CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210557Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Division Diretcor
CDTL Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND)
Office of Drug Evaluation (ODE) III
Division of Bone, Reproductive, and Urologic Products (DBRUP)
Clinical Memorandum

June 25, 2019

To: NDA 210557

From: Christina Chang, M.D., M.P.H. – Clinical Team Leader, DBRUP

Through: Audrey Gassman, M.D., – Deputy Division Director, DBRUP

This memorandum serves to amend information contained Section 1.3 in the June 21, 2019 Summary Review for Vyleesi.

Vyleesi is a drug-device combination product containing the active ingredient bremelanotide (BMT), a synthetic heptapeptide and melanocortin receptor (MCR) agonist, in a prefilled syringe. Vyleesi was approved on June 21, 2019 for the treatment of premenopausal women with acquired, general hypoactive sexual desire disorder (HSDD).

In the Summary Review finalized on June 21, 2019, a table in Section 1.3 (titled Patient Experience Data) was inadvertently truncated. The complete table is shown below.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
x	**The patient experience data that were submitted as part of the application include:**			
	x	Clinical outcome assessment (COA) data, such as		Section 8.1.1 Study Endpoints
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	x	Patient-focused drug development or other stakeholder meeting summary reports[1]		Section 8.1.1 Study Endpoints
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

[1] FDA Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction held on October 26 and 27, 2014, respectively. https://www.federalregister.gov/documents/2014/09/26/2014-22983/patient-focused-drug-development-public-meeting-and-scientific-workshop-on-female-sexual-dysfunction

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/s/

CHRISTINA Y CHANG
06/25/2019 03:40:37 PM
Amendment to Section 1.3 of UniReview

AUDREY L GASSMAN
06/25/2019 03:42:11 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210557
Priority or Standard	Standard
Submit Date(s)	March 23, 2018
Received Date(s)	March 23, 2018
PDUFA Goal Date	June 23, 2019 (After Extension)
Division/Office	DBRUP
Review Completion Date	June 21, 2019
Established Name	Bremelanotide
(Proposed) Trade Name	(Vyleesi)
Pharmacologic Class	melanocortin receptor (MCR) agonist
Code name	
Applicant	AMAG Pharmaceuticals, Inc.
Formulation(s)	Subcutaneous injection
Dosing Regimen	One injection, as needed, not to exceed more than one dose in a 24-hour period and not to exceed 8 doses per month
Applicant Proposed Indication(s)/Population(s)	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Premenopausal women with acquired, generalized HSDD

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OPQ Office of Pharmaceutical Quality
OPDP Office of Prescription Drug Promotion
OSI Office of Scientific Investigations
OSE Office of Surveillance and Epidemiology
DBRUP Division of Bone, Reproductive, and Urologic Products
DEPI Division of Epidemiology
DMEPA Division of Medication Error Prevention and Analysis
DRISK Division of Risk Management
DCaRP Division of Cardiorenal Products
DDDP Division of Dermatology and Dental Products

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Glossary

ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotropic hormone
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
α-MSH	α-melanocyte-stimulating hormone
AUC	area under the plasma concentration-time curve
BLA	biologics license application
BMI	body mass index
BMT	bremelanotide
BP	blood pressure
bpm	beats per minute
cAMP	cyclic adenosine monophosphate
CAVGDOSE	average plasma concentration during dosing days
CDF	cumulative distribution function
CDRH	Center for Devices and Radiological Health
CI	clinical investigator
CNS	central nervous system
COA	clinical outcome assessment
CPK	creatinine phosphokinase
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DBRUP	Division of Bone, Reproductive, and Urologic Products
DCaRP	Division of Cardiovascular and Renal Products
DDDP	Division of Dermatology and Dental Products
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMEPA	Division of Medication Errors and Prevention and Analysis
DMF	Drug Master File
DMV	dorsal motor nucleus of the vagus
DSM	Diagnostic and Statistical Manual of Mental Disorders
eCDF	electronic cumulative distribution function
ECG	electrocardiogram
EDQ	Elements of Desire Questionnaire
EIC	Expected Introduction Concentration

EMITT	expanded modified intent-to-treat
EOS	end of study
ETASU	Elements to Assure Safe Use
F0	initial generation
F1	first filial generation
F2	second filial generation
FDA	Food and Drug Administration
FSAD	female sexual arousal disorder
FSD	female sexual dysfunction
FSEP-R	Female Sexual Encounter Profile–Revised
FSFI-D	Female Sexual Function Index–Desire Domain
FSDS-DAO	Female Sexual Distress Scale–Desire/Arousal/Orgasm
FSH	follicle stimulating hormone
GAQ	General Assessment Questionnaire
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
GLP-1	glucagon-like peptide-1
HED	human equivalent dose
HPA	hypothalamic pituitary adrenal
HR	heart rate
HSDD	hypoactive sexual desire disorder
HTN	hypertension
ICH	International Conference on Harmonisation
ICV	intracerebroventricular
IN	intranasal
IND	investigational new drug
ISS	integrated summary of safety
IV	intravenous
K_i	inhibitory constant
LD	lactation day
LFT	liver function test
MAR	missing at random
MCR	melanocortin receptor
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MMRM	Mixed-Effect Model Repeated Measure
MOE	margin of exposure

NDA	new drug application
NOAEL	no-observed-adverse-effect level
NOEL	no observable effect level
OLE	open-label extension
PBO	placebo
PD	pharmacodynamics
PHQ	Patient Health Questionnaire
PK	pharmacokinetics
PPY	peptide YY
PRN	as needed
PRO	patient-reported outcome
QD	once a day
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous
SNRI	serotonin and norepinephrine reuptake inhibitor
SOC	system organ class
SSE	satisfactory sexual event
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TK	toxicokinetic
ULN	upper limit of normal

1 Executive Summary

1.1. Product Introduction

Vyleesi is a drug-device combination product containing the active ingredient bremelanotide (BMT), a synthetic heptapeptide and melanocortin receptor (MCR) agonist, in a prefilled syringe. BMT is a new molecular entity and is not currently approved for use for any indication in any country. AMAG Pharmaceuticals (the Applicant) is seeking the marketing authorization for BMT 1.75 mg SC injection, using an autoinjector, for the treatment of premenopausal women with acquired, generalized, hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to co-existing medical condition, problems with the relationship, or the effects of a medication or drug substance. The product is proposed for use, as needed, at least 45 minutes prior to each sexual encounter. Consecutive doses should be taken at least 24 hours apart. Using more than eight doses in a month is not recommended.

APPEARS THIS WAY ON ORIGINAL

1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

We recommend approval of Bremelanotide (BMT), tradename Vyleesi, 1.75 mg subcutaneous injection for the treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women. HSDD is defined as absent or low desire for sexual activity that causes marked distress or interpersonal difficulty that is not accounted for by co-existing medical or psychiatric conditions, use of medications or drug substances, or problems within a relationship. HSDD is "acquired" if symptoms begin after a period of relatively normal sexual function and is "generalized" if symptoms are not limited to certain types of stimulation, situations, or partners. BMT is a melanocortin receptor agonist but the mechanism by which BMT improves the symptoms of HSDD is unknown.

HSDD can adversely impact emotional and psychological well-being and the relationship with the partner. Currently, only one drug (Addyi) is FDA-approved for the treatment of acquired, generalized HSDD. Approval of BMT adds a new therapy to the treatment armamentarium.

The Applicant conducted two, 6-month, randomized, placebo-controlled trials to evaluate the efficacy and safety of BMT in premenopausal women with acquired, generalized HSDD. BMT 1.75 mg or placebo was injected subcutaneously as needed and was used, on average, 2-3 times per month. Sexual desire was measured with the Female Sexual Function Index-Desire Domain (FSFI-D), on a scale of 1.2 to 6.0 using a 28-day recall. Distress was measured by Question 13 of the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO) instrument, which asked about bother or distress on a scale of 0 to 4 using a 30-day recall. From a baseline median of 1.8 for the sexual desire score, BMT-treated subjects had a median improvement of 0.6 compared to a median change of 0 for placebo. From a baseline median of 3 for the distress score, BMT-treated subjects had a median improvement of 1 compared to a median change of 0 for placebo. These treatment differences were statistically significant.

The safety profile of BMT is acceptable for use as-needed. As noted previously, most subjects used BMT infrequently during the phase 3 trials (two to three times per month on average). Very few subjects used more than 8 doses of BMT per month.

We do not recommend more than 8 doses per month. There is very limited safety information with more than 8 doses per month, and more frequent dosing carries an increased risk of focal hyperpigmentation. More frequent dosing will also increase the length of time per month when blood pressure is increased.

Notable adverse reactions included transient increases in blood pressure and reductions in heart rate, focal hyperpigmentation, and nausea.

BMT transiently increased mean systolic and diastolic blood pressure by 3 mmHg and transiently decreased heart rate by 2 bpm. These changes usually returned to baseline by 12 hours post-dosing without a cumulative effect. These transient blood pressure increases with up to 8 doses per month are not expected to appreciably increase the risk of cardiovascular disease in the indicated population, which is generally at low cardiovascular risk. This risk can be adequately mitigated with labeling including a warning for transient blood pressure increases and a contraindication in patients with uncontrolled hypertension or known cardiovascular disease. Because of the risk of additive blood pressure effects with stacked doses, labeling will also recommend that consecutive doses be separated by at least 24 hours. This is important to communicate because a fraction of subjects (3.9%) used consecutive doses of BMT less than 12 hours apart in the phase 3 trials.

BMT caused focal hyperpigmentation (face, gingiva and breasts) in 1% of subjects in the phase 3 trials, and more commonly in the black population. Reversibility was documented in one-half of cases during the period of follow-up. A higher incidence of focal hyperpigmentation was seen with daily dosing for 16 days. This risk will be labeled in the Warnings and Precautions section of labeling, and as noted above, is one of the reasons for not recommending more than eight doses per month.

Other common adverse reactions included flushing, injection site reactions and headache. These are included in the Adverse Reactions section of labeling.

There were few BMT-exposed pregnancies in the clinical program. Nonclinical studies could not identify a no observed effect level (NOEL) in developmental toxicity studies. Therefore, labeling recommends effective contraception and to promptly discontinue BMT if pregnancy is suspected. Because inadvertent pregnancy is expected given the indication and population, we are requiring the Applicant to conduct two pregnancy-related postmarketing studies (observational pregnancy registry and retrospective epidemiology study) to evaluate the effect of BMT on pregnancy outcomes. We are also requiring a lactation study to assess the effect of BMT on breastfed neonates.

There was one case of liver injury (serum transaminases 40X upper limit of normal (ULN), total bilirubin (b) (4) X ULN) following the 20th dose and 1 year of BMT use. Extensive work up did not identify the etiology. This was classified as a possible but not probable case of drug-induced liver injury (DILI). There was no other signal for DILI in the database, such as outliers of serum transaminase elevations. This case will be described In the Adverse Reactions section of labeling and we will continue to monitor for liver toxicity in the postmarketing setting.

No additional risk management interventions beyond labeling and routine pharmacovigilance are needed.

We conclude that the benefits of BMT outweigh its risks when used according to labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hypoactive sexual desire disorder (HSDD) is defined as absent or low desire for sexual activity that causes marked distress or interpersonal difficulty and is not accounted for by co-existing medical or psychiatric conditions, use of medications or drug substances, or problems within a relationship. Survey data suggest that approximately 8% of premenopausal women in the United States are affected by HSDD.[1] • HSDD is "acquired" if symptoms begin after a period of relatively normal sexual function and is "generalized" if symptoms are not limited to certain types of stimulation, situations, or partners. • HSDD can adversely impact emotional and psychological well-being and relationships with the partners.[2] • HSDD is usually chronic. The etiology is unknown.	Acquired, generalized HSDD is a chronic condition that can adversely affect a woman's physical and emotional well-being and relationship with her partner.

[1] West SL et al., 2008. Prevalence of Low Sexual Desire and Hypoactive Sexual Desire Disorder in a Nationally Representative Sample of US Women. Arch Intern Med, 168(13):1441-1449.

[2] FDA Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction held on October 26 and 27, 2014, respectively. https://www.federalregister.gov/documents/2014/09/26/2014-22983/patient-focused-drug-development-public-meeting-and-scientific-workshop-on-female-sexual-dysfunction

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Addyi (flibanserin) is the only FDA-approved medication for HSDD and is indicated for premenopausal women with the acquired and generalized form. It is taken daily at bedtime. • Compared to placebo: – The median improvement in satisfying sexual events (SSEs) was 0.5 to 1.0 event per month from a mean baseline of 2-3 events per month – The mean improvement in sexual desire was 0.3 to 0.4 from a mean baseline of 1.8-1.9, assessed with the Female Sexual Function Index-desire domain (FSFI-D), on a scale of 1.2 to 6.0. – The mean improvement in distress was 0.3 to 0.4 from a mean baseline of 3.2-3.4, assessed with Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R), which rated bother on a scale of 0 to 4. • Addyi is not widely used. The key risks associated with Addyi are hypotension, syncope, and central nervous system (CNS) depression, which are exacerbated when Addyi is taken concomitantly with alcohol, moderate to strong CYP3A4 inhibitors, and in the presence of hepatic impairment. Addyi's current labeling has a Boxed Warning and contraindication for use with alcohol, moderate or strong CYP3A4 inhibitors, and hepatic impairment due to severe hypotension and syncope. Because of the risks of hypotension and syncope associated with the alcohol interaction, Addyi is only available through a risk evaluation and management strategy (REMS) program; certification of prescribers and pharmacists is required to ensure and document that patients receive counseling regarding these risks.	Addyi is the only approved drug for HSDD. New treatment options would be useful.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In two, 6-month, randomized trials in 1247 premenopausal women with generalized, acquired HSDD, bremelanotide (BMT) 1.75 mg injected subcutaneously, as needed, improved sexual desire and associated distress compared to placebo. Women used, on average, two to three injections per month. • Sexual desire was measured using the FSFI-D. Distress was measured by Question 13 of the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO) instrument, which asks about bother or distress on a scale of 0 to 4. • The median improvement in FSFI-D was 0.6 for BMT compared to 0 for placebo. The median improvement in distress was 1 for BMT compared to 0 for placebo. • For patients who completed the trials, a higher percentage of BMT-treated patients had at least a 1.2-point improvement from baseline in the FSFI-D score compared to placebo, and a higher percentage of BMT-treated patients had at least a 1-point improvement from baseline in the FSDS-DAO Q13 score compared to placebo. • These thresholds (1.2-point increase in the FSFI-D score and 1-point decrease in the FSDS-DAO Q13 score) are meaningful change scores and were derived from patients who identified as having experienced a meaningful improvement based on multiple anchor measures. • The recall period for the key instruments was approximately one month, which may not have been optimal for assessing improvements around the time of the few injections per month. This would be expected to bias the trial towards the null hypothesis of no difference between treatment groups because patients would presumably be factoring in most days when they had not received BMT during the one-month recall. • BMT did not improve the number of SSEs, which was evaluated as a key secondary endpoint. We do not require an improvement in SSEs for drugs intended to treat HSDD, only that these drugs improve low desire and associated distress, which are the hallmark symptoms of HSDD. SSEs are not part of the diagnostic criteria for HSDD. • The efficacy of BMT has not been established in postmenopausal women.	In premenopausal women with generalized, acquired HSDD, BMT 1.75 mg injected subcutaneously, as needed, leads to modest improvements in low sexual desire and associated distress – the hallmark symptoms of HSDD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The primary safety database includes 1057 subjects who received BMT in phase 3 trials. • Most subjects used BMT infrequently; on average, subjects used BMT two to three times per month and few used BMT more than seven times per month (1.6% or 9/620 in the placebo-controlled phase 3 trials and 1.3% or 9/678 in their uncontrolled extensions). However, 3.9% of subjects in the phase 3 trials took at least two BMT doses less than 12 hours apart even though they were instructed to inject no more than one dose in a 24-hour period. *(continued below)*	• The overall safety profile of BMT is acceptable for an as-needed drug. • The duration of the treatment effect after an injection has not been adequately characterized. • We do not recommend more than 8 doses per month. There is very limited safety information with more than 8 doses per month. Daily dosing for 16 days considerably increased the risk of focal hyperpigmentation. More frequent dosing will also increase the length of time per month when blood pressure is increased. • We do not recommend injecting consecutive doses more frequently than every 24 hours. In the phase 3 trials, most subjects injected at least 24 hours apart. There is a risk of additive blood pressure effects with stacked doses.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management (continued)	• Compared to placebo, BMT transiently increased mean systolic and diastolic blood pressure by 3 mm Hg, and transiently decreased heart rate by 2 bpm. These changes returned to baseline prior to the next scheduled BMT dose without a cumulative effect, which supports the proposed dosing interval of at least 24 hours between injections. • The phase 3 trials excluded women with uncontrolled hypertension or known cardiovascular disease and had limited information on women with well-controlled hypertension. • The safety of BMT has not been established in postmenopausal women. This population had greater variability in BMT exposure and has a higher background rate of cardiovascular disease than premenopausal women. • BMT caused focal hyperpigmentation in about 1% of subjects in the phase 3 trials. When BMT was administered daily for 8 consecutive days, the incidence of focal hyperpigmentation was 38%. There does not appear to be an increased risk in developing nevi that are atypical or undergo malignant transformation, although the duration and extent of exposure in the phase 3 trials limits definitive conclusions. These focal pigmentary changes occurred in cosmetically important areas such as the face, gingiva, and breasts and occurred more frequently in women with darker skin. Resolution of pigmentary changes did not occur in all women during the period of follow-up. *(continued below)*	• These transient blood pressure increases with up to 8 doses per month are not expected to appreciably increase the risk of cardiovascular disease in the indicated population, which is generally at low cardiovascular risk. This risk can be adequately mitigated with labeling including: – A contraindication in patients with uncontrolled hypertension or known cardiovascular disease. – A warning regarding transient increases in blood pressure and transient decrease in heart rate in Section 5. • A Limitation of Use for postmenopausal women, who generally have a higher background risk of cardiovascular disease and in whom efficacy has not been established. • The risk of focal hyperpigmentation is described in the Warnings and Precautions section. Prescribers are alerted to instruct patients to seek care if pigmented areas develop or have changes that are of concern.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management (continued)	• Use of BMT in premenopausal women to improve sexual desire increases the risk of BMT exposure during pregnancy and lactation. Available nonclinical data show fetal harm, and a no observed effect level could not be established. Human pregnancy data in the clinical program were too limited. There is also no information on whether BMT is secreted in breast milk. • Nausea was the most common adverse reaction during the placebo-controlled trials and their uncontrolled extensions. Up to 40% of BMT-treated subjects experienced nausea, compared to 1% of placebo-treated subjects. About 8% of patients discontinued BMT due to nausea and 13% of patients required anti-emetics to manage their symptoms. • Other common adverse reactions (≥5%) included flushing, injection-site reactions, headache, and vomiting. Less common adverse reactions (2% to <5%) included cough, fatigue, hot flushes, paresthesias, dizziness and nasal congestion. Elevated creatinine phosphokinase levels occurred in 1.3% of patients exposed to BMT compared to 0% with PBO. • One case of hepatic injury with serum transaminases elevated above 40X upper limit of normal (ULN) and total bilirubin 7X ULN was reported in 52-year-old subject 10 days after her last BMT injection (1 year after start of study drug and 20th total dose). Extensive work up did not identify the etiology. This was classified as a possible but not probable case of drug-induced liver injury (DILI) . There was no other signal for DILI in the database, such as outliers of serum transaminase elevations.	• Labeling recommends effective contraception when using BMT and to promptly discontinue BMT if pregnancy is suspected. Because inadvertent pregnancy is expected given the indication and population, we are requiring the Applicant to conduct two pregnancy-related postmarketing studies – a pregnancy registry and a retrospective cohort study to evaluate the effect of BMT on pregnancy outcomes. We are also requiring a lactation study to assess the effect of BMT on breastfed neonates. • Nausea is described in the Warnings and Precautions section. Providers are alerted that anti-emetics may be necessary. Other common adverse reactions are labeled in Section 6. • The single case of acute hepatitis is described in Section 6 Adverse Reactions. We will monitor for postmarketing cases of liver injury associated with BMT use. • No additional risk management interventions beyond labeling and routine pharmacovigilance are required.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	Section 8.1.1 Study Endpoints
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	x	Patient-focused drug development or other stakeholder meeting summary reports			Section 8.1.1 Study Endpoints
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
X	Patient experience data that was not submitted in the application but was considered in this review.[3]				

[3] FDA Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction held on October 26 and 27, 2014, respectively. https://www.federalregister.gov/documents/2014/09/26/2014-22983/patient-focused-drug-development-public-meeting-and-scientific-workshop-on-female-sexual-dysfunction

2 Therapeutic Context

2.1. Analysis of Condition

In the fourth edition (text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) published by the American Psychiatric Association, HSDD is characterized as a deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty.[4] Additionally, HSDD cannot be better accounted for by a general medical, other psychiatric, or a substance or drug-related condition. HSDD is further classified as either acquired (symptoms beginning after a period of relatively normal sexual function) or lifelong (present since the individual became sexually active). HSDD can also be either generalized (not limited to certain types of stimulation, situations, or partners) or situational (only occurs with certain types of stimulation, situations, or partners). In DSM-5, however, HSDD is no longer listed as a single diagnostic entity because HSDD was combined with female sexual arousal disorder (FSAD) into a new condition—female sexual interest/arousal disorder.[5] For this application, the Applicant is seeking an indication of acquired, generalized HSDD in premenopausal women.

Survey data suggest that approximately 8% of U.S. premenopausal women may have HSDD. HSDD can cause emotional and psychological distress and significantly impact the relationship with the partner. There is an ongoing debate in the scientific community whether sexual desire is a constant phenomenon or if it ebbs and flows from day to day; however, the general condition of low or absent sexual desire is considered chronic in the majority of patients. The etiology of acquired HSDD is unknown.

2.2. Analysis of Current Treatment Options

Addyi® (flibanserin 100-mg oral tablets), available since 2015 for the treatment of HSDD in premenopausal women, is the only medical treatment approved by the FDA for HSDD in the U.S. Addyi® was shown to increase satisfactory sexual events (SSEs) (median treatment difference from placebo (PBO) of 0.5 to 1.0 event per month) and to increase the Female Sexual Function Index-Desire Domain (FSFI-D) score (mean treatment difference from PBO of 0.3-0.4 on a scale ranging from 1.2 to 6.0).

[4] Diagnostic and Statistical Manual of Mental Disorder (DSM), Washington, DC: American Psychiatric Association: DSM-III-R, published in 1987; DSM-IV, published in 1994; DSM-IV, Primary Care Version, published in 1995; DSM-IV-TR (text revision), published in 2000.

[5] DSM-5, published in 2013.

Addyi® is taken daily at bedtime because administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system depression. Because of these risks, the use of Addyi® beyond 8 weeks is not recommended if symptomatic improvement is not seen. Additionally, these risks are exacerbated when alcohol is taken at the same time as Addyi®; therefore, alcohol use is contraindicated in patients taking Addyi®. To mitigate these risks, a Boxed Warning was included in Addyi®'s labeling and a REMS program with Elements to Assure Safe Use (ETASU) was implemented, requiring prescribers and pharmacists to counsel patients on Addyi®'s interaction with alcohol. The use of Addyi® has been limited to date.

Testosterone has been used off-label in women for the treatment of sexual disorders, including HSDD.[6] However, response to therapy may be difficult to assess, as testosterone levels are not correlative with HSDD symptoms. Moreover, chronic testosterone administration may have adverse effects on lipid profile, hair growth and skin conditions such as acne. Safety data on long-term testosterone use in women with this condition are lacking. Notably, a testosterone patch was available briefly in Europe for treatment of HSDD but was not approved in the United States.[7]

Nonpharmacological interventions—such as cognitive behavior therapy, sex therapy, or couples' therapy—have been reported to decrease symptom severity in women with HSDD;[8] however, evidence from adequate and well-controlled clinical trials demonstrating effectiveness of these types of psychological therapies is needed.

[6] Wierman ME et al., 2014. Androgen therapy in women: a reappraisal: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 99(10):3489-510.

[7] In 2006, Intrinsa TTS (testosterone transdermal system) was approved in Europe for the treatment of HSDD in surgically menopausal women who are on concomitant estrogen therapy. In 2012, the marketing authorization holder, Warner Chilcott, voluntarily withdrew the marketing authorization for "commercial reasons."

[8] Frühauf S et al., 2013. Efficacy of Psychological Interventions for Sexual Dysfunction: A Systematic Review and Meta-Analysis. Arch Sex Behav, 42(6):915-33.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant initially developed BMT for intranasal (IN) administration for male erectile dysfunction (ED) (under IND 61706) (b) (4) investigational new drugs (INDs) have now been withdrawn. (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The clinical program for the HSDD indication was conducted under IND 64119, initially submitted by Palatin Technologies, Inc. The current Applicant (AMAG Pharmaceuticals, Inc.) acquired the rights to the new drug application (NDA) on 20Nov2017. Major milestone submissions and communications are listed in Table 1 below. Pertinent advice and agreements are summarized thereafter.

Table 1. Regulatory History: Major Milestones and Communications IND 64119

IND 64119	Date	Comment
Initial IND submission	8Feb2002	(b) (4)
Type C guidance meeting	23Jan2008	
Type C guidance meeting	20Jan2011	
EOP2 meeting	9Apr2013	
SPA	21Jun2013	Non-agreement letter to SPA sent 5Aug2013
Type A meeting follow-up to SPA non-agreement letter	5Nov2013	
WRO COA endpoints	2May2014	
Type C meeting Clinical/COA issues	8Sep2016	
WRO Clinical Pharmacology issues	1Nov2016	
Pre-NDA meeting	18Sep2017	

Abbreviations: EOP2 end-of-phase 2, SPA special protocol assessment, WRO written response only, COA clinical outcome assessment, HSDD hypoactive sexual desire disorder

Initial IND Submission

The initial IND submission proposed a phase 1, double-blind, PBO-controlled, dose-escalation study to evaluate the safety, tolerability, and pharmacodynamic effect of SC BMT administration in healthy female subjects (PT-141-2002-14F). Subsequently, a phase 2b study

(PT-141-2005-53FB) was conducted in pre- and postmenopausal women with FSAD to explore the efficacy and safety of 10 mg IN BMT.

Type C Meeting (23Jan2008; minutes dated 20Feb2008)

Results of the phase 2b study (PT-141-2005-53FB) were discussed:

- Although greater responses were seen in postmenopausal women, this group also experienced more frequent adverse events (AEs) of nausea/vomiting and increased blood pressure (sustained elevations in mean systolic blood pressure (SBP) of 9 to 10 mm Hg and mean diastolic blood pressure (DBP) of 5 mm Hg of at least 4 hours duration). Overall, there were more discontinuations from the BMT group than PBO group, driven largely by AEs of nausea/vomiting and blood pressure increases.
- The Division of Bone, Reproductive, and Urologic Products (DBRUP) voiced concerns that the 10-mg IN dose may be too high, noting that the development program will need to provide enough safety data to support cardiovascular safety, particularly in postmenopausal women.

(b) (4)

- Any instruments to be used to demonstrate efficacy should be validated in the target population and agreed-upon by DBRUP prior to use in phase 3 trials. Validation of the instruments is necessary for those instruments that will be used for labeling claims and included in the statistical hypothesis.

Following this meeting, the SC formulation was carried forward to reduce the variability in systemic exposure and potentially decrease the incidence of AEs. The Applicant also opted to limit the development program to premenopausal women.

Type C Meeting (20Jan2011; minutes dated 18Feb2011)

The design of a phase 2b, randomized, PBO-controlled, dose-finding trial (PT-141-54, hereafter referred to as Study 54) to evaluate the efficacy and safety of SC BMT in premenopausal women with FSAD and/or HSDD was discussed. DBRUP stressed including blood pressure

threshold as withdrawal criteria and the use of 24-hour ambulatory blood pressure monitoring following the first dose of study drug.

(b) (4)

- Regarding study PT-141-54, provide available information about exposure at different sites (i.e., anterior thigh or the abdomen). DBRUP recommended that subjects record the injection site location used so that the Applicant can determine whether there are any differences in exposure between the sites.

(b) (4)

- The optimal frequency with which to evaluate sexual desire (daily, weekly, monthly, or only with treatment) has not been determined.

Advice Letter (dated 18Jul2011)

- Following a review of safety data and supporting rationale, DBRUP agreed with the revised doses to be used in Study 54: 0.75 mg, 1.25 mg, and 1.75 mg BMT.
- For the analysis of change from baseline in the number of SSEs, provide all SSEs that occur during a given month as well as SSEs that were associated directly with the "as needed" use of active drug or PBO treatment.
- DBRUP recommended pharmacokinetic sampling longer than 4 hours postdose to adequately characterize the pharmacokinetics (PK) of BMT following SC administration.

End-of-Phase 2 Meeting (9Apr2013; minutes dated 30Apr2013)

Preliminary results of Study 54 and design of phase 3 trials were discussed.

- The Applicant clarified that most of the subjects who participated in Study 54 had a primary diagnosis of HSDD.
- The Applicant's chosen patient-reported outcome (PRO) instruments (FSFI-D and the Female Sexual Distress Score/Desire Arousal Orgasm or FSDS-DAO) were not considered optimal (see Trial Design, Coprimary Endpoints discussion in Section 8.1.1). There were also concerns regarding the enrollment criteria for FSFI and FSDS-DAO (see Trial Design, Inclusion Criteria in Section 8.1.1).

- Primary and secondary endpoint selection (see Trial Design, Study Endpoints discussion in Section 8.1.1).
- Blood pressure and HR monitoring (see Blood Pressure Elevations discussion in Section 8.2.6).
- The average time (from first use or the number of uses) to onset of a significant clinical benefit should be determined.
- Address the potential for BMT to affect the adrenal-cortisol axis.
- Address the potential for BMT-associated suicidality. Consider incorporating the Columbia Suicide Severity Rating Scale in the phase 3 program.

Protocol Intended for Two Identical Phase Trials (BMT-301 and BMT-302).

Submitted for review under special protocol assessment (submitted by Applicant 20Jun2013).

DBRUP Issued a Special Protocol Assessment Non-Agreement Letter (5Aug2013)

- DBRUP commented on the endpoints and PRO instruments (see discussion in Section 8.1.1).
- DBRUP requested that the Applicant provide analysis based on administration site (abdomen versus thigh) to evaluate whether one site may be driving the overall efficacy.
- Based on the PK profile of the product, the Applicant was advised to propose a period within which efficacy due to BMT use can be established.
- DBRUP requested that the safety database be consistent with guidelines per the International Conference on Harmonisation (ICH) for chronically administered drugs.[9] These exposures must occur at the dose or dose range believed to be efficacious.
- The Applicant was asked to clarify, with justification, how the baseline number of SSEs should be counted during the PBO run-in period (i.e., total number SSEs versus only SSEs occurring with the use of PBO).
- The Applicant was asked to provide details on sample-size calculation, such as the assumed treatment differences between the two treatment groups for the change from baseline in number of SSEs and change from baseline in the FSFI-D respectively and the simulation method.
- DBRUP was concerned that the reminder telephone calls (approximately 10 days after each visit) may influence data capture and, in turn, bias trial outcome. A standard script to be used during these reminder calls was requested.
- The average time (from first use or the number of uses) to onset of a significant clinical benefit may be assessed as a secondary endpoint.

[9] ICH Harmonised Tripartite Guideline *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions E1* (October 1994), accessed 9May2019, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf.

- For the coprimary endpoints and key secondary endpoints, to assess the sensitivity of missing data, DBRUP recommended repeating the primary efficacy analyses for subjects who complete the double-blind treatment period.
- DBRUP recommended a longer stability period of 60 days at room temperature for the auto-injectors.
- The product used in phase 3 clinical trials should be the final, to-be-marketed product.

Type A Meeting (5Nov2013; minutes dated 5Dec2013)

This meeting followed the special protocol assessment non-agreement letter.

- The Applicant agreed with DBRUP's recommendation that two positive, phase 3, PBO-controlled trials with 24 weeks of active treatment conducted in North America would be required to support an NDA.
- DBRUP noted that in the phase 2 trial (Study 54), BMT was used infrequently and questioned how an as-needed (PRN) dosing regimen may be supported.
- DBRUP noted the incongruence between the Applicant's statement that sexual desire is best conceptualized as a cumulative, nonintermittent experience assessed over a prolonged period (e.g., a month) and the proposed PRN dosing regimen for BMT.
- DBRUP reiterated the concern regarding long recall period with the FSFI-D (28 days) that may increase that difficulty in detecting and attributing to the drug a treatment difference.
- DBRUP did not agree with the use of a (b) (4) window for treatment effect in the absence of exposure and modeling data to support this period.
- DBRUP recommended that the Applicant incorporate the use of a simple diagnostic tool into its phase 3 program to allow healthcare providers to readily and accurately diagnose HSDD before treating the patient. DBRUP asked the Applicant to propose a method that would demonstrate a correlation in diagnosing the condition between using the simple tool and using the more complex instruments.
- DBRUP recommended evaluating two doses of BMT in the phase 3 trials.

Written Response Only (2May2014)

- FSFI-D: Recall period and the content validity issues further discussed (See Trial Design discussion in Section 8.1.1). Four options were provided to the Applicant with respect to FSFI-D and recall periods.
- (b) (4)

Type C Meeting (8Sep2016; minutes dated 23Sep2016)

This was a clinical/clinical outcome assessment (COA)–focused meeting.

- The Applicant was asked to provide efficacy, safety, and PK data by injection site for three groups: subjects who had only abdominal injections; subjects who only had thigh injections; and subjects who had both abdominal and thigh injections.
- The Applicant proposed a major change in endpoint hierarchy before unblinding the phase 3 data (see Trial Design, Study Endpoints in Section 8.1.1).
- DBRUP strongly disagreed (b) (4)
- DBRUP did not agree (b) (4)
- Based on use during phase 3, it seems unlikely that sufficient safety data from enough patients (n=100) will be collected in order to support daily use over (b) (4) weeks as required. Accordingly, labeling may limit use to the dosing regimen observed in the trials (e.g., a maximum of six doses in a 28-day period).
- DBRUP reiterated the request for a specific plan to characterize the onset and duration of treatment effect that will support the Dosage & Administration instructions of the product label.
- PROs that have not been validated (e.g., the General Assessment Questionnaire (GAQ), or specifically, question 3 in the GAQ) cannot be used to support labeling claims.
- DBRUP requested an abuse potential assessment because BMT is a new molecular entity that acts on the central nervous system.
- If there are a significant number of women enrolled with male partners with ED, present a subgroup analysis of the data comparing efficacy in women whose partners have ED compared with those who do not.

Written Response Only (11Nov2016)

This was a clinical pharmacology–focused meeting under IND 64119.

- DBRUP requested a drug-drug interaction (DDI) study with an oral anti-diabetic medication to assess any glucose altering interaction.
- BP monitoring discussion (see Section 8.1.1).
- DBRUP requested additional clinical information on all BP outliers and any episode of hypertension in Study 32, in which subjects had controlled essential hypertension.

- A hormonal contraceptive study was strongly recommended prior to approval to better assess potential changes in pharmacodynamic parameters such as changes in BP and HR in women of reproductive potential.
- A Human Factors study should be conducted to assess whether the product can be appropriately administered by the intended users, for the intended uses, and for the intended-use environments.

Pre-NDA Meeting (18Sep2017; minutes dated 17Oct2017)

- Presentation of data and pooling strategy were discussed.
- DBRUP requested focused safety assessment relating to hepatic injury and blood pressure, including patient narratives for those with liver injury as well as outlier blood pressure data (SBP>160 mm Hg or change >20 mm Hg, DBP>100 mm Hg or change >20 mm Hg) or heart rate (HR) values (HR >100 beats per minute (bpm) or change >20 bpm).
- The Applicant should provide additional details to describe the process for determining meaningful change in the efficacy assessments.
- DBRUP reiterated the recommendation for a new ambulatory blood pressure monitoring (ABPM) study given the safety signals already observed (see Section 8.2.6).
- The time to onset for drug effect used in labeling should be based on the dosing instruction used in the pivotal phase 3 studies, i.e., “at least 45 minutes before anticipated sexual activity.”
- DBRUP requested information regarding the induction effect of BMT on CYP enzymes.
- DBRUP requested a risk assessment of the immunogenicity of BMT because even peptides as short as seven to eight amino acids can be immunogenic.
- Patients with hypertension or elevated blood pressures were largely excluded in the clinical program. Implication on labeling was discussed.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Four clinical sites participating in Studies 301 and 302 were primarily selected for inspection because of high enrollment and level of site-specific efficacy findings relative to overall efficacy. One of these sites was also selected because of a delayed reporting of a clinically significant AE (hepatic injury). An inspection of the Applicant was also conducted.

Based on the results of these inspections, the Office of Scientific Investigations concluded that Studies 301 and 302 appear to have been conducted adequately and that the data generated by these sites and submitted by the Applicant appear acceptable to support the indication sought. There were no human subject protection issues that could affect data integrity, and there were no data integrity issues with respect to efficacy and safety findings. For details, see Office of Scientific Investigations summary review by Roy Blay, PhD, dated 17Jan2019.

4.2. Product Quality

Vyleesi (BMT) injection is a drug-device combination product designed to deliver a single 1.75 mg BMT dose via subcutaneous injection of a sterile 0.3 mL solution.

BMT is a synthetic cyclic heptapeptide prepared (b) (4)

While there are numerous potentially related substances formed during synthesis, four main impurities Imp A, B, C, and D have been identified. Suitable controls for these related substances as well as for unspecified impurities have been established consistent with levels qualified from the nonclinical perspective. Three potential genotoxic impurities were identified. However, the Applicant has adequately demonstrated that the (b) (4) reduces these materials to acceptable levels.

The drug substance is stable for (b) (4) months when stored at (b) (4) C. Suitable controls have been established to ensure the identity, strength, quality, and purity of the drug substance. The drug product is a prefilled syringe containing 0.3 mL of an aqueous solution containing the equivalent of 1.75 mg BMT, and glycerin. Solution pH is adjusted to (b) (4) with hydrochloric acid and/or sodium hydroxide. The osmolality is (b) (4)

The (b) (4) syringe consists of a (b) (4) 1-mL typ (b) (4) glass barrel with a (b) (4) stopper/piston (b) (4) stainless steel ½" 29-gauge needle, and a rigid needle shield. A leachables/extractables study and toxicologic evaluation confirmed the compatibility of all components.

The drug product manufacturing process consists of preparation (b) (4) As a product for subcutaneous injection, assurance of sterility is critical for safe use by patients.

Adequate component sterilization, environmental conditions and monitoring, process validation, container closure (syringe) integrity, and drug product testing (sterility and endotoxins) have been demonstrated. Overall, the Applicant has adequately demonstrated that the manufacturing process is robust and suitable for ensuring the sterility of the product.

Specified degradation products Deg A, B, C, D, and (b) (4) Both specified and unspecified degradation products have been qualified through a 91-day toxicology study. Appropriate limits have been established in the drug product specification.

An expiration dating period of 36 months at or below 25°C has been established for the drug product, but it should not be frozen.

Overall, the Applicant has provided sufficient product quality information including the specifications necessary to ensure the identity, strength, quality, purity, potency, and performance of the prefilled syringe and assembled autoinjector at release and through the expiration dating period.

All facilities associated with the manufacture, packaging, and control of the drug substance and finished product have acceptable Current Good Manufacturing Practices status. The claimed categorical exclusion from the requirement for preparation of an environmental assessment in accordance with 21 CFR 25.31(b) is acceptable based on a calculated Expected Introduction Concentration (EIC-aquatic) significantly below 1 ppb. For detailed product quality review, refer to the Office of Product Quality Integrated Quality Assessment review by Mark Seggel, PhD, dated 10Apr2019.

4.3. Clinical Microbiology

This product is not an antimicrobial agent; this section is not applicable.

4.4. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) was consulted to evaluate device design, performance, and controls and, in accordance with 21 CFR Part 4, to assess compliance with medical device good manufacturing practices of the autoinjector component.

CDRH-Office of Device Evaluation has determined that the autoinjector component (i.e., (b) (4) of this drug-device combination product is comparable to the (b) (4) autoinjector used in the phase 3 clinical trials. Adequate device performance requirements (i.e., essential device performance criteria such as delivered volume and ejection force) have been established. The stability of the device was demonstrated and a suitable program for continued monitoring of device stability was established. Overall, the (b) (4) is suitable for the intended use.

CDRH-Office of Compliance concluded that adequate documentation demonstrating compliance with the applicable sections of the medical device Quality System Regulation under 21 CFR 820 has been provided in the application. The application therefore complies with the requirements for a drug-device combination product under 21 CFR Part 4.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Introduction

BMT is a nonselective, high-affinity ligand and agonist for MCRs, of which there are five subtypes. For the purposes of this application, the pharmacologically relevant receptors are MC4R (b) (4) MC3R, and MC1R. BMT is the first compound to be designated a melanocortin receptor agonist for purposes of NDA approval. Nonclinical studies to support NDA approval were conducted in mouse, rat, rabbit, ferret, dog, and monkey by the intravenous (IV), subcutaneous, and intranasal routes. Published nonclinical studies on BMT use the code name PT-141.

Pharmacology

Receptor binding

BMT is a synthetic cyclic heptapeptide analog of α-melanocyte-stimulating hormone (α-MSH). The relative binding affinity of BMT for the five MCR subtypes is: MC1R > MC4R > MC3R > MC5R. BMT has little to no affinity for MC2R (the adrenocorticotropic hormone (ACTH) receptor expressed on the adrenal gland; K_d >1000 nM). There were no data presented for binding of BMT to the MCRs of nonclinical species (other than MC1R in the mouse). For that reason, pharmacodynamic effects are the most reliable indicators of activity in nonclinical species.

There was no off-target activity of BMT against a panel of receptors at therapeutically relevant concentrations based on in vitro studies.

Distribution and function of MCRs

Activity of BMT in target organs is determined by the distribution of melanocortin receptors to which it binds. MC1R is expressed on melanocytes; its activation leads to production of melanin. Expected pharmacology for BMT binding to MCR1 is enhanced pigmentation, which was observed in dogs and in humans. It is also expressed on cells of the immune system and may play a role in regulating the inflammatory response.

MC4R is expressed on neurons of the CNS. It is expressed at high density in the paraventricular region of the hypothalamus and in the dorsal motor nucleus of the vagus (DMV) in the hindbrain. Peripheral expression is less well characterized, but it is expressed on nerve endings of the penis. Melanocortin induction of penile erection has been shown to be modulated by MC4R.

MC3R is expressed in the CNS and gastrointestinal (GI) tract. It may have overlapping functions with MC4R. BMT can induce emesis, which may be related to MC3R expression.

It is expected that a therapeutic dose of BMT will yield tissue concentrations that are sufficient to produce pharmacological activity at the MC1R, MC4R, and possibly MC3R.

The Applicant proposes that the therapeutic effect for HSDD occurs [redacted] (b) (4)

Safety Pharmacology

BMT was negative for CNS and respiratory safety. Gastrointestinal (emetic) effects were demonstrated in the ferret at doses estimated to be near the therapeutic dose range. Emesis was also incidentally observed in several studies in the dog. It is not known whether the emetic effect is due to a direct effect on the stomach or is a centrally mediated effect.

To evaluate CV safety, standard in vitro studies were conducted and BMT was found negative for proarrhythmia risk. However, there was no single adequate in vivo study that evaluated CV parameters. Rather, the Applicant relied on weight of evidence from a series of studies conducted in the rat, dog, and monkey to support CV safety. In vivo studies were conducted by the IV, SC, and intranasal routes. There were no findings for the effect of BMT on electrocardiogram (ECG) parameters, as measured in the dog and monkey, by the intranasal route. The effect of BMT on blood pressure parameters was examined in rat, dog, and monkey and yielded positive findings in the rat and dog, but no findings in the monkey. In the rat and dog, both blood pressure (BP) and heart rate (HR) were elevated by BMT. No observed effect levels (NOELs) were obtained in the dog that were approximately half the human therapeutic dose based on area under the plasma concentration-time curve (AUC). Weight of evidence therefore indicates that elevated BP and HR are possible following BMT exposure, and that the threshold for CV changes to appear in the rat and the dog are near the human therapeutic range based on AUC. The likely mechanism of action, based on literature, is activation of central MC4 and/or MC3 receptors. These positive findings are mitigated by the lack of response by the monkey at doses that were 3.6X the proposed human dose. Elevated BP has been observed in humans following therapeutic doses of BMT.

ADME

The absorption, distribution, metabolism, excretion (ADME) of BMT was characterized in single- and multiple-dose studies in both sexes of mouse, rat, rabbit, ferret, dog, and monkey by the SC, IV, and intranasal routes.

Absorption

Focusing on the therapeutically relevant subcutaneous route of administration, absorption across species was rapid (≤1 hour), and exposure was proportional to dose. Bioavailability was 100%. There were no significant differences between sexes. Volume of distribution was low, and the time course of elimination was rapid ($T_{1/2}$=1 to 2 hours).

Distribution

BMT binding to protein for nonclinical species was 32%, 6%, and 13% for mouse, rat, and dog, respectively. Mean values for BMT protein binding in human serum was 13% and closely resembles protein binding in the dog. There was no evidence for distribution to blood cells.

In a mouse radiolabel distribution study, subcutaneous BMT was found to distribute quickly and widely to tissues and organs. Most tissues had peak radioactivity concentrations at 0.5 hours postdose (the first evaluation time point). In males and females, the tissues showing the highest peak concentrations of radioactivity (after the dose site) reflected the routes of excretion: kidney, liver, small intestine, and pancreas. Males additionally showed high concentrations in the bulbo-urethral gland.

Relevant to the mechanism of action, BMT was shown to cross the blood–brain barrier, but with a significant delay. Radioactivity concentrations in the cerebellum, cerebrum, medulla, and spinal cord peaked at a low level, 24 hours after injection in males and 4 hours after injection in females. The reason for this sex difference is unknown. The average peak radiolabel concentration (ng equivalents ^{14}C-BMT/g tissue) in the CNS was approximately 1000 in both males and females (approximately 10% of plasma concentration), which, if assumed to be all parent compound, is equal to a tissue concentration of 1000 nM, well above the inhibitory constant (K_i) for the MC4 receptor of 14 nM. Clearance from the CNS was slow relative to systemic clearance, and measurable concentrations that were 3 to 6X the plasma concentration remained at 28 days postdose in both male and female mice.

In female mice, low levels of radioactivity were measured for up to 28 days postdose in uterus and ovary. In males, radioactivity slowly crossed the blood-testis barrier, peaking at low levels at 24 hours postdose, and then was slowly cleared.

BMT was not found to be specifically-associated with melanin-containing tissues such as the eye and the skin, lessoning a concern for toxicity in these tissues.

Distribution in pregnant animals was not assessed. It is not known whether BMT crosses the placenta or into milk.

Metabolism

In vitro metabolism was characterized in mouse, rat, dog, and human hepatocytes. In vitro, no unique human metabolites were found. As expected, in vitro metabolism of BMT was accomplished by hydrolysis of peptide bonds.

In vivo metabolism was characterized only in the mouse. There was one major metabolite (M3), the synthetic amino acid D-phenylalanine, that accounted for 11.3% and 8.3% of the dose in males and females, respectively and is not known to have melanocortin receptor activity.

Human metabolism in vivo was similar. Conversion of BMT to M3 occurs between 4 and 8 hours and is complete by 24 hours. Thus, the time that BMT circulates in its pharmacologically active form is limited.

Excretion

BMT was rapidly excreted in urine and feces after SC dosing in the mouse. Hepato-biliary and renal excretion were the major routes of elimination. Excretion profiles were similar across sex with renal and fecal excretion being nearly equal. The excretion profile in the human was similar.

Comparative toxicokinetics

The Applicant did not provide an analysis of dose equivalency across species but did provide a table with all the collated toxicokinetics (TK) data. Inspection of this data showed that equivalent doses based on mg/m^2 in the mouse produced higher exposures than in the dog. Based on human equivalent dose (HED) in mg/kg and assuming proportionality, exposure in nonclinical species was comparable to human for the mouse and pregnant rabbit, and lower in the rat and dog.

General Toxicology

Single-dose toxicity

Single-dose toxicity studies by the SC route showed that BMT was well tolerated by mouse and dog. In the mouse, there were significant clinical signs at the maximum tolerated dose of 150 mg/kg. In the dog, single-dose studies were conducted up to 15 mg/kg and were well tolerated other than for injection-site reactions. Rats were intolerant of SC dosing; and by the IV route a maximum tolerated dose of 1.5 mg/kg was set. However, mortality above that dose, starting at 2 mg/kg, was not explained. Acute dose toxicity by the intranasal route was not achieved in rat, dog, or monkey. Overall, species sensitivity by the SC route was rat > dog > mouse. Studies in the rabbit were conducted for reproductive toxicity and the rabbit, like the rat, was found to be extremely sensitive and intolerant to treatment with BMT, although no single-dose maximum tolerated dose was defined.

Repeat dose toxicity

Pivotal repeat-dose studies to assess the nonclinical toxicity of BMT were conducted in mice and dogs following once-a-day SC administration for up to 26 and 32 weeks, respectively. A 4-week nonpivotal study in the rat was also conducted by the SC route.

Mouse: BMT administered at 15, 30, or 75 mg/kg/d SC for 26 weeks was well-tolerated by the mouse. The primary toxicity was skin reactions at the high dose. There were mild reactive changes in liver and kidney that were not considered adverse. A trend for increased body weight and food consumption was observed at the high dose during the treatment period. However, by the end of the recovery period, food consumption and group mean body weights in the 75 mg/kg/day group were lower than controls. TK: Exposures were stable or slightly increased over the duration of the study. There were no sex differences. Based on these findings, NOEL=30 mg/kg/day. At that dose, the margin of exposure (MOE) compared to the proposed human dose based on AUC on day 180 was 56.

Dog: BMT administered at 2, 8, or 20 mg/kg/d for 32 weeks was tolerated overall, but there were treatment-related findings that included stereotypic behavior, black discoloration of the hair, injection-site reactions, decreased body weight gain, mild liver enzyme elevation, and, in females only, increased adrenal weight without corresponding histology. These findings were likely due to exaggerated pharmacology of BMT. The Applicant did not consider any of these findings adverse and set the no-observed-adverse-effect level (NOAEL) at the high dose. The review team preferred a more conservative NOAEL of 2 mg/kg, which still produced exposures that were approximately 10-fold greater than the proposed therapeutic dose.

Rat: Most of the repeat-dose studies carried out in the rat were conducted by the intranasal route, which allowed for longer duration dosing. We briefly mention rat studies in this summary to highlight the fact that in a more sensitive species such as the rat, dose-dependent weight loss is one of the signs of BMT activity. We also note that in two of the repeat-dose intranasal studies in the rat (28- and 90-day), vacuolization of the adrenal cortex was observed in males. Interestingly, in the two-year carcinogenicity studies, males that were intranasally dosed over the same range as in the repeat-dose tox studies were found to have benign cortical adenomas, which did not rise to the level of significance as a tumor finding.

Comment on adrenal findings

There were findings in the adrenal gland in three species: rat, rabbit, and dog. In the rat, vacuolation in the adrenal cortex was found (without a corresponding increase in weight), and the Applicant conducted a dedicated study to characterize the finding, ultimately concluding that it was not treatment related. In the pregnant rat, ACTH and corticosterone were found to be significantly elevated with treatment. Unfortunately, adrenal weight and histopathology was not done in that study. In the pregnant rabbit, adrenal weights were elevated, but no

histopathology was carried out. In the dog, adrenal weights were elevated, but there was no corresponding histopathology. ACTH and cortisol or corticosterone measurements were not conducted as part of the latter two studies. Thus, there was no single nonclinical study that looked for an association between morphological changes in the adrenal glands and that also measured ACTH and cortisol or corticosterone.

We speculate that if there is an effect of BMT on the adrenal gland, it is not direct. BMT does not bind to MCR2, which is the only melanocortin receptor that is expressed on the adrenal gland and binds ACTH. Rather, if BMT affects the adrenals, it is likely via an indirect mechanism. One possibility is that BMT may stimulate production of corticotropin releasing hormone in the hypothalamus, which would subsequently cause ACTH production to increase in the pituitary and then subsequently act on the adrenals.

Summary

No frank toxicity of BMT was observed in repeat-dose toxicity studies in mouse, rat, and dog. Findings could largely be characterized as exaggerated pharmacology, with the primary pharmacodynamic effect being reduced body weight gain and in males, penile erection. Overall, we conclude that, at low dose ranges, or in less sensitive species such as the mouse, peripheral effects of BMT will dominate (nausea, vomiting, skin darkening). Very high exposures that can elevate tissue concentrations in the brain can begin to influence the hypothalamic-pituitary-adrenal (HPA) axis and autonomic systems. An unanswered question about the therapeutic use of BMT for HSDD is how it can exert its putative effect on brain circuitry to transiently elevate sexual response without also affecting other physiological functions.

Genetic Toxicity

Genetic toxicity was assessed in a standard panel of in vitro and in vivo studies and was found to be negative.

Carcinogenicity

The carcinogenic potential of BMT was assessed in 2-year studies conducted in the mouse and the rat. BMT was found negative for tumorigenicity.

Mouse: The mouse study was conducted by the SC route at doses of 3, 9, and 15 mg/kg/d. There were no treatment-related tumor findings, and the NOAEL was set at the high dose. By body surface area, the MOE at the NOAEL compared to the human therapeutic dose is 41X. The MOE based on exposure can be estimated from TK values. Exposures were stable over the course of the study up to 1 year and were consistent with other measurements obtained in the mouse by the SC route. Based on C_{max} values obtained at 1 year, the MOE is 141X for males and 183X for females.

Rat: The rat study was conducted by the intranasal route at comparatively low doses: 0.5, 2.5, and 5 mg/kg/d. There were no treatment-related tumor findings and the NOAEL was set at 5 mg/kg/d. By body surface area, the MOE at the NOAEL is 27X compared to the human therapeutic dose. By exposure, the MOE changes dramatically depending on whether it is calculated from plasma values taken at 3 months versus 19 months. As was observed in other, shorter duration repeat-dose toxicity studies by either the SC or intranasal routes, exposures in the rat decline over time with repeat dosing. Thus, based on C_{max}, the MOE determined from initial exposure values is 2X to 3X but declines to less than half the human exposure at the end of the study.

Reproductive Toxicity

Fertility

Fertility studies were conducted in male and female mice by the subcutaneous route and in male rats by the intranasal route.

Females: In a study conducted in mice by the SC route, there was no effect of BMT on female fertility indices when mice were dosed 14 days prior to mating through gestation day (GD) 15 at doses up to 150 mg/kg/d, which is 639X the human therapeutic dose based on AUC. There were also no findings for embryotoxicity.

Males: There were no effects of BMT on male fertility indices, as tested in mice by the SC route up to 75 mg/kg/d. There were also no findings in the rat, but that study was conducted by the intranasal route at much lower exposures.

Embryofetal toxicity and pre- and postnatal development

Embryofetal toxicity studies were conducted in multiple species (mouse, rat, rabbit, and dog). Due to excessive maternal toxicity in the rabbit, and limitations of dosing in the rat, the definitive segment 2 and segment 3 studies were conducted in the mouse and the dog.

Mouse: In the mouse, a combined Segment 2/3 study was conducted by the subcutaneous route. Pregnant mice were dosed at 30, 75, and 150 mg/kg/d from GD6 through lactation day (LD) 28. Conclusions from the study were:

- There was no evidence for teratogenicity.
- There was maternal toxicity (reduced body weight and body weight gain) at the high dose.
- There was no evidence of embryofetal toxicity through organogenesis (GD15).

- There was, however, evidence of reduced pup viability and developmental delays if dosing continued through parturition and weaning. This was probably due to reduced food consumption and weight gain in the dams. In the high dose group, lower pup body weight was propagated into the F2 generation. Consequently, a developmental NOEL could not be set.

Dog: In the Beagle dog, which is a nonstandard species for reproductive toxicity, eight pregnant animals/dose were dosed at 2, 8, or 20 mg/kg/d from GD18 to 35. The study was terminated near the end of gestation, on GD57. The number of litters evaluated was five to seven per dose. There was maternal toxicity at the mid and high dose, in the form of inappetence and lower body weight gain. Discoloration (blackening) of the coat was also noted. Regarding embryotoxicity, there was no evidence for teratogenicity, but there was some evidence for embryofetal toxicity (post-implantation loss) at all doses. Consequently, a developmental NOEL was not set.

Given the findings in the mouse and the dog, we conclude that BMT is unlikely to affect fertility in humans but has the potential to cause fetal harm if dosing occurs during pregnancy.

Abuse Potential

Abuse potential was assessed in a standard series of behavioral studies in the rat that were reviewed by Dr. Katherine Bonson of the Controlled Substance Staff. It was concluded from the results of these studies that the abuse potential for BMT is negligible.

Immunotoxicity

Immunotoxicity was based on a risk assessment evaluation. No in vivo nonclinical studies were done to address immunogenicity. The following conclusion was made by the Office of Pharmaceutical Quality reviewers (Davinna Ligons and Susan Kirshner) who evaluated in vitro data submitted by the Applicant:

“A competitive binding assay demonstrates that BMT most likely does not bind human leukocyte antigen class II alleles, which is required to drive an anti-drug antibody response. Consistent with these findings, pharmacokinetic and clinical efficacy responses do not appear to be impacted by anti-drug antibody responses.”

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

5.3.1. Primary Pharmacology

BMT is a synthetic analog of α-MSH and a nonselective agonist for MCRs. MCRs are G-protein coupled receptors functionally coupled to adenylyl cyclase and mediate their effects by activating cyclic adenosine monophosphate (cAMP)-dependent signaling pathways. There are five MCR subtypes.[10]

- MC1R is expressed on melanocytes and some immune cells. It regulates the production of melanin, and some immune functions.
- MC2R is expressed on the adrenal cortex. Its endogenous agonist is ACTH. It is not sensitive to α-MSH or BMT.
- MC3R is expressed in the CNS, GI tract, kidney, and some immune cells. It regulates autonomic functions and some immune functions.
- MC4R is expressed in the CNS and some peripheral nerves. It regulates feeding and energy homeostasis and erectile activity in males.
- MC5R is expressed on exocrine glands and some immune cells. It regulates exocrine secretion and some immune functions.

Relative binding affinity of BMT for the MCRs (derived from the species shown in parentheses) is: MC1R (mouse)>MC4R (human)>MC3R (human)>MC5R (human)>MC2R (species not stated). K_i values reported by the Applicant are 0.7, 14, 98, 225, and >1000 nM. The relevant receptors for this application are MC4R, MC3R, and MC1R. (b) (4)

There were no data presented for binding of BMT to the MCRs of other nonclinical species, but literature states that MC4Rs are highly conserved across many species, with, for example, 93% amino acid sequence identity conserved between rat and human.[11]

BMT was shown to be an agonist at MC4R in functional assays (Studies PL-03 and PL-35). BMT induced cAMP production in MC4R-transfected human embryonic kidney (HEK) 293 cells with a mean EC_{50} of 1.1 nM. Thus, the EC_{50} is about 10-fold lower than the K_i derived from binding experiments. The maximum cAMP level was 825 pmol/10^6 cells, which was 68% of the response produced by α-MSH.

[10] For reviews, see Catania A et al., 2004. Targeting Melanocortin Receptors as a Novel Strategy to Control Inflammation. Pharmacol Rev, 56(1):1–29; Cone RD, 2006. Studies on the Physiological Functions of the Melanocortin System. Endoc Rev, 27(7):736–749; Yang Y, 2011. Structure, Function and Regulation of the Melanocortin Receptors. Eur J Pharmacol, 660(1): 125–130.

[11] Tao Y-X, 2010. The Melanocortin-4 Receptor: Physiology, Pharmacology, and Pathophysiology. Endoc Rev, 31(4):506–543.

It is expected that a therapeutic dose of BMT will yield tissue concentrations that are sufficient to produce pharmacological activity at the MC4R. Human PK data show that the C_{max} following a single 1.75 mg injection of BMT is 72.8 ng/mL. Assuming 13% bound (see Section 5.1 of this review for protein binding data), this yields a free concentration in plasma of 63 nM, well above the K_i for binding to MCR1 and MCR4. Also, MC3R might be partially bound.

Specificity of BMT action is determined by the distribution of melanocortin receptors to which it binds. Distribution of MCRs in the brain has been extensively characterized in many nonclinical species. In the rat, MC4R is present at highest density in the hypothalamus, midbrain, and brainstem.[12] Areas of expression of MC4 and MC3 receptors often overlap.

While BMT concentration in peripheral tissues may be close to the levels in plasma, BMT access to the CNS, the proposed target for therapeutic action, is limited. Distribution studies (discussed below) indicate that BMT concentration in the brain peaks several hours later than in plasma and reaches only approximately 10% of the maximal plasma-free concentration. This implies that MC4Rs in the brain might be only partially activated.

Functions Mediated by MC4 Receptors

As would be expected from their widespread distribution in the brain, MC4 receptors mediate a diverse array of physiological functions and behaviors.[13] For the purposes of explaining the findings of the animal toxicology studies, we will focus on four aspects of the expected pharmacology of BMT.

1. Energy homeostasis and feeding behavior.

   MC4R has been primarily associated with energy homeostasis and has been extensively investigated in obesity research. Although the brain circuitry regulating feeding behavior and body weight is complex, it is clear from many animal studies that agonism at the MC4R reduces body weight and that antagonism leads to obesity. Knock out of the MC4R in the mouse produces animals that are obese, hyperphagic, and hyperinsulinemic.[14] In mice,

[12] Nahon J-L, 2006. The Melanocortins and Melanin-Concentrating Hormone in the Central Regulation of Feeding Behavior and Energy Homeostasis. C R Biol, 329:623–638; Mountjoy KG et al., 1994. Localization of the Melanocortin-4 Receptor (MC4-R) in Neuroendocrine and Autonomic Control Circuits in the Brain. Mol Endocrinol, 8:1298–1308.

[13] Adan RAH and WH Gispen, 1997. Brain Melanocortin Receptors: From Cloning to Function. Peptides, 18(8):1279–1287; Wikberg JE and F Mutulis, 2008. Targeting Melanocortin Receptors: An Approach to Treat Weight Disorders and Sexual Dysfunction. Nat Rev Drug Discov, 7(4):307–323; Tao Y-X, 2010. The Melanocortin-4 Receptor: Physiology, Pharmacology, and Pathophysiology. Endoc Rev, 31(4):506–543; Mul JD et al., 2013. Melanocortin MC4 Receptor-Mediated Feeding and Grooming in Rodents. Eur J Pharmacol, 719:192–201.

[14] Cone RD, 2006. Studies on the Physiological Functions of the Melanocortin System. Endoc Rev, 27(7):736–749; Huszar D et al., 1997. Targeted Disruption of the Melanocortin-4 Receptor Results in Obesity in Mice. Cell, 88:131–141.

central administration of the MC4R agonist MT-II inhibits basal insulin release.[15] Expected pharmacology following administration of an MC4R agonist in nonclinical models include reduced feeding and weight loss, reduced insulin production and possible glucose elevation.

2. Sexual function. Induction of penile erection by melanocortin agonists in multiple species, including humans, has long been noted.[16,17] Nonclinical studies submitted by the Applicant (Study # PL-05, PL-06, PL-08, PL-22, PL-23, PL-24, PL-25, and PL-36), as well as studies in available literature[18] have demonstrated that melanocortins likely induce penile erection via activation of the MC4 receptor expressed on neurons, primarily those that are located in the hypothalamic region of the brain as well as spinal cord, but possibly also some that are located in penile tissue. Direct action of melanocortins on the corpus cavernosum was not found.

   Induction of erections in male animals is a pharmacodynamic effect of BMT. In the rat, induction of erection by BMT has a bell-shaped dose-response curve, with maximal effect at 1 µg/kg IV (PL-36) and an estimated AUC of 275 ng.hr/mL. In the rhesus monkey, 2.5 µg/kg IV induces erection (PL-05; no dose response determined, no AUC available). Effects in human males have been described in published literature, at systemic exposures comparable to those of the rat, which supports the use of the rat as valid test species for BMT.[19] As noted previously, the clinical development of BMT for ED is no longer being actively pursued and the corresponding IND has been inactivated.

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[15] Tao Y-X, 2010. The Melanocortin-4 Receptor: Physiology, Pharmacology, and Pathophysiology. Endoc Rev, 31(4):506–543.

[16] King SH et al., 2007. Melanocortin Receptors, Melanotropic Peptides and Penile Erection. Curr Top Med Chem, 7(11):1098–1106.

[17] Rosen RC et al., 2004. Evaluation of the Safety, Pharmacokinetics and Pharmacodynamic Effects of Subcutaneously Administered PT-141, a Melanocortin Receptor Agonist, in Healthy Male Subjects and in Patients With an Inadequate Response to Viagra. Int J Impotence Res, 16, 135–142; Ückert S et al., 2014. Melanocortin Receptor Agonists in the Treatment of Male and Female Sexual Dysfunctions: Results From Basic Research and Clinical Studies. Expert Opin Investig Drugs, 23(11):1477-1483.

[18] Van der Ploeg LHT et al., 2002. A Role for the Melanocortin 4 Receptor in Sexual Function. PNAS, 99(17):11381–11386; Martin WJ et al., 2002. Activation of Melanocortin MC4 Receptors Increases Erectile Activity in Rats Ex Copula. Eur J Pharmacol, 454:71–79; Molinoff PB et al., 2003. PT-141: A Melanocortin Agonist for the Treatment of Sexual Dysfunction. Ann N Y Acad Sci, 994:96–102; Shadiack AM et al., 2007. Melanocortins in the Treatment of Male and Female Sexual Dysfunction. Curr Top Med Chem, 7:1137–1144; Shadiack AM and S Althof, 2008. Preclinical Effects of Melanocortins in Male Sexual Dysfunction. Int J Impot Res, 20:S11–S16.

[19] Diamond LE et al., 2004. Double-Blind, Placebo-Controlled Evaluation of the Safety, Pharmacokinetic Properties and Pharmacodynamic Effects of Intranasal PT-141, a Melanocortin Receptor Agonist, in Healthy Males and Patients with Mild-to-Moderate Erectile Dysfunction. Int J Impot Res, 16:51–59.

3. Autonomic functions

   The high density of MC4Rs in the hypothalamus and the DMV suggests their involvement in the regulation of many types of autonomic output.[20] We focus here on the cardiovascular system and, briefly, the GI system, in order to explain findings that were observed in clinical studies alone and both clinical and nonclinical studies.

   - *Cardiovascular function*

     The role of the melanocortin system in the regulation of hemodynamics is very complex and not completely understood.[21] The circuitry that has been described to date involves the hypothalamus, brain stem, and spinal cord, MC4 and MC3 receptors, $\alpha-$ and $\gamma-$MSH, and feedback from peripheral tissues, including the kidney.[22]

     It is beyond the scope of this document to fully describe this system. Rather, we will highlight what is known about MC4 receptors specifically, and in the Safety Pharmacology subsection below, discuss the findings obtained by the Applicant using BMT.

     Literature studies describing the cardiovascular response to MC4R activation have shown that cardiovascular effects vary depending on the species, the type of MC4R agonist used, the route of administration, the site of administration, that is, which region of the brain or brainstem is stimulated, and whether administration is acute or chronic.[23] In rodents, direct activation of MC4 receptors in the DMV by injection of α-MSH into the brainstem produces bradycardia and hypotension.[24] In contrast, injection of α-MSH intracerebroventricularly (ICV), targeting the MC4 receptors of the hypothalamus, produces the opposite effect: tachycardia and hypertension.[25] Increased HR and BP have also been noted when the MC4R agonist MT-II is perfused ICV, and the effect is mediated by adrenergic activation.[26] Mixed results have been obtained when

[20] For reviews, see Tao Y-X, 2010. The Melanocortin-4 Receptor: Physiology, Pharmacology, and Pathophysiology. Endoc Rev, 31(4):506–543; Adan RAH and WH Gispen, 1997. Brain Melanocortin Receptors: From Cloning to Function. Peptides, 18(8):1279–1287.

[21] do Carmo JM et al., 2017. Role of the Brain Melanocortins in Blood Pressure Regulation. Biochim Biophys Acta Mol Basis Dis, 1863:2508–2514.

[22] See Wikberg JE and F Mutulis, 2008. Targeting Melanocortin Receptors: An Approach to Treat Weight Disorders and Sexual Dysfunction. Nat Rev Drug Discov, 7(4):307-323.

[23] Rinne P et al., 2012. Hemodynamic Actions and Mechanisms of Systemically Administered Alpha-MSH Analogs in Mice. Peptides, 38:150–158.

[24] Li S-J et al., 1996. Melanocortin Antagonists Define Two Distinct Pathways of Cardiovascular Control by α- and γ-Melanocyte-Stimulating Hormones. J Neurosci, 16(16):5182–5188.

[25] Ni X-P et al., 2006. Central Receptors Mediating the Cardiovascular Actions of Melanocyte Stimulating Hormones. J Hypertens, 24:2239–2246.

[26] Kuo JJ et al., 2004. Role of Adrenergic Activity in Pressor Responses to Chronic Melanocortin Receptor Activation. Hypertension, 43[part 2]:370–375.

comparing acute versus chronic administration. The acute hypertensive response of α-MSH abates with chronic administration via the ICV route,[27] a result that was not duplicated with MT-II.[28] It has been suggested that functional responses to melanocortins may depend on the balance between MC4 and MC3 receptors, and that obesity may also play a role.[29]

In humans, subcutaneous infusion of an MC4R agonist leads to slightly elevated blood pressure, and subjects with loss-of-function mutations in MC4R have a reduced incidence of hypertension.[30] Prior clinical experience in males with BMT also indicates that a hypertensive response to MC4R activation is the more likely response.[31]

- *GI function*

  MC4 receptors are expressed on vagal afferents, and the stomach and duodenum are innervated by MC4R vagal afferents and efferents. Injection of melanocortin agonists into either the DMV or nucleus tractus solitarius decreases phasic gastric contractions. There is also evidence the MC4 receptors are expressed on enteroendocrine L cells in the GI tract.[32] Thus, MC4R agonists can play a role in slowing gastric emptying, which could affect drug absorption. The effect of BMT on the kinetics of drug absorption and drug-drug interaction was investigated in a nonclinical study in the mouse but no effect was found. BMT was found to have emetic activity in the ferret.

4. HPA axis

   The presence of MC4 receptors at high density in the periventricular region of the hypothalamus indicates that the melanocortin system influences the HPA axis; however, there is not a large body of literature defining what these effects might be. MC4Rs are expressed on both magnocellular and parvocellular neurons in the paraventricular nucleus of the hypothalamus. Magnocellular neurons project to the posterior pituitary

[27] Hill C and JC Dunbar, 2002. The Effects of Acute and Chronic Alpha Melanocyte Stimulating Hormone (Alpha-MSH) on Cardiovascular Dynamics in Conscious Rats. Peptides, 23:1625–1630.

[28] Kuo JJ et al., 2003. Hypothalamic Melanocortin Receptors and Chronic Regulation of Arterial Pressure and Renal Function. Hypertension, 41[part 2]:768–774.

[29] da Silva AA et al., 2006. Does Obesity Induce Resistance to the Long-Term Cardiovascular and Metabolic Actions of Melanocortin 3/4 Receptor Activation? Hypertension, 47:259–264.

[30] Greenfield JR et al., 2009. Modulation of Blood Pressure by Central Melanocortinergic Pathways. N Engl J Med, 360:44–52.

[31] Rosen RC et al., 2004. Evaluation of the Safety, Pharmacokinetics and Pharmacodynamic Effects of Subcutaneously Administered PT-141, a Melanocortin Receptor Agonist, in Healthy Male Subjects and in Patients with an Inadequate Response to Viagra. Int J Impot Res, 16, 135–142.

[32] Panaro BL et al., 2014. The Melanocortin-4 Receptor Is Expressed in Enteroendocrine L Cells and Regulates the Release of Peptide YY and Glucagon-Like Peptide 1 In Vivo. Cell Metab, 20(6):1018–1029.

(neurohypophysis) and secrete vasopressin and oxytocin; parvocellular neurons project to the median eminence and secrete releasing factors (corticotropin-releasing hormone, thyrotropin-releasing hormone, etc.) that stimulate release of hormones from the anterior pituitary (adenohypophysis). In the rat, ICV injection of MT-II has been shown to induce synthesis of corticotropin releasing hormone (and presumably ACTH), followed by a rise in plasma corticosterone.[33] MC4 receptors also play a role in grooming behavior in rodents, which may be tied to a stress response.[34] In the description of the MC4R knockout mouse no particular emphasis was placed on distruption of the HPA axis, which indicates that melanocortins may play a more limited, modulatory role. Effects on the HPA axis were infrequently monitored in nonclinical studies for this application. Treatment-related elevated ACTH and corticosterone was noted in only one study in the pregnant rat (996-029) that used IV dosing at maternally toxic levels.

Drug mechanism related to indication: A mechanism of action for the treatment of HSDD in females has not been established. There were no studies submitted by the Applicant investigating the effect of BMT on sexual behavior in female animals. There are a few published studies that indicate that melanocortins in general, and BMT in particular, can induce sexual receptivity in the female rat.[35] BMT is effective in female rats for solicitation behaviors following either subcutaneous administration or following infusion into the lateral ventricles or medial preoptic area.[36]

5.3.2. Secondary Pharmacology

MC1 Receptor

Because BMT binds with higher affinity to MC1 receptors than to MC4Rs, secondary pharmacology mediated by the MC1 receptor is expected. Activation of the MC1 receptor leads to melanin production by melanocytes, producing hyperpigmentation. Treatment with BMT produced blackening of the coat in the dog and hyperpigmentation was noted in clinical

[33] Lu X-Y et al., 2003. Interaction Between Alpha-Melanocyte-Stimulating Hormone and Corticotropin-Releasing Hormone in the Regulation of Feeding and Hypothalamo-Pituitary-Adrenal Responses. J Neurosci, 23(21):7863–7872.

[34] Mul JD et al., 2013. Melanocortin MC4 Receptor-Mediated Feeding and Grooming in Rodents. Eur J Pharmacol, 719:192–201.

[35] Nocetto C et al., 2004. Evidence That the Effect of Melanocortins on Female Sexual Behavior in Preoptic Area Is Mediated by the MC3 Receptor: Participation of Nitric Oxide. Behav Brain Res, 153:537–541; Pfaus JG et al., 2004. Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist. Proc Natl Acad Sci U S A, 101(27):10201–10204.

[36] Pfaus JG et al., 2004. Selective Facilitation of Sexual Solicitation in the Female Rat by a Melanocortin Receptor Agonist. Proc Natl Acad Sci U S A, 101(27):10201–10204; Pfaus JG et al., 2007. Bremelanotide: An Overview of Preclinical CNS Effects on Female Sexual Function. J Sex Med, 4(suppl 4):269–279.

studies. Melanocortins also act as anti-inflammatory and antipyretics via MC1R agonism,[37] but this effect was not assessed in nonclinical studies.

Other Receptors

BMT (1µM) showed weak activity at the muscarinic acetylcholine (M) and the alpha-2 adrenergic receptor, and there was some evidence of binding to vasoactive intestinal peptide 1 and neuropeptide Y receptors. Weak activity at serotonin transporters was reported, equal in magnitude to activity at dopamine transporters. Thus, if BMT acted as a weak selective serotonin reuptake inhibitor (SSRI), some indirect activation of 5-hydroxytryptamine receptors might occur. Binding at these off-target receptors occurred at concentrations that are not therapeutically relevant.

5.3.3. Safety Pharmacology

Twenty studies were conducted to assess safety pharmacology and are broken down as follows:

- CNS safety: One in vivo study in the male rat
- Cardiovascular safety: Two in vitro and 12 in vivo studies in dog, rat, and monkey
- Respiratory safety: One in vivo study in the male rat
- Gastrointestinal safety: Four in vivo studies in the male ferret

CNS Safety

Male rats were dosed intravenously with 10, 75, and 300 µg/kg, and assessed using the Irwin test. The animals showed a dose- and time-dependent change in 'typical' behavior, a poorly described parameter. No other changes in 26 specific behaviors (including tremor, convulsion, etc.) were observed. The Applicant did not set a NOAEL. TK obtained in a different study (91-0501) showed that an IV dose of 250 µg/kg produced an AUC of 69 ng.hr/mL, which is 25% of the therapeutic AUC.

There were no findings in the CNS study, but dosing (by the IV route) did not reach therapeutically relevant concentrations.

Cardiovascular Safety

Cardiac safety studies were negative for cardiac arrhythmia, but positive for elevated HR and BP at high multiples of human exposure.

The Applicant's tabulated summary (2.6.3) of cardiovascular safety pharmacology studies lists 2 in vitro studies and 11 in vivo studies in dog and monkey. In addition, one drug-drug interaction study was conducted in the rat to determine whether coadministration of BMT and sildenafil

[37] Catania A et al., 2004. Targeting Melanocortin Receptors as a Novel Strategy to Control Inflammation. Pharmacol Rev, 56(1):1–29.

would affect CV parameters. These studies, plus several others conducted to evaluate CV safety, are listed either under the safety pharmacology section (4.2.1.3) or the general toxicology section (4.2.3.2.) of the submission.

The two in vitro studies, a human Ether-à-go-go Related Gene (hERG) channel assay and a cardiac action potential assay, followed standard study designs and were negative.

In vivo studies were conducted by the IV, SC, and intranasal routes. ECG studies were conducted in the dog and monkey, by the intranasal route, and were negative. The effect of BMT on blood pressure was examined in rat, dog, and monkey and yielded positive findings in the rat and dog. However, no one study met all the criteria necessary to be considered a valid good laboratory practice (GLP) study for assessing CV safety. For that reason, conclusions regarding CV safety are based on weight of evidence from the in vivo studies described below.

Cardiovascular Assessment: Single-Dose Studies in the Dog by the IV and SC Routes

Three studies were conducted by the IV route in the dog, one of which included dosing by the SC route for comparison. These studies were conducted in 2008 and 2009, after the other safety pharmacology studies had been completed and after the single-dose general toxicology studies in the dog had been conducted. Even though these studies did not meet GLP criteria, the continuous monitoring for BP and HR changes, acquired by telemetry, was far superior to the limited BP and HR measurements made in the single-dose general toxicology studies that the Applicant has cited to support cardiovascular safety. For that reason, results of these studies are presented in detail below, and are used in the overall assessment of cardiovascular response to BMT.

<u>12513 02 01B: Exploratory Pharmacokinetic Study and Cardiovascular Evaluation of Bremelanotide in Beagle Dogs</u>

Non-GLP. This study compared administration of BMT via the IV versus the SC route and had both PK and CV endpoints. The SC doses (0.01, 0.1, 1, 3, and 10 mg/kg) ranged 10-fold higher than the IV doses in order to produce adequate exposure. The IV doses used (0.1 and 1 mg/kg) were higher than the doses used in the two other preliminary studies (SP-SPG-2299 and SP-SPG-2403) that were similarly conducted. Dosing formulations were not verified.

Methods

HR and systolic and diastolic blood pressures were monitored continuously using telemetry for 4 hours before dosing, 4 hours after dosing, and then every 60 minutes thereafter through 24 hours after dosing. ECGs were not recorded. Blood samples for plasma drug level analysis were collected prior to dosing, at 15 and 30 minutes, and at 1, 2, 4, and 8 hours after dosing. The results are reported in Palatin Study Report #PL-76 (Section 4.2.2.2).

Results

Clinical signs: There was excessive stretching and/or panting at all dose levels. CV parameters: There were dose- and time-dependent increases in mean BP and HR for both the IV and SC route. The greatest increase was observed for 10 mg/kg SC, which produced a mean 28% increase in BP over the 4-hour continuous monitoring period. Blood pressure values were consistently elevated over the highest predose values for an average of 25 minutes following dosing and remained elevated up to 19 hours after dosing. BMT administered at 1 mg/kg IV and SC produced average increases of 14.2% and 19% in blood pressure, respectively, over the same period. HR also increased in a dose- and time-dependent manner.

The onset and duration of the BP effect was dose-dependent, and the peak effect at the lower doses lagged behind the T_{max}, which was 0.5 to 0.7 hours. The peak effect on BP at 1 mg/kg IV or SC was approximately 4 to 6 hours postdose. The peak effect on BP for a 10 mg/kg SC dose was approximately 1 hour.

HR was also increased in a dose-dependent way by BMT, and the dynamics of the response were also dose-dependent. In contrast to BP, HR tracked closely with T_{max} at all doses, and effects occurred at lower doses than for BP.

NOEL for increased BP

<0.1 mg/kg IV	MOE=0.5X the human therapeutic AUC
0.1 mg/kg SC	No TK data was available at this dose. A 10-fold higher dose of 1 mg/kg SC, which produced large effects on HR and BP, had an MOE of 5.3X the human therapeutic AUC. The high dose of 10 mg/kg SC, AUC=19856 nM.hr, is 72X the observed human AUC at the therapeutic dose. (Human therapeutic AUC=276 ng.hr/mL or 276 nM.hr. C_{max}=73 ng/mL=73 nM)

The NOEL for increased HR was *lower* than the NOEL for increased BP.

NOEL for increased HR

<0.1 mg/kg IV	MOE=0.5X the human therapeutic AUC
0.01 mg/kg SC	No TK data available at this therapeutic dose

Data from the other two preliminary studies conducted by the IV route in the male Beagle dog were consistent with the previously described study. The two studies had identical study design, but the first study used only two animals and yielded only qualitative results and is not reviewed here. The second study (SP-SPG-2403) showed that BMT infused stepwise at 0.051 mg/kg and 0.205 mg/kg induced a significant increase in HR at the high

dose that resolved at the 24-hour time point. BMT did not significantly affect mean arterial blood pressure, systolic or diastolic, but there were trends toward increased values for all three parameters. Compared to the human therapeutic C_{max}, the lower dose was 2X and the higher dose was 8.8X the human plasma level.

Two single-dose general toxicology studies (131-007 and 131-008) conducted by the subcutaneous route in the dog were cited by the Applicant in support of cardiovascular safety. The Applicant reported both as being negative for cardiovascular effects. We disagreed, based on sparse sampling in 131-007, and on positive findings for increased HR in 131-008. Neither study had ECG measurements. Brief summaries of these studies are given below.

131-007: Range-Finding Toxicity Study of BMT Administered Subcutaneously to Beagle Dogs
Doses: 3, 6, 9, 12 mg/kg. N=2 males (M)/2 females (F). Non-GLP. No TK.

Blood pressure (systolic, diastolic), was measured prior to dosing and at 15, 30, 45, 60, 75, and 90 minutes postdose. Two measurements were made at each time point, and an average value was recorded. HR was also reported. The Applicant reports no effect, but there were not enough measurements taken to create accurate BP averages.

131-008: Single-Dose Toxicity Study of BMT Administered Subcutaneously to Beagle Dogs
Doses: 9, 12, 15 mg/kg. N=4M/4F. GLP. Blood samples were taken but no TK was reported.

Blood pressure and HR were measured following each bioanalytical collection (predose and at approximately 15 and 30 minutes, and 1, 3, 6, and 24 hours postdose). Three measurements were recorded, and the calculated average was reported.

In males, HR was significantly elevated in the 12 mg/kg and 15 mg/kg dose groups at 3 hours postdose (page 120 of the study report), which is well past the T_{max}. In females, there were significantly elevated HRs in all treated groups at 1 and 3 hours postdose and in the highest dose group also at 30 minutes postdose, indicating slightly greater sensitivity of the females. The largest increase (37%) was observed at the 1-hour time point at the high dose. There were no significant trends for altered BP, only sporadic differences.

The Applicant set the NOEL at 15 mg/kg, but we disagree based on elevated HR that was dose and time-dependent in males and females, so no NOEL was set. From other TK studies, 9 mg/kg has an AUC of 15625 ng.hr/mL by the SC route in the dog which is 56.6X the human therapeutic exposure.

This study is consistent with the range-finding studies in demonstrating that BMT can produce elevated HR. The lack of a finding for increased BP in this study may have been due to the comparatively sparse sampling, which also had a lot variability.

Summary Statement for Single-Dose CV Studies in the Dog

Of the five in vivo CV studies in the dog that were conducted, the three that utilized continuous recording detected elevated HR and BP. The two that did not use continuous recording did not measure changes in BP, even when doses were higher. One picked up increased HR.

Although the dose-dependence of the cardiovascular effects was not well-defined in the dog, it seems that the effect on HR appeared at lower doses than the effect on blood pressure. A firm NOEL for CV effects was not established, but no effect levels were in the range of 0.5X the human therapeutic dose, based on AUC.

Cardiovascular Assessment: Single-Dose Studies in the Monkey by the IN Route

Two single-dose studies (WTAW-103 and 3133) conducted in the monkey by the intranasal route were also cited by the Applicant in support of cardiovascular safety. Each was conducted in males only (N=4). Both were GLP, and both have ECG measurements. However, because BP was monitored more intensively in study 3133, it was deemed better to use for weight of evidence.

Study 3133

Doses were 0.05, 0.2, and 1 mg/kg. Hemodynamic and cardiovascular assessment: Baseline measurements were taken over 30 minutes and hemodynamic and CV parameters were monitored for 2 hours postdose (every 5 minutes). ECGs: once during the pretreatment period and once at 15 minutes prior to each dosing (baseline period), and at 15, 30, 45, 60, 75, 90, 105, and 120 minutes postdose. Other parameters were recorded 30 minutes prior to and every 15 minutes postdosing: cardiac output,[38] pulmonary arterial wedge pressure, pulmonary vascular resistance, respiration rate (visual), right and left cardiac work, right and left ventricular stroke work, stroke volume, and systemic vascular resistance.[39]

Results

There was no mortality. One animal in the mid-dose group had an erection that lasted for one hour.

[38] Cardiac output was recorded at least three times over a period of 3 minutes.

[39] Calculated values for pulmonary vascular resistance, right and left cardiac work, right and left ventricular stroke work, stroke volume, and systemic vascular resistance.

There were no effects of BMT on BP, or on any other cardiovascular or ECG parameters. No NOAEL was determined. Because exposure was not measured in this study, an MOE was estimated using data from a different study (PL-10). It is known from PK studies (see WTAD-100) that bioavailability via intranasal administration is highly variable. The mean of the three AUC values by the intranasal route was 991 ng.hr/mL, which is 3.6X the human therapeutic dose by AUC.

Cardiovascular Assessment: Single-Dose Pharmacodynamic Study in the Rat

PL-40: Cardiac Safety Pharmacology of Bremelanotide in the Rat Alone and in Combination With a Nitrate or Sildenafil

The Applicant cited this study to support cardiovascular safety because one arm of the experiment used BMT alone and yielded useful data.

Doses: 0.003, 0.1, 1 mg/kg administered intravenously; N=6M/dose

Results

BMT increased BP and HR in a dose-dependent manner. The Applicant stated that peak efficacy (parameter not specified) in the rat is 0.003 mg/kg and the LD_{50} is 2 mg/kg. Thus, changes in BP became significant only at a dose approaching toxic levels (1 mg/kg). The increase in HR did not reach significance. These findings are consistent with those obtained in the dog. TK data obtained from female rats is: 276 ng.hr/mL at 1 mg/kg IV, which is approximately equal to human AUC.

Cardiovascular Assessment: Repeat-Dose Studies in the Dog

Several repeat-dose studies conducted in the dog by the intranasal and subcutaneous routes were cited by the Applicant in support of cardiovascular safety. Of these, the study that had the highest quality data was a 28-day repeat dose study, using the intranasal route (WTAW-107). Briefly, this study dosed three male dogs at 0.65 mg/kg and assessed ECGs, HR, and BP. There were no findings, other than episodes of *hypo*tension in one dog. Exposure: From study PL-18 the AUC for a dose of 0.65 mg/kg administered intranasally is 126.2 ng.hr/mL (see p3). This is approximately half the human therapeutic dose. Other repeat dose studies are reviewed under Section 5.5. of this review, general toxicology, and showed no CV effects.

Summary and Conclusions for All Nonclinical CV Safety Studies

Briefly, BMT *can* produce elevated BP and HR when administered IV or SC in the dog and the rat. Although TK data were not available for all doses tested, it can be estimated that the threshold for CV changes to begin to appear in the rat and the dog are near the human therapeutic range based on AUC. In the dog, BP ranged as much as 25% higher at 72X the

human therapeutic dose. Negative findings in some single-dose and repeat-dose studies were likely due to inadequate exposure or monitoring.

In the monkey, there were no findings for effects on ECG or CV parameters following intranasal dosing. The NOEL was 3.6X the human therapeutic dose based on AUC, and monitoring was adequate. The highest dose tested was 20X higher.

Respiratory Safety

BMT was evaluated for its effect on respiration in the unrestrained conscious male Wistar rat following a single intravenous dose of 10, 75, or 300 µg/kg and found negative. The NOEL was >300 µg/kg. The MOE based on body surface area was >1.6X.

Gastrointestinal Safety

The emetic effect of BMT was assessed in four different studies in male ferrets. The ferret is a standard animal model for testing emesis/anti-emetics. (The rat does not have an emetic response.) Emesis occurred following BMT doses of 9 mg/kg SC (Study 04-037), 30 µg/kg and 75 µg/kg IV (Study 20010474PGF), and 300 µg/kg and 500 µg/kg intranasal (Studies 03-112 and 20010666PGF). The Applicant states that no true dose-dependence was established in any of these studies. However, we note that there was a clear threshold for the emetic response, which occurred at doses that were estimated to be comparable to the human therapeutic dose.

5.4. ADME/PK

Comparison of TK Across Species

TK by the subcutaneous route was obtained in mouse, rat, rabbit, ferret, and dog. There was also limited TK information from intranasal dosing in the monkey. In general, absorption by the SC route was complete, and exposure was proportional to dose. Absorption was rapid, and elimination occurred over a time course of several hours. There were no striking sex differences, and no evidence for accumulation. There was no evidence of saturation of exposure with dose. In a few studies, there was evidence of declining exposure with repeat-dosing.

The Applicant did not provide an analysis of dose equivalency across species but did provide a table with all the TK data collated (see Table 2.6.4-9 Summary of Exposure: Comparison Across Species, page 71 of the PK written summary in Module 2.6.4 of the NDA submission).

Highest doses delivered

Rat: 3.5 mg/kg (0.56 mg/kg HED)	C_{max} 353 ng/mL, AUC 1306 ng·hr/mL
Mouse: 75 mg/kg (6.1 mg/kg HED)	C_{max} 32,150 ng/mL, AUC 56,700 ng·hr/mL
Pregnant Rabbit: 150 mg/kg (48 mg/kg HED)	C_{max} 108,728 ng/mL, AUC 475,631 ng.hr/mL
Dog: 40 mg/kg (22 mg/kg HED)	C_{max} 49,300 ng/mL, AUC 140,700 ng·hr/mL

Human TK: (Study PT-141-56) BMT administered SC at a dose of 1.75 mg (0.03 mg/kg or 1.1 mg/m^2) resulted in mean C_{max} of 72.8 ng/mL (approximately 73 nM), and a mean $AUC_{0\text{-}inf}$ value of 276 ng·hr/mL (276 nM.hr). Assuming proportionality of dose, exposure in nonclinical species was comparable to human for the mouse and pregnant rabbit, and lower in the rat and dog based on human equivalent dose (HED).

PK parameters

Bioavailability for the SC route was assessed for only one species, the dog, and was found to be essentially 100%. Bioavailability for the intranasal route was assessed in dog and monkey and was predictably much less: 32% in the monkey and approximately 7% in the dog.

Volume of distribution and clearance

In the female rat, following IV administration, the volume of distribution was 0.34 L/kg and 0.38 L/kg for doses of 0.25 mg/kg or 1 mg/kg, respectively, and clearance was 63 mL/min/kg and 61 mL/min/kg (Study 91-0501).

In the male dog, following IV administration, volume of distribution was small, 0.5 L/kg and 0.4 L/kg for an 0.1 mg/kg or 1.0 mg/kg IV dose, and clearance was low: 12 mL/min/kg and 8.4 mL/min/kg, respectively. (See Table 2.6.4-1 Mean (± SE) Pharmacokinetic Parameters of IV and SC Bremelanotide in Beagle Dogs, page 25 of the PK written summary in Module 2.6.4 of the NDA submission).

Exposure was roughly proportional to dose, but the Applicant did not provide graphical analysis of dose proportionality or of dose equivalence across species.

Table 2. ADME/PK Results

Type of Study	Major Findings
Absorption Mouse: PL-34, PL-41, PL-54, PL-53 Rat: PL-16, 8360928 Rabbit: 04-014, PL-44 Ferret: 04-037 Dog: PL-76, 996-034, PL-17, PL-26, PL-42, PL-43, PL-50, PL-51, PL-18 Monkey: PL-10	In general, BMT administered by the SC route was rapidly absorbed (T_{max} <1 hour) and rapidly cleared ($T_{1/2}$ <2 hours in mice and dogs, ≤3 hours in rat). Clearance was roughly biphasic, and was seen in rat IV, rabbit SC, dog SC, and monkey IV.
Distribution: Protein Binding Values for plasma protein binding were reported in three studies: 5151 (b) (4) 2001), 7545 (b) (4) 2003), and 100040177 (b) (4) 2017). The first two studies used ultrafiltration to test binding of a 10μM sample. The last used equilibrium binding of 1μM BMT and assessed partitioning to blood cells.	Binding to human serum protein varied from a low of 3% (Study 7545, test concentration 10μM) to a high of 21% (Study 5151, test concentration 10μM). Study 100040177 was intermediate at 16% (test concentration 1μM). Mean of these three values is 13%. We note that the clinical pharmacology team is allowing the value of 21% in the label. Protein binding to nonclinical species was 32%, 6%, and 13% for mouse, rat, and dog, respectively.

Type of Study	Major Findings
Tissue Distribution in the Mouse *Study 8349336: Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-Bremelanotide Following Subcutaneous Administration to Mice* Methods: Male and female B6C3F1/Crl mice were dosed with 30 mg/kg BMT by the SC route. A 30 mg/kg dose corresponds to a HED of 2.44 mg/kg. The proposed human therapeutic dose is 1.75 mg or 0.03 mg/kg for a 60 kg woman. Thus, the dose administered in this distribution study was 81X the proposed human dose. Urine was collected at 0 to 8 and 8 to 24 hours postdose, and at 24-hour intervals through 168 hours postdose. Feces were collected at 24-hour intervals through 168 hours postdose. After each 24-hour excreta collection through 144 hours postdose, cage rinse samples were collected. Two animals/sex/time point were prepared for quantitative whole-body autoradiography (QWBA) at 0.5, 4, 8, 24, 48, 72, 168, 336, and 672 hours postdose. The last three timepoints correspond to 7, 14, and 28 days, respectively.	Exposure: AUC_{0-t} for BMT in plasma in male and female mice represented 13.8% and 16.6%, respectively, of the total radioactivity in plasma, indicating the presence of circulating metabolite(s). The mean blood to plasma concentration ratios were <1 through 24 hours postdose, indicating that there was no distribution to the cellular component of blood. Tissue distribution: [^{14}C]-BMT-related radioactivity was quickly and widely distributed in tissues and organs and there were no notable gender differences. Most tissues had peak radioactivity concentrations at 0.5 hours postdose (the first evaluation time point). In males and females, the tissues showing the highest peak concentrations (after the dose site) reflected the routes of excretion: kidney, liver, small intestine, and pancreas. Males additionally showed high concentrations in the bulbo-urethral gland. Relevant to the mechanism of action, BMT was shown to cross the blood brain barrier, but with a significant delay. Radioactivity concentrations in the cerebellum, cerebrum, medulla, and spinal cord peaked at a low level, 24 hours after injection in males, and 4 hours after injection in females. The reason for the sex difference for this distribution is unknown. The average peak radiolabel concentration (ng equivalents ^{14}C-BMT/g tissue) in the CNS was approximately 1000 in both males and females (approximately 10% of plasma concentration), which, if assumed to be all parent compound, is equal to a tissue concentration of 1000 nM, well above the K_i for the MC4 receptor of 14 nM. Clearance from the CNS was slow, and measurable concentrations that were 3 to 6X the plasma concentration remained at 28 days postdose in both male and female mice. In female mice, low levels of radioactivity were measured for up to 28 days postdose in uterus and ovary. In males, radioactivity slowly crossed the blood-testis barrier, peaking at low levels at 24 hours postdose, and then was slowly cleared. [^{14}C]-BMT-related radioactivity was not found to be selectively associated with melanin-containing tissues. The elimination of drug-derived systemic radioactivity was essentially complete by 28-days postdose.

Type of Study	Major Findings
Metabolism *Study 8349337* This study characterized the in vitro metabolic profile of BMT in mouse, rat, dog, and human hepatocytes. Unfortunately, this study did not include rabbit hepatocytes.	In agreement with Study 7514-124, BMT was found to be relatively stable in human and dog hepatocyte incubations, and moderately metabolized in rat and mouse hepatocytes. The hydrolysis metabolite (M5) was the only major metabolite found in human and dog hepatocytes. In mouse hepatocytes, M5 and M4 (a secondary metabolite formed via the amide hydrolysis of M5 between the aspartic acid and histidine residues) predominated, and in rat hepatocytes, M33 (formed via the hydrolysis between the tryptophan and lysine residues of M4), along with M3, M4, and M5 were found. All other metabolites were relatively minor across species, and no human unique metabolite nor any disproportionately expressed metabolite was detected in hepatocyte incubations. The primary metabolic pathway involved the hydrolysis of the amide bond between the N-acetyl-norleucine moiety and aspartic acid to form M5. A second-step amide hydrolysis of M5 between the aspartic acid and histidine residues produced M4, which further underwent hydrolysis between the tryptophan and lysine residues to form M33. A double amide hydrolysis of BMT (between arginine and tryptophan; and between tryptophan and lysine) by loss of tryptophan residue yielded M24. In addition, M3 was identified as a D-phenylalanine, which further formed M1 via aromatic hydroxylation.
Metabolism *Study 8349336: Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-Bremelanotide Following Subcutaneous Administration to Male and Female Mice* In vivo metabolism was not characterized for the other nonclinical species.	Bremelanotide underwent moderate metabolism in male and female mice to produce 21 radioactive components, of which eight were identified/characterized by LC-MS. Amide hydrolysis was the predominant biotransformation pathway. M3 (D-phenylalanine), the sole major metabolite, cumulatively accounted for 11.3% and 8.3% of the dose in male and female mice, respectively. Observed primarily in feces and to a lesser extent in urine, resulted from double amide hydrolysis of BMT at the histidinyl-D-phenylalanine and D-phenylalanyl-arginine bonds. Minor metabolites are not listed here.
Excretion *Study 8349336: Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-Bremelanotide Following Subcutaneous Administration to Mice*	Excretion: ^{14}C-BMT-derived radioactivity was rapidly excreted in urine and feces after SC dosing. Approximately 86.4% and 82.2% of the dose was excreted in the first 48 hours in male and female mice, respectively. Excretion profiles were similar across sex with renal and fecal excretion being nearly equal in abundance. Hepato-biliary and renal excretion were the major routes of elimination.

Type of Study	Major Findings
Enzyme Inhibition/Induction and Drug-Drug Interaction *Study 46818* Human liver microsomes pooled from 20 subjects were used to investigate the potential of PT-141 to inhibit human liver microsomal CYP 450 isozymes (CYP 1A2, CYP 2A6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4). The incubations were performed in the absence or presence of five concentrations of PT-141, i.e., 10, 25, 50, 100, and 200μM.	No clinically meaningful levels of inhibition were observed. BMT did not inhibit the activity of CYP isozymes 1A2, 2C9, 2D6, or 2E1. At 200μM, BMT caused inhibition of CYP 2C19 (approximately 85%) and CYP 3A4 (approximately 60%), and marginal inhibition of CYP 2A6 (approximately 40%). There was no inhibition of these three CYP isozymes at 20μM (Study 46818). For CYP 2C19, BMT decreased V_{max}, while the K_m remained unchanged, suggesting a noncompetitive mechanism of inhibition. The K_i was determined graphically to be approximately 35μM. For CYP 3A4, each substrate exhibited a pattern consistent with competitive inhibition by BMT. The K_i of BMT using substrates testosterone and midazolam were graphically determined to be approximately 60μM and approximately 16μM, respectively. However, in the case of nifedipine, graphically, the K_i was determined to be approximately 35μM.
Enzyme Inhibition/Induction and Drug-Drug Interaction *Study 100026669* Two other enzymes assayed.	At concentrations up to 10μM, BMT showed minimal inhibition of the CYP isozymes 2B6 and 2C8.
P450 Induction *Study MD-3-3-474-1827* This non-GLP study determined if treatment with BMT induced the expression of CYP 450 enzyme genes in human primary hepatocytes in vitro.	The panel of P450s selected for this study included CYP 1A2, CYP 2B6, CYP 3A4, CYP 2C19, and CYP 2A6. Bremelanotide demonstrated little to no potential to induce gene expression for CYP enzymes.
Drug-Drug Interaction *Study 100026666* This non-GLP study tested the in vitro inhibition of drug transporters by BMT in absorption assays using fluorimetry as the detection method. BMT at a concentration of 1mM was incubated for 20 minutes at 37ºC with OCT2, BCRP, OAT1, OAT3, OATP1B1, and OATP1B3 in human recombinant CHO-K1 cells, and with P-gp in MDR1-MDCKII cells.	Bremelanotide caused low inhibitory activity against all seven transporters. Inhibition was 20.9% for OATP1B3, 12.0% for P-gp, and 5.0% for OAT3. This level of inhibition is not clinically relevant.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Drug-Drug Interaction
In vivo study
This study tested the effect of BMT on the kinetics of absorption of orally administered drugs. It was submitted in response to an information request by the NDA review team (SDN 39, 14Dec2018, Appendix 1). BMT is known to reduce gastric contractility and to therefore slow gastric emptying, which could alter the kinetics of drug absorption. Briefly, BMT was administered SC to mice plus or minus orally administered furosemide, naltrexone, or naltrexone.</td><td>None of the drugs affected BMT pharmacokinetics, nor did BMT affect kinetics of the drugs tested.</td></tr>
<tr><td>TK Data: General Toxicology Studies
Study 996-028 (mouse)
A 26-week SC study with 4-week recovery

Study 996-003 (dog)
A 39-week SC dose toxicity study

To get a sense of comparative exposure for the species used in the pivotal repeat-dose toxicology studies, the table to the right shows values for C_{max} and AUC for equivalent doses (based on mg/m^2) in the mouse and dog (average of M/F on D1 of dosing).</td><td>
<table>
<tr><th></th><th>Study 996-028 (mouse)
15 mg/kg=45 mg/m^2</th><th>Study 996-003 (dog)
2 mg/kg=40 mg/m^2</th></tr>
<tr><td>C_{max} (D1)</td><td>9806</td><td>1946</td></tr>
<tr><td>AUC (D1)</td><td>15093</td><td>3855</td></tr>
</table>

This comparison shows that equivalent doses in the mouse produced higher exposures than in the dog on a mg/m^2 basis.</td></tr>
</table>

Type of Study	Major Findings
TK Data: Reproductive Toxicology *Study 996-026* Mouse female fertility NOEL=150 mg/kg/d	AUC: At the NOEL, $AUC_{0\text{-}inf}$=176379 ng.hr/mL and the MOE was 639X based on AUC.
TK Data: Reproductive Toxicology *Study 996-033* Effect of BMT on embryo fetal development in dogs No developmental NOEL set	AUC: At doses of 2, 8, and 20 mg/kg/d, exposures were approximately 17X, 85X, and 274X the human therapeutic exposure of 276 ng.hr/mL.
TK Data: Reproductive Toxicology *Study 996-032* Pre- and postnatal developmental toxicity study, including maternal function and TK in B6C3F1 mice Doses: 30, 75, and 150 mg/kg/d NOEL for maternal toxicity=75 mg/kg/d NOEL for reproductive performance of the F0 generation=150 mg/kg/g NOEL for development of the F1 generation >150 mg/kg/d NOEL for development of the F2 generation=75 mg/kg/d	Exposures in this study were approximately 118X, 327X, and 702X the human therapeutic exposure based on AUC averaged for GD6 and GD15 low, mid, and high dose, respectively.
TK Data: Carcinogenicity Studies *Study 996-007* A 2-year oncogenicity study of BMT in B6C3F1 mice Doses: 3, 9, 15 mg/kg/d SC NOAEL=15 mg/kg/d	By body surface area, the MOE compared to the human therapeutic dose is 41X. The MOE based on based on C_{max} values obtained at 1 year is 141X for males and 183X for females.
Study 996-008 A 2-year intranasal oncogenicity study of BMT in SD rats Doses: 0.5, 2.5, 5 mg/kg/d NOAEL=5 mg/kg/d	By body surface area, the MOE is 27X compared to the human therapeutic dose. By exposure, the MOE changes dramatically depending on whether it is calculated from plasma values taken at 3 months versus 19 months. As was observed in other, shorter duration repeat-dose toxicology studies by either the SC or intranasal routes, exposures in the rat decline over time with repeat dosing. Thus, based on C_{max}, the MOE determined from initial exposure values is 2 to 3X but declines to less than half the human exposure at the end of the study.

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, GLP good laboratory practice, IV intravenously, K_i inhibitory constant, LC-MS liquid chromatography–mass spectrometry, MOE margin of exposure, NOEL no observable effect level, NOAEL no-observed-adverse-effect level, P-gp P-glycoprotein, SC subcutaneous

5.5. General Toxicology

Study 996-028

A 26-week subcutaneous dose toxicity study of BMT in B6C3F1 mice with a 4-week recovery group.

Key study findings

There were no new toxicities that had not been previously observed in the mouse for shorter duration studies.

- At 75 mg/kg/day (the high dose), there was an increased incidence of scabbed areas, sparse hair, and white hair in males and females.
- A trend for increased body weight and food consumption was observed at the high dose during the treatment period. However, by the end of the recovery period, food consumption and group mean body weights in the 75 mg/kg/day group were lower than controls.
- There were signs of mild reactive changes in the liver and kidney. There was a dose-dependent mild increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) particularly in females at termination. There were small (approximately 10% to 12%) but statistically significant increases in relative liver and kidney weights in males and females, primarily at the mid and high doses, that did not have corresponding histopathology, and were considered reactive.
- TK: Exposures were stable or slightly increased over the duration of the study. There were no sex differences.

Based on these findings, NOEL=30 mg/kg/day. At that dose, MOE compared to the proposed human dose based on AUC on day 180 was 56X.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 15, 30, 75 mg/kg/d
Route of administration: Subcutaneous
Formulation/Vehicle: 2.5% glycerin in sterile water
Species/Strain: Mouse / B6C3F$_1$
Number/Sex/Group: 30 sex/group plus 10 animals in the low and high dose groups for recovery
Age: 5 weeks
Satellite groups/unique design: 90/sex/group for TK; none
Deviation from study protocol affecting interpretation of results: No

Table 3. Observations and Results From Study 996-028: Changes From Control

Parameters	Major Findings
Mortality	Two control females, one male and one female at 15 mg/kg/day, and one male and one female at 30 mg/kg/day were found dead during the course of the study. None were considered treatment-related.
Clinical signs	Cage side observations conducted twice daily. Detailed clinical observations conducted weekly. Clinical signs consisted of alopecia observed at greater frequency in the high-dose group (90% of males and 65% of females) than in controls (33% in males and 35% in females) during the treatment period. Scabbed areas were observed only in the high-dose group (40% of males and 35% of females). Only one animal had a scabbed area during the recovery period. White colored hair was observed only at the high dose (23% of males and 10% of females). Alopecia and white coloration of hair were observed throughout the recovery period.
Body weights	Prior to randomization and then weekly. At the high dose, body weights were significantly decreased in males during Weeks 2 and 3 and in females during Weeks 3 and 4. However, for the remainder of the 26-week dosing period, treated animals generally had higher body weights than control animals. No significant differences were observed during the 4-week recovery period.
Ophthalmoscopy	No treatment-related findings
Hematology	Hemoglobin and MCH were slightly higher in both male and female treated groups with no dose-response relationship.
Clinical chemistry	There was a dose-dependent mild increase in serum transaminases (AST and ALT) particularly in females at termination. There were no test article–related effects on clinical chemistry analytes at recovery.
Gross pathology	There was an increased incidence (approximately 25% male and female) of alopecia in the high-dose group at terminal necropsy. Mild alopecia was also observed at the injection site in males (2/20 left flank and 3/20 right flank).
Organ weights	There were small (approximately 10% to 12%) but statistically significant increases in liver and kidney weight in males and females, primarily at the mid and high doses. Other significant changes consisted of decreased weights of mandibular salivary gland and seminal vesicles in high-dose males. Relative spleen weight in high-dose females at the end of the recovery period was significantly higher than the controls (0.419% versus 0.290%), which was unexplained. Microscopic examination identified no test article-related abnormalities in the spleen of these animals, and spleen weights in the 75 mg/kg/day terminal necropsy females were normal. Therefore, the increased spleen weight in the recovery females was considered spurious and of no toxicological significance.
Histopathology Adequate battery: Yes	Test article related microscopic changes occurred in the skin and at the injection site, primarily at the high dose. In males these findings included alopecia/ hypotrichosis, epidermal hyperplasia, fibrosis, chronic inflammation, and erosion/ ulcer. In females, fibrosis, epidermal hyperplasia, and acute inflammation were observed. The incidence of skin alopecia in males was 0, 1, 1 and 6 out of 20 for control, 15, 30 and 75 mg/kg/day groups, respectively. In females the incidence of skin alopecia was 1, 2, 2 and 5 in control and dosed groups, respectively. Severity was minimal to mild. The incidence of alopecia at the high dose did not decrease during the recovery period.

Parameters	Major Findings
TK	Bremelanotide was rapidly absorbed following SC dosing at all three dose levels, with T_{max} occurring 20 to 60 minutes postdose. Mean T_{max} occurred slightly later at the highest dose but did not change following multiple SC doses. A dose-related increase in average C_{max} and $AUC_{0-\infty}$ was observed in male and female mice at all three study intervals (Days 1, 90, and 180). The data were highly variable; however, there did not appear to be a difference in exposure between male and female mice, and exposure was comparable to previously conducted mouse studies at these doses.

Abbreviations: ALT alanine aminotransferase, AST aspartate aminotransferase, AUC area under the plasma concentration-time curve, MCH mean cell hemoglobin, SC subcutaneous

Study 996-003

A 39-week subcutaneous dose toxicity study of BMT in dogs.

Key study findings

- Treatment-related clinical findings included stereotypic behavior, black discoloration of the hair and thickening of the skin at injection sites. Stereotypic behavior was generally limited to the first week of dosing.
- Body weights were reduced by approximately the same amount (approximately 10%) at all doses in males and in a dose-dependent manner in females (maximum approximately 10%).
- Liver enzyme elevation occurred in all drug-treated groups. Although treatment increased some hepatic enzymes primarily in females, no hepatic macroscopic or microscopic pathology was reported.
- There was treatment related increase in adrenal gland weight in females (significant at the high dose only) with no corresponding adrenal histopathological changes.
- TK: Systemic exposure *decreased* at all doses over the course of the study (approximately 30%), which was unexplained.

The Applicant discounted changes in body weight, elevated liver enzymes, and increased adrenal weight and set the NOAEL at the high dose, 20 mg/kg/d. We disagree. Body weight changes are likely due to action of the drug and are mildly adverse. Other changes are likely reactive. Based on changes in body weight, we set the NOAEL for females at 2 mg/kg and do not set a NOAEL for males. Compared to AUC at 2 mg/kg in Week 24 of the study, MOE is 10.7X.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 8, 20 mg/kg/d
Route of administration: Subcutaneous
Formulation/Vehicle: 2.5% glycerin in sterile water
Species/Strain: Dog/Beagle
Number/Sex/Group: 4/sex/group
Age: 18 months
Satellite groups/ unique design: None; all animals used for TK at 4, 12, and 24 weeks
Deviation from study protocol affecting interpretation of results: None

Table 4. Observations and Results From Study 996-003

Parameters	Major Findings
Mortality	None
Clinical signs	Performed weekly. Drug-related clinical findings consisted of stereotypic behavior, black discoloration of the hair and thickening of the skin at injection sites. Stereotypic behavior included forepaw padding, stretching, rolling, crouching, and yawning in a dose response-related pattern; increasing doses increased the number and types of behavior observed. These occurred in all treated animals but were generally limited to the first week of study. A generalized darkening of the brown hair, noted as black discoloration, was observed in all treated animals beginning in Week 7. This change gradually resulted in a coat color that was black and white (instead of the normal distribution of brown, black, and white). There was no apparent effect on the white or black hair, only the replacement of brown hair with black. There was no dose-response or sex relationship. Thickening of the skin at the injection sites was observed in both sexes treated with 8 mg/kg/day and 20 mg/kg/day as early as Week 5 of the study. The skin thickening and leathery appearance continued to increase which necessitated the decision to move dosing to the caudal region in Week 19 of the study. By Week 21, most observations for thickened and leathery skin at the original injection site were no longer present and none were present by Week 23. For new injection sites thickening was noted in Weeks 23 and 24 for four animals.
Body weights/Food consumption	Weekly. Body weights were slightly reduced by approximately the same amount at all doses in males and in a dose-dependent manner in females. Weekly. Decreased food consumption was observed in males in the mid- and high dose groups and all treated females during the first week. Following Week 1, food consumption increased and tended to higher than respective controls.
Ophthalmoscopy	Conducted pretest and prior to necropsy. No treatment-related effects.
ECG	ECG and indirect limb BP determined on all animals prior to dosing and one hour following dosing on Weeks 4, 12, and 24. No qualitative or quantitative ECG abnormalities were associated with treatment at Week 24. There were no drug-related effects on the systolic, diastolic, or mean arterial blood pressure measurements. There was however, a large variability in the data but were not considered treatment related due to the lack of dose-dependency or relative change from pretest values. No changes in heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc intervals were reported associated with treatment.

Parameters	Major Findings
Indirect blood pressure	Blood pressure of each animal was measured and recorded pretest and in Weeks 4, 12, and 24, prior to dosing and one hour (±15 minutes) following dosing. Blood pressure measurements are reported using three consecutive readings that have the MAP within 20 mm Hg. There were no test article-related effects noted on the systolic, diastolic, or mean arterial blood pressure measurements. There was a large variability in the data, but they were not considered to be test article related due to the lack of dose-dependency or the relative change from pretest values.
Hematology	Pretest and at Weeks 4, 12, and 24. There were statistically significant decreases in erythrocytes, hemoglobin, and hematocrit in the low dose group females at Weeks 8 through 24 and in the mid-dose group at Week 24. There was a decrease (approximately 6%) in platelet counts in the high dose group expressed as mean K/mm^3.
Clinical chemistry	Pretest and at Weeks 4, 12, and 24. No treatment-related effects.
Urinalysis	Collected for at least 16 hours. No treatment-related effects.
Gross pathology	Not presented.
Organ weights	Males: The absolute and relative right cauda epididymis were significantly increased at the mid- and high doses, and both epididymides were elevated at the high dose. There was no dose response and there were no microscopic findings, so this was not considered toxicologically important. Females: There was a trend toward decreased liver weight in females that was significant only when normalized to brain weight at the high dose. There was a statistically significant increase in adrenal weight in a dose related manner. Although adrenal gland weight was significantly increased with treatment in females, no microscopic pathology was observed.
Histopathology Adequate battery: Yes Peer review: Yes (for adrenal glands only)	Injection-site reactions: Hemorrhage, pigment, inflammation, fibrosis, and degeneration/regeneration of skeletal muscle fibers in the panniculus carnosus (subcutaneous layer of striated muscle). The Applicant noted that increased melanin in the medulla of hair shafts was difficult to discern due to skin sites having black hair. Liver: No pathologic findings were reported for liver although liver enzymes were elevated with treatment. Adrenals: No hypertrophy confirmed by peer review. Peer review was conducted on the control and high dose females to confirm that there was no hypertrophy of the adrenal cortex. The reviewing pathologist agreed with the study pathologist that no detectable hypertrophy was present.
Sperm analysis	A section of the right vas deferens was utilized for videotaping a prepared sperm sample for automated evaluation of sperm motility (viability). The right cauda epididymis was separated, weighed, and used for manual (visual) assessment of sperm concentration. Slides were prepared for assessment of sperm morphology from the motility preparations. The right testis was frozen and used to prepare samples for analysis of spermatid head count. Treatment showed no effect on sperm motility, sperm concentration/gram cauda epididymis, and total sperm concentration per cauda epididymis. Also, the number of homogenization-resistant spermatids as well as percentage of abnormal sperm were similar among groups.
TK	Blood samples (approximately 2 mL) were collected from four animals/sex/group via the jugular vein predose and at 0.5, 1, 2, 4, and 8 hours postdose on Day 1, and Weeks 12 and 24. The animals were not fasted prior to blood collection. C_{max} and AUC decreased at Week 24 compared to values reported for Day 90. Mean plasma $AUC_{0\text{-}inf}$ values decreased by approximately 30% from Day 1 to Week 24 in both males and females at all three dose levels.

Abbreviations: AUC area under the plasma concentration-time curve, BP blood pressure, ECG electrocardiogram, Mean Arterial Pressure (MAP), TK toxicokinetics

General Toxicology: Additional Studies

Intranasal Repeat-Dose Studies in the Rat

Three repeat-dose toxicity studies (14-, 28-, and 90-day) were conducted by the intranasal route in the rat and are briefly discussed below. Of note was a special evaluation of adrenal tissue sections from the 28- and 90-day studies to evaluate a finding of vacuolization in the adrenal cortex that occurred in both studies (Study 490-001). The Applicant deemed the finding nonadverse but did not provide an explanation for what might have caused it. Limited TK was available from the 14- and 28-day studies; plasma was collected for TK but not analyzed for the 90-day study.

Study 490-001: PT-141

Review of adrenal tissue sections from rats in 28-day and 90-day studies. Conducted by (b) (4) on 9Aug2002. Finalized independent pathology report based on slides from Studies 103-004 (28-day with 14-day recovery) and 131-003 (90-day with 28-day recovery).

Sections evaluated:

- 28-day study (131-004): All rats in the high-dose and control groups and the males in the low-dose and mid-dose groups. Doses were 3, 4, and 5 mg/kg. N=15/sex control and high dose. N=10/sex low and mid-dose.
- 90-day study (131-003): All rats in all groups. Doses were 0.2, 1, and 3 mg/kg. N=15/sex control dose. N=21/sex dosed groups.
- Adrenal sections were also evaluated for rats from those studies after a recovery phase. 5/sex from low- and high-dose groups in the 28-day study and N=5/sex from all groups in the 90-day study).
- Microscopic findings were graded for relative severity on a scale of 1 to 5.

Table 5. Results: Incidence of Cytoplasmic Vacuolation in Adrenal Cortex in BMT Studies 103-004 and 103-004

Study 103-004	**Control**	**3 mg/kg**	**4 mg/kg**	**5 mg/kg**
After 28-day dosing	4/10	5/10	6/10	6/10
After 14-day recovery period	3/5	—	—	2/5
Total incidence of vacuolation	7/15 (47%)	5/10 (50%)	6/10 (60%)	8/15 (53%)
Study 131-003	**Control**	**0.2 mg/kg**	**1 mg/kg**	**3 mg/kg**
After 90-day dosing	3/10	4/16	5/16	7/16
After 28-day recovery period	1/5	2/5	2/5	1/5
Total incidence of vacuolation	4/15 (27%)	6/21 (29%)	7/21 (33%)	8/21 (38%)

Abbreviations: BMT bremelanotide

Females were not affected in either study. Vacuoles were discrete round clear vacuoles distributed among few to several mid-zonal cells in the zona fasciculata. Those discernible at low magnification were recorded as grade 2. Grade 1 was used for similar vacuoles, although

smaller or fewer, found at high magnification. All vacuolations were mostly grade 1 except one or two male rats with grade 2 in each study group. From these findings it was concluded that the cytoplasmic vacuolations were sex-related and had no relationship to PT-141 dose levels or duration of treatment.

These studies did not include measurements of corticosterone or ACTH, so it is not known whether there was any physiological change associated with the histopathology findings.

5.6. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

For reasons that are unclear, the standard Ames test was conducted twice for BMT, using identical methods. Two different lots were used.

Ames Test Results for Sample: Bremelanotide/GLP-1000-0618 and GLP-2000-PT-141A

Key study findings

- BMT was found not mutagenic against any of the tester strains, either directly or with S9 metabolic activation in either test.

GLP compliance: Yes
Test system: *Salmonella typhimurium, TA98,* TA100, TA1535, TA1537
Escherichia coli WP2 up to 5000 µg/plate; +/-S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

In Vitro Mammalian Chromosomal Aberration Test in Chinese Hamster Ovary Cells With Bremelanotide/C122-002

Key study findings

- BMT was negative for the induction of structural or numerical chromosomal damage.

GLP compliance: Yes
Test system: Chinese hamster ovary cells.
Doses: 1009, 2017, 3026, 4035, or 5043 µg/mL (by weight); +/-S9
Actual doses adjusted for peptide purity: Expt #2: 802, 1604, 2406, 3208, 4009 µg/mL (approximately 800µM to 4mM)

Formulation analysis showed that concentrations were approximately 20% below the targeted concentration (Study C122-002, Appendix II Dose Formulation Analysis[40]).

Duplicate cultures were exposed to the test article with and without metabolic activation for 4 hours. An additional set of duplicate cultures was exposed to the test article without metabolic activation continuously for 19 hours. Colcemid (final concentration of 0.1 µg/mL) was present for the final two hours of incubation.

Results

Cytotoxicity

Measurements of cytotoxicity and myocardial infarction were highly variable and difficult to interpret for both BMT and the positive controls.

Structural Chromosomal Damage (percentage of metaphase cells with structural aberrations)

BMT was found negative. Number of cells scored: 200/dose.

Numerical Chromosomal Damage (polyploidy index)

BMT was found negative. Number of cells scored: 400/dose.

Study Validity

The conduct of the study was acceptable, even though some aspects of design did not meet standard criteria. A high-test concentration was achieved, and given that BMT is a peptide, it is likely that it did not achieve access to the cell interior, which would account for the negative findings. We accept the findings and will include them in weight of evidence for genotoxicity.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Mouse Micronucleus Test Results for Bremelanotide/GLP-2000-PT-141

Key study findings

- BMT was found to be not clastogenic in the mouse micronucleus assay.
- Although TK measurements were not done, using TK data from study 996-009 (PL-41) the top dose in this study produced an exposure of approximately 17-18,000 ng.hr/mL, which is approximately 100X the human therapeutic AUC.

[40] See Table 4, pages A2–13, available at \\cdsesub1\evsprod\nda210557\0002\m4\42-stud-rep\423-tox\4233-genotox\42331-in-vitro\c122-002.pdf

GLP compliance: Yes

Test system: BALB/c mice, bone marrow micronuclei; single oral doses of 6.25, 12.5, and 25 mg/kg

Study was deemed valid. However, a number of experimental details were not provided.

Other Genetic Toxicity Studies

Genotoxicology testing for impurities was conducted and found negative.

5.7. Carcinogenicity

Standard 2-year carcinogenicity studies for BMT in the mouse and rat were conducted. The mouse study was conducted by the SC route, and the rat study was conducted by the intranasal route, (b) (4) MT was found not carcinogenic in either species.

Mouse: 104-week subcutaneous dose oncogenicity study of BMT in B6C3F1 mice. Study #996-007. Doses of 0, 3, 9, or 15 mg/kg were administered daily in a vehicle of 2.5% glycerin in sterile water at a dose volume of 4 mL/kg. N=60/sex/group for the main study and 18/sex/group for TK.

Rat: 104-week intranasal oncogenicity study of BMT in Sprague-Dawley rats. Study #996-008. Doses of 0, 0.5, 2.5, or 5 mg/kg were administered daily in a vehicle of 2.5% glycerin in sterile water at a dose volume of 25 µL to the right naris only. The basis for dose selection was maximum feasible dose by the intranasal route. N=60/sex/group for the main study and 5/sex/group for TK.

5.7.1. Key Study Findings

Mouse

Overall, BMT did not affect survival. A slight but treatment-related increase in body weight was observed in both male and female mice, especially during the first half of the study. There were no treatment related tumor findings. BMT was found not carcinogenic in the mouse. NOAEL=15 mg/kg/d. By body surface area, the MOE compared to the human therapeutic dose is 41X. The MOE based on exposure can be estimated from TK values. Exposures were stable over the course of the study up to 1 year and were consistent with other measurements obtained in the mouse by the SC route. Based on C_{max} values obtained at 1 year, the MOE is 141X for males and 183X for females.

Rat

Treated groups had slightly increased survival compared to controls. For body weight, males showed no effect of treatment, and in females, there was a trend toward slightly lower body weight. There were no treatment-related tumor findings. The statistical reviewer noted a significant pairwise comparison at the high dose for incidence of benign cortical adenoma in males, and uterine stromal polyps in females. However, these did not show a significant dose-response relationship, and therefore, were not considered to be positive findings. Therefore, BMT was found negative for oncogenic potential. NOAEL for carcinogenicity was 5 mg/kg/d by the intranasal route. By body surface area, the MOE is 27X compared to the human therapeutic dose. By exposure, the MOE changes dramatically depending on whether it is calculated from plasma values taken at 3 months versus 19 months. As was observed in other, shorter duration repeat-dose toxicity studies by either the SC or intranasal routes, exposures in the rat decline over time with repeat dosing. Thus, based on C_{max}, the MOE determined from initial exposure values is 2X to 3X but declines to less than half the human exposure at the end of the study.

5.7.2. Adequacy of Carcinogenicity Studies:

Mouse and rat study protocols were approved on 30 March 2004, by the Center for Drug Evaluation and Research, Executive Carcinogenicity Assessment Committee; the final studies were reviewed and deemed adequate on 28 May 2013.

5.8. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Three studies were conducted to evaluate fertility and early embryonic development. One study was conducted in female mice by the subcutaneous route. One study was conducted in male mice by the subcutaneous route, and another study was conducted in the male rat by the intranasal route. Because this is a female indication, only the female mouse study is presented.

Bremelanotide: Study of Female Fertility and Embryo-Fetal Development in Mice/996-026

Key study findings

- No effect of treatment with BMT was noted in fertility indices, uterine implantation data, gravid uterine weights, fetal body weights, fetal sex ratios, or fetal external, visceral, and skeletal examinations.
- The maternal lowest observed adverse effect level was 30 mg/kg/day based on a dose-related increase in the incidence of females with irritation at the injection sites, including sparse hair at all treatment levels and scabbing in the high dose animals.
- The NOEL for both female fertility and developmental toxicity was 150 mg/kg/day, the highest dose evaluated.

- No TK measurements were done for this study, but TK data were obtained from pregnant mice at the same doses in Prenatal and Postnatal Development Study 996-032 (TK Study PL-53). Using measurements taken on the first day of dosing, at the low dose of 30 mg/kg/d, $AUC_{0\text{-}inf}$ was 31194 ng.hr/mL, which is 113X the human therapeutic AUC. At the high dose of 150 mg/kg/d, $AUC_{0\text{-}inf}$ was 176379 ng.hr/mL and the MOE was 639X based on AUC.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0, 30, 75, and 150 mg/kg/d (two control groups)
Route of administration: Subcutaneous
Formulation/Vehicle: 2.5% glycerin in sterile water
Species/Strain: Mouse/B6C3F1/Crl
Number/Sex/Group: 30 F/group
Satellite groups: No TK (refer to study PL-53 for TK data obtained at the same doses)
Study design: Animals were dosed 14 days prior to mating through GD15
Deviation from study protocol affecting interpretation of results: None

Table 6. Observations and Results From Study 996-026

Parameters	Major Findings
Mortality	One mouse each in the 30, 75, and 150 mg/kg/day groups died during the study. In addition, one mouse each in the vehicle control 1, 30, and 150 mg/kg/day groups was euthanized in extremis. Clinical observations and macroscopic findings were unremarkable and the mortality of mice in these groups was considered unrelated to treatment.
Clinical signs	Examined daily. Treatment-related irritation at the injection site was observed in all treatment groups.
Body weights	Maternal body weights, body weight change, food consumption, and organ weights were unaffected.
Necropsy findings (mating/fertility index, *corpora lutea*, preimplantation loss, etc.)	The mating indices for the treated and both controls groups was 100%. The percentage fertility and fecundity indices for controls 1 and 2 and for the 30, 75 and 150 mg/kg/day groups were 96.6, 93.3, 80.6, 86.7 and 83.3, respectively. While treated groups were all lower than controls, the differences were not statistically significant. The mean copulatory interval in the treated groups ranged from 2.0 to 2.8 days compared to about 2.8 in the controls. Uterine and ovarian examinations: The total number of GD17 pregnancies in the control 1 and 2 and the three drug-treated groups were 24, 27, 19, 23 and 24, respectively. Two animals each in control group 1 and the low dose group, and one animal in the mid-dose group delivered prior to GD17. The number of corpora lutea, uterine implantations, viable fetuses, resorptions, preimplantation loss, and post-implantation loss for the treated groups were comparable to controls.

Abbreviations: GD gestation day, HD: high dose

Embryo-Fetal Development

The effect of BMT on embryo-fetal-development was investigated in eight studies in mice, rats, rabbits, and dogs. The rabbit was found not suitable for reproductive toxicity testing due to maternal and developmental toxicity. The Applicant has chosen to use the studies in the mouse and dog by the SC route to support labeling; in the mouse, this took the form of a combined embryofetal/pre- and postnatal development study. These are fully reviewed below.

Bremelanotide: Study for Effects on Embryo-Fetal Development in Dogs/996-033

Key study findings

- The maternal lowest observed effect level was 2 mg/kg/day based on clinical findings of stereotypic behavior (stretching, yawning, etc.), inappetence, and lower gestation body weight gain predominately observed during the treatment period (GD18-35). In addition, excessive shedding and discolored hair (black) were evident beginning later in the treatment period (approximately GD33) and persisting through to termination.
- The Applicant's developmental NOEL was considered 20 mg/kg/day, the highest dose level evaluated. However, based on increased pre- and post-implantation loss in all treated groups, we conclude that no developmental NOEL can be set.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2, 8, 20 mg/kg/d
Route of administration: Subcutaneous
Formulation/Vehicle: 2.5% glycerin in sterile water
Species/Strain: Dog/Beagle ages 13 to 44 months
Number/Sex/Group: 8
Satellite groups: None
Study design: Timed mated female animals were treated from GD18-35 and euthanized on GD57.
Deviation from study protocol affecting interpretation of results: None

Table 7. Observations and Results From Study 996-033

Parameters	Major Findings
Mortality	None
Clinical signs	Treatment-related clinical findings of stereotypic behavior (stretching, yawning, etc.), inappetence, excessive shedding, and black discolored hair were observed at all doses.
Body weights	Lower body weight gain was observed in all treated groups during the dosing period and correlated with lower food consumption. Body weight was reduced by approximately 9% in the low and high dose groups at the end of dosing, and by approximately 6% in the mid-dose group. Following completion of the dosing period, animals resumed normal eating behavior and body weight gain values for the treated animals were similar to controls at termination on GD57.
Necropsy findings (Cesarean section data)	No test article-related maternal macroscopic findings were observed in the treated animals. • The pregnancy index was 87.5, 62.5, and 87.5% in the 2, 8, and 20 mg/kg/day groups and was comparable to controls at 75.0%. • Preimplantation and post-implantation loss was slightly higher in the treated groups in comparison to controls, but differences were not statistically significant or dose-dependent. The low number of animals evaluated make it difficult to establish statistical significance for any changes that might occur. • Likewise, all other uterine implantation data (number of corpora lutea), implantation sites, viable fetuses, litter size, and number of resorptions and fetal sex ratios were similar to controls and unaffected by treatment. • No effect of treatment was evident on gravid uterine weights, adjusted GD57 body weight, and adjusted body weight gains (GD6 to 57) in the treated groups.
Necropsy findings (offspring malformations, variations, etc.)	The Applicant indicates that no effect of treatment with BMT was evident from fetal body weight or fetal external, visceral, or skeletal evaluations. We disagree about fetal body weight, noting that body weight was reduced 12% for both males and females combined at the high dose. We also note that the low number of litters evaluated make it difficult to establish statistical significance for any changes that might occur.
TK	Plasma samples were collected on GD18 and GD35 and were similar at the two timepoints. Mean T_{max} (0.7 to 1.0 hours) was unaffected by dose level and did not change following multiple SC doses. Plasma exposure was dose-related on GD18 and GD35, with a slight increase in C_{max} and a slight decrease in $AUC_{0-\infty}$ following repeated dosing. Based on AUC averaged across the two timepoints, exposures were approximately 17X, 85X, and 274X the human therapeutic exposure of 276 ng.hr/mL.

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, GD gestation day, SC subcutaneous, TK toxicokinetics

Combined Embryofetal and Prenatal and Postnatal Development Study in the Mouse

Study title/number: Bremelanotide: A Pre- and Postnatal Developmental Toxicity Study, Including Maternal Function and Toxicokinetics, in B6C3F1 Mice/996-032

Key study findings

- No treatment-related mortality was observed in the initial generation (F0) females or second filial generation (F2) generation animals.

- A treatment-related decrease in F1 pup survival was observed during LD0-4 where nursing F0 female mice were being treated at 150 mg/kg/day; however, this decrease in survival did not persist after LD4.
- No treatment-related macroscopic findings were observed in the F0 females or first filial generation (F1) and F2 generation mice.
- Treatment-related clinical findings of tremors were seen in a few F0 females during the first 3 days of dosing (GD6-8) at the high dose. Other effects at this dose level included lower body weights, body weight gain, and food consumption early in lactation (LD0-14). Reproductive performance of the F0 female mice was unaffected.
- In the F1 generation, treatment-related effects consisted of clinical findings (decreased activity, thin appearance, and patches of white hair), lower body weights (lactation and postweaning), and a delay in development (eye opening, vaginal opening, and preputial separation) at all dose levels. In addition, lower food consumption was evident postweaning (Weeks 1 to 8) for F1 pups from F0 female mice dosed at 75 and 150 mg/kg/day. There were no behavioral findings (motor activity, learning and memory) and reproductive performance was unaffected at any dose.
- In the F2 generation from the high dose group, treatment-related lower body weights were noted during lactation.
- The NOEL for maternal toxicity was 75 mg/kg/day based on clinical findings (tremors), lower body weight, body weight gain, and food consumption at 150 mg/kg/day.
- The NOEL for reproductive performance of the F0 generation females was 150 mg/kg/day, the highest level evaluated.
- A NOEL for growth and development of the F1 generation mice was not achieved since treatment-related effects were noted in the F1 generation mice at all doses. The NOEL for behavior and reproductive performance was >150 mg/kg/d.
- The NOEL for growth and development of the F2 mice was 75 mg/kg/day based on lower pup body weights observed at 150 mg/kg/day on LD4-10.
- Exposures in this study were approximately 118, 327, and 702X the human therapeutic exposure based on AUC averaged for GD6 and GD15 at the low, mid, and high dose, respectively.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0, 30, 75, 150 mg/kg/d
Route of administration: Subcutaneous
Formulation/Vehicle: 2.5% Glycerin in sterile water
Species/Strain: Mouse/B6C3F1/Crl: BR
Number/Sex/Group: 30 F/group

Satellite groups: 60 F/dosed group and 10 F/control group for TK. TK samples were taken from half the animals per group on GD6 and half on GD15 at 0.25, 0.5, 1, 3, and 8 hours postdose. Control TK samples were collected at 0.5 hours postdose. On LD28, samples were collected from the main study treated groups and vehicle control group 1 at the same timepoints.

Study design: Animals were dosed from GD6 through LD28[41] (implantation through weaning). Litters Culled on Day 4.

Deviation from study protocol affecting interpretation of results: None

Table 8. Observations and Results From Study 996-032

Generation	Major Findings
F0 dams	• Tremors were sporadically observed in seven animals during the first 3 days of dosing at the high dose. There was scabbing and sparse hair in all groups at the injection site. There were no treatment-related macroscopic observations. • Gestation body weights and body weight gain in the treated groups were comparable to controls and unaffected by treatment. However, during lactation (LD0 to 14), mean body weights were lower in the high dose group. Body weight gain during this period for this group was comparable to controls and final weights were slightly above controls. • Early in the lactation period (LD4-7) food consumption was significantly lower in the treated groups (24% to 28% lower at the high dose). This was consistent with lower body weight and body weight gain during this time and was considered indicative of a treatment-related response. Food consumption after LD7 was not analyzed due to an increased incidence in food spillage, which necessitated exclusion of data for a large number of animals in all groups. • Parturition data: The number of F0 females delivering litters was 22, 26, 27, 28, and 26 in the Vehicle Control 1, Vehicle Control 2, 30, 75, and 150 mg/kg/day groups, respectively. Likewise, the fertility indices were 76.7%, 86.7%, 90.0%, 93.3%, and 86.7%. • The mean number of pups (live plus dead)/litter on LD0 in the treated groups ranged from 9.04-10.37 and was comparable to vehicle controls 1 and 2 (10.04 and 10.05, respectively). Gestation Length and Stillborn Indices in the treated groups were comparable to controls and unaffected by treatment. • Toxicokinetics: A dose-proportional increase in C_{max} and $AUC_{0-\infty}$ was observed at all three study intervals. Mean T_{max} was unaffected by dose level but occurred earlier on LD28 compared to GD6 and GD15. Exposures in this study were approximately 118X, 326X, and 615X the human therapeutic exposure based on AUC.

[41] The F1 offspring were potentially exposed to PT-141 in utero and as neonates during the lactation period but were not dosed directly.

Generation	Major Findings
F1 generation	• The viability index (mean % pups surviving LD0-4) was reduced at the high dose. Values were 94.67% and 97.27% for the vehicle controls, and 92.65%, 90.76%, and 79.59% in the 30, 75, and 150 mg/kg dose groups. • The Lactation Index (mean % pups postcull to LD28) was unaffected by treatment. F1 pup sex ratios were unaffected by treatment. • Post-weaning, during the F1 growth and evaluation period, one control male and two males in the mid-dose group died. No cause of death was determined. • Decreased activity and thin appearance; localized areas of white discolored hair. • There were lower body weights in all treated groups during preweaning and postweaning periods. The decrease in pup body weights was less evident at birth with weights ranging from 4% to 7% lower than controls. However, this difference increased markedly LD4-28, ranging from 10% to 27% lower than controls. Mean F1 pup body weights continued to be significantly lower postweaning (LD35) and ranged from 6% to 15% lower than controls. These lower F1 pup body weights during lactation in the treated groups were not dose-responsive but were considered treatment related. • Postweaning, during the premating period, food consumption in males was lower in the two highest dose groups. Likewise, premating food consumption in females at 75 and 150 mg/kg/day was lower in comparison to controls, but unlike in the males, these values were less likely to be statistically significant. These differences were considered related to treatment with BMT. Food consumption during subsequent gestation and lactation were considered similar among treated and control groups. • Physical development: Mean age at eye opening was statistically greater in all treated groups and averaged 15.9 to 16.1 days in comparison to control 1 and 2 at 14.7 and 14.8 days, respectively. The delay in eye opening was indicative of developmental retardation and was consistent with the lower body weight of these pups. • Righting reflex was unaffected as was pinna detachment. • Sexual maturation: Onset of vaginal opening in females and preputial separation in males. Mean age at preputial separation was greater in the treated groups and in most instances was statistically significant. Vaginal opening was also delayed, but this delay was only significant at the low dose. • Body weight on the day sexual maturation was achieved for both males and females was lower in comparison to controls and in most instances statistically significant. These lower body weights and delay in maturation are suggestive of developmental retardation; however, this delay in maturation did not impact reproductive performance or fertility of the F1 generation. • Neurological assessment: Auditory response was unaffected by treatment. Motor activity in treated pups (male and female) was generally comparable to controls. Learning and memory as determined from passive avoidance testing were unaffected by treatment. • Reproduction: There was no effect of treatment on reproductive performance or fertility of the F1 animals. Mating indices among the treated groups and controls were 100%. Fertility and Fecundity indices in the treated groups ranged from 83.3% to 86.7% and were comparable to the 80% to 90% in controls. • Mean number of days-to-mating (copulatory interval) in treated groups was unaffected by treatment. • Number of F1 females delivering litters, mean number of pups (live plus dead)/litter on LD0, gestation length, stillborn indices, and mean litter size on LD4, 7, and 10 in treated F1 pups were unaffected by treatment. • Macroscopic findings: No treatment-related macroscopic observations were noted in F1 pups (stillborn, died on study, culled on LD4, and LD35 scheduled euthanasia) at necropsy.

Generation	Major Findings
F2 generation	• Survival: F2 pup survival LD0 to 4 and LD0 to 10 was similar among all groups and unaffected by treatment. The Viability Index (mean % pups surviving LD0 to 4) was 96%, 83%, and 97% in the 30, 75, and 150 mg/kg/day groups, respectively, and was comparable to controls (95% and 82% in vehicle control 1 and 2, respectively). Similarly, the lactation index (mean % pups surviving LD4-10) was 95%, 99%, and 97% in the 30, 75, and 150 mg/kg/day groups, respectively, and was comparable to controls (98% and 99% in vehicle control 1 and 2). • Body weight: Mean F2 pup body weights in the treated groups at birth (LD0) were similar to controls and unaffected by treatment. However, on LD4, 7, and 10, pup weights were lower (3-10%) at the high dose and considered to be treatment-related. • Macroscopic evaluation: No treatment-related findings. • Male/Female ratio: F2 pup sex ratios were unaffected by treatment.

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, F1 first filial generation, F2 second filial generation, LD lactation day

Overall Conclusions From the Pivotal Reproductive Toxicity Studies

Mouse

- There was no evidence for an effect on fertility.
- There was no evidence for teratogenicity.
- There was no evidence of embryofetal toxicity through organogenesis (GD15).
- There was, however, evidence of reduced pup viability and developmental delays if dosing continued through parturition and weaning. This was probably due to reduced food consumption and weight gain in the dams.
- Exposures were >100X the human therapeutic dose.

Dog

- There was no evidence for teratogenicity.
- There was some evidence for embryofetal toxicity (post-implantation loss)
- Exposures were >10X the human therapeutic dose

A nonpivotal study in the rat that achieved exposures 1X to 2X the therapeutic dose supports the finding that there is no teratogenicity and no embryotoxicity through organogenesis.

5.9. Other Toxicology Studies

Impurity qualification: There were no structural alerts for impurities in the drug substance.

A total of six studies were conducted to address qualification of impurities and to assess toxicity of degradants: two in vitro genotoxicity studies, and four repeat-dose general toxicology

studies in the mouse. All the studies met GLP and quality assurance standards and none revealed any new toxicities. Four specified impurities were adequately qualified.

Immunotoxicity: In vitro studies for immunotoxicity were conducted. A risk assessment for immunotoxicity was made by Office of Pharmaceutical Quality reviewers and found to be low.

Abuse potential: Animal abuse-related studies were conducted in the rat. Our review determined that none of these studies (general behavior, self-administration, and physical dependence) showed abuse-related signals with BMT.

6 Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology recommends approval of this NDA. The key review issues with specific recommendations and comments are summarized in the table below.

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness and/or safety	• Two pivotal phase 3 studies (BMT-301 and BMT-302) demonstrated the safety and efficacy of BMT for the proposed indication of HSDD.
General dosing instructions	• The recommended dosage of BMT is 1.75 mg administered subcutaneously as needed at least 45 minutes before anticipated sexual activity. Patients should not administer more than one dose within 24 hours or more than eight doses per month (see the Clinical Safety section for further details). • The optimal window for BMT administration has not been fully characterized. Patients may decide the optimal time for BMT administration based on their own experience on duration of effect on desire and any adverse reactions such as nausea. Some patients may experience nausea at 1 to 3 hours postdose.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is needed for patients with mild or moderate renal or hepatic impairment. Use with caution in patients with severe renal or hepatic impairment due to potential for increased frequency and severity of adverse events (e.g., nausea and vomiting) that are commonly related to BMT. • Avoid using BMT when taking oral medications, such as antibiotics, which are particularly dependent on threshold concentrations for efficacy. Consider discontinuing or withholding BMT if there is a delayed drug effect of concomitant oral medications when a quick onset of drug effect is desired (e.g., pain relief). Avoid using BMT with a naltrexone containing oral product that is intended to treat alcohol and opioid addiction.
Labeling	Refer to Section 11.1 of this review for the review team's recommendations.
Bridge between the to-be-marketed and clinical trial formulations	None. The formulation and administration device are the same for the clinical trial and to-be-marketed products.
Other (specify)	None.

6.2. Summary of Clinical Pharmacology Assessment

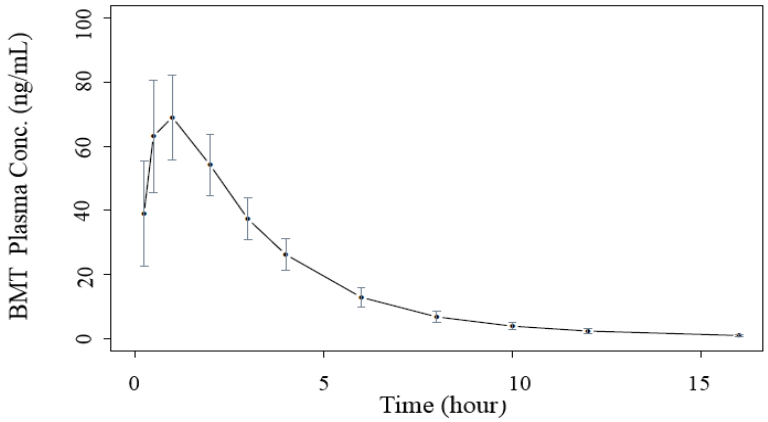
6.2.1. Pharmacology and Clinical Pharmacokinetics

BMT is an agonist for melanocortin receptors. The mechanism by which BMT improves the symptoms of HSDD in females is unknown.

Absorption

The plasma concentration-time profile of BMT following a 1.75 mg SC injection is shown in Figure 1. After a SC dose of 1.75 mg BMT, the average plasma C_{max} and $AUC_{0\text{-}inf}$ of BMT were 72.8 ng/mL and 276 hr·ng/mL, respectively, with a median T_{max} of approximately 1.0 hours (range: 0.5 - 1.0 hours). In other studies, such as Study PT-141-54, the median T_{max} was reported to be around 0.6 hours. Absolute bioavailability following SC administration is 100%. At BMT single doses ranging from 0.3 mg to 10 mg, BMT systemic exposure increased in a less than dose proportional manner. C_{max}, but not $AUC_{0\text{-}t}$, appeared to reach a plateau at the 7.5 mg dose level.

Figure 1. Mean (SD) Plasma Concentration vs. Time Profile for BMT 1.75 mg SC via Autoinjector in Study PT-141-56



N=36
Abbreviations: BMT bremelanotide, SC subcutaneous

Distribution

Twenty one percent (21%) of BMT binds to human serum protein. The mean ± standard deviation (SD) volume of distribution after a single subcutaneous administration of BMT is 25.0±5.8 L.

Metabolism

The primary metabolic pathway of BMT involves multiple hydrolyses of the amide bond of the cyclic peptide and eventually the formation of the major (inactive) metabolite M3, a single amino acid diphenylalanine. BMT undergoes minimal hepatic metabolism.

Excretion

After reaching C_{max}, plasma concentrations of BMT decline in a biphasic manner, with a mean terminal half-life of 2.7 hours (range: 1.9 to 4.0 hours). Following administration of a radiolabeled dose, 65% of the total radioactivity was recovered in urine and 23% in feces.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended BMT dose is 1.75 mg administered as a SC injection via an autoinjector pen into the abdomen or thigh. Patients should administer BMT at least 45 minutes before sexual activity. Some patients may experience nausea at 1 to 3 hours postdose. The duration of effect on desire is unknown. Therefore, patients may decide the optimal time for BMT administration based on their own experience on duration of effect and any adverse reactions. The maximum recommended dosing frequency is once per 24 hours and no more than eight times per month based on the safety profile of the product, particularly the hypertensive findings (see the Clinical Safety section). In addition, only a few subjects in the phase 3 studies used BMT more than seven times per month.

Therapeutic Individualization

Renal impairment

In a dedicated renal impairment study, the mean values of C_{max} of BMT in subjects with normal renal function, and in those with mild, moderate, or severe renal impairment were comparable, while BMT $AUC_{0\text{-}inf}$ increased 2-fold in subjects with severe renal impairment, 1.5-fold in subjects with moderate renal impairment, and 1.2-fold in patients with mild renal impairment compared to subjects with normal renal impairment, respectively. No dosing adjustments are needed for patients with mild to moderate renal impairment. BMT should be used with caution in patients with severe renal impairment, because of the observed increase in frequency and severity of AEs (e.g., nausea and vomiting) that are commonly related to BMT.

Hepatic impairment

In a dedicated hepatic impairment study, the exposure of BMT (C_{max} and AUC) was comparable between subjects with normal hepatic function and subjects with mild hepatic impairment. No dose adjustment is needed in subjects with mild hepatic impairment. BMT mean C_{max} and AUC

values were 1.3- and 1.7-fold higher for subjects with moderate hepatic impairment relative to subjects with normal hepatic function. The increased exposure of BMT is unlikely to have a clinically significant impact on safety. BMT can be used in subjects with moderate hepatic impairment.

No PK information is available in subjects with severe hepatic impairment. BMT exposure is expected to be higher in subjects with severe hepatic impairment than moderate impairment as there is a trend of decreasing BMT clearance with declining hepatic function. BMT should be used with caution in subjects with severe hepatic impairment, because of the potential increase in frequency and severity of AEs (e.g., nausea and vomiting) that are commonly related to BMT.

Drug-drug interaction (DDI)

The Applicant conducted five clinical DDI studies to characterize the potential interactions of SC BMT with oral medications that may be commonly used in the target population of women with HSDD. These concomitant medications include antihypertensive medications, anti-depressant/weight loss medications, oral contraceptives, an oral antidiabetic agent metformin, and selected concomitant medications with the potential to increase blood pressure (BP), including pseudoephedrine, phentermine, celecoxib, and indomethacin. Of 17 studied drugs, all had delayed T_{max} when taken with BMT, six drugs (hydrochlorothiazide, losartan, furosemide, naltrexone, bupropion and indomethacin) had mean C_{max} values decreased by >25% and one drug (naltrexone) had mean AUC decreased by >25%.

Based on these results, we speculate that BMT decreases gastric motility—typically characterized by delayed T_{max} and lower C_{max} with modest impact on the AUC of concomitant medications. The Applicant also hypothesized that BMT slows gastric emptying by activating MC4R in enteroendocrine cells in the gut, with subsequent release of GI hormones (glucagon-like peptide-1 (GLP-1) and peptide YY) that suppress gastric motility.

Given that BMT is used on an as-desired basis with limitation of eight doses per month and phase 3 trials showed on average two to three doses per month, it is unlikely that BMT will compromise the long-term efficacy of drugs for chronic use. However, patients should avoid using BMT when taking oral medications, such as antibiotics, which are particularly dependent on threshold concentrations for efficacy. In addition, patients may consider discontinuing or withholding BMT if there is a delayed drug effect of concomitant oral medications when a quick onset of drug effect is desired (e.g., pain relief). Lastly, patients should avoid using BMT when receiving a naltrexone-containing oral formulation indicated for treatment of alcohol dependence and opioid addiction due to the potential for therapeutic failure.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 9. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	BMT is an agonist for melanocortin receptors. The exact mechanism by which BMT improves the symptoms of HSDD in females is unknown.
Active moieties	BMT
QT prolongation	No QT interval prolongation of clinical concern was observed at a single intranasal dose of 20 mg BMT (with a mean C_{max} that was 2.5-fold higher than at the therapeutic dose of 1.75 mg SC BMT).
General Information	
Bioanalysis	LC-MS/MS methods were used to measure BMT concentrations in plasma.
Healthy vs. patients	The Applicant did not conduct a dedicated clinical study comparing BMT PK between healthy subjects and HSDD patients. Population PK analysis showed that the exposures of BMT were similar between healthy women and women with HSDD.
Drug exposure at steady state (Mean ± SD)	There is no BMT accumulation expected upon sequential once daily dosing (Half-life 2.7 hours). Therefore, steady-state exposures are expected to be similar to single-dose SC administration of 1.75 mg BMT; C_{max} and $AUC_{0\text{-}inf}$ values are 72.8±13.5 ng/mL and 276±40 hr*ng/mL, respectively.
Range of effective dose or exposure	1.75 mg SC (the only dose that has been assessed and demonstrated to be effective in the phase 3 trials.)
Maximally tolerated dose or exposure	The 10 mg BMT dose was the highest dose tested (and tolerated) and was designated as the maximum tolerated dose.
Pharmacodynamics	Exposure-response analysis showed a greater degree of BP increases with increasing BMT doses. Study AMAG-BMT-HSDD-101 showed no cumulative BP increase upon sequential BMT dosing (once per day for 16 days).
Dose proportionality	Following SC administration, BMT systemic exposure (C_{max} and $AUC_{0\text{-}t}$) increased in a less than dose proportional manner in the dose range of 0.3 to 10 mg. C_{max} appeared to reach a plateau at the 7.5 mg dose level.
Accumulation	There is no accumulation upon sequential daily dosing of BMT.
Variability	Following SC administration, BMT CV% values are 18% and 14% for C_{max} and $AUC_{0\text{-}inf}$, respectively.
Absorption	
Bioavailability	Absolute bioavailability is about 100% following SC administration
T_{max}	1.0 (0.5 to 1.0) hours; Median (min to max)
Food effect	N/A
Distribution	
Volume of distribution	25.0±5.8 L
Plasma protein binding	21% bound to human plasma protein

Elimination	
Terminal elimination half-life (mean ± SD)	2.7±0.6 hour
CL/F (mean ± SD)	6.5±1.0 L/hr
Metabolism	
Fraction metabolized (% dose)	58.5% of dose is recovered in feces and urine as BMT metabolites.
Primary metabolic pathway(s)	The primary metabolic pathway of BMT involves multiple hydrolyses of the amide bond of the cyclic peptide. There is no active metabolite. M3, the single amino acid diphenylalanine, is the major metabolite in plasma and urine.
Excretion	
Primary excretion pathways (% dose) ± SD	64.8% of the radiolabeled dose was found in urine, indicating renal is the primary excretion pathway for BMT.
In Vitro Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	BMT is unlikely to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 or induce CYP1A2, CYP2B6, CYP3A4, CYP2C19, and CYP2A6 at the clinically relevant dose.
Inhibition/induction of transporter systems	BMT is unlikely to inhibit transporters OCT2, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and P-gp at the clinically relevant dose.

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, BP blood pressure, CV coefficient of variation, HSDD hypoactive sexual desire disorder, LC-MS/MS liquid chromatography–mass spectrometry/mass spectrometry, MC4R melanocortin receptor 4, PK pharmacokinetics, SC subcutaneous, SD standard deviation

6.3.2. Clinical Pharmacology Questions

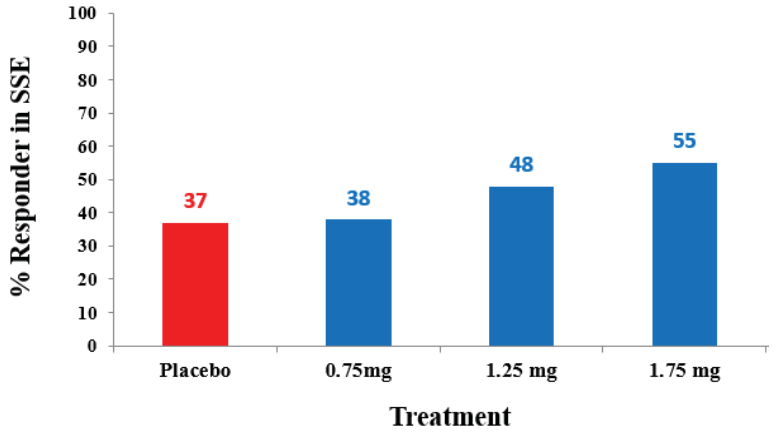
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The 1.75 mg SC dose of BMT was selected for pivotal phase 3 trials (BMT-301 and BMT-302) based on safety and efficacy results obtained in phase 2 trial Study PT-141-54.

Study PT-141-54 was a 14-week, multicenter, randomized, PBO-controlled, parallel-group, dose-finding study to evaluate the efficacy and safety of three fixed doses of subcutaneous BMT in premenopausal women with FSAD and/or HSDD. The primary efficacy endpoint was change in the number of SSEs from baseline (28-day period) to the end of study (EOS) (final 28 days of randomized therapy). As shown in Figure 2, a dose-response relationship on percentage of responders with one more SSE compared to baseline was observed within the dose range of 0.75 mg to 1.75 mg. Among three studied dose groups, only the highest dose group, 1.75 mg, met the primary efficacy endpoint (Table 10). Additionally, the 1.75 mg dose showed improvement in some exploratory secondary efficacy endpoints including the mean change from baseline to EOS in total FSFI, FSDS-DAO, and GAQ question 3. Safety data in Study PT-141-54 suggested that self-administration of BMT 1.75 mg SC was generally well-tolerated. Most commonly reported treatment-emergent adverse events (TEAEs) were nausea, injection-site reactions, flushing and headache. Most TEAEs were mild or moderate in intensity and resolved spontaneously. The frequency of AEs was similar between the BMT 1.25 mg (65%) and BMT

1.75 mg (71%) groups. Overall, based on the safety and efficacy profiles observed in Study PT-141-54, the 1.75 mg SC dose of BMT was selected for phase 3 trials.

Figure 2. Percentage of Responder, Defined as at Least One More SSE Compared to Baseline, in PBO, 0.75 mg, 1.25 mg, and 1.75 mg of BMT in Study PT-141-54



Abbreviations: BMT bremelanotide, SSE satisfactory sexual event, PBO placebo

Table 10. Summary of Primary Efficacy Endpoint in Study PT-141-54

Primary Endpoint	PBO	BMT (mg) 0.75	BMT (mg) 1.25	BMT (mg) 1.75
Change from baseline in number of SSEs				
Mean Δ from baseline	0.2	0.6	0.7	0.8
Median Δ from baseline	0.0	0.0	0.0	1.0
Estimate of treatment minus placebo	NA	0.00	0.00	1.00
p-value (compared with placebo)	NA	0.4430	0.0807	0.0215

Abbreviations: BMT bremelanotide, SSEs satisfactory sexual events, PBO placebo
Source: Table 11-7 from Study PT-141-54 study report

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

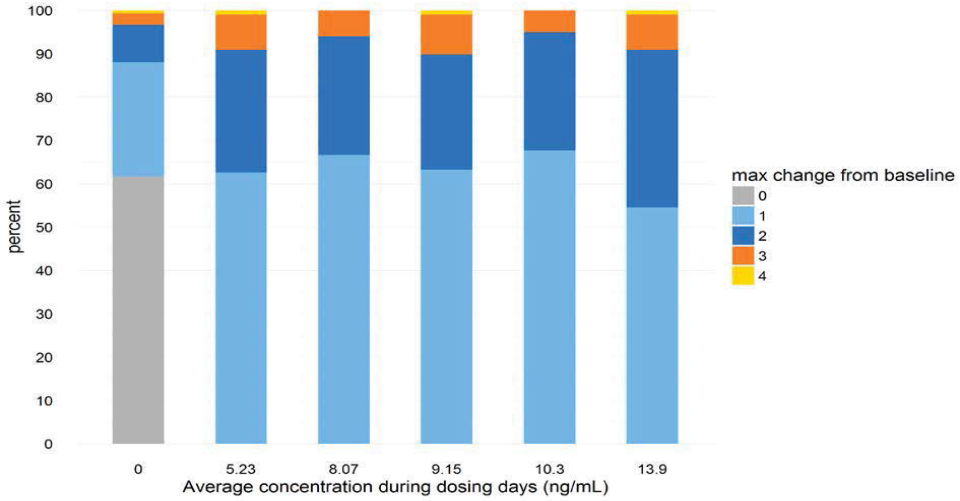
Yes. The proposed regimens are supported by clinical efficacy, safety, PK and pharmacodynamic (PD) data. The safety and efficacy of BMT 1.75 mg for the treatment of HSDD have been demonstrated in two phase 3 trials (BMT-301 and BMT-302). Both of these trials met their coprimary efficacy endpoints of improving desire and reducing distress associated with low desire. The key secondary efficacy endpoint of evaluating the number of SSEs did not reach statistical significance between treatment groups in either study. This result is not consistent with the phase 2 dose-finding study where statistically significantly higher numbers of SSEs were observed in the BMT group compared to placebo (see Table 10). The reason for this discrepancy is not known. Post-hoc analysis of the two phase 3 trials showed that the percentage of SSEs (number of SSEs per total number of sexual encounters) was 65% in the

BMT 1.75 mg group and 49% in the PBO group; this difference was nominally statistically significant ($p<0.0001$). Although the SSEs did not reach statistical significance, the results from the two coprimary endpoints (see Section 8) was sufficient to support approval.

Exposure-Response for Efficacy

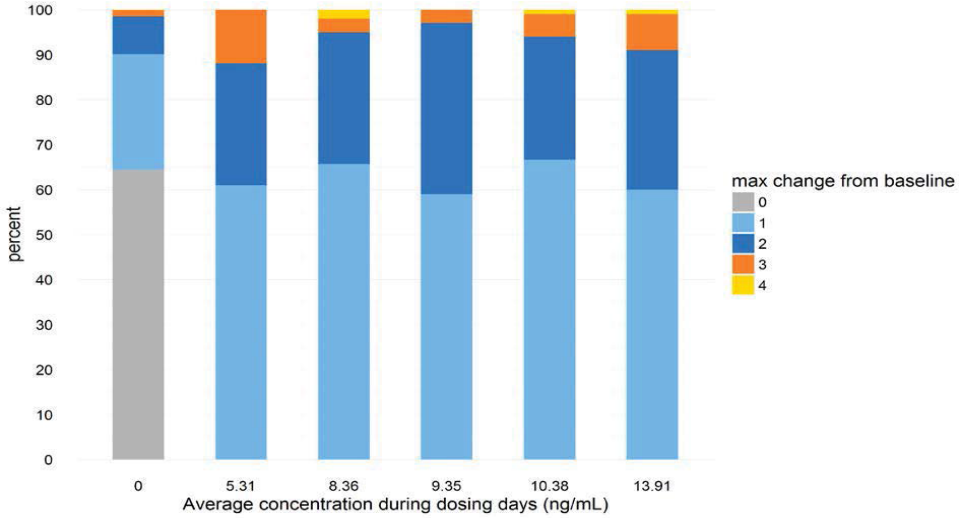
In the phase 3 trials, the coprimary efficacy endpoints were changes from baseline to end of study in the desire domain from the Female Sexual Function Index (FSFI-D; also referred to as the FSFI Questions 1 and 2) and in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO Question 13) (See Section 8 for further details). There were no significant exposure-response relationships for BMT on the coprimary efficacy endpoints FSFI (Q1 and Q2) scores as well as FSDS-DAO (Q13) in the range of exposure for BMT 1.75 mg. The observed FSFI-Q1 and FSFI-Q2 maximum change from baseline (baseline defined as the score at the time of randomization) for each subject during the randomization period versus corresponding model-predicted average plasma concentration during dosing days (CAVGDOSE) in Studies PT-141-54, BMT-301 and BMT-302 are shown in Figure 3 and Figure 4. As shown in the figures, more than 60% of the PBO subjects had no improvement in FSFI-Q1 and FSFI-Q2 score (i.e., maximum change from baseline=0), while all the subjects who received active doses had a maximum improvement across visits in FSFI-Q1 and FSFI-Q2 score by at least 1 point compared to baseline (Mean improvements in FSFI Q1 and Q2 from baseline are shown in Figure 12 under Section 8). As the CAVGDOSE values increased, there was generally a trend of an increasing percentage of subjects achieving improvement by at least 2 points. However, the trend was weak due to the variability in the data. Overall, while BMT 1.75 mg showed a positive response compared to PBO, there was no evident exposure-response relationship for the primary efficacy endpoints within the range of exposure for BMT 1.75 mg.

Figure 3. Observed FSFI-Q1 Maximum Change From Baseline vs. Model-Predicted Average Concentration During Dosing Days in Studies PT-141-54, BMT-301, and BMT-302



The average BMT concentrations were binned into six groups. The group with average BMT concentrations 0 was subjects who did not administer any active dose (e.g., placebo subjects). The remaining five groups were from subjects who received active doses (0.75, 1.25 and 1.75 mg) and each group had roughly the same number of subjects. The x-axis values were calculated as the (min + max)/2 of each group's average BMT concentrations values
Abbreviations: BMT bremelanotide, FSFI-Q1 Female Sexual Function Index–Question 1
Source: Figure 12 on page 50 of Applicant's population PKPD report PPK1819

Figure 4. Observed FSFI-Q2 Maximum Change From Baseline vs. Model-Predicted Average Concentration During Dosing Days in Studies PT-141-54, BMT-301, and BMT-302



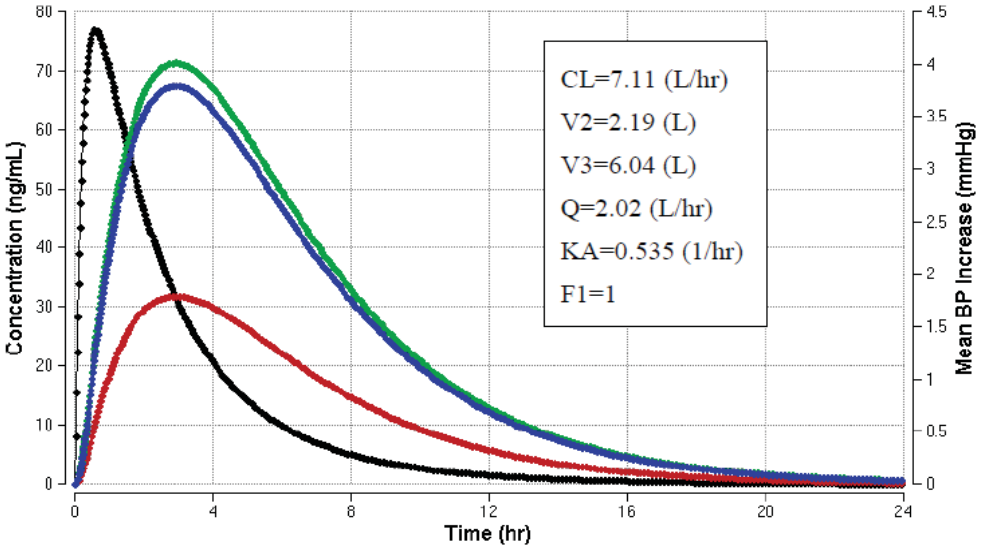
Abbreviations: BMT bremelanotide, FSFI-Q2 Female Sexual Function Index–Question 2
Source: Figure 16 on page 57 of Applicant's population PKPD report PPK1819

Exposure-Response for Safety

Blood pressure

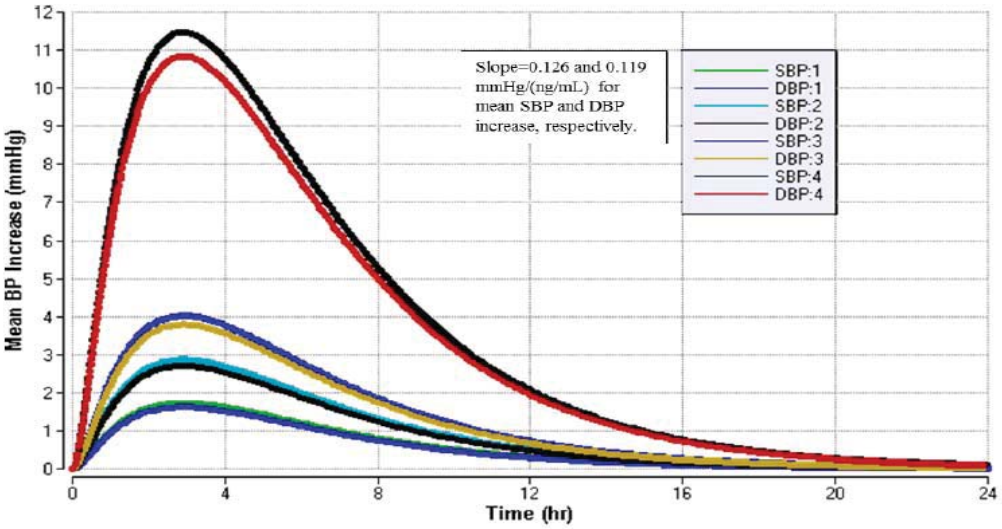
There was a clear association between BMT's effect on BP and BMT concentrations. The largest mean SBP and DBP increases occurred with peak BMT concentrations in the peripheral compartment. Simulated concentrations in the plasma and peripheral compartment and mean BP increase after a single SC dose of 1.75 mg BMT are shown in Figure 5. The largest mean SBP increase was predicted to be 1.7, 2.9, 4.0 and 11.5 mm Hg after a single SC dose of 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT, respectively (Figure 6 and Table 11). The predicted mean increase for DBP was slightly lower than that for SBP, for a given dose.

Figure 5. Simulated Typical BMT Concentrations in Plasma and Peripheral Compartment and Mean Blood Pressure Increase After Single SC Dose of 1.75 mg BMT



Black line concentrations in the plasma, red line concentrations in the peripheral compartment, green line mean SBP increase, blue line mean DBP increase
Abbreviations: BMT bremelanotide, SC subcutaneous, SBP systolic blood pressure, DBP diastolic blood pressure
Source: Figure 41, page 106 of Applicant's population PKPD report PPK1819

Figure 6. Simulated Mean Systolic Blood Pressure and Diastolic Blood Pressure Increases After a Single SC Dose of 0.75 mg,1.25 mg, 1.75 mg, and 5 mg BMT



Runs 1, 2, 3 and 4 were for 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT, respectively.
The underlying PK model contained the following parameters: CL=7.11 L/hr, V2=2.19 L, V3=6.04 L, Q=2.02 L/hr, KA=0.535 /hr, and F1=1.
The mean SBP and DBP increases were calculated as the product of slope × concentration in the peripheral compartment.
The slope values of 0.126 and 0.119 mmHg/(ng/mL) were the median from the bootstrap results for the typical slope for SBP and DBP, respectively (PPK1819, Table 9 and Table 10).
The simulations were conducted using the software Berkeley Madonna Version 8.3.18.

Abbreviations: BMT bremelanotide, SC subcutaneous, SBP systolic blood pressure, DBP diastolic blood pressure
Source: Figure 1, page 4 of Applicant's response to Information Request of 15Aug2018

Table 11. Simulated Largest Mean Systolic Blood Pressure and Diastolic Blood Pressure Increases After Single SC Dose of 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT

Dose (mg)	Largest Mean SBP Increase (mmHg) with Slope=0.126 mmHg/(ng/mL)	Largest Mean DBP Increase (mmHg) with Slope=0.119 mmHg/(ng/mL)
0.75	1.72	1.63
1.25	2.87	2.71
1.75	4.02	3.80
5	11.5	10.8

The Cmax in the peripheral compartment was 31.9 ng/mL for the 1.75 mg dose. The Cmax in the peripheral compartment for other doses was calculated assuming dose proportionality.
The largest mean SBP and DBP increases were calculated as the product of slope × the Cmax in the peripheral compartment, with slope=0.126 and 0.119 mmHg/(ng/mL), respectively, for SBP and DBP.

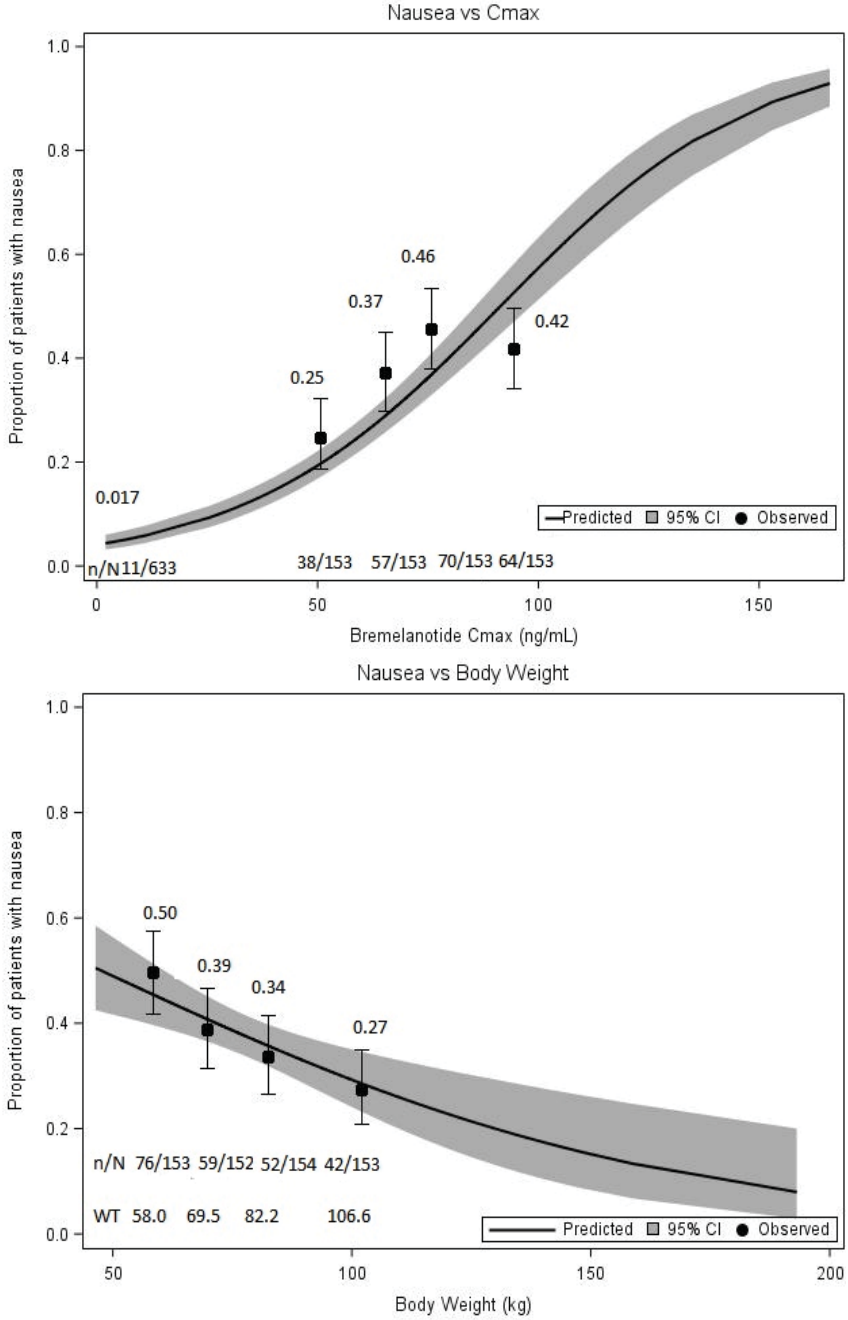
Abbreviations: BMT bremelanotide, SC subcutaneous, SBP systolic blood pressure, DBP diastolic blood pressure
Source: Table 1 on page 4 of Applicant's response to Information Request of 15Aug2018

Incidence of vomiting and nausea

There was a clear relationship between BMT exposure and odds of experiencing vomiting, nausea, and nausea severity. The plasma concentrations of BMT were body weight dependent with higher body weight subjects having lower exposures than lower body weight subjects for

the same fixed dose. The probability of nausea increases with C_{max} (Figure 7). Lower body weight subjects have higher drug exposure and were observed to have a higher risk of vomiting and nausea.

Figure 7. Predicted and Observed Probability of Nausea by C_{max} and Body Weight



Data were from 1245 subjects from study 301 and 302 receiving BMT 0 mg and 1.75 mg SC in the plot for C_{max} (top) and were from 612 subjects receiving BMT 1.75 mg SC in the plot for body weight (bottom). Observed (dots) and model predicted probabilities (line) with 95% CI is (shaded area) based on a logistic model plotted at the median of individual C_{max} or body weight values.
Abbreviations: BMT bremelanotide, SC subcutaneous
Source: Created by FDA reviewer using data file "nausea.xpt."

QTc assessment

Study PT-141-2005-28 showed no significant QTc prolongation following a single intranasal (IN) dose of 20 mg BMT. The supra-therapeutic BMT dose (20 mg IN) produced a mean BMT C_{max} value (192±108 ng/mL) of approximately 2.5-fold the mean C_{max} (72.8±13.5 ng/mL) at the therapeutic dose of 1.75 mg SC. Considering a maximum 2-fold increase in BMT AUC (and a lesser degree of increase in C_{max}) in patients with renal or hepatic impairment patients, the QT study covers the worst-case scenario for BMT exposure.

Overall, based on the exposure-response analysis for both safety and efficacy along with the QTc assessment, BMT 1.75 mg SC is appropriate for the general population of HSDD patients.

Onset and duration of drug effect

BMT is recommended to be administered at least 45 minutes before sexual activity. The onset time of 45 minutes is based on the observed T_{max} of 1.0 hour following SC administration and is consistent with instructions given to subjects in phase 3 trials.

Regarding the duration of drug effect, the Applicant initially proposed that (b) (4)

(b) (4)

(b) (4)

we recommend stating in the label that the optimal window for BMT administration has not been fully characterized.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. BMT exposure was higher in subjects with renal impairment and hepatic impairment. Comments for each specific population are provided below.

Renal impairment

In a dedicated renal impairment study (Study BMT-115), the PK profile of BMT following a 1.75 mg single SC dose in subjects with mild, moderate, and severe renal impairment relative to demographically matched controls with normal renal function was investigated. The mean BMT C_{max} values in subjects with normal renal function and mild, moderate, and severe renal impairment were comparable (Table 12). BMT AUC_t and $AUC_{0\text{-}inf}$ appeared to be higher in subjects with mild to severe renal impairment compared to subjects with normal renal function. Subjects with severe renal impairment have mean AUC that was 2-fold higher than that in subjects with normal renal function.

Table 12. Mean ± SD PK Parameters of BMT in Subjects With Normal Renal Function and Mild, Moderate, and Severe Renal Impairment in Study BMT-115

	Treatment Group			
PK Parameters	**Normal Renal Function N=8**	**Mild Renal Impairment N=8**	**Moderate Renal Impairment N=8**	**Severe Renal Impairment N=8**
C_{max} (ng/mL)	76.5±24.6	81.6±8.69	56.4±14.5	74.8±29.6
T_{max} (h) median (range)	1.0 (0.5–1.0)	0.75 (0.50–1.00)	2.0 (0.5–2.0)	1.0 (1.0–3.0)
$AUC_{0\text{-}t}$ (ng*h/mL)	258±60.0	306±54.9	388±134	517±152
$AUC_{0\text{-}inf}$ (ng*h/mL)	263±62.3	313±55.4	399±140	528±154
$T_{1/2}$ (h)	2.85±0.58	3.20±0.82	4.88±1.37	5.42±1.61
CL/F (L/h)	7.04±1.98	5.74±1.00	4.94±1.92	3.55±0.95

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, SD standard deviation, PK pharmacokinetics

Safety Results

Severity of TEAEs was greater in subjects with severe renal impairment (normal renal function: mild TEAEs 50%, moderate TEAEs 25%, severe TEAEs 0%; severe renal impairment: mild TEAEs 0%, moderate TEAEs 88%, severe TEAEs 13%). The incidence of nausea and vomiting was higher in subjects with severe renal impairment (normal renal function: nausea 25%, vomiting 13%; severe renal impairment: nausea 50%, vomiting 25%).

Based on these findings, BMT should be used with caution in patients with severe renal impairment. No dosage adjustments are recommended for patients with mild to moderate renal impairment.

Hepatic impairment

A dedicated hepatic impairment study (Study BMT-116) indicated a comparable BMT exposure between subjects with mild hepatic impairment and those with normal hepatic function. But BMT C_{max} and AUC increased by 1.3-fold and 1.7-fold respectively in subjects with moderate hepatic impairment, relative to those with normal function. The slightly increased exposure is not likely to have clinically significant effect on safety. No PK information is available in subjects with severe hepatic impairment, but BMT exposure is expected to be higher in subjects with severe hepatic impairment as there was an increasing trend between BMT exposure and decreasing hepatic function. BMT should be used with caution in patients with severe hepatic impairment because of a potential increase in frequency and severity of AEs (e.g., nausea and vomiting) that are commonly related to BMT treatment. The PK parameters of BMT in subjects with various degrees of hepatic impairment are shown in Table 13.

Table 13. Mean ± SD PK Parameters of BMT in Subjects With Normal Hepatic Function and Mild or Moderate Hepatic Impairment in Study BMT-116

	Treatment Group		
PK Parameters	**Normal Hepatic Function N=8**	**Mild Hepatic Impairment N=8**	**Moderate Hepatic Impairment N=8**
C_{max} (ng/mL)	48.4±10.9	53.3±11.5	61.1±15.0
T_{max} (h) median (range)	1.0 (0.5-1.08)	0.75 (0.50-1.00)	0.5 (1.0-2.0)
AUC_{0-t} (ng*h/mL)	198±40.8	248±71.5	336±90.1
AUC_{0-inf} (ng*h/mL)	204±42.4	254±72.6	344±93.3
$T_{1/2}$ (h)	3.46±0.67	3.53±0.73	4.33±0.61
CL/F (L/h)	8.88±1.59	7.38±2.04	5.34±1.06

Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, SD standard deviation, PK pharmacokinetics

Age

BMT is only proposed for use in premenopausal women. The mean (SD) age of subjects in the phase 3 trials is 39 (7) years old. Population PK analysis showed that age is not a significant covariate for BMT PK. Therefore, dose adjustment based on age is not needed for this population.

Injection site

Based on pooled PK data from Studies PT-141-56, PT-141-54, BMT-301, and BMT-302, the observed C_{max} after a thigh injection was 10.5% lower on average than that after an abdominal

injection but the difference was not statistically significant (Table 14). Overall, there is no significant difference in BMT PK between the two injection sites.

Table 14. Summary of Observed C_{max} (ng/mL) Values for BMT 1.75-mg Dose, Thigh vs. Abdominal Injection

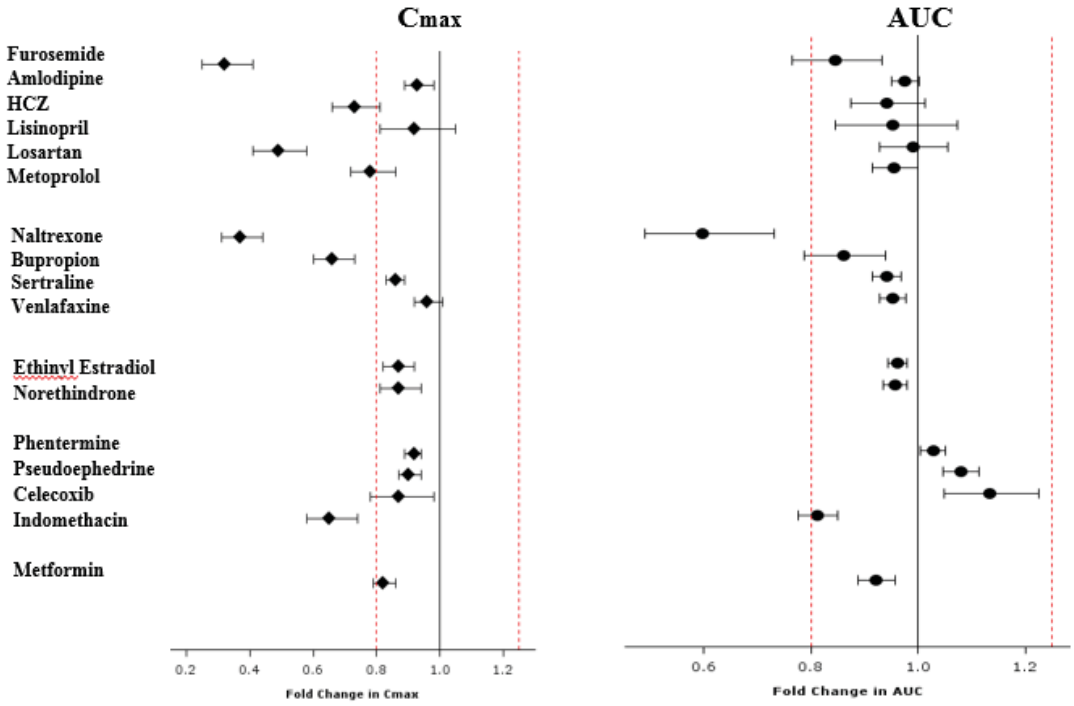
Site	N	Mean	SD	Min	Median	Max
Thigh	246	68.8	17.5	25.4	68	153
Abdomen	493	76.8	20.3	8.6	75	166

Each subject only had one injection site (either thigh or abdomen). There was no subject who had both injection sites.
Abbreviations: BMT bremelanotide, SD standard deviation

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. The Applicant conducted five clinical DDI studies to characterize the potential interaction of SC BMT with medications that may be commonly used in the target population of HSDD (premenopausal women). These concomitant medications include antihypertensive medications (BMT-101), anti-depressant medications/weight loss medication (BMT-103), oral contraceptives (BMT-104), selected medications with the potential to increase BP (BMT-105) and the antidiabetic agent metformin (BMT-118). The study results showed that out of 17 studied drugs, all had delayed T_{max} when taken with BMT, six drugs (hydrochlorothiazide, losartan, furosemide, naltrexone, bupropion and indomethacin) had mean C_{max} values decreased by >25% and one drug (naltrexone) had mean AUC decreased by >25% (Figure 8 and Table 15).

Figure 8. Effects of BMT 1.75 mg SC on PK Exposures of Orally Administered Medications in BMT Studies 101, 103, 104, 105, and 118



*A forest plot of the GMRs with associated 90% CIs for C_{max} and AUC with two dotted vertical lines at 80% and 125% of the GMR
Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, PK pharmacokinetics, GMR geometric mean ratio, CI confidence intervals, HCZ hydrochlorothiazide

Table 15. Effects of BMT 1.75 mg SC on T_{max} Values of Orally Administered Medications in BMT Studies101, 103, 104, 105, and 118

	Geometric Mean Ratio (%) [90% CI]			
Parent Drug or Active Metabolites	**C_{max} (ng/mL)**	**AUC_t (hr•ng/mL)**	**T_{max}+PBO (h)**	**T_{max}+BMT (h)**
Furosemide	32.25 [25.42-40.91]	84.50 [76.50-93.35]	1.5 [0.25, 3.0]	3.0 [1.0, 10.0]
Amlodipine	93.54 [89.47–97.79]	97.55 [94.94–100.23]	5.5 [4.0, 12.0]	7.0 [5.0, 12.0]
Hydrochlorothiazide	73.20 [66.05–81.12]	94.20 [87.51–101.39]	2.0 [1.0, 2.5]	3.0 [2.0, 5.0]
Lisinopril	92.34 [81.01–105.25]	95.22 [84.43–107.38]	5.0 [4.0, 6.0]	5.0 [4.0, 8.0]
Losartan	49.15 [41.40–58.35]	98.95 [92.81–105.49]	1.0 [0.5, 2.5]	2.5 [0.5, 5.0]
Metoprolol	78.38 [71.56–85.84]	95.57 [91.36–99.97]	1.5 [1.0, 4.0]	3.0 [1.5, 6.0]
Naltrexone	36.93 [31.07–43.90]	59.82 [48.97–73.09]	2.0 [1.5, 3.0]	5.0 [1.5, 12.0]
6β-naltrexol	63.97 [59.79–73.06]	79.19 [72.63–86.33]	2.3 [1.5, 3.0]	5.0 [1.5, 10.0]
Bupropion	66.10 [59.79–73.06]	86.04 [78.78–93.97]	2.0 [1.5, 4.0]	5.0 [1.5, 12.0]

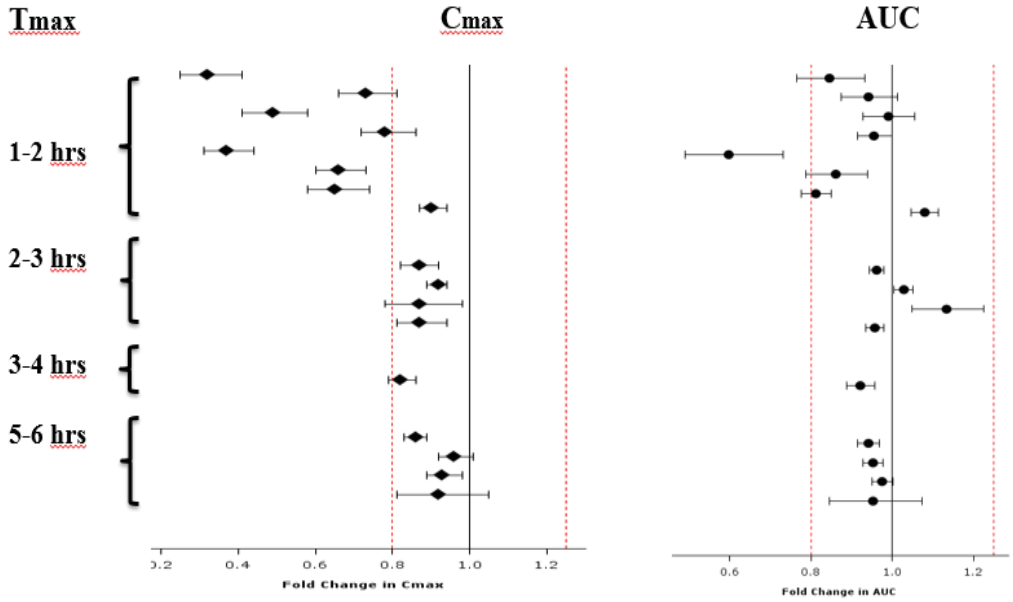
Parent Drug or Active Metabolites	Geometric Mean Ratio (%) [90% CI] C_{max} (ng/mL)	AUC_t (hr•ng/mL)	T_{max}+PBO (h)	T_{max}+BMT (h)
Hydroxybupropion	87.74 [84.65–90.94]	86.50 [66.85–111.92]	3.0 [0, 8.0]	2.5 [0, 12.0]
Threo-hydrobupropion	85.98 [82.14–90.01]	95.66 [71.49–128.00]	4.0 [1.5, 8.0]	6.0 [0, 12.0]
Erythro-hydrobupropion	94.93 [89.55-100.62]	79.19 [72.63–86.33]	3.0 [0, 8.0]	2.5 [0, 12.0]
Sertraline	86.01 [82.88–89.27]	94.05 [91.35–96.84]	6.0 [3.0, 12.0]	10.0 [5.0, 12.0]
Venlafaxine	96.30 [91.55–101.29]	95.19 [92.75–97.69]	5.0 [3.0, 8.0]	6.0 [3.0, 10.0]
Ethinyl Estradiol	86.66 [81.93–91.66]	96.15 [94.45–97.88]	2.6 [1.5, 6.0]	3.5 [1.0, 10.0]
Norethindrone	87.00 [80.75–93.73]	95.68 [93.49–97.92]	2.5 [1.0, 6.0]	2.5 [1.0, 10.0]
Phentermine	91.53 [89.07–94.05]	86.04 [78.78–93.97]	3.0 [1.5, 10.0]	5.0 [2.5, 12.0]
Pseudoephedrine	90.26 [86.83–93.83]	107.93 [105.07–110.86]	2.0 [1.5, 3.0]	3.0 [1.5, 8.0]
Celecoxib	87.32 [77.74–98.08]	113.37 [104.78–122.67]	2.5 [1.0, 6.0]	5.0 [1.0, 10.0]
Indomethacin	65.29 [57.74–73.83]	81.20 [77.60–84.96]	1.5 [0.6, 2.5]	2.5 [1.0, 8.0]
Metformin	82.09 [78.62–85.72]	92.23 [88.95–95.64]	4.0	4.0

For T_{max}, median, minimum, and maximum are shown
Abbreviations: AUC area under the plasma concentration-time curve, BMT bremelanotide, PBO placebo, CI confidence interval, SC subcutaneous

Mechanism of Interaction

In vitro data suggest that BMT does not inhibit or induce drug metabolizing isozymes at the therapeutic dose, and thus BMT is unlikely to affect the PK of other drugs. Interestingly, clinical DDI studies showed that BMT altered the PK of orally administered drugs with different metabolic profiles. The Applicant hypothesized that BMT slows gastric motility by activating melanocortin 4 receptor in enteroendocrine cells in the gut, with subsequent release of GI hormones (GLP-1 and Peptide YY) that suppress gastric emptying. The Applicant attempted to test this hypothesis in rats and submitted the study report on 15Nov2018. However, the results of these studies are conflicting and could not support their hypothesis. Nonetheless, based on data from these drug interaction studies, the Applicant's hypothesis of decreased gastric motility appears reasonable, given the delayed T_{max}, a lower C_{max} and a smaller change in AUC of orally administered medications. In addition, the effect of BMT seems to be more pronounced on concomitant medications with T_{max} around 1 to 2 hours (Figure 9).

Figure 9. Effects of BMT 1.75 mg SC on PK Exposures of Orally Administered Medications With Victim Drugs Grouped by Their T_{max} Values in BMT Studies101, 103, 104, 105, and 118



Abbreviations: BMT bremelanotide, SC subcutaneous, PK pharmacokinetics

Clinical Significance of Conducted DDI Studies

When BMT is taken with Contrave® (naltrexone and bupropion), a product indicated for weight management, C_{max} and AUC of naltrexone decreased by 73% and 40%, respectively, and active metabolite 6-β-naltrexol had a 46% decrease in C_{max} and 20% decrease in AUC. Based on the magnitude of exposure decrease, BMT may affect the efficacy of Contrave® if used frequently. However, considering that BMT is used on an intermittent basis and subjects in phase 3 trials used BMT on average two to three times per month, the occasional use of BMT is unlikely to affect the long-term efficacy of Contrave®. It should be noted that naltrexone, as a single-drug formulation, is also indicated for treatment of alcohol dependence and opioid addiction (e.g., ReVia® as oral tablets). Although no dedicated DDI study was conducted with an oral naltrexone alone formulation, coadministration with BMT may result in a marked decrease in naltrexone exposure. Therefore, patients should avoid using BMT when receiving a naltrexone containing oral product that is intended to treat alcohol and opioid addiction due to the more severe consequence of treatment failure.

When coadministered with BMT, antihypertensive medications including hydrochlorothiazide, losartan, furosemide had a significant decrease in C_{max} but minimal change in AUC. Given that AUC was not significantly affected in any of these interactions and BMT is used only occasionally as needed, these DDI results are not clinically relevant to warrant any changes in dosing recommendations in labeling. Lastly, although AUC change does not appear clinically significant, indomethacin is used for acute pain, and decreased C_{max} or delayed T_{max} may affect

its onset of analgesic action. Therefore, patients may consider discontinuing or withholding BMT if they experience a delayed effect in pain relief when taking indomethacin.

Labeling Recommendation on Appropriate Management Strategy

BMT causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. Given that BMT is used on an as-needed basis with limitation of eight doses per month, it is unlikely that BMT will compromise the long-term efficacy of drugs for chronic use. However, patients should avoid using BMT when taking oral medications, such as antibiotics, which are particularly dependent on threshold concentrations for efficacy. In addition, patients may consider discontinuing or withholding BMT if there is a delayed drug effect of concomitant oral medications when a quick onset of drug effect is desired (e.g., pain relief). Lastly, patients should avoid using BMT with an orally administered naltrexone containing product for treatment of alcohol dependence and opioid addiction due to the high impact of therapeutic failure.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 16. Clinical Trials Relevant to NDA 210557

Trial Identifier	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	Patients Enrolled	Study Population	Centers and Countries
Controlled Studies to Support Efficacy and Safety								
BMT-301	NCT02333071	Phase 3, DB/PC	BMT 1.75 mg SC vs. PBO	Desire, distress (primary); SSEs (key secondary)	6 months	643 (324 BMT/ 319 PBO)	HSDD with or without decreased arousal	U.S., Canada
BMT-302	NCT02338960	Phase 3, DB/PC	BMT 1.75 mg SC vs. PBO	Desire, distress (primary); SSEs (key secondary)	6 months	604 (303 BMT/ 301 PBO)	HSDD with or without decreased arousal	U.S., Canada
PT-141-54	NCT01382719	Phase 2, dose finding	BMT 0.75, 1.25, 1.75 mg vs. PBO	SSEs (primary)	14 weeks	397 (298 BMT/ 99 PBO)	FSAD and/or HSDD	U.S., Canada
Studies to Support Safety								
BMT-301 OLE		Long-term OLE	1.75 mg BMT SC	Safety, exploratory endpoints	52 weeks	363	HSDD with or without decreased arousal, completed BMT-301	U.S., Canada
BMT-302 OLE		Long-term OLE	1.75 mg BMT SC	Safety, exploratory endpoints	52 weeks	321	HSDD with or without decreased arousal, completed BMT-302	U.S., Canada

Trial Identifier	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	Patients Enrolled	Study Population	Centers and Countries
Other Studies Pertinent to Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
PT-141-2002-11		Alcohol interaction and PK/ hemodynamic study: DB/PC crossover	IN 10, 20 mg	PK, BP	1 week	24	Healthy M/F	U.S. (1)
PT-141-2005-23		Nitroglycerin interaction	IN 5, 15 mg	Safety (BP)	21 days	36 (18M/18F)	Healthy males and females	U.S. (1)
PT-141-2005-28		TQT study	IN 5, 20 mg	Safety (QT)	2 days	264 (132M/132F)	Healthy males and females	U.S. (1)
PT-141-2006-32		Effect on controlled hypertension	IN 5, 10 mg	Safety (BP/ABPM)	4 days	140 (77M/85F)	Male or female subjects with essential HTN (Stage 1 or 2)	U.S. (32)
[redacted]								(b) (4)
BMT-101		DDI with antihypertensive medications	1.75 mg SC	PK/PD	Up to 14 days	163	Healthy pre-and postmenopausal women	U.S. (1)
BMT-103		DDI-SSRI/SNRI/ naltrexone and bupropion	1.75 mg SC	Safety (PK/PD)	Single dose	127	Healthy females	U.S. (1)
BMT-104		PK study with hormonal contraceptives (norethindrone/ethinyl estradiol oral contraceptive)	1.75 mg SC	PK	4 days (15 days pretreat-ment with OCPs)	36	Healthy females	U.S. (1)
BMT-105		PK study with pseudoephedrine, phentermine, celecoxib, and indomethacin	1.75 mg SC	PK/PD (ABPM)	Single dose	144 (78M/66F)	Healthy male and females	U.S. (1)

Trial Identifier	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	Patients Enrolled	Study Population	Centers and Countries
BMT-115		PK study: Impaired renal function	1.75 mg SC	Safety/PK	Single dose	32 (16M/16F)	M and F subjects with normal renal function and those with renal impairment (mild, mod, severe)	Canada (2)
BMT-116		PK study: Impaired hepatic function	1.75 mg SC	Safety/PK	Single dose	24 (20M/4F)	M and F subjects with normal hepatic function and mild and moderate hepatic dysfunction	U.S. (2) Canada (1)
BMT-117		Abuse potential	1.75, 3.5, 5.25 mg SC	Safety/PK	Single dose	56 (38M/18F)	Recreational drug users, M and F	U.S. (1)
BMT-118		PK study using the antidiabetic agent, metformin	1.75 mg SC	PK	Single dose	36 (19M/17F)	Healthy M and F	U.S. (1)
Other Supportive Safety Studies								
PT-141-2004-52FB	N/A	PD study: Change in vaginal pulse amplitude and TSI	20 mg IN	Efficacy/safety	Single dose	45F (18 pre-MP/ 27 post-MP)	FSAD	U.S. (2–3)
PT-141-2005-53FB	NCT00425256	Arousal study	10 mg IN	Efficacy/safety	8 weeks (10 doses)	163F (76 pre-MP/ 87 post-MP)	FSAD	U.S. (28)

Abbreviations: BMT bremelanotide, OLE open-label extension, NCT national clinical trial, PBO placebo, DB/PC double-blind/placebo-controlled, PK pharmacokinetics, pre-MP premenopausal, post-MP postmenopausal, M male, F female, SC subcutaneous, IN intranasal, TSI treatment satisfaction index, BP blood pressure, ABPM ambulatory blood pressure monitoring, SSE satisfactory sexual event, DDI drug-drug interaction, SSRI/SNRI selective serotonin reuptake inh bitor/serotonin and norepinephrine reuptake inhibitor, OCP oral contraception pill, FSAD female sexual arousal disorder, HSDD hypoactive sexual desire disorder, TID three times a day, PD pharmacodynamics, HTN hypertension, BMI body mass index

7.2. Review Strategy

The efficacy of BMT for the proposed indication was assessed using the datasets submitted by the Applicant (Study Data Tabulation Model and Analysis Data Model). The quality of data submitted was sufficient for analysis and there were no identified issues with data quality that impeded the review. The data were also queried using the JumpStart program. No significant issues were noted.

The efficacy assessment focuses on two phase 3 trials BMT-301 and BMT-302. The primary efficacy analysis performed by the Applicant for the coprimary analysis was reproduced. Additional supportive and sensitivity analyses were performed to assess the robustness of the efficacy results to missing data, determine if the treatment effect persists throughout the entire double-blind period, and examine the long-term efficacy. Other analyses were performed to examine the clinical meaningfulness of the treatment. Further analyses relating to the secondary endpoint, change in number of SSEs from baseline, were performed. This endpoint was originally a coprimary endpoint and, with DBRUP's concurrence, was demoted to a secondary endpoint prior to unblinding of data. The primary analysis for this endpoint was not statistically significant. Additionally, the usage of study drug was explored along with additional analyses to examine the appropriateness of the 28-day recall period used for the coprimary endpoints.

The safety review of BMT focused on the pooled core data from phase 3 trials BMT-301 and BMT-302 and separate analyses of the extension phase data (BMT-301-extension and BMT-302-extension) to support longer-term safety. The Applicant's Integrated Summary of Safety (ISS) included three additional phase 2 studies (one in the HSDD population and two in the FSAD population) and 18 additional controlled and uncontrolled phase 1/2 studies in non-HSDD/FSAD subjects. These data were less applicable but were reviewed in the setting of global safety issues (e.g., liver toxicity, pregnancy, etc.). Data from the intranasal route was of limited clinical value because of the differences in pharmacokinetic and safety profiles between formulations.

Efficacy data were reviewed by statistical, clinical outcomes assessment, and clinical reviewers, whereas safety information was reviewed by clinical reviewers. The Applicant's primary analyses were reproduced by the review team. Our analyses are presented if they differ significantly from the Applicant's analyses. The review team also performed additional supportive safety analyses as necessary.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trials BMT-301 and BMT-302

Primary Objective

- Evaluate efficacy of 1.75 mg as needed dose of SC BMT for HSDD (in premenopausal females with or without concurrent decreased sexual arousal).

Secondary Objectives

- Evaluate efficacy of 1.75 mg BMT SC compared to PBO in premenopausal women in the double-blind core study, assessed by subject responses to questionnaires measuring sexual function, treatment satisfaction, and distress associated with sexual function.
- Evaluate safety of 1.75 mg BMT SC compared to PBO in premenopausal women in 6-month double-blind core study.

Trial Design

The Applicant conducted two clinical trials to support efficacy of one dose of BMT, 1.75 mg. Studies BMT-301 and BMT-302 (hereafter referred to as 301 and 302) were of identical design; both were multicenter, randomized (1:1), PBO-controlled, parallel group trials conducted in the United States and Canada, and compared fixed-dose BMT (1.75 mg SC) to PBO on an as-needed basis (not to exceed one dose within a 24-hour period) in premenopausal women with HSDD. A total of 91 clinical sites participated in 301 and 84 clinical sites participated in 302.

The selected dose was determined by the phase 2 dose-finding trial (Study 54) that evaluated three doses of as-needed BMT (0.75, 1.25, and 1.75 mg) and PBO for 12 weeks. The BMT 1.75 mg SC dose was the only dose that showed statistically significant increases in SSEs (median 1.0, p=0.02) and FSFI-D (median 0.6, p=0.001) and this dose was chosen for the phase 3 trials. Although the SSEs did not reach statistical significance in Phase 3, the results from the two coprimary endpoints were sufficient to support approval.

Trial Endpoints

Studies 301 and 302 evaluated the same primary and secondary endpoints. Three major patient-reported outcome (PRO) measures were used in these two trials: The FSFI-D, FSDS-DAO question 13, and Female Sexual Encounter Profile–Revised (FSEP-R) question 10. Table 17 below shows their positions in the endpoint hierarchy. The coprimary endpoints were assessed with instruments approximately once per month.

Table 17. Endpoint Position, Definition, and Assessment Schedule for BMT Studies 301 and 302

Endpoint Position	Assessment *If COA, specify name and type*	Concept	Endpoint Definition	Assessment Frequency
Coprimary (PRO)	FSFI-D	Sexual desire	Change from baseline to EOS in desire domain from FSFI Q1 and Q2	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Every 4 weeks** ☐ Assessment at cross-over or early discontinuation
Coprimary (PRO)	FSDS-DAO Q13, "Bothered by low desire"	Distress by low sexual desire	Change from baseline to EOS in score for feeling bothered by low sexual desire as measured by FSDS-DAO Q13	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Every 30 days** ☐ Assessment at cross-over or early discontinuation
Secondary (PRO)	FSEP-R Q10, "Satisfying sexual event"	Satisfaction with sexual event	Change from baseline to EOS in number of SSEs that occurred within 16 hours of study drug dosing and reported within 72 hours	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Within 24 hours of each sexual encounter** ☐ Assessment at cross-over or early discontinuation

Abbreviations: FSFI-D Female Sexual Function Index–Desire Domain, FSDS-DAO Female Sexual Distress Scale–Desire/Arousal/Orgasm, FSEP-R Female Sexual Encounter Profile–Revised, Q question, COA clinical outcome assessment, PRO patient-reported outcome, EOS end of study, SSE satisfactory sexual event

Female Sexual Function Index–Desire Domain

The first coprimary endpoint is the change from baseline to EOS in the desire domain of the FSFI. The FSFI is a multidimensional 19-item self-report questionnaire developed to assess female sexual function in women with HSDD.[42] The instrument consists of six domains: sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. The version employed in Studies 301 and 302 used a 4-week recall period.

The assessment of desire in the FSFI Desire Domain (FSFI-D) includes introductory instructions that define desire as "a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex." Item 1 asks, "How often did you feel sexual desire or interest?" with response options ranging from 5 (almost always or always) to 1 (almost never or never). Item 2 asks, "How would you rate your

[42] Rosen R et al., 2000. The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function. J Sex Marital Ther, 26(2):191–208.

level (degree) of sexual desire or interest?" with response options ranging from 5 (very high) to 1 (very low or none at all).

The FSFI produces a total score; however, only the desire domain score was used as a coprimary endpoint. The FSFI-D consists of questions 1 and 2. The desire domain score is calculated as the sum of the two items multiplied by a factor of 0.6. The score range is 1.2 to 6.0, with higher scores indicating greater levels in sexual desire.

Female Sexual Distress Scale–Desire/Arousal/Orgasm Question 13

The secondary coprimary endpoint is the change from baseline to EOS in the score for feeling "bothered" by low sexual desire as measured by FSDS-DAO Q13. FSDS-DAO question 13 is a single item from a 13-item self-report questionnaire[43] that asks women to evaluate how often a given problem has "bothered you or caused you distress" over the past 30 days. Response options to FSDS-DAO question 13 (0 to 4) ranged from "never," "rarely," "frequently," to "always." Higher score indicates greater sexual distress. This question is virtually identical to question 13 in the Female Sexual Distress Scale–Revised (FSDS-R),[44] which has been accepted by DBRUP and used in other previous programs. The FSDS-R-Q13 also uses a 30-day recall period and asks, "How often did you feel bothered by low sexual desire?"

Female Sexual Encounter Profile–Revised Question 10 Satisfying Sexual Event

The change from baseline to EOS in the number of SSEs, determined from Study Medication and Sexual Encounter eDiary, was evaluated as a key secondary endpoint. Patients reported if they had an injection, the time and site of an injection, if they had a sexual encounter, and the time of that encounter. Subjects were instructed to record all injections in the eDiary. Subjects were also asked to complete the FSEP-R if a sexual encounter was reported.

FSEP-R question 10 is a single item from a 10-item self-report questionnaire designed to identify a satisfactory sexual event. Question 10 of the FSEP-R asks, "Did you consider this sexual encounter satisfactory for you?" FSEP-R question 10 is rated on a yes/no response scale. A subject was counted as having an SSE if the subject reported an encounter and answered "yes" to question 10. For the SSE to be counted in the secondary endpoint, it must have

[43] DeRogatis L et al., 2014. Reliability and Validity of the Female Sexual Distress Scale–Desire/Arousal/Orgasm Instrument in a Phase 2B Dose-Ranging Study of Bremelanotide. Poster presented at the 167th Annual Meeting of the American Psychiatric Association, 3–7May2014, New York, NY. https://www.palatin.com/assets/PAL-P4078-APA-DeRogatis-FSDS-DAO-Reliability-and-Validity-Poster-0421-2-1.pdf

[44] DeRogatis L et al., 2008. Validation of the Female Sexual Distress Scale–Revised for Assessing Distress in Women With Hypoactive Sexual Desire Disorder, J Sex Med, 5:357–364.

occurred within 16 hours of study drug and been recorded within 72 hours of the sexual encounter.

Regulatory History and Discussion Regarding Endpoint Selection

The Applicant did not provide a PRO evidence dossier for review. However, DBRUP had previously agreed on the acceptability of the FSFI-D and FSDS-DAO question 13 as coprimary endpoints during the IND phase of development. Both FSFI-D and FSDS-R were used to support labeling claims in another HSDD application.

The Applicant began their development program using SSEs and sexual arousal as coprimary endpoints in women with female sexual arousal disorder. Once the clinical program focused on HSDD, DBRUP recommended assessing SSEs (limited to those directly related to dosing) and sexual desire as coprimary efficacy endpoints and assessing reduction in distress related to HSDD as a key secondary endpoint. Given the proposed PRN dosing regimen, establishing efficacy using the number of total SSEs would not be acceptable. Success with PRN dosing would require demonstration of statistical significance and clinically meaningful treatment effects (the instruments used to measure these endpoints are discussed below).

On 27Oct2014 and 28Oct2014, FDA held a patient-focused drug development meeting and scientific workshop, respectively, to seek perspectives from patients and other stakeholders regarding the development of drugs intended to treat female sexual dysfunction, specifically disorders of sexual interest and arousal.[45] At the scientific workshop, practitioners and patients stated that SSEs were less relevant and should not be required to be evaluated as a coprimary efficacy endpoint for HSDD because this disorder is characterized by reduced sexual desire and related distress.

[45] See Patient-Focused Drug Development Public Meeting and Scientific Workshop on Female Sexual Dysfunction web page, accessed 9May2019, https://www.federalregister.gov/documents/2014/09/26/2014-22983/patient-focused-drug-development-public-meeting-and-scientific-workshop-on-female-sexual-dysfunction. See also public meeting minutes The Voice of the Patient, a series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative: Female Sexual Dysfunction, accessed 9May2019, https://www.fda.gov/downloads/Drugs/NewsEvents/UCM453718.pdf.

Subsequently, on 10Oct2016, the Applicant submitted protocol amendments for Studies 301 and 302, changing the endpoint hierarchy. The coprimary efficacy endpoints were revised to the change from baseline in sexual desire score (as measured by the FSFI-D) and the change from baseline in distress score (as measured by the FSDS-DAO question 13); change from baseline in the number of SSEs related to drug administration was relegated to the secondary endpoint. This was done prior to data lock and was considered acceptable in principle. However, DBRUP conveyed the following concerns that should be addressed in the application:

- Studies 301 and 302 were powered based on SSEs and the FSFI-D items. The Applicant was asked to clarify how altering the endpoint hierarchy at this time would affect study power and sample size.
- Characterization of the product's onset and duration of action, relative to the time of injection, should be linked to the primary endpoint(s). The Applicant should address how assessment of these aspects of treatment effect would be affected by the proposed change in endpoints.

On 27Oct2016, FDA published a draft guidance for industry entitled *Low Sexual Interest, Desire, and/or Arousal in Women: Development Drugs for Treatment* (October 2016).[46] In the draft guidance, the FDA recognized that the endpoint decisions should reflect the primary symptoms targeted by the drug. Since the diagnosis of HSDD is not contingent on any predefined baseline SSEs, assessment of the change from baseline in the number of SSEs as a primary endpoint is not essential for demonstrating the drug's efficacy. Similarly, because the diagnostic criteria of HSDD outlined in the DSM-IV-TR include associated distress, the drug's treatment benefit should demonstrate a reduction in distress associated with low sexual desire. As such, the draft guidance outlines acceptable approaches in endpoint selection. One approach, utilized in previous development programs, is to assess the change from baseline in SSEs and the change from baseline in sexual desire scores as coprimary endpoints, and associated distress as a secondary endpoint. Alternatively, associated distress may replace SSEs as a coprimary efficacy endpoint, downgrading SSEs to a secondary endpoint. Therefore, the Applicant's revised endpoint hierarchy prior to database lock is consistent with this draft guidance.

Regulatory History and Discussion Regarding PRO Selection

Concerns regarding FSFI–D

- Concerns were raised regarding the use of the FSFI-D using a 28-day recall over daily recall. It was unclear why the optimal assessment of desire was over a 4-week period when a woman is expected to experience acute improvement in her sexual desire around the time of dosing of the PRN drug. Concerns with the 28-day recall period

[46] Draft guidance for industry *Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment* (October 2016), accessed 9May2019, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM526362.pdf.

relate to (1) being able to accurately detect change in the score of sexual desire due to the PRN-dosed drug (with a 3-hour half-life and intermittently used), and (2) the difficulty in recalling feelings of sexual desire that are not recent. These issues will likely lead to increased variability in responses, making it more difficult to detect a treatment effect even if a true treatment effect exists. Use of a daily diary would capture sexual desire close to the time of drug administration and allow for more accurate evaluation of the relationship between dosing and sexual desire. Diary fatigue could be alleviated by limiting daily diary periods to selected weeks during the treatment period.

- FDA considers the evidence to support the content validity of the FSFI-D to be limited. Sexual desire is a multicomponent concept that does not appear to be well-defined and measured by the two items in FSFI-D, which may not adequately evaluate the individual core components of desire (e.g., wanting to have sex, initiating sex, thinking about sex, receptivity to sex, etc.), and therefore make it difficult to determine which component is driving the change. Any treatment benefit without adequate items in the assessment to assess comprehensively and specifically the individual components of desire, would make it difficult to understand and accurately describe in labeling. The FDA's content validity concerns for the sexual desire domain arise from the multi-barreled instructions that make it unclear what is driving any change identified on the assessment (e.g., receptivity, sexual fantasies, or initiating sexual activity). For example, if only one component (e.g., sexual fantasies) is increased with the drug, but other components (e.g., wanting, initiating, or feeling receptive to sexual activity) have not improved, a score change suggesting improvement could be shown; however, it is unclear whether this represents a meaningful benefit to patients. FDA's also concerned with the response scale relate to the response option of "almost always or always" feeling sexual desire or interest (question 1) and a response indicating a "very high" level of sexual desire or interest (question 2). For example, it is unclear whether women experiencing sexual desire all or most of the time would identify this as a benefit, or whether this could represent a different concern to women.

The Applicant was given the following options (2May2014, Type C meeting minutes):

1. Use existing qualitative research to develop a modified FSFI-D for use in clinical trials.
2. Use FSFI-D and 28-day recall as proposed. Include as secondary endpoints a daily assessment that includes individual items for each of the specific components of desire. These results may serve as supportive information to help FDA better interpret any positive findings on the primary endpoint based on the current FSFI items.
3. Use FSFI-D but remove the multi-barreled instructions of the current FSFI-D, such that women focus only on the aspect of interest in having a sexual experience when responding to the existing FSFI desire items.
4. Use FSFI-D and 28-day recall as proposed, without modifying the assessment or completing any daily assessment of the individual components of desire.

Notably, the content validity of the FSFI-D has been used previously to support the approval of another HSDD product. The relevance and importance of the concepts assessed were affirmed in the 2014 PFDD meeting on female sexual dysfunction. The Applicant chose option 2 and conducted the phase 3 trials using the 28-day recall FSFI-D. The trials also incorporated two versions of the Elements of Desire Questionnaire (EDQ), both a 4-week recall version (completed at the scheduled visits) and a daily version that was to be self-administered 7 days prior to scheduled visits. The EDQ was an exploratory questionnaire evaluating sexual feelings and interest. (See *Exploratory endpoints* section below). The thinking was that the daily EDQ may bridge and give confidence for the monthly EDQ and subsequently the 28-day recall of the FSFI. See subsection Additional Analyses Conducted in Individual Trials in Section 8.1.3 for results of the daily EDQ assessment.

Exploratory endpoints

A number of exploratory endpoints were also evaluated including the General Assessment Questionnaire (GAQ) and Elements of Desire Questionnaire (EDQ). These instruments, which are summarized below, provided supportive data but were not sufficiently robust to support labeling claims.

General Assessment Questionnaire

The GAQ is a self-report questionnaire containing five general questions pertaining to treatment in the trials. The first four questions ask participants how they changed from the start of the trial in certain aspects (e.g., desire). Responses to questions 1 through 4 are on an integer scale of 1 to 7, where a response of 1 corresponds to very much worse, 4 corresponds to no change, and 7 corresponds to very much better. Question 5 asks subjects which treatment they believe they have been taking in the last 4 weeks. The GAQ was given to patients at each clinical visit during the treatment period of the study.

Question 3 of the GAQ, “Compared to the start of the study (prior to taking the study drug), to what degree do you think you benefited from taking the study drug?,” was used by the Applicant as an anchor for determining a clinically meaningful change in desire and distress.

Elements of Desire Questionnaire daily diary version/4-week recall version

The EDQ is a self-report diary. Two versions of the EDQ were administered. The 4-week (monthly) recall version was administered at each clinical visit. The daily diary version was administered every day during the 7 days preceding Visits 2, 3, 6, and 9. Both versions have nine questions related to sexual feelings and interest.

Safety endpoints

The safety endpoints evaluated included AEs, physical examination, BP and vital sign measurements (centrally read), ECGs (centrally read by a cardiologist), clinical laboratory tests (centralized facility), and the Beck Scale for Suicidal Ideation. Laboratory tests included chemistry (fasting), hematology, hormones (ACTH, sex hormone binding globulin, α-MSH, prolactin, cortisol, oxytocin, follicle stimulating hormone (FSH), estradiol), HIV, biomarkers (not further specified for possible future testing), urinalysis, serum pregnancy, urine pregnancy (local laboratory), and urine screen for drugs/alcohol. Urine pregnancy testing and confirmatory serum testing were assessed at each visit for all subjects. Any positive urine pregnancy test result was confirmed immediately by a serum pregnancy test. Subjects were instructed to contact the investigator if their menses was delayed more than 14 days. PK samples were obtained postdose (15–45 minutes, 46–90 minutes, >90 minutes) at Visit 3 of the core study only.

Trial Population

Studies 301 and 302 enrolled premenopausal women with acquired, generalized HSDD who were generally healthy without history of serious health conditions but could have had stable chronic conditions, such as controlled HTN and controlled diabetes. However, known cardiovascular disease was an exclusionary criterion. The diagnosis of HSDD was based on the Diagnostic Screening Guide for HSDD and was completed by the licensed health care provider. Eligibility for the double-blind study was based on the following inclusion/exclusion criteria and screening blood pressure criteria. Any subject with a lesion that could represent premalignant or malignant melanoma would be referred to a dermatologist. If confirmed to be malignant, these subjects were excluded from the trial.

Inclusion Criteria

- Written informed consent.
- Premenopausal female at least 18 years of age, (menopausal status based on the Stages of Reproductive Aging Workshop criteria).
- Per the subject, previously experienced “normal sexual function” in the past for a period of at least 2 years.
- Willing to engage in sexual activities at least one time per month during the trial.
- Currently in a stable (≥6 months) relationship with a partner (male or female).
- If partner is male, partner had scored “not impotent,” “minimally impotent,” or “moderately impotent” on the Massachusetts Male Aging Study assessment.
- HSDD according to the Diagnostic Screening Guide for ≥6 months before screening, including categorization as acquired and generalized.
- Was willing and able to understand and comply with study requirements.
- Negative serum pregnancy test at screening regardless of childbearing potential. If the subject’s partner is male, the subject has used the same method of contraception for 3

months prior to screening and is willing to continue during the entire study. In cases where single barrier birth control had been used, a second barrier method must be started at screening. Acceptable forms of contraception are surgical sterilization of subjects or male partner, hormonal contraceptives, intrauterine device, Essure® (transcervical sterilization), double barrier contraception. Protocol Amendment 1 specified that contraception is not required for monogamous females with a female partner.

- Normal pelvic exam at screening.
- A clinically acceptable Pap test defined as normal, or atypical squamous cells of undetermined significance with negative HPV at screening or documented within 12 months before screening.
- Has all the following at screening:
  - Patient Health Questionnaire-9 (PHQ-9) total score <10 (mild depression or none)
  - PHQ-9 score for question 9 is 0 (no suicidal thoughts or thoughts of self-harm)
  - Either FSFI total score is ≤26 (for HSDD with or without decreased arousal) or FSFI desire domain score is ≤5 (if HSDD without decreased arousal)
  - FSDS-DAO total score is >18 (range 0 to 60)
- Has or has had all the following at Visit 2 (end of 28-day screening period):
  - At least one sexual encounter since screening visit
  - For subjects reporting fewer than three sexual encounters (one or two events) since the screening visit, there was no requirement regarding question 10 of the FSEP-R questionnaire (pertaining to SSEs) for the percentage of SSEs being satisfactory
  - For subjects reporting four or more sexual encounters since screening, the answer to FSEP-R for percentage of SSEs being satisfactory must be “yes” for no more than half of the encounters (≤50%)
  - For subjects having three sexual encounters, the answer to FSEP-R Q10 must have been “yes” for no more than two of the encounters (<100%)

Rescreening of screen failures was allowed if either of the following was the sole reason: (1) the PHQ-9 score is 10 through 13; or (2) BP criteria was out of range.

Exclusion Criteria

- Any condition that is unstable or uncontrolled despite treatment.
- Participated in a previous BMT study.
- Received other investigational drug/devices within 30 days or at any time during study participation.
- Donated blood within 30 days of screening or anytime during study.
- History of unresolved sexual trauma or abuse.
- Pregnant or nursing.
- Has any FSD other than acquired HSDD with or without decreased arousal (e.g., lifelong anorgasmia, sexual pain disorder, sexual aversion disorder, primary diagnosis of FSAD).

- Has FSD caused by untreated endocrine disease (e.g., hypopituitarism, hypothyroidism, diabetes mellitus).
- Has acute or chronic hepatitis.
- Has had hepatitis C, or infectious blood disorders such as HIV; myocardial infarction; stroke, or any malignancies (treated or untreated) within the past 5 years.
- Active moderate to severe vaginitis or a clinically significant vaginal infection.
- Has had an active or chronic clinically significant sexually transmitted disease within 6 months before screening.
- Any urologic or gynecologic condition such as condyloma, uterine fibroids, vulvar or vaginal lesions, vulvodynia, or pelvic pain that may contribute to impaired sexual activity and function or be a cause of FSD or that may interfere with subject's ability to comply with study procedures.
- Has had any of the following general conditions within the 6 months before screening:
  - Clinically unstable angina or clinically unstable arrhythmia
  - Significant CNS diseases, such as spinal cord injury or multiple sclerosis
  - AST or ALT more than three times ULN
  - Serum creatinine >2.5 mg/dL
  - Any other clinically significant abnormal laboratory test result
- Has used any of the following types of medications:
  - Treatment with any implanted or injected testosterone product within the 6 months
  - Within the 3 months and during study, use of (1) neuroleptics (e.g., risperidone);(2) lithium (e.g., lithium carbonate); (3) antidepressants (e.g., amitriptyline, fluoxetine, bupropion); (4) mood stabilizers (e.g., valproate); (5) benzodiazepines (e.g., lorazepam, diazepam); (6) cognitive enhancers or stimulants (e.g., donepezil or amphetamine/dextroamphetamine); (7) centrally acting antihypertensives (e.g., clonidine); (8) any other prescription, nonprescription, herbal, or nutritional supplement known to affect sexual arousal or desire [e.g., St. John's wort, black cohosh, dehydroepiandrosterone (DHEA), DHEA-sulfate]; or (9) γ-aminobutyric acid (GABA) agonists (e.g., zolpidem, eszopiclone)
  - Topical testosterone within the 30 days before screening; the subject must also agree to remain off testosterone, androgenic compounds or any of the excluded medications for the duration of the study
- History of, diagnosed with, and/or is taking or has received treatment for psychosis, bipolar disorder, depression, and/or alcohol/substance abuse within the 6 months before screening. (Note: history of depression that is no longer present is not exclusionary).
- History of suicide attempt or at increased risk for suicide according to the Beck Scale for Suicidal Ideation. Any subject with a score >0 on questions 1 through 5 and/or question 20 is not eligible and should be referred to their physician as appropriate.
- Is receiving any treatment for HSDD (e.g., psychotherapy, physical therapy) at the time of screening.

- Has a current diagnosis of uncontrolled hypertension (>140/90 mm Hg) defined as:
  - Two sequential assessments (approximately 4 minutes apart and no more than 15 minutes apart, after being seated quietly for at least 5 minutes prior to the first reading) at levels above 140 mm Hg SBP or 90 mm Hg DBP; subjects who meet either of these criteria at two separate visits at least 24 hours apart will be excluded from study participation and advised to consult their primary care physician for follow-up
  - Treatment for HTN that has been changed at least once in the 4 weeks before screening
- Is unwilling to forego any medications, herbal treatments, dietary supplements, or psychotherapy intended to enhance sexual function during the course of the trial.
- Has any condition that, in the investigator's opinion, would interfere with the subject's ability to provide informed consent, to comply with study instructions, or that might confound the interpretation of the study results.
- Has any condition that would endanger the participant if she participated in this study.
- Has had a hysterectomy with bilateral oophorectomy.
- Has had a hysterectomy without bilateral oophorectomy (or any other procedure that affects menses cycles, e.g., endometrial ablation) *and* meets one or more of the following:
  - Age was >50 years at screening
  - Was menopausal by Stages of Reproductive Aging Workshop menstrual cycle criteria before the hysterectomy
  - FSH was >40 mIU/mL at screening
  - Estradiol was <20 pg/mL at screening

Based on the entry criteria, the population enrolled in these two phase 3 trials consisted of primarily healthy women and may differ from the larger population of women who would consider using this product if it is approved. Importantly, women with melanoma and uncontrolled HTN (defined as repeated measures of BP>140/90 mm Hg) were excluded from participating in the trials.

Trial Conduct

Each trial involved a 4-week, no-drug, screening period (Weeks 1 to 4), followed by a 4-week single-blind PBO run-in period (Weeks 5 to 8) that served as each subject's baseline, followed by a 24-week randomized double-blind period (Weeks 9 to 32). During the double-blind period, subjects were randomized 1:1 to BMT 1.75 mg or identical PBO subcutaneously and instructed to use study drug approximately 45 minutes prior to anticipated sexual activity on an as-needed basis. At the beginning of the single-blind PBO run-in period, subjects were trained to use the autoinjector device and self-administered an in-clinic dose of single-blind placebo medication. Subjects were re-trained to use the autoinjector device and self-administered an in-clinic dose of randomized study drug at the beginning of the double-blind period. Randomization was

conducted using the interactive voice response system and was blocked by country. Dosing was not to exceed more than one dose within 24 hours and not more than 12 doses in a 4-week period. There was no further restriction on the number of doses per week. Following training, subjects self-administered the study drug in either the anterior thigh or abdomen using the single-use autoinjector. The 45-minute window was based on the PK profile of BMT, but sexual activity could start any time after drug administration.

Table 18. Schedule of Events

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Core study week	1	5	9	13	17	21	25	29	32
Days since last visit	—	28±3	28±3	28±3	28±3	28±3	28±3	28±3	28±3
Study Procedure	**Screening**	**Treatment**							**EODBP/ET**
Safety									
Pregnancy (urine hCG)	X	X	X	X	X	X	X	X	X
Vital signs	X	X[f]	X[f]	X	X	X	X	X	X
12-lead ECG	X		X						X
Assess AEs		X	X	X	X	X	X	X	X
Concomitant treatments		X	X	X	X	X	X	X	X
Clinical laboratory tests[1]									
Chemistry	X		X			X			X
Hematology	X		X			X			X
HIV test	X								
Pregnancy (serum hCG)	X								X
FSH (if needed)	X								
Estradiol (if needed)	X								
Urinalysis	X		X			X			X
Drug/alcohol screen (urine)	X								
Hormone tests			X[h]						
Study drug									
In-clinic dosing		X	X						
Dispense 4-week supply		X (SB)	X (DB)	X (DB)	X (DB)	X (DB)	X (DB)	X (DB)	
At-home dosing		X (SB)	X (DB)	X (DB)	X (DB)	X (DB)	X (DB)	X (DB)	
Collect used/unused study drug			X	X	X	X	X	X	X
Other samples									
Blood collection for possible biomarkers testing			X						X
Blood collection for PK analysis			X						

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Core study week	1	5	9	13	17	21	25	29	32
Days since last visit	—	28±3	28±3	28±3	28±3	28±3	28±3	28±3	28±3
Study Procedure	**Screening**	**Treatment**							**EODBP/ET**
Questionnaires									
PHQ-9	X								
DSDS	X								
MMAS Q (male partner)	X								
FSDS-DAO	X	X	X	X	X	X	X	X	X
FSFI	X	X	X	X	X	X	X	X	X
EDQ									
Monthly version	X	X	X	X	X	X	X	X	X
Daily version (eDiary device)	X	X	X		X	X		X	X
BSS	X		X						X
GAQ			X	X	X	X	X	X	X
WITS-9			X	X	X	X	X	X	X
FSEP-R (eDiary device)	X	X	X	X	X	X	X	X	X
Dosing diary		X	X	X	X	X	X	X	X
Study medication at-home dosing and sexual encounter questions		X	X	X	X	X	X	X	

[1] Central Laboratory
Abbreviations: AEs adverse events, BSS Beck Scale of Suicidal Ideation, DB double-blind, DSDS decreased sexual desire screener, ECG electrocardiogram, EDQ Elements of Desire Questionnaire, EODBP/ET end of double-blind period or end of treatment (if subjects do not continue into extension phase), FSDS-DAO Female Sexual Distress Scale–Desire/Arousal/Orgasm, FSEP-R Female Sexual Encounter Profile-Revised, FSH follicle stimulating hormone, GAQ General Assessment Questionnaire, hCG human chorionic gonadotropin, MMAS-Q Morisky Medication Adherence Scale, PHQ-9 Patient Health Questionnaire-9, PK pharmacokinetics, SB single-blind, WITS-9 Women's Inventory of Treatment Satisfaction
Source: Table 3 BMT-301 CSR, page 26; BMT-302, page 27

During the trial, subjects were dispensed one kit (six doses) with one additional kit (six doses) given upon request during each 4-week period. Subjects were to return all used and unused autoinjectors before any additional kit was dispensed. An eDiary device was used to record the time and date when study drug was self-administered, as well as the number of used and unused autoinjectors returned. Following the 6-month double-blind portion (core study phase), subjects were offered enrollment into a 52-week extension study (301-extension or 302-extension), each conducted under a separate protocol.

Electronic diary devices were provided at the screening visit. The FSEP-R and daily EDQ (obtained 7 days prior to the scheduled visit) were to be completed at home while all other questionnaires were completed at the clinic visit. Subjects were to bring the devices to each visit and the staff would download the data. They were required to complete the FSEP-R after each sexual encounter whether or not they used the study drug prior to the encounter. FSEP-R was also used to record the date, time and location of all injections and sexual encounters and SSEs. A sexual encounter was defined by the Applicant as "any act involving sexual contact with genitalia and/or oral mucosa and includes intercourse, oral sex, anal sex, and masturbation (by self or a partner)." Subjects were required to use study drug before sexual encounters and engage in sexual activity at least once before the next scheduled visit to remain enrolled in the study. Data entered after 72 hours would be flagged as a late entry.

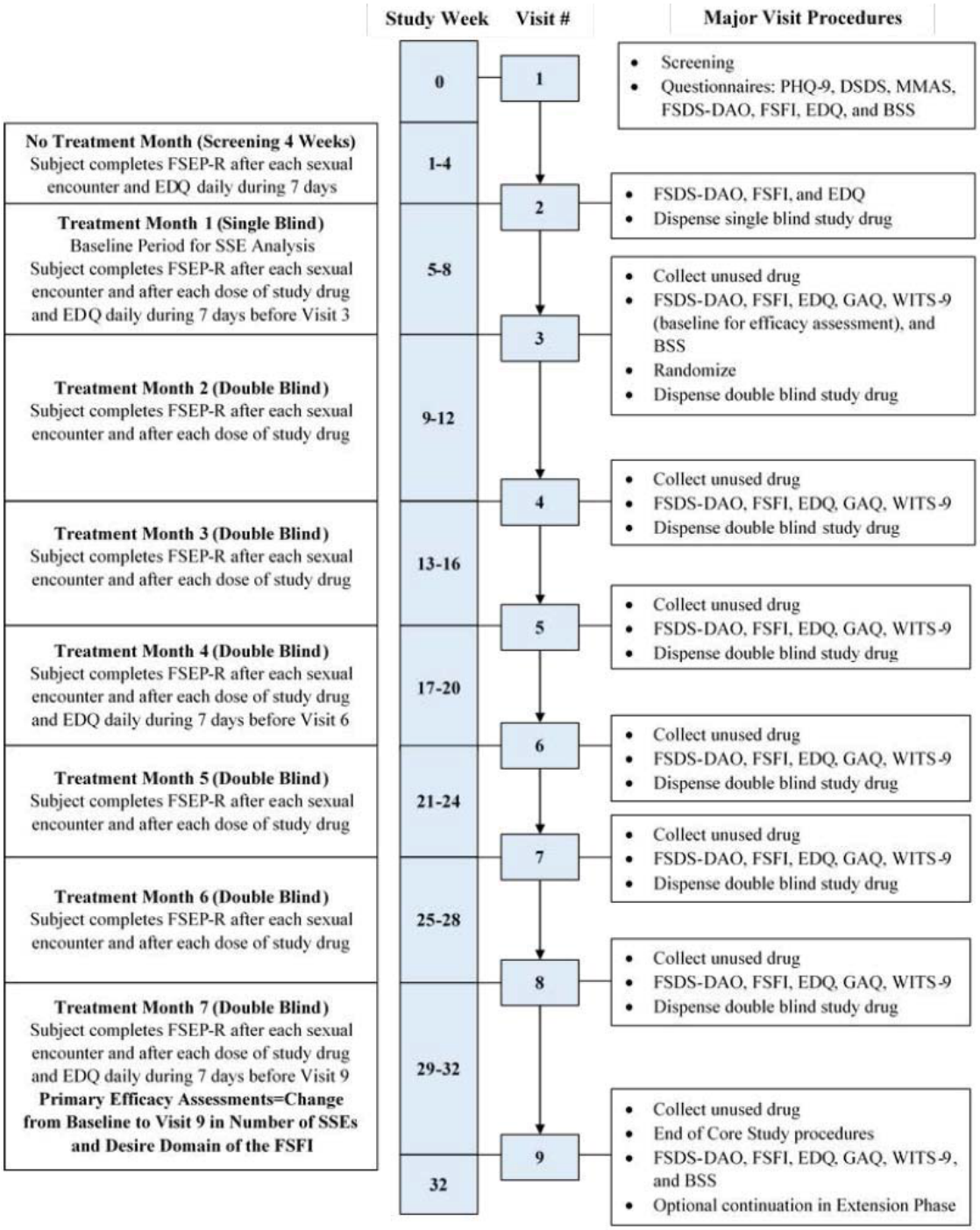
All visits queried the last menses, alcohol use, if the subject's partner changed, AEs, concomitant medications, weight, vital signs, pregnancy testing, other laboratory testing, if scheduled, review of FSEP-R, and collection of used/unused medication.

One telephone visit occurred between each visit to remind subjects about the need for birth control; the need for at least one sexual encounter; the need to complete the eDiary and daily EDQ, if applicable 7 days prior to the next visit; and reminders to take study drug before any sexual encounter; not to take more than one dose in a 24 hour period; to record time and location of all injections; and to contact the investigator if menses is delayed. The interview also assessed compliance and AEs. DBRUP reviewed the standard script for the telephone encounters and concluded that the scripts would not result in bias in how AEs were elicited or reported.

Subjects were instructed not to use lubricants containing menthol, nicotine, other "enhancers," botanical oils or extracts during sexual encounters. Nausea and vomiting, which may be related to study drug, were managed with an antiemetic.

Treatment compliance was monitored using the dates the drug was dispensed to each subject and the number of autoinjectors returned. The subject was also to use the eDiary to record drug use and the number of used/unused autoinjectors returned.

Figure 10. Study Design and Schedule of Assessments



Abbreviations: BSS Beck Suicidal Ideation Scale, DSDS decreased sexual desire screener, EDQ Elements of Desire Questionnaire, FSDS-DAO Female Sexual Distress Scale–Desire/Arousal/Orgasm, FSEP-R Female Sexual Encounter Profile-Revised, FSFI Female Sexual Function Index, GAQ – General Assessment Questionnaire, MMAS Morisky Medication Adherence Scale, PHQ-9 Patient Health Questionnaire-9, SSE satisfactory sexual event, WITS-9 Women's Inventory of Treatment Satisfaction
Source: 1 Applicant Figure 1, BMT-301 Clinical Study Report page 21/1127

Subjects were removed from participation under the following conditions:

- If predose BP exceeded 140 mm Hg for SBP or 90 mm Hg for DBP (on two sequential readings, after at least 5 minutes of rest, at least 4 minutes apart and less than 15 minutes apart) and if readings remained elevated upon repeat assessment (at least 18 hours later), the subject was withdrawn.
- If postdose BP exceeded 160 mm Hg SBP and 95 mm Hg DBP and remained elevated upon repeat assessment (at least 18 hours later) the subject was withdrawn. The subject could also be withdrawn at the discretion of the investigator for SBP between 140 and 160 mm Hg or DBP between 90 and 95 mm Hg.
- If monthly in-clinic BP was >140 mm Hg SBP or >90 mm Hg DBP on two readings and if readings remained elevated upon repeat assessment (at least 18 hours later), the investigator was to discuss the subject with the medical monitor prior to withdrawing her from the study.
- If pregnant, subjects will be followed for outcome of pregnancy (either delivery or early termination). Live births will be followed for 3 months. Spontaneous pregnancy loss will be classified as a serious adverse event (SAE).
- Other reasons: Noncompliance with questionnaires at Visit 3, use of prohibited medication, change in sexual partners, subject request, if investigator decides that it is in the subject's best interest, or if the Applicant terminates the study.

Screen failures could be rescreened once if (1) PHQ-9 score was 10 to 13 (indicating moderate depression) and was the sole criterion for screen failure or (2) BP was the sole reason for screen failure.

Statistical Analysis Plan

Analysis Populations

Modified intent-to-treat population

The modified intent-to-treat (MITT) population consisted of all randomized subjects who received at least one dose of double-blind study drug and have at least one double-blind follow-up visit. The primary efficacy analysis uses the MITT population.

Randomized population

The randomized population consisted of all subjects randomized to a double-blind treatment group.

Safety population

The safety population consisted of all randomized subjects who received at least one dose of double-blind study drug.

Expanded modified intent-to-treat population

The expanded modified intent-to-treat (EMITT) population consisted of all subjects who left the clinic with outpatient double-blind study drug, did not terminate prior to leaving the clinic at Visit 3, and can provide data on any efficacy endpoint after Visit 3. The EMITT population was used by the Applicant for sensitivity analysis.

Multiple Testing Procedure

All endpoints were tested at two-sided α=0.05. The coprimary endpoints were tested first, and both needed to be significant to test the secondary endpoints. There was one key secondary endpoint and 12 additional ranked secondary endpoints. The secondary endpoints were tested in a prespecified hierarchy. The testing procedure terminated at the first endpoint that does not achieve statistical significance. Any statistical tests performed on efficacy endpoints after the testing procedure terminated will be considered exploratory. Because the key secondary endpoint was not significant in Studies 301 and 302, the 12 other secondary endpoints were considered exploratory and will not be discussed any further.

Missing Data

In the absence of eDiary data for FSEP-R, it was assumed that zero encounters and SSEs had occurred. Subjects with missing data on one of the coprimary endpoints were excluded from the primary efficacy analyses of that endpoint. The Applicant's sensitivity analyses in the EMITT population used the screening value at Visit 2 as the baseline value when the Visit 3 value was missing. The EMITT analysis also used baseline carried forward imputation for subjects with no postbaseline values. The Applicant performed additional sensitivity analyses using multiple imputation to impute missing data for the coprimary endpoints for all subjects in the MITT population.

Statistical Analysis Method

The coprimary and key secondary endpoint were analyzed using a Wilcoxon rank-sum test, with the MITT population used in the primary analysis. The Applicant's multiple imputation sensitivity analysis tests the change from baseline to the end of the double-blind period for the coprimary endpoints using a general linear model. The primary analysis of the key secondary endpoint, number of SSEs, excludes all SSEs recorded more than 72 hours after the encounter. The Applicant performed sensitivity analyses including all recorded SSEs.

Protocol Amendments

There were four amendments to the study protocol (5Jan2015, 10Aug2015, 3Aug2016, and 10Oct2016).

The Applicant requested changing the number of SSEs from a coprimary endpoint to a secondary endpoint and replacing it with decrease in distress as a coprimary endpoint at an 8Sep2016 meeting with FDA. The Applicant cited data from phase 2 Study 54 and an 28Oct2014 FDA panel on Female Sexual Interest/Arousal Disorder to justify the change in endpoints. The panel recommended using SSEs as a secondary endpoint and distress as a primary endpoint. FDA acknowledged that altering the endpoints was acceptable if done prior to database lock (meeting minutes dated 23Sep2016). The change in endpoint hierarchy is reflected in the 10Oct2016 protocol amendment. SSEs that occurred within 16 hours but recorded more than 72 hours after the encounter were also excluded from primary analyses (10Oct2016).

The Applicant made numerous changes to the inclusion and exclusion criteria. Key changes in the protocols include (1) adding withdrawal BP criteria of 140/90 mm Hg (5Jan2015); (2) continuing BP assessment of subjects with elevated readings until the BP returned to an acceptable level (5Jan2015); (3) requesting that the investigator discuss with the medical monitor any subjects who meet elevated BP criteria before withdrawing those subjects from the trials (10Aug2015); (4) adding urine pregnancy testing to local study sites (in addition to central readings) to more quickly identify pregnancies (5Jan2015); and (5) editing inclusion criterion 13 regarding the percentage of satisfactory events recorded in the FSEP-R to allow one or two events having no requirements and changing the requirement for three events to having less than 100% being satisfactory (i.e., up to two of three events could be satisfactory). This change was made after consulting with multiple experts/advisors in HSDD who also are investigators on the study and who confirm many patients have satisfactory events but still have decreased desire causing marked distress (3Aug2016).

Additional amendments related to analyses:

- The Applicant eliminated the efficacy of long-term therapy in the open-label extension phase from assessment as a secondary endpoint due to the lack of a comparison group (3Aug2016).
- An Independent Anchor Assessment Committee was formed as a result of discussions with the FDA during the Type C meeting on 8Sep2016, regarding evaluation of multiple anchors and determining minimal clinically important differences of the coprimary, key secondary, and first nine other secondary endpoints based on blinded data from Studies 54, BMT-301, and BMT-302 (10Oct2016).
- It is conceivable that the Applicant was aware from blinded data that the results of SSEs (the original coprimary endpoint) would not meet statistical significance prior to unblinding since neither treatment or PBO arm showed any improvement. However, the change in endpoint was consistent with input from the Public Workshop and subsequent draft FSD Guidance and was agreed to by DBRUP. Amendments related to the change in the endpoint hierarchy did not appear to have had a significant impact on the integrity of the trial.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that the clinical trials were conducted in accordance with the ethical principles of Good Clinical Practice. No clinical studies from sites outside the United States or Canada were submitted to support the Applicant's application.

Patient Disposition

A total of 1,267 subjects were randomized into core study phases of Studies 301 and 302 (653 to BMT and 614 to PBO). Of the randomized subjects, 1,247 (98.4%, 643 in BMT group and 604 in PBO group) received at least one dose of study drug and were included in the safety population. Of these, 1,202 subjects (95%) also completed at least one double-blind follow-up visit and were included in the MITT population. The proportions of BMT subjects completing the double-blind period (56-58%) were considerably lower than PBO subjects (72-84%) in both trials.

Table 19 shows the distribution of patient disposition/discontinuations in both phase 3 trials. Table 20 shows the reason for treatment discontinuation.

Table 19. Patient Disposition

	Study 301			Study 302		
Population	BMT N (%)	PBO N (%)	Total N (%)	BMT N (%)	PBO N (%)	Total N (%)
Randomized	327 (100)	326 (100)	653 (100)	308 (100)	306 (100)	614 (100)
Safety	324 (99.1)	319 (97.9)	643 (98.5)	303 (98.4)	301 (98.4)	604 (98.4)
MITT	314 (96.0)	316 (96.9)	630 (96.5)	282 (91.6)	290 (94.8)	572 (93.2)
Completer	190 (58.1)	274 (84.0)	464 (71.1)	173 (56.2)	219 (71.6)	392 (63.8)

Abbreviations: BMT bremelanotide, MITT modified intent-to-treat, PBO placebo
Source: Reviewer's analysis created from ADDS.xpt

Table 20. Reason for Treatment Discontinuation

	Study 301			Study 302		
Reason for Treatment Discontinuation	BMT N (%)	PBO N (%)	Total N (%)	BMT N (%)	PBO N (%)	Total N (%)
Completed double-blind period	190 (58.1)	274 (84.0)	464 (71.1)	173 (56.2)	219 (71.6)	392 (63.8)
Adverse event	60 (18.3)	3 (0.9)	63 (9.7)	55 (17.9)	9 (2.9)	64 (10.4)
Change of partner	3 (0.9)	0 (0)	3 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow-up	23 (7.0)	11 (3.4)	34 (5.2)	29 (9.4)	18 (5.9)	47 (7.7)
Noncompliance with study drug	5 (1.5)	1 (0.3)	6 (0.9)	4 (1.3)	8 (2.6)	12 (2.0)
Other	9 (2.8)	7 (2.2)	16 (2.5)	3 (1.0)	6 (2.0)	9 (1.5)
Physician decision	2 (0.6)	1 (0.3)	3 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Prohibited medications	2 (0.6)	2 (0.6)	4 (0.6)	2 (0.6)	7 (2.3)	9 (1.5)
Withdrawal by subject	33 (10.1)	27 (8.3)	60 (9.2)	38 (12.3)	35 (11.4)	73 (11.9)

Reason for Treatment Discontinuation	Study 301 BMT N (%)	Study 301 PBO N (%)	Study 301 Total N (%)	Study 302 BMT N (%)	Study 302 PBO N (%)	Study 302 Total N (%)
Pregnancy	0 (0)	0 (0)	0 (0)	2 (0.6)	2 (0.7)	4 (0.7)

Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADDS.xpt

Adverse events were the most common reason for drug discontinuation, with approximately 18% of subjects exposed to BMT discontinuing due to AEs compared to 1% to 3% in the PBO group across both trials. Discontinuation rates were similar in both trials. See the safety section below for details.

Protocol Violations/Deviations

There were no imbalances in the number of important protocol deviations (Table 21) across the phase 3 double-blind phase and across treatment arms in both trials. There was a 1% to 2% increase in deviations in safety assessments in the BMT group. Review of the protocol violations/deviations (addv.xpt and Listings 16.2.1.9) shows deviations that frequently occurred by category. Most subjects with protocol deviations were not discontinued, unless specifically stated below.

Table 21. Important Protocol Deviations

Protocol Deviation	Study 301 PBO	Study 301 BMT	Study 302 PBO	Study 302 BMT
Inclusion criteria	8 (2.5%)	8 (2.4%)	10 (3.3%)	10 (3.2%)
Exclusion criteria	4 (1.2%)	4 (1.2%)	3 (1.0%)	2 (0.6%)
Study drug	18 (5.5%)	22 (6.7%)	10 (3.3%)	8 (2.6%)
Safety assessments	31 (9.5%)	35 (10.7%)	25 (8.2%)	31 (10.1%)
Lab/endpoint data	1 (0.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)
Visit window	0	0	0	1 (0.3%)
Informed consent	1 (0.3%)	4 (1.2%)	3 (1.0%)	2 (0.6%)
Prohibited medication	9 (2.8%)	4 (1.2%)	6 (2.0%)	4 (1.3%)
Overdose/misuse	35 (10.7%)	33 (10.1%)	2 (0.7%)	2 (0.6%)
Other	4 (1.2%)	3 (0.9%)	2 (0.7%)	0

Abbreviations: BMT bremelanotide, PBO placebo
Source: Table 14.1.9 CSR 301 and 302

Comments on Protocol Deviations (Studies 301/302)

- Inclusion criteria deviations: Did not meet FSEP-R criteria (≤50%); screening pregnancy test not done (subject was not randomized); elevated predose BP; screen failure but given study drug; HSDD severity not assessed (subject was not enrolled); acquired and situational HSDD enrolled (Subject (b) (6) pap not done or delayed; birth control switched; PHQ-9 total score=10 at screening visit; those conducting HSDD interviews were not qualified; and partner change

- Exclusion criteria deviations: Prohibited medications (i.e., Ambien, Effexor, diazepam XL dose); hypertension (HTN) medication changed; elevated BP and completed study; plasma donation (subject was rescreened); started medication for attention deficit disorder (Vyvanse) and was excluded from study; failed exclusion criterion of FSH >40 mIU/mL at screening (subject remained in study); partial hysterectomy prior to screening and FSH value was 59 (subject remained in study); history of squamous cell on back (subject was early terminated); history of bipolar disorder (subject was excluded from study); no encounters between V4 and V9 (subject was terminated); suicide attempt (subject completed core phase, but not allowed to enter extension phase).
- Study drug deviations: Two doses in 24-hour period; time of in-clinic injection deviated from protocol (after noon); temperature excursions of study drug; dose not entered into LogPad; injection <45 minutes after removal from refrigerator; dosing after noon on in-clinic days, not returning all medicine, did not return eDiary; subject given two kits at Visit 3 (per subject request); subject had two unscheduled study drug resupplies (27Jul2015 and 24Aug2015) while under Amendment 1.
- Assessment of safety deviations included: No post-clinic visit phone calls; postdose BP out of range (up to 53 minutes); no ECG or physical exam at early termination visit; breast exam not completed; serum or urine pregnancy test not competed; subject with elevated BP and subject not monitored until BP back to normal, or not repeated; end-of-treatment visit not completed; 1 hour postdose BP done earlier.
- Lab/data endpoint deviations included: EDQ incomplete for many subjects (0 to 6 days incomplete).
- Informed consent deviations included: signed incorrect version; not reconsented.
- Overdose/misuse deviations: See Section 8.2.12 for description of overdose/misuse in phase 3 clinical program.

Many subjects completed fewer than 7 days of daily EDQ (ranging from 0 to 6 days) prior to scheduled visit(s). The Applicant intended to use data from the daily EDQ to support the use of the monthly EDQ and in turn the 28-day recall of the FSFI-D. However, a significant number of patients (31% in Study 301 and 36% in Study 302) had 3 or fewer days of data.

Table of Demographic Characteristics

BMT is intended for use only in premenopausal women. Postmenopausal women, defined as amenorrhea for >12 months, were excluded from phase 3.

Table 22 shows the demographic characteristics of randomized subjects in both studies. Demographics were balanced between treatment groups and between phase 3 studies. Most subjects were enrolled from the United States (>95%) and were white women (85%) between the ages of 30 to 45 years. Other racial groups (non-white, non-black) were under-represented. Among the subjects, body weight and BMI spanned all categories (>18.5 kg/m^2); there were few underweight participants. Approximately 75% were reported to be of childbearing potential,

with the remainder surgically sterile (24%). Hormonal contraceptives were used by 18% to 20% of subjects.

Table 22. Demographic Characteristics of Randomized Population

	Study 301			Study 302		
Demographic Parameters	**BMT (N=327) n (%)**	**PBO (N=326) n (%)**	**Total (N=653) n (%)**	**BMT (N=308) n (%)**	**PBO (N=306) n (%)**	**Total (N=614) n (%)**
Sex						
Male	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Female	327 (100)	326 (100)	653 (100)	308 (100)	306 (100)	614 (100)
Age						
Mean years (SD)	38.5 (7.0)	38.6 (7.2)	38.5 (7.1)	38.5 (7.2)	39.2 (6.9)	38.8 (7.1)
Median (years)	39	39	39	39	40	40
Min, max (years)	21, 56	19, 55	19, 56	20, 54	19, 52	19, 54
Age group						
<30 years	32 (9.8)	40 (12.3)	72 (11.0)	35 (11.4)	32 (10.5)	67 (10.9)
30–45 years	234 (71.6)	227 (69.6)	461 (70.6)	217 (70.5)	211 (69.0)	428 (69.7)
>45 years	61 (18.7)	59 (18.1)	120 (18.4)	56 (18.2)	63 (20.6)	119 (19.4)
BMI						
<18.5	1 (0.3)	5 (1.5)	6 (0.9)	7 (2.3)	4 (1.3)	11 (1.8)
≥18.5, <25	113 (34.6)	118 (36.2)	231 (35.4)	110 (35.7)	108 (35.3)	218 (35.5)
≥25, <30	95 (29.1)	80 (24.5)	175 (26.8)	84 (27.3)	87 (28.4)	171 (27.9)
≥30	118 (36.1)	123 (37.7)	241 (36.9)	107 (34.7)	107 (35.0)	214 (34.9)
Race						
White	274 (83.8)	272 (83.4)	546 (83.6)	267 (86.7)	266 (86.9)	533 (86.8)
Black or African American	46 (14.1)	46 (14.1)	92 (14.1)	30 (9.7)	30 (9.8)	60 (9.8)
Asian	2 (0.6)	3 (0.9)	5 (0.8)	5 (1.6)	4 (1.3)	9 (1.5)
American Indian or Alaska Native	3 (0.9)	1 (0.3)	4 (0.6)	2 (0.7)	1 (0.3)	3 (0.5)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Multiple	1 (0.3)	3 (0.9)	4 (0.6)	3 (1.0)	2 (0.7)	5 (0.8)
Other	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.3)	3 (1.0)	4 (0.7)
Ethnicity						
Hispanic or Latino	33 (10.1)	31 (9.5)	64 (9.8)	22 (7.1)	23 (7.5)	45 (7.3)
Not Hispanic or Latino	294 (89.9)	295 (90.5)	589 (90.2)	286 (92.9)	283 (92.5)	569 (92.7)
Region						
United States	321 (98.2)	318 (97.5)	639 (97.9)	296 (96.1)	289 (94.4)	585 (95.3)
Canada	6 (1.8)	8 (2.5)	14 (2.1)	12 (3.9)	17 (5.6)	29 (4.7)

Abbreviations: BMI body mass index, BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADSL.xpt

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The mean duration of HSDD in the enrolled patient population was about 5 years (range 6 months to 30 years). Most subjects had >70% of their sexual encounters with absent/reduced sexual excitement/pleasure. History of uncontrolled HTN was an exclusion criterion. HTN was present at baseline in 5% to 6% of subjects, with 3% to 5% taking concurrent antihypertensive medications. Presence/absence of HTN was balanced between groups. Two subjects enrolled

had a cardiovascular history, although history of myocardial infarction and stroke were exclusion criteria. Diabetes was reported in 1% of subjects. Smoking status was not an exclusionary criterion and was not captured. The rate of hysterectomy was slightly greater in the PBO group (5.3% BMT versus 7.3% PBO) and the rate of endometrial ablation was higher in the BMT group (5.3% versus 2.3% PBO).

For the 1,202 subjects in the MITT population, 634 (52.7%) subjects overall reported taking medications during the trials (54.4% in the BMT group versus 51.2% in the PBO group). No concomitant medication was taken by at least 10% of subjects in the MITT population overall or either treatment group. The incidence and type of concomitant medications taken by subjects during the trials were similar between treatment groups except for the use of ondansetron, which was reported for more subjects in the BMT group (7%) than in the PBO treatment group (1.2%), consistent with the higher incidence of nausea reported with BMT use. The incidence and type of concomitant medications taken by subjects during the trials were similar between treatment groups for all other concomitant medications.

About 90% of subjects received concomitant medications in the extension studies. Of the medications used, ibuprofen was the most common medication used (26% of subjects).

The enrolled population was healthy premenopausal women with a limited number of stable medical conditions (e.g., controlled HTN and diabetes). This population may not mirror the full extent of the population of women who may have chronic or more advanced medical conditions or those at higher cardiovascular risk and want to take BMT, if it is approved.

Treatment Compliance, Concomitant Medications

Treatment compliance

Over 98% of autoinjectors dispensed during the double-blind phase were returned (used and unused) across the BMT and PBO groups in both phase 3 studies. Some subjects did not adhere to the limit of one dose per 24-hour period; this is further discussed in the Overdose/Misuse Summary in Section 8.2.12.

Concomitant medication

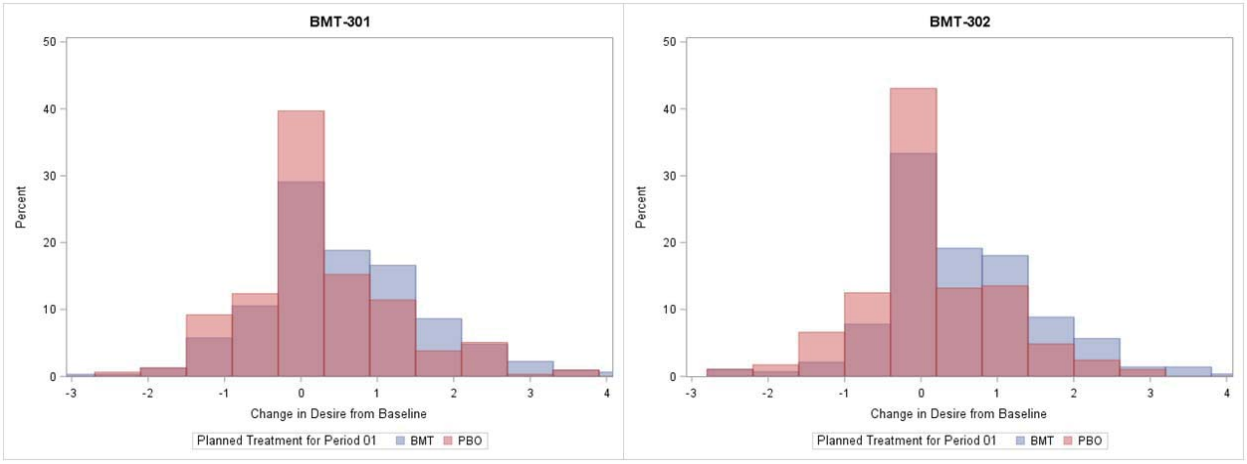
The rate of prohibited concomitant medication use was negligible between groups, BMT groups (2% to 3%) versus PBO (1.0%). The types of concomitant medication used did not affect the efficacy results.

Efficacy Results: Coprimary Endpoints

Increase in sexual desire

Figure 11 displays a histogram for the distribution of the change in desire (assessed using FSFI-D) by treatment group in Studies 301 and 302. The distribution of the change in desire differs by treatment group, but there is a substantial amount of overlap. The most frequent change in desire from baseline is zero in both treatment groups.

Figure 11. Distribution of Change in Desire From Baseline to End of Study



Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADEFF1.xpt

The Applicant's primary analysis in the MITT population was replicated. The results (Table 23) are highly significant in favor of BMT for both studies (p<0.001), though the magnitude of effect is not large. Mean desire scores assessed using FSFI-D increased by 0.54 and 0.63 in the BMT group and by 0.24 and 0.21 in the PBO group for Studies BMT-301 and BMT-302, respectively. The FSFI-D score ranges from a minimum of 1.2 to a maximum of 6.

Table 23. Primary Efficacy Analysis for Change in Desire

	BMT-301		BMT-302	
	BMT 1.75 N=313	PBO N=315	BMT 1.75 N=282	PBO N=288
Baseline mean (SD)	2.09 (0.85)	2.02 (0.80)	2.04 (0.83)	2.05 (0.83)
Mean change (SD)	0.54 (1.11)	0.24 (0.99)	0.63 (1.04)	0.21 (0.92)
Median change	0.6	0	0.6	0
Mean Difference	0.30		0.42	
P-value	<0.001		<0.001	

P-values are computed from a Wilcoxon Rank-Sum test.
Abbreviations: BMT bremelanotide, PBO placebo, p-value probability-value, SD standard deviation
Source: Reviewer's analysis created from ADEFF1.xpt

The MITT analysis excludes individuals with no follow-up visit during the double-blind period. Study 301 had 23 patients (13 BMT and 10 PBO) and Study 302 had 42 patients (26 BMT and 16

PBO) that were randomized but were not included in the MITT population. Additionally, two subjects in the MITT population of Study 301 (one BMT and one PBO) and two subjects in the MITT population of Study 302 (two PBO) were missing baseline values for desire and were excluded from the primary efficacy analysis.

A larger number of subjects who received BMT were excluded from the primary efficacy analysis in both trials. To assess whether these exclusions biased the study results, sensitivity analyses were performed using all randomized patients. First, a change of 0 in the FSFI-D was imputed for any individual missing baseline or EOS data. The imputation was later repeated with a change of -0.6 and -1.2. The values 0, -0.6, and -1.2, were chosen as it is unlikely that subjects who withdrew prior to a postbaseline assessment experienced improvement from baseline. A worst-case scenario imputation was also performed, where any missing values were imputed to the worst possible score for subjects randomized to BMT and the best possible score for subjects randomized to PBO. This scenario is implausible but determines if the missing values could change efficacy results. The randomized population sensitivity analyses are presented in Table 24. All analyses were nominally significant in favor of the BMT group using a Wilcoxon rank-sum test except the worst-case scenario imputation for Study 302, which had a mean improvement favoring the PBO group. The Wilcoxon rank-sum test was selected for the sensitivity analyses as it is less affected than the mean by the large outliers produced by the imputation. These sensitivity analyses support that the excluded subjects do not alter the primary efficacy conclusions.

Table 24. Missing Data Sensitivity Analysis for Desire

		BMT-301		BMT-302	
		BMT 1.75 N=327	PBO N=326	BMT 1.75 N=308	PBO N=306
Change of 0 when data are missing	Mean (SD)	0.52 (1.09)	0.23 (0.98)	0.57 (1.00)	0.20 (0.90)
	Difference (p-value)	0.28 (<0.001)		0.38 (<0.001)	
Change of -0.6 when data are missing	Mean (SD)	0.49 (1.11)	0.21 (0.99)	0.52 (1.05)	0.16 (0.91)
	Difference (p-value)	0.28 (<0.001)		0.36 (<0.001)	
Change of -1.2 when data are missing	Mean (SD)	0.46 (1.14)	0.19 (1.01)	0.47 (1.11)	0.13 (0.95)
	Difference (p-value)	0.27 (0.001)		0.35 (<0.001)	
Worst-case scenario for efficacy when data are missing	Mean (SD)	0.41 (1.32)	0.37 (1.23)	0.34 (1.50)	0.44 (1.32)
	Difference (p-value)	0.04 (0.037)		-0.10 (0.032)	

P-values are computed from a Wilcoxon Rank-Sum test and are nominal
Abbreviations: BMT bremelanotide, PBO placebo, p-value probability-value, SD standard deviation
Source: Reviewer's analysis created from ADEFF1.xpt and ADDS.xpt

Sensitivity analyses were performed to evaluate whether efficacy was driven by subjects who withdrew early and if BMT produced a long-term benefit. The primary analysis used the change of desire assessed using FSFI-D from baseline to EOS. The EOS visit depended on how long a patient remained in the study and could occur 4 weeks after randomization (Week 12) or 24 weeks after randomization (Week 32). As shown earlier in Table 19, the BMT treatment arms had a lower proportion of subjects who completed the double-blind treatment period; thus,

improvements in patients who withdrew from the study early and did not receive long-term benefit could have driven efficacy results.

To address the effect of subjects who withdrew early on the efficacy findings, separate sensitivity analyses were performed for individuals who completed the study and those that did not. In addition, a 50% trimmed mean analysis was performed for the randomized population to address the long-term efficacy of BMT compared to PBO. All individuals with missing data at the end of the 24-week double-blind treatment period were assumed to be in the bottom 50% of efficacy results within a trial arm. This analysis determines if the top 50% of patients in the treatment group did better than the top 50% of patients in the PBO group at the end of the double-blind period. This method ignores the EOS efficacy results for individuals who discontinued the study early and likely more heavily penalizes the BMT arm, which had higher dropout rates.

The results of these sensitivity analyses are presented in Table 25. The change in desire is nominally significant in favor of the study drug among completers but is not nominally significant for those who withdrew from the study early, indicating that the overall efficacy results are driven by patients who completed the study. The 50% trimmed mean analysis is nominally significant for Study 302 (p<0.001) and almost nominally significant for Study 301 (p=0.075), providing support that BMT produced long-term improvement in desire compared to PBO.

Table 25. Sensitivity Analyses for Long-Term Efficacy of Bremelanotide on Desire

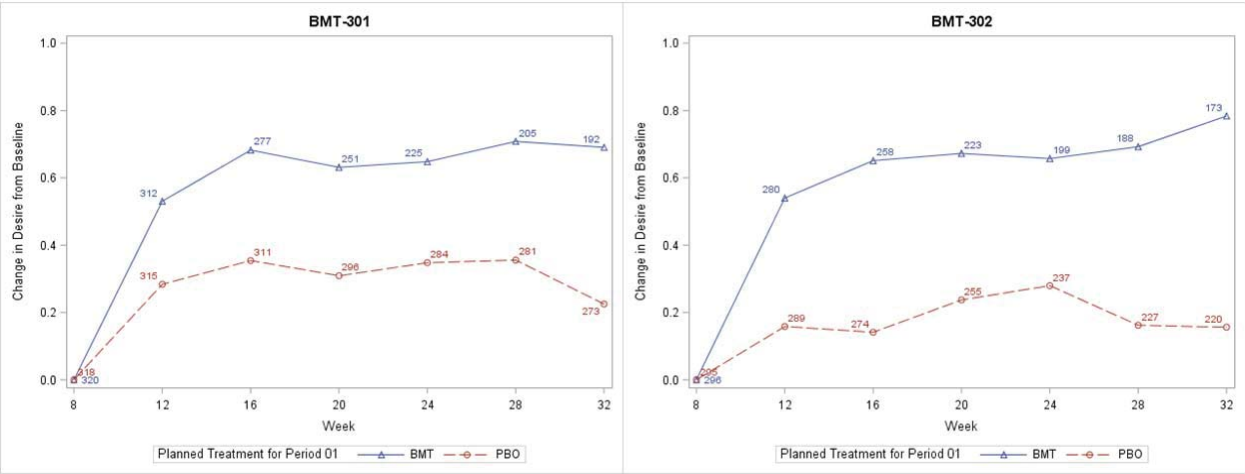
		BMT-301		BMT-302	
		BMT 1.75	**PBO**	**BMT 1.75**	**PBO**
Completed double-blind period	N	190	273	173	218
	Mean (SD)	0.69 (1.12)	0.24 (0.99)	0.80 (1.07)	0.16 (0.91)
	Difference (p-value)	0.45 (<0.001[1])		0.64 (<0.001[1])	
Did not complete double-blind period	N	123	42	109	70
	Mean (SD)	0.30 (1.05)	0.21 (1.05)	0.34 (0.91)	0.36 (0.95)
	Difference (p-value)	0.08 (0.810[1])		-0.02 (0.728[1])	
50% trimmed mean analysis	N	163	163	154	153
	Mean (SD)	0.97 (0.96)	0.75 (0.86)	0.96 (0.95)	0.55 (0.71)
	Difference (p-value)	0.22 (0.075[2])		0.41 (<0.001[2])	

[1] P-values are computed from a Wilcoxon Rank-Sum test and are nominal
[2] P-values are computed from a permutation test with 500,000 permutations and are nominal
Abbreviations: BMT bremelanotide, PBO placebo, p-value probability-value
Source: Reviewer's analysis created from ADEFF1.xpt and ADDS.xpt.

Exploratory analyses were conducted to examine the change in this endpoint over time. Figure 12 below displays the mean change in desire assessed using FSFI-D from baseline by treatment group during the double-blind period. Because the coprimary endpoint was assessed using a 4-week recall, efficacy results at the listed week on the x-axis measure desire during both that week and the three weeks prior to that week (e.g. Week 8 measures efficacy results from weeks 5-8). Week 8 represents the end of the baseline period of the study. The numbers on the

graph represent the sample size at each visit. In this exploratory analysis, a noticeable increase in the mean appears to occur in both the BMT and PBO arms at Week 4 of the double-blind treatment period (corresponding to Week 12 in the figure below). There appears to be a slight further increase in the mean change of desire in the BMT group after Week 12, while the change appears to remain relatively stable in the PBO group. The effect of missing data at each visit due to dropout is not accounted for in this analysis. Efficacy conclusions from a Mixed-Effect Model Repeated Measure (MMRM) analysis which uses a missing at random assumption are the same.

Figure 12. Mean Change in Desire From Baseline by Study Week



Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADEFF1.xpt

Table 26 displays the change in the individual components of the FSFI-desire domain from baseline to EOS in the MITT population. There is a nominally significant difference in the change from baseline for both individual questions and the magnitude of change is similar for both questions; the analysis of the individual items is not adjusted for multiplicity. Efficacy results are not driven by a single question in the FSFI-D.

Table 26. Change in Components of Desire in FSFI-Q1 and FSFI-Q2

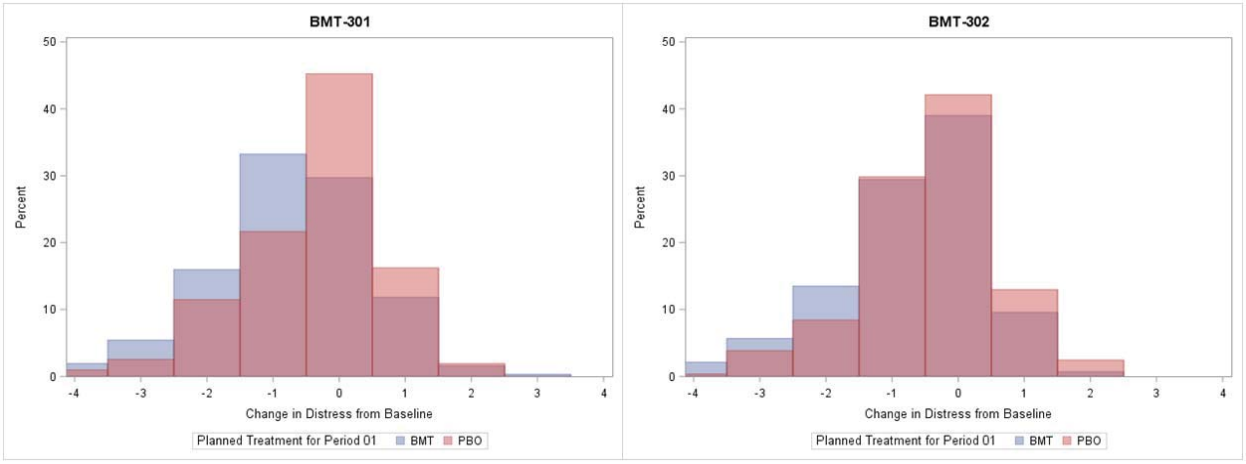
		BMT-301		BMT-302	
		BMT 1.75	PBO	BMT 1.75	PBO
Change from baseline in FSFI-Q1	N	313	315	282	288
	Mean (SD)	0.44 (1.00)	0.22 (0.95)	0.49 (0.93)	0.18 (0.87)
	Difference (p-value)	0.23 (0.004)		0.31 (<0.001)	
Change from baseline in FSFI-Q2	N	313	315	282	288
	Mean (SD)	0.45 (0.99)	0.18 (0.86)	0.55 (0.95)	0.16 (0.82)
	Difference (p-value)	0.27 (<0.001)		0.39 (<0.001)	

P-values are computed from a Wilcoxon Rank-Sum test and are nominal
Abbreviations: BMT bremelanotide, FSFI-Q1 Female Sexual Function Index–Question 1, FSFI-Q2 Female Sexual Function Index–Question 2, PBO placebo, p-value probability-value, SD standard deviation
Source: Reviewer's analysis created from ADEFF1.xpt

Decrease in distress

Figure 13 displays a histogram for the distribution of the change in distress (as measured by question 13 in the FSDS-DAO) by treatment group in Studies 301 and 302. The distributions indicate that subjects in the BMT group experienced a larger reduction in distress, but there is a substantial amount of overlap between the two distributions.

Figure 13. Distribution of Change in Distress From Baseline to End of Study



Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADEFF1.xpt

The Applicant's results were verified and presented in Table 27. The analysis is highly significant in favor of BMT with a p-value less than 0.001 in Study 301 and a p-value equal to 0.005 in Study 302. The response to FSDS-DAO Q 13 ranges from 0 (no distress) to 4 (most distress).

Table 27. Primary Efficacy Analysis for Change in Distress

	BMT-301		BMT-302	
	BMT 1.75 N=313	PBO N=314	BMT 1.75 N=282	PBO N=285
Baseline mean (SD)	2.86 (0.95)	2.84 (0.87)	2.86 (0.94)	2.93 (0.88)
Mean change (SD)	-0.73 (1.20)	-0.36 (1.08)	-0.71 (1.14)	-0.42 (1.05)
Median change	-1	0	-1	0
Mean Difference	-0.37		-0.29	
P-value	<0.001		0.005	

P-values are computed from a Wilcoxon Rank-Sum test
BMT bremelanotide, PBO placebo, SD standard deviation
Source: Reviewer's analysis created from ADEFF1.xpt

The MITT population again excludes 23 patients in Study 301 (13 BMT and 10 PBO) and 42 patients in Study 302 (26 BMT and 16 PBO) who were randomized but had no follow-up visit during the double-blind period. Another three subjects in Study 301 (one BMT and two PBO) and four subjects in Study 302 (four PBO) were excluded from the primary efficacy analysis due

to missing baseline values for distress. One additional PBO subject in Study 302 was excluded due to a missing value at EOS.

Sensitivity analyses were performed using all randomized patients to determine the potential impact that missing data from these subjects had on efficacy results. First, a change of 0 in distress was imputed for any individual missing baseline or EOS data. The imputation was later repeated with a change of 1. The values of 0 and 1 represent no change or a slight increase in distress from baseline and were considered plausible changes for subjects with missing data. Additionally, multiple imputation sensitivity analyses were performed. A total of 20 multiples were created. Missing EOS values were imputed using a linear regression model that included the treatment group, baseline value of distress, age group, injection site, disease group, race and ethnicity, and baseline values for desire and total scores for the FSFI and FSDS instruments. Rubin's rules were used to estimate the difference in means between the treatment groups from a linear regression model that used the same covariates from the imputation model.

Imputed values for subjects in the PBO group were based on the missing at random (MAR) assumption. The mean of the imputed values in the BMT group were shifted by a constant value compared to the mean under the MAR assumption. A mean shift of 1 or 2.1 was used in the imputation. This imputation and analysis approach assumes that change in distress is normally distributed, an assumption that may not be appropriate for this endpoint. A semi-parametric imputation model based on predictive mean matching could be used instead to avoid the normality assumption. However, shifting the mean of the imputed value by a constant is more difficult to implement and may not be as appropriate for a semi-parametric imputation model. Finally, a worst-case scenario imputation was performed, with missing values imputed to the worst score for subjects in the BMT group and the best score for subjects in the PBO group, to determine if the missing values could change efficacy results. The sensitivity analyses are presented in Table 28. All sensitivity analyses are nominally significant for Study 301.

In Study 302, the PBO group had a larger mean reduction from baseline in distress than the BMT group in the worst-case scenario imputation. However, this scenario is implausible. The efficacy results are nominally significant when imputing a value of 0 or 1 for every subject with missing data. The results are also nominally significant when assuming that missing values in the PBO group are MAR and missing values in BMT group are shifted by a mean of 1 or a mean of 2.1 compared to the MAR imputation model. The imputation model with a mean shift of 2.1 in BMT subjects just barely meets the threshold for nominal statistical significance (p=0.048). The results would no longer be nominally significant with a slightly larger shift in the mean. The change from baseline in distress for individuals who completed the study was slightly under -0.7 and anchor-based analyses of electronic cumulative distribution function (eCDF) curves indicated that a decrease of 1 could be considered a clinically meaningful change (\\CDSESUB1\evsprod\NDA210557\0012).

A shift of 2.1 in the average change from baseline FSDS-DAO Q13 score represents a large departure from the MAR assumption and a large change in distress. From a clinical perspective, the efficacy results are robust and the sensitivity analyses support that the excluded subjects are unlikely to influence the efficacy conclusions.

Table 28. Missing Data Sensitivity Analysis for Distress

		BMT-301		BMT-302	
		BMT 1.75 N=327	PBO N=326	BMT 1.75 N=308	PBO N=306
Change of 0 when data are missing	Mean (SD)	-0.70 (1.19)	-0.35 (1.06)	-0.65 (1.11)	-0.39 (1.02)
	Difference (p-value)	-0.35 (<0.001[1])		-0.26 (0.010[1])	
Change of 1 when data are missing	Mean (SD)	-0.66 (1.23)	-0.31 (1.09)	-0.56 (1.19)	-0.32 (1.07)
	Difference (p-value)	-0.35 (<0.001[1])		-0.24 (0.024[1])	
MI with shift of 1 in change for BMT group	Mean (SD)	-0.69 (1.22)	-0.36 (1.08)	-0.63 (1.18)	-0.41 (1.05)
	Difference (p-value)	-0.32 (<0.001[2])		-0.22 (0.002[2])	
MI with shift of 2.1 in change for BMT group	Mean (SD)	-0.64 (1.28)	-0.36 (1.09)	-0.52 (1.31)	-0.41 (1.05)
	Difference (p-value)	-0.28 (0.001[2])		-0.11 (0.048[2])	
Worst-case scenario for efficacy when data are missing	Mean (SD)	-0.61 (1.37)	-0.46 (1.21)	-0.44 (1.48)	-0.59 (1.23)
	Difference (p-value)	-0.15 (0.006[1])		0.14 (0.824[1])	

[1] P-values are computed from a Wilcoxon Rank-Sum test and are nominal
[2] P-values are computed from the multiple imputation pooled parameter estimate of the effect of treatment from a linear regression model adjusted for baseline value of FSDS-Q13, age group, injection site, disease group, race and ethnicity, and baseline values for FSFI, FSDS, and FSFI-D, and are nominal
Abbreviations: BMT bremelanotide, MI multiple imputation, PBO placebo, p-value probability-value, SD standard deviation, diff difference
Source: Reviewer's analysis created from ADEFF1.xpt

Other sensitivity analyses were performed to determine if BMT produced a long-term benefit in distress by looking at efficacy within completers and dropouts and performing a 50% trimmed mean analysis on the randomized population. The results of these sensitivity analyses are presented in Table 29. The change in distress is nominally significant in favor of the study drug among completers but is not nominally significant for those that dropped out, indicating that the overall efficacy results are driven by patients who completed the study. The 50% trimmed mean analysis is nominally significant for Study 301 (p<0.035) and, though not nominally significant, produced a small p-value for Study 302 (p=0.090), providing further support that BMT produced long-term improvement in distress compared to PBO.

Table 29. Sensitivity Analyses for Long-Term Efficacy of Bremelanotide on Distress

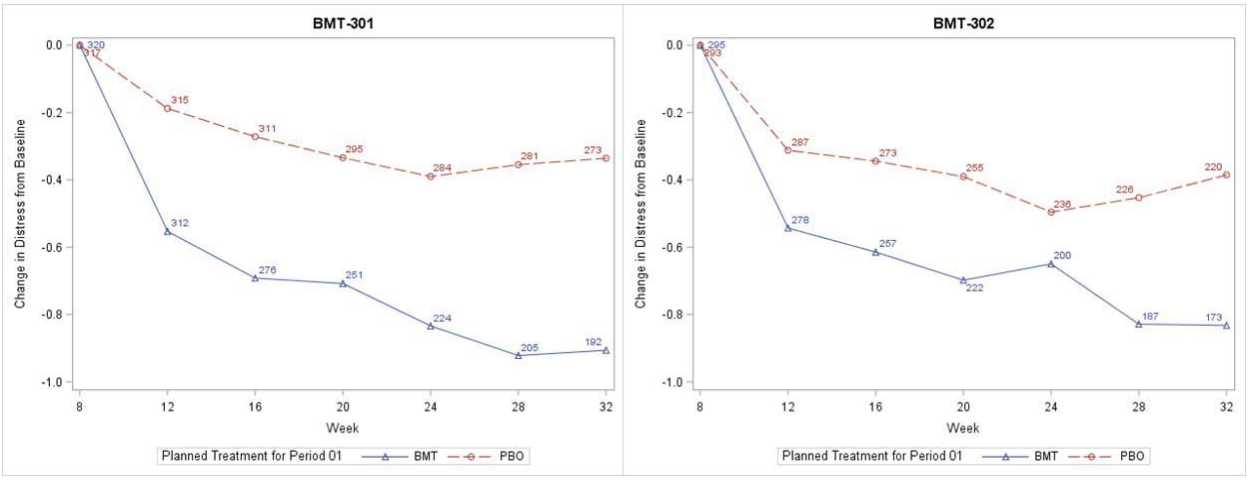
		BMT-301		BMT-302	
		BMT 1.75	PBO	BMT 1.75	PBO
Completed double-blind period	N	190	272	173	217
	Mean (SD)	-0.91 (1.23)	-0.35 (1.05)	-0.86 (1.24)	-0.39 (1.03)
	Difference (p-value)	-0.56 (<0.001[1])		-0.46 (<0.001[1])	
Did not complete double-blind period	N	123	42	109	68
	Mean (SD)	-0.46 (1.11)	-0.43 (1.29)	-0.48 (0.93)	-0.50 (1.10)
	Difference (p-value)	-0.03 (0.5128[1])		0.02 (0.6891[1])	
50% trimmed mean analysis	N	163	163	154	153
	Mean (SD)	-1.21 (1.04)	-0.90 (0.90)	-1.05 (1.11)	-0.82 (0.81)
	Difference (p-value)	-0.31 (0.025[2])		-0.23 (0.090[2])	

[1] P-values are computed from Wilcoxon Rank-Sum test and are nominal
[2] P-values are computed from a permutation test with 500,000 permutations and are nominal
Abbreviations: BMT bremelanotide, PBO placebo, P-value probability-value, SD standard error
Source: Reviewer's analysis created from ADEFF1.xpt

Exploratory analyses were conducted to examine the change in this endpoint over time. Figure 14 displays the mean change in distress from baseline by treatment group by study week. Because the co-primary endpoint was assessed using a 4-week recall, efficacy results at the listed week on the x-axis measure distress during both that week and the three weeks prior to that week (e.g. Week 8 measures efficacy results from weeks 5-8). Week 8 represents the end of the baseline period of the study. The numbers on the graph represent the sample size at each visit. A notable decrease in mean distress occurs in the BMT groups at Week 4 of the double-blind treatment period (corresponding to Week 12 in the figure below), with a smaller decrease in the placebo groups. Afterwards, the mean distress appears to continue a downward trend across several study weeks in both treatment groups.

The effect of missing data at each visit due to dropout is not accounted for, but efficacy conclusions from an MMRM analysis which uses a missing at random assumption are the same.

Figure 14. Mean Change in Distress From Baseline by Study Week



Abbreviations: BMT bremelanotide, PBO placebo, p-value probability-value
Source: Reviewer's analysis created from ADEFF1.xpt

Efficacy Results: Secondary and Other Relevant Endpoints

Increase in satisfying sexual events

As SSEs were a key secondary endpoint, the Applicant's results were verified and presented in Table 30. The difference between treatment groups is not statistically significant in either study (p=0.764 in Study 301 and p=0.702 in Study 302). Change in the number of SSEs was originally a coprimary endpoint. Numerically, the difference between groups in the number of SSEs is small and there is little change in the number of SSEs from baseline. As per statistical testing plan, no further evaluation of other endpoints are warranted.

Table 30. Primary Efficacy Analysis for Change in Number of Satisfactory Sexual Events

	BMT-301		BMT-302	
	BMT 1.75 N=314	PBO N=316	BMT 1.75 N=282	PBO N=290
Baseline mean (SD)	0.72 (0.98)	0.81 (1.12)	0.78 (1.07)	0.70 (0.95)
Mean change (SD)	-0.02 (1.44)	-0.09 (1.35)	0.01 (1.34)	-0.04 (1.20)
Median change	0	0	0	0
(1st quartile, 3rd quartile)	(-1,0)	(-1,0)	(-1,1)	(-1,0)
Mean Difference	0.07		0.06	
P-value	0.76		0.70	

P-values are computed from Wilcoxon Rank-Sum test
BMT bremelanotide, PBO placebo, p-value probability-value, SD standard deviation
Source: Reviewer's analysis created from ADEFF1.xpt

Further examination of the number of reported sexual encounters did not provide evidence that the BMT group increased the number of encounters. At almost every visit, the PBO group had a higher number of encounters. The group difference was very minimal despite the BMT group having a numerically higher number of SSEs at most visits. The data demonstrated a lack of increase in the number of SSEs with BMT, however, an improvement in SSEs is not a requirement for a drug intended to treat HSDD. SSEs are more distal from the onset of sexual desire and are potentially impacted by other factors. In addition, the diagnosis of HSDD does not take into account SSEs. A drug intended for HSDD need only show an improvement in the hallmark symptoms of HSDD—low sexual desire and associated distress. As per the statistical testing plan, no further evaluation of other endpoints are warranted.

Efficacy by Subgroup

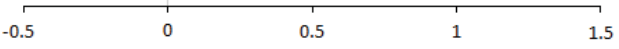
Results of subgroup analyses of change in desire are shown in Figure 15 and Figure 16. Treatment differences and the associated 95% confidence intervals are displayed by racial, ethnic, age, BMI, desire score, and injection-site subgroups for Study 301 and Study 302, respectively. Figure 17 and Figure 18 display the estimate and 95% confidence interval of the difference in means between the treatment groups for the change in distress from baseline to EOS within racial, ethnic, age, BMI, baseline desire score, and injection subgroups for Studies 301 and 302, respectively. Confidence intervals were computed from two sample t-tests with unequal variance. A Wilcoxon rank-sum test was used to analyze treatment differences within

the subgroups. Due to the small number of patients belonging to the Asian, American Indian, Pacific Islander, multiple and other race categories, only two subgroups were created based on race, white and nonwhite. Additionally, due to the small number of patients classified as underweight by BMI, the underweight category was combined with the healthy BMI category. Additional subgroup analyses using the combined treatment effects from studies 301 and 302 were performed but are not shown.

A point estimate greater than 0 for desire indicates results numerically favored BMT within a subgroup, while a point estimate less than 0 for distress indicates results numerically favored BMT within a subgroup. The point estimate favored BMT over PBO within every examined subgroup except for nonwhites in Study 301, though the sample size was not large (48 BMT, 50 PBO) and the efficacy result for nonwhites in Study 302 strongly favored BMT. The confidence intervals from the individual and combined trials show no strong evidence for a differential treatment effect by race, ethnicity, age, BMI, baseline desire or injection site.

Figure 15. Forest Plot of Subgroup Analysis for Change in Desire: Study BMT-301

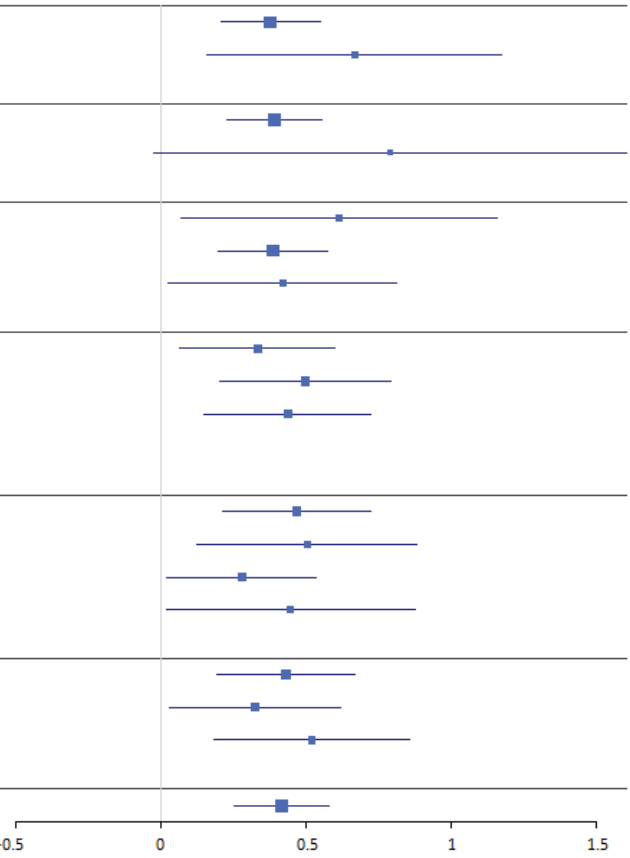
Subgroup	Sample Size BMT	Sample Size PBO	Mean Change from Baseline BMT	Mean Change from Baseline PBO
Race				
White	265	265	0.53	0.17
Non-White	48	50	0.57	0.64
Ethnicity				
Non-Hispanic	281	284	0.53	0.21
Hispanic	32	31	0.64	0.48
Age				
< 30	31	39	0.35	0.32
30 - 45	225	221	0.56	0.2
> 45	57	55	0.57	0.33
BMI				
Underweight/Healthy	111	120	0.44	0.2
Overweight	91	79	0.4	0.18
Obese	111	116	0.76	0.32
Baseline Desire Score (FSFIQ1Q2)				
= 1.2	112	120	0.83	0.68
= 1.8	48	45	0.8	0.07
= 2.4	88	96	0.4	-0.06
> 2.4	65	54	0.03	-0.08
Injection Site				
Both	126	141	0.55	0.17
Abdomen	98	90	0.59	0.35
Thigh	89	84	0.47	0.23
Overall				
	313	315	0.54	0.24



Abbreviations: BMT bremelanotide, FSIQ1Q2 Female Sexual Function Index–Questions 1 and 2; PBO placebo, BMI body mass index

Figure 16. Forest Plot of Subgroup Analysis for Change in Desire: Study BMT-302

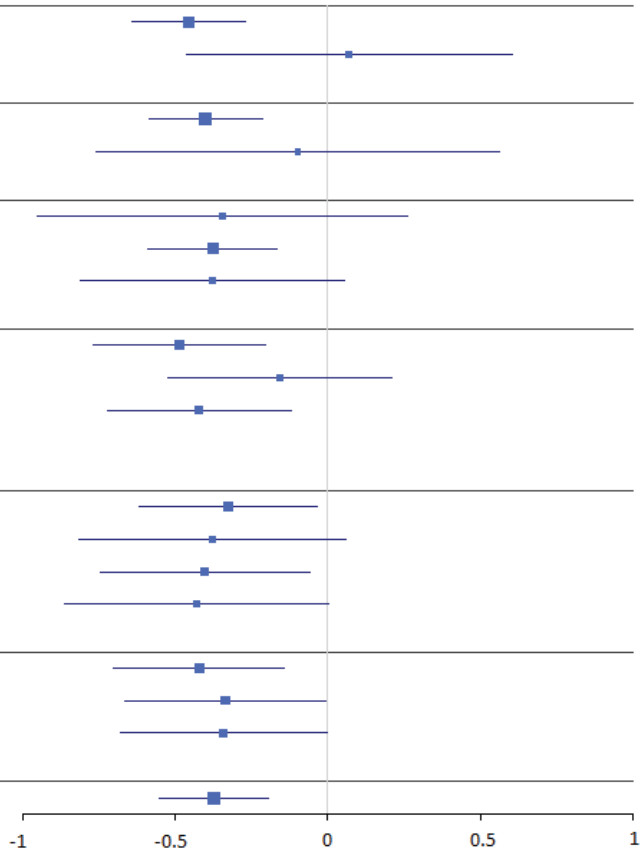
Subgroup	Sample Size BMT	Sample Size PBO	Mean Change from Baseline BMT	Mean Change from Baseline PBO
Race				
White	245	250	0.6	0.22
Non-White	37	38	0.78	0.11
Ethnicity				
Non-Hispanic	265	270	0.6	0.21
Hispanic	17	18	1.02	0.23
Age				
< 30	31	30	0.74	0.12
30 - 45	198	200	0.59	0.21
> 45	53	58	0.68	0.26
BMI				
Underweight/Healthy	107	109	0.54	0.2
Overweight	77	82	0.62	0.12
Obese	98	97	0.73	0.29
Baseline Desire Score (FSFIQ1Q2)				
= 1.2	103	101	0.95	0.48
= 1.8	47	50	0.82	0.31
= 2.4	86	90	0.45	0.17
> 2.4	46	47	0.03	-0.42
Injection Site				
Both	135	132	0.59	0.16
Abdomen	85	87	0.58	0.26
Thigh	62	69	0.76	0.24
Overall				
	282	288	0.63	0.21



Abbreviations: BMT bremelanotide, FSFIQ1Q2 Female Sexual Function Index–Questions 1 and 2, PBO placebo, BMI body mass index

Figure 17. Forest Plot of Subgroup Analysis for Change in Distress: Study BMT-301

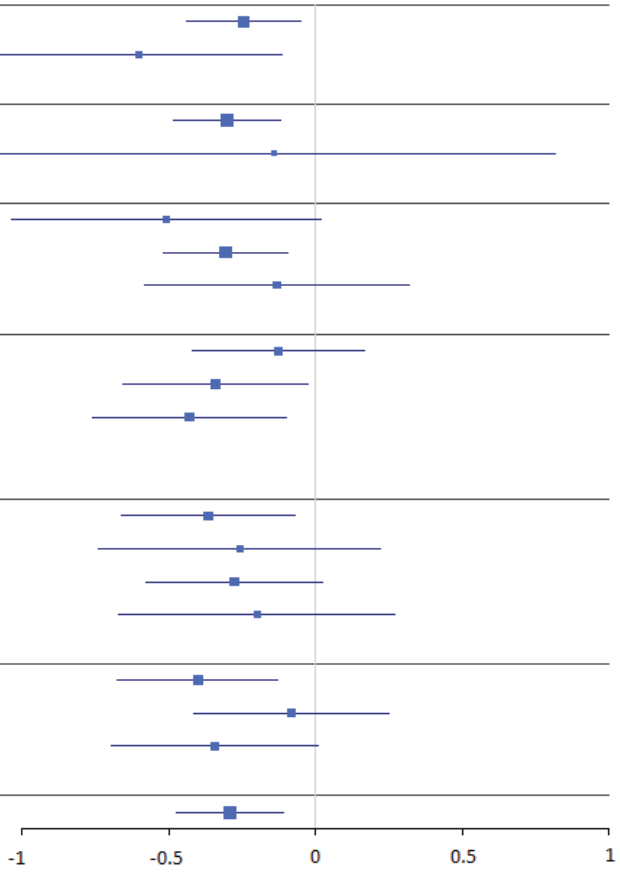
Subgroup	Sample Size BMT	Sample Size PBO	Mean Change from Baseline BMT	Mean Change from Baseline PBO
Race				
White	265	264	-0.73	-0.28
Non-White	48	50	-0.73	-0.8
Ethnicity				
Non-Hispanic	281	283	-0.71	-0.31
Hispanic	32	31	-0.94	-0.84
Age				
< 30	31	39	-0.81	-0.46
30 - 45	225	221	-0.69	-0.32
> 45	57	54	-0.84	-0.46
BMI				
Underweight/Healthy	111	120	-0.72	-0.23
Overweight	91	79	-0.55	-0.39
Obese	111	115	-0.89	-0.47
Baseline Desire Score (FSFIQ1Q2)				
= 1.2	112	120	-0.77	-0.44
= 1.8	48	44	-0.83	-0.45
= 2.4	88	96	-0.72	-0.31
> 2.4	65	54	-0.62	-0.19
Injection Site				
Both	126	140	-0.78	-0.36
Abdomen	98	90	-0.72	-0.39
Thigh	89	84	-0.67	-0.33
Overall				
	313	314	-0.73	-0.36



Abbreviations: BMT bremelanotide, FSFIQ1Q2 Female Sexual Function Index–Questions 1 and 2, PBO placebo, BMI body mass index

Figure 18. Forest Plot of Subgroup Analysis for Change in Distress: Study BMT-302

Subgroup	Sample Size BMT	PBO	Mean Change from Baseline BMT	PBO
Race				
White	245	247	-0.69	-0.44
Non-White	37	38	-0.86	-0.26
Ethnicity				
Non-Hispanic	265	269	-0.71	-0.41
Hispanic	17	16	-0.76	-0.62
Age				
< 30	31	30	-0.74	-0.23
30 - 45	198	197	-0.7	-0.4
> 45	53	58	-0.72	-0.59
BMI				
Underweight/Healthy	107	108	-0.61	-0.48
Overweight	77	81	-0.64	-0.3
Obese	98	96	-0.88	-0.45
Baseline Desire Score (FSFIQ1Q2)				
= 1.2	103	100	-0.82	-0.45
= 1.8	47	50	-0.96	-0.7
= 2.4	86	88	-0.65	-0.38
> 2.4	46	47	-0.33	-0.13
Injection Site				
Both	135	132	-0.73	-0.33
Abdomen	85	85	-0.67	-0.59
Thigh	62	68	-0.73	-0.38
Overall				
	282	285	-0.71	-0.42



Abbreviations: BMT bremelanotide, FSFIQ1Q2 Female Sexual Function Index–Questions 1 and 2, PBO placebo, BMI body mass index,

Dose/Dose Response

The BMT 1.75 mg dose was chosen based on the preliminary findings of safety and efficacy in phase 2b (Study PT-141-54), a randomized, double-blind, dose-finding (0.75 mg, 1.25 mg, and 1.75 mg) study of 12 weeks in duration. The primary endpoint in this phase 2b trial was change from baseline to EOS in the number of SSEs. The basis for the dose selection is discussed in further detail in the Clinical Pharmacology section. Although only one active dose (1.75 mg) was evaluated in the phase 3 trials, later in this review we discuss the association between number of doses and improvement in desire and distress.

Additional Analyses Conducted on Individual Trials

Clinical Meaningfulness of Treatment Difference: Exploratory Responder Analysis

To interpret clinical meaningfulness of the results from the primary analysis of change in desire and change in distress, based on our recommendation, the Applicant convened an Independent Anchor Assessment Committee to assess the within-patient meaningful change of FSFI-D and FSDS-DAO Q13.[47] The Committee recommended an FSFI-D score change of ≥0.6 and FSDS-DAO Q13 score change of ≥1.0 as within-patient meaningful change scores. We agree with the Committee's recommendation on the within-patient meaningful change of ≥1.0 for FSDS-DAO-Q13. However, we conclude that a higher within-patient meaningful change score of 1.2 points for FSFI-D is more appropriate than the 0.6 point that the Applicant proposed. The anchor-based methods suggested a cut point in the range from 0.6 to 1.2. The results from exit surveys and interviews of patients who reported having experienced meaningful changes showed an average change score of 1.2. Triangulating the results of the anchor-based methods and patient exit survey and interviews, a change score of 1.2 is more appropriate for use as the meaningful within-patient change score.

The Applicant performed exploratory responder analyses in the MITT population for both co-primary endpoints using the change from baseline to EOS. The Applicant used a change in 0.6 to define responders for the FSFI-D score and used a change of -1 to define responders for the FSDS-DAO Q13 score. The Applicant's analyses were verified along with additional exploratory responder analyses based on a change of 1.2 for FSFI-D score (which was determined to be more appropriate than a change of 0.6 for a responder definition). The responder analysis was also examined using a change of -2 in FSDS-DAO Q13 score to determine whether the responder analysis for FSDS-DAO Q13 was reasonably robust.

As treatment discontinuation rates were much higher in the BMT treatment groups compared to placebo, additional exploratory analyses were performed to determine if a higher percentage of patients were experiencing an increase in desire and decrease in distress at the end of the double-blind treatment period in the BMT treatment groups. A total of 39.5% and 38.7% of MITT patients in the BMT group and 13.3% and 24.5% of MITT patients in the Placebo group did not complete the double-blind treatment period in Study BMT-301 and Study BMT-302, respectively. A composite responder definition was used where patients were only considered responders if they both completed the study and experienced an increase of 1.2 or greater for FSFI-D or a decrease of 1 or less in FSDS-DAO Q13. In this analysis, the absolute difference in the percentage of responders with BMT and the percentage of responders with placebo in Study BMT-301 was 6% for the FSFI-D (24% for BMT; 18% for placebo) and 6% for FSDS-DAO Q13 (37% for BMT; 31% for placebo). In Study BMT-302, the absolute difference in the percentage of responders with BMT and the percentage of responders with placebo was

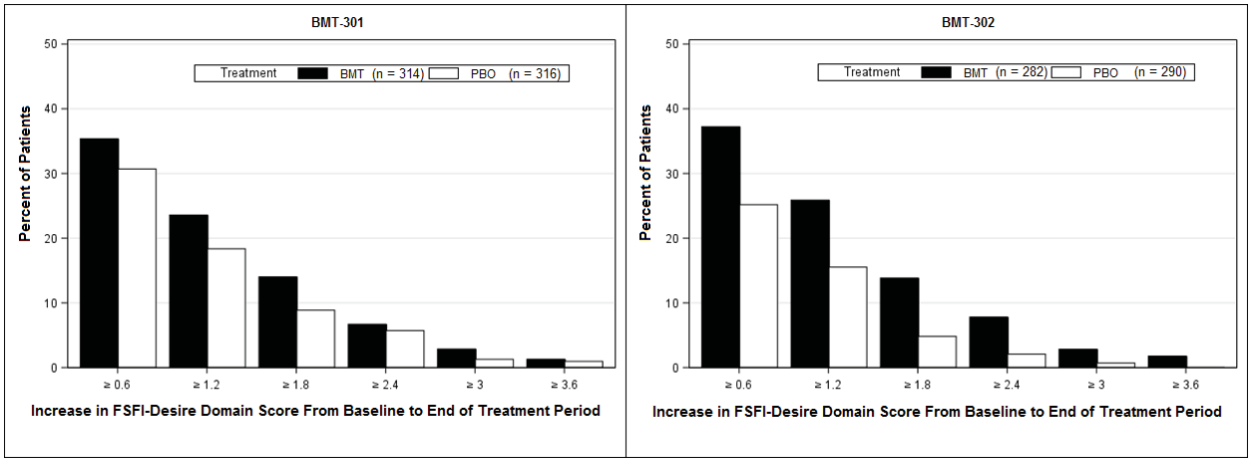
[47] The rationale and decision-making process of the Independent Anchor Assessment Committee are described in Appendix D of the pre-NDA meeting package under IND 64119.

10% for the FSFI-D (26% for BMT; 16% for placebo) and 1% for FSDS-DAO Q13 (33% for BMT; 32% for placebo).

Figure 19 displays the percent of the MITT patients in the two Phase 3 trials who completed the double-blind treatment period and achieved various levels of increase in the FSFI-Desire Domain Score from baseline (higher scores indicate increased sexual desire). The proportion of patients that completed the double-blind treatment period and experienced an increase in desire is slightly greater in the bremelanotide group for every cutoff value.

Patients who did not complete the double-blind treatment period or were missing baseline scores are not considered to have experienced an increase in FSFI-D score at the end of the double-blind treatment period.

Figure 19. Percent of Patients (MITT Population) Who Completed the Treatment Period and Achieved Various Levels of Increases in the FSFI-Desire Domain Score

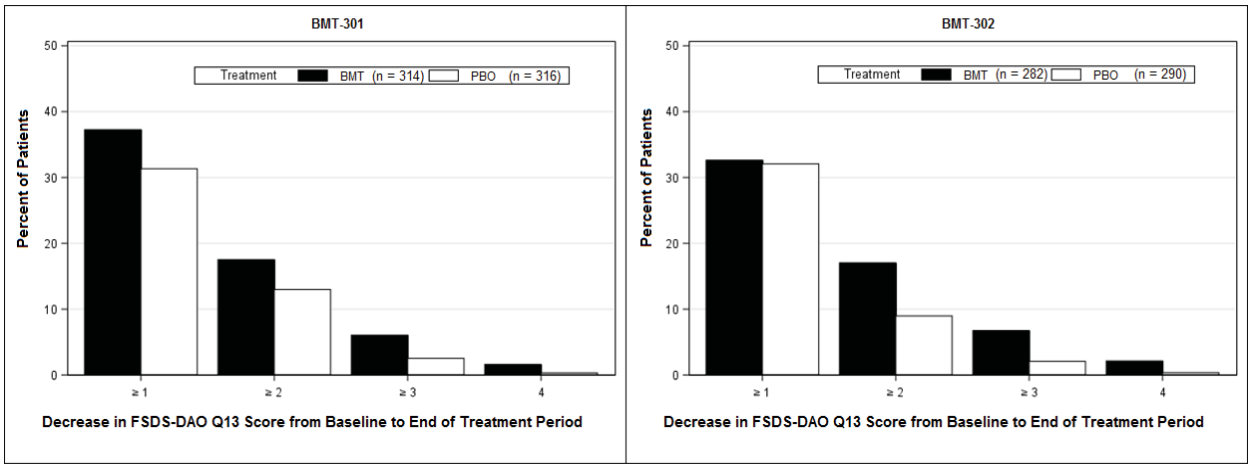


Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADEFF1.xpt and ADSLS.xpt.

Figure 20 displays the percent of the MITT patients in the two clinical trials who completed the treatment period and achieved various levels of decrease in the FSDS-DAO Q13 score from baseline (higher scores indicate greater reduction in distress). The proportion of patients that completed the double-blind treatment period and experienced a decrease in distress is slightly greater in the bremelanotide group for every cutoff value.

Patients who did not complete the double-blind treatment period or were missing change from baseline scores are not considered to have experienced a decrease in FSDS-DAO Q13 score at the end of the double-blind treatment period.

Figure 20. Percent of Patients (MITT Population) Who Completed the Treatment Period and Achieved Various Levels of Reductions in the FSDS-DAO Q13 Score



Abbreviations: BMT bremelanotide, PBO placebo
Source: Reviewer's analysis created from ADEFF1.xpt and ADSL.xpt

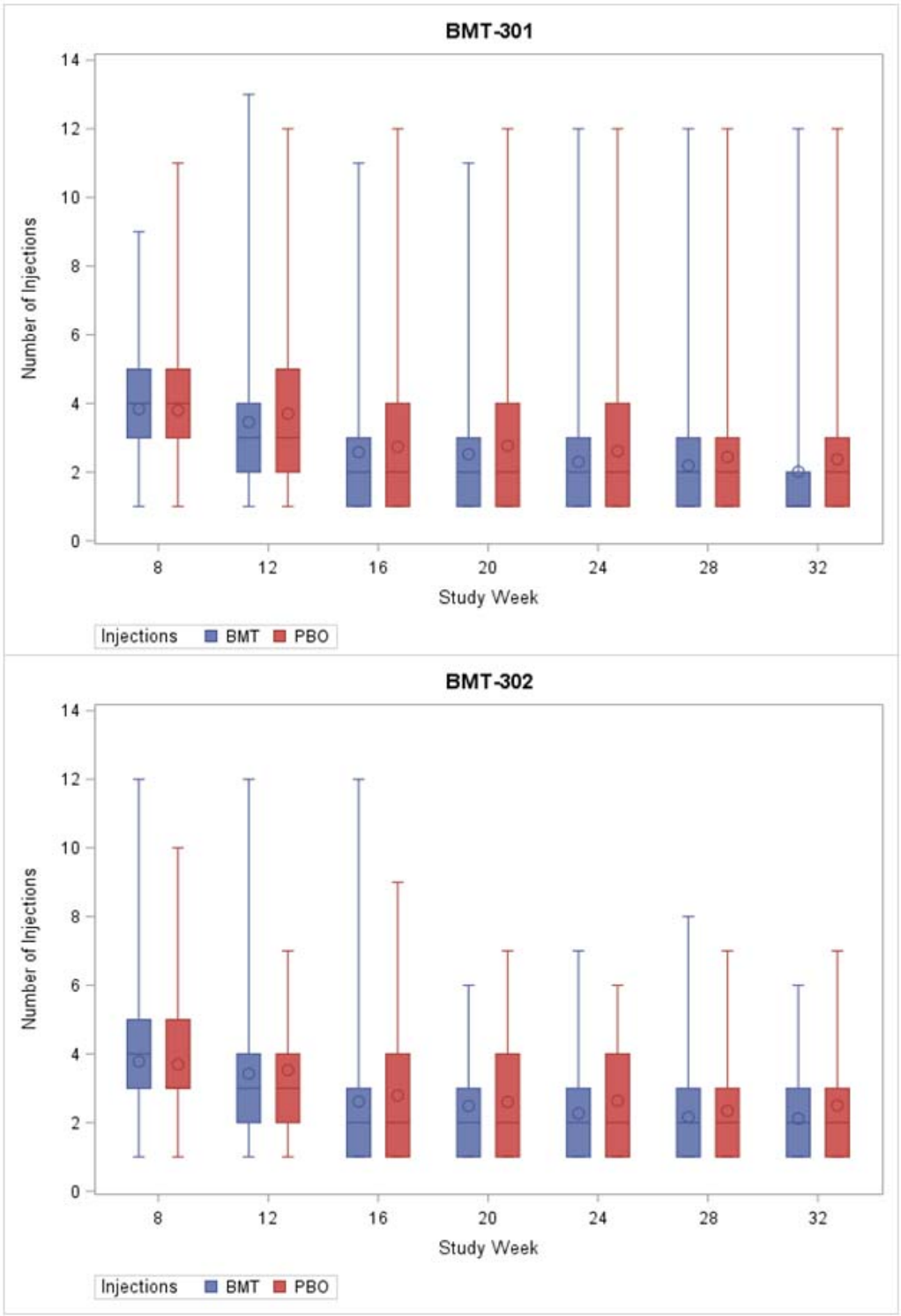
GAQ-Q3

Exploratory responder analyses based on the GAQ-Q3 provided further support to the coprimary endpoint findings.

Number of injections

Figure 21 displays boxplots for the distribution of the number of injections during the 4-week periods prior to each clinical visit during the single- and double-blind treatment periods. The number of injections at the listed week on the x-axis measures the total number of injections during both that week and the three weeks prior to that week (e.g., Week 8 measures the number of injections from Weeks 5 through 8). The bottom of the box represents the 25th percentile and the top of the box represents the 75th percentile for the number injections. The circle denotes the average number of injections and the line inside the box is the median number of injections. The line above the box marks the maximum value and any line below marks the minimum value. Subjects were given an injection at the clinic during the beginning of study Week 5 (beginning of the single-blind PBO run-in period) and the beginning of study Week 9 (end of the single-blind PBO run-in period), which are included in the number of injections for Weeks 8 and 12, respectively. On average, patients in the BMT group had fewer injections for every treatment period after the single-blind period; however, the number of injections did not differ by much between treatment groups. After Week 12, more than 75% of subjects in the BMT group had three or fewer injections and over 25% had only one injection. Subjects were instructed to take at least one injection every 4 weeks. The plot only includes the reported number of injections. Subjects who did not report any injections during a study month were not included in the number of injections for that time period, but only a small number of subjects did not report any injections during a study month while still enrolled in the study.

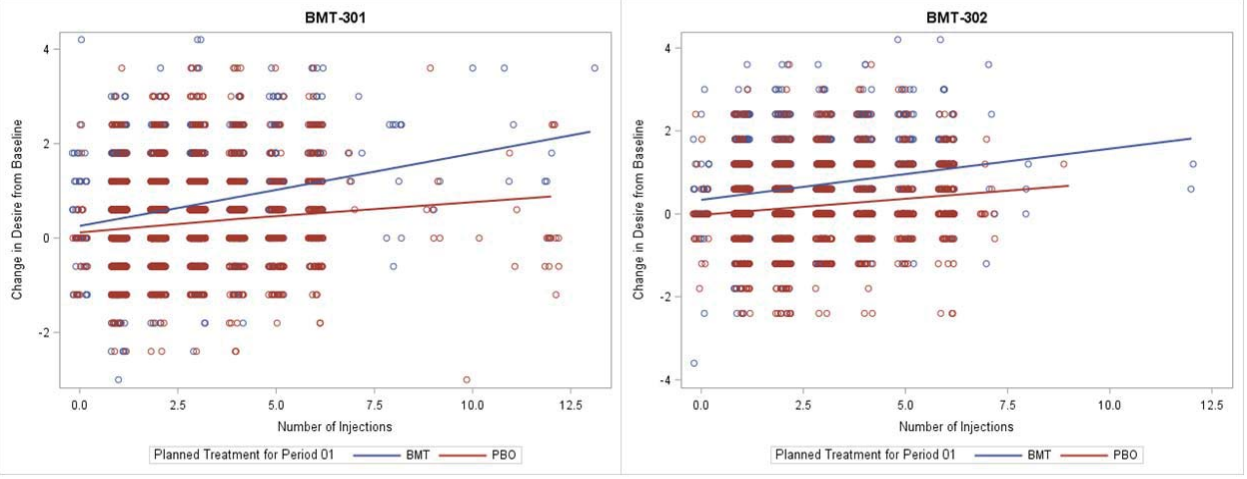
Figure 21. Distribution of the Number of Injections during Placebo Lead-In and Double-Blind Treatment Period:



Week 8 represents the end of single-blind placebo treatment; Week 32 represents end of 24-week double-blind period
Abbreviations: BMT bremelanotide, PBO placebo

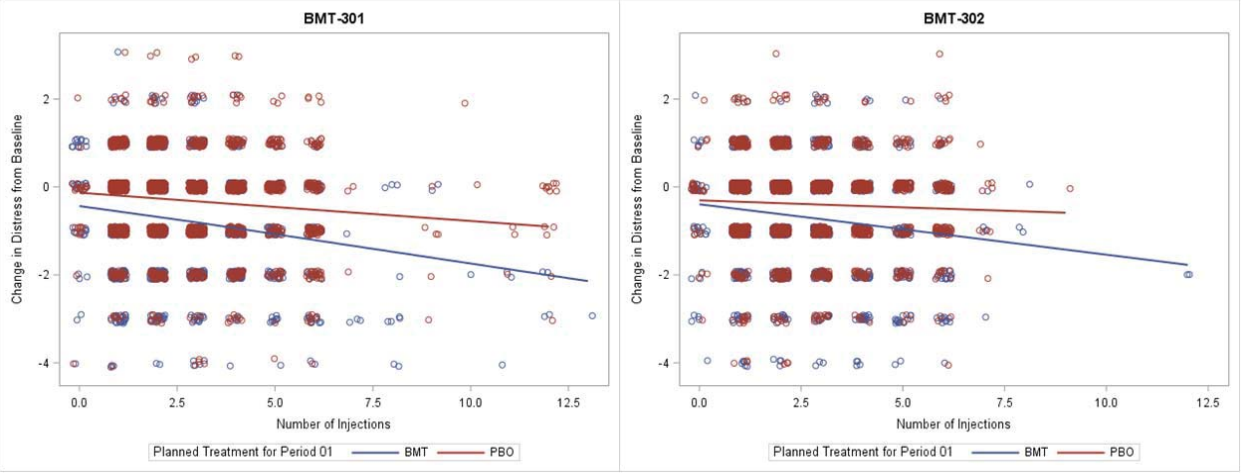
Analyses were conducted to determine if there was a relationship between the number of injections used and the change in desire and distress. Figure 22 and Figure 23 display scatter plots for the change from baseline in desire and distress, respectively, and the number of injections used during the reported recall period. Locally estimated smoothing is also displayed in the scatter plot. The curves show a trend that an increase in the number of injections is associated with an increase in desire and a decrease in distress. The relationship between the number of injections and the change in desire and distress is stronger in the BMT group than the PBO group, though the association in the BMT group appears weak. There is almost no relationship between the number of injections and the change in desire and distress for the PBO group. The stronger association between the number of injections and the change in desire and distress for the BMT group provide support for the drug being efficacious, although it appears the effects of the drug on desire and distress are modest.

Figure 22. Change in Desire From Baseline Compared to the Number of Injections Used in the 30 Days Prior to Study Visit During the Double-Blind Treatment Period



Abbreviations: Abbreviations: BMT bremelanotide, PBO placebo

Figure 23. Change in Distress From Baseline Compared to the Number of Injections Used in the 30 Days Prior to Study Visit During the Double-Blind Treatment Period



Abbreviations: BMT bremelanotide, PBO placebo

Comparison of EDQ Daily Diary Version With 4-Week Recall Version

Due to concerns that the 4-week recall period used for the primary endpoints might not accurately capture the effect of the drug, additional exploratory analyses were performed comparing the EDQ daily diary with the monthly version (4-week recall). Although the EDQ was not used as a primary endpoint, it contains multiple questions related to sexual desire. The exploratory analyses indicated that daily diary responses were moderately correlated with the monthly version and results were generally consistent between the two versions. However, there were several key limitations to these analyses, including the daily diary only covering 1-week out of the 4-week recall period covered by the monthly version and only being administered before four study visits.

8.1.3. Assessment of Efficacy Across Trials

The Applicant conducted two identical, adequate and well-controlled, phase 3, randomized, PBO-controlled clinical trials in premenopausal women with HSDD using two coprimary endpoints: sexual desire (FSFI-D) and distress (FSDS-Q13). Both trials were conducted in accordance with our recommendations during development and as outlined in the 2016 draft guidance on developing drugs to treat low sexual interest, desire, and/or arousal in women with respect to the enrolled population (U.S. and Canada only), trial duration and design, efficacy endpoints, method of data capture, and clinical outcome assessment instruments.

Efficacy results were consistent across both trials, providing confirmatory evidence. There was a statistically significant but modest median increase in desire and decrease in distress for BMT compared to PBO in both trials. Although these median increases were numerically small, responder analyses showed that a greater proportion of BMT-treated women reported improvement in their desire and distress than PBO-treated women. Most sensitivity analyses

also favored BMT. Both trials failed to demonstrate a significant effect for BMT on the number of SSEs, but, as noted previously, improvement in SSEs is not a requirement for approval for drugs intended to treat HSDD.

8.1.4. Integrated Assessment of Effectiveness

We conclude that the evidentiary standard for establishing effectiveness has been met. The efficacy data submitted in this application consistently demonstrate in two adequate and well-controlled trials in premenopausal women with acquired, generalized HSDD, that treatment with BMT 1.75 mg subcutaneous injections, when taken on an as-needed basis, resulted in:

- Statistically significant increases in sexual desire, and
- Statistically significant reductions in distress ("feeling bothered") associated with low sexual desire.

In Studies 301 and 302, women treated with BMT had a median increase from baseline to EOS in the sexual desire score, as measured by the FSFI-D score, of 0.6 compared to a median increase of 0 for women who took PBO. Women treated with BMT also had a median decrease from baseline to EOS in the distress score of 1 compared to a median decrease of 0 for women who took PBO. In both phase 3 trials, for both sexual desire and distress, the difference between the BMT group and PBO were statistically persuasive.

To evaluate potential clinical meaningfulness, anchor-based exploratory responder analyses were conducted for sexual desire and distress. The proportions of responders were higher in BMT-treated women than PBO-treated women for both sexual desire and distress. In Study 301, 24% of BMT-treated subjects reported meaningful improvement in the FSFI-D score compared to 18% of PBO-treated patients. In Study 302, 26% of BMT-treated subjects reported meaningful improvement in the FSFI-D score compared to 16% of PBO-treated subjects. For sexual distress measured using the FSDS-DAO Question 13, 37% of BMT-treated subjects reported meaningful improvement in Study 301 compared to 31% of PBO-treated subjects. In Study 302, 33% of BMT-treated subjects reported meaningful improvement in sexual distress compared to 32% of those given PBO. Although the median difference between treatment arms was small for both coprimary endpoints, some women have improved response to treatment.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review targeted premenopausal women with HSDD and was conducted using the Applicant's Integrated Summary of Safety as a guide. The Applicant included a total of 23 studies in the ISS; however, safety from the two phase 3 trials, including extension periods, and

one phase 2 study in HSDD was the primary focus. Many of the other studies were single dose or included women with non-HSDD diagnoses. Additional studies included only male subjects (n=20) and were not included. Pertinent datasets were queried to assess consistency with the values reported by the Applicant. During drug development, several issues required particular attention:

- Elevations in blood pressure and decreases in pulse were seen during ambulatory BP assessment in the phase 2 study (Study 54) following a single BMT dose. The effect peaked within the first 4 hours and was in the magnitude of mean maximum increases of 3.1 mm Hg and 3.2 mm Hg, for SBP and DBP, respectively, and a mean maximum decrease in HR of 6.6 bpm (PBO-subtracted) (b) (4) (b) (4) (b) (4) Other MCR-4 agonists have had nonclinical signals of elevations in BP. Published data for a non-U.S. study for another MCR-4 agonist showed increased BP effects in humans.[48] A premarket dedicated ABPM was required and was conducted during the review cycle, prompting a major amendment that extended the review by 3 months.
- Proposed labeling recommending subjects not administer more than one dose within 24 hours by default allows daily dosing. As the average usage was two to three doses per month, and not more than one dose per week, there are limited data to support daily dosing.
- A total of 16.8% of subjects in the phase 3, misused the study medication by taking more than one dose in a 24-hour period and as close together as 5 minutes apart. While the number of AEs did not appear to increase with early dosing, the effect on BP was not captured and remains unknown.
- BMT stimulates MCR-1 and caused hyperpigmentation/skin discoloration in 13 (1%) BMT-treated subjects compared to 0 events in PBO. The effects were more common in black individuals (4.1%) compared to white individuals (0.6%) in the double-blind phase. Half of all subjects affected did not report resolution.
- A single case of hepatoxicity, initially thought to be consistent with Hy's law case, was reported in a subject in the phase 3 extension (Study 301E) after receiving 20 doses of BMT. The peak effect of the liver function test abnormalities was not captured due to delayed presentation by the patient; however, an extensive evaluation by the Applicant did not identify a cause for the incident. There was no rechallenge. Internal and external hepatology experts deemed the event "possibly" related to the study drug.

[48] Greenfield J, Miller J, Keogh J, Henning E, Satterwhite J, Cameron G. et al. Modulation of Blood pressures by central melanocortinergic pathways. New England Journal of Medicine. 2009; 360:44-52.

8.2.2. Review of the Safety Database

Overall Exposure

Overall exposure and duration of exposure to BMT 1.75 mg SC are shown in Table 31 and Table 32 below. Calculation of the exposure using the Applicant's tabulation in the response to Filing Issues Identified letter (dated 3Aug2018) was difficult due to the inclusion of populations other than the targeted population (such as men), different doses, and different routes of administration. In the response to Information Request (dated 14Aug2018), the Applicant submitted the following numbers with supporting tables:

- Number of women exposed for at least 6 months=639 (ICH E1 goal, 300 to 600)
- Number of women exposed for at least 12 months=366 (ICH E1 goal, 100)
- Total number of female patients who received BMT doses≥1.75 mg SC = 1155
- Total number of female subjects who received BMT dose≥1.75 mg SC=1641 (ICH E1 goal, 1,500)

The ICH E1 guideline states that the "total number of *individuals* treated with the investigational drug, including short-term exposure, will be about 1,500." Based on this, and the belief that HSDD patients are similar to healthy subjects, the 1,641 total number is relevant, and the Applicant has achieved sufficient exposure numbers.

Table 31. Enumeration of Subjects for BMT SC 1.75 mg Development Program

	Treatment Group	
Clinical Trial Groups	**BMT 1.75 mg SC**	**PBO**
Completed phase 1 (clinical pharmacology)		
Single dose	919	117
Multiple dose	30	28
Phase 1 subtotal	949	145
Completed phase 2–3 (clinical trials for proposed indication)		
PBO-control,[3] fixed dose		
BMT-301	324	319
BMT-302	303	301
PT-141-54 (1.75 mg SC)	98	97
Uncontrolled, long-term		
301-Extension	363[1]	—
302-Extension	321[2]	—
Phase 2–3 subtotals		
Single-dose subtotal	919	117
Multiple-dose subtotal	1185[3]	745
Grand total	2104	862

[1] 124 on BMT in core + 239 previously on PBO in core
[2] 130 on BMT in core +191 previously on PBO in core
[3] Subtract out 254 subjects to account for those in core and extension to get unique number of subjects
Abbreviations: BMT bremelanotide, SC subcutaneous, PBO placebo

Table 32. Duration of Exposure—BMT 1.75 mg SC

	Core Studies		Core/EXT Studies Combined	All BMT 1.75 mg SC in Phase 2/3 Trials Core/EXT/Study 54
Variable	PBO (N=620) n (%)	BMT 1.75 mg (N=627) n (%)	BMT 1.75 mg (N=1057) n (%)	BMT 1.75 mg (N=1155) n (%)
Any exposure	620 (100)	627 (100)	1057 (100)	1155 (100)
≥1 Month	614 (99.0)	611 (97.4)	1025 (97.0)	1107 (95.8)
≥2 Months	602 (97.1)	561 (89.5)	932 (88.2)	1011 (87.5)
≥3 Months	575 (92.7)	503 (80.2)	840 (79.5)	914 (79.1)
≥4 Months	547 (88.2)	456 (72.7)	765 (72.4)	777 (67.3)
≥5 Months	526 (84.8)	410 (65.4)	700 (66.2)	702 (60.8)
≥6 Months	462 (74.5)	346 (55.2)	639 (60.5)	639 (55.3)
≥12 Months	—	—	366 (34.6)	366 (31.7)
≥16 Months	—	—	137 (13.0)	NC
≥18 Months	—	—	NC	119 (10.3)

Abbreviations: BMT bremelanotide, SC subcutaneous, NC not complete, EXT extension, PBO placebo
Source: Summary of Clinical Safety, Table 6, page 25

Relevant Characteristics of Safety Population

The safety population was predominantly enrolled from the United States and is generalizable relative to age and the menopausal status. The racial demographics reflect the general U.S. population among white and black subjects. The safety population was defined as all subjects who were randomized and received at least one dose of the double-blind study medication (in clinic or as outpatients). Analyses were performed by the actual treatment received. The demographic data are similar to the MITT efficacy population, defined as all subjects in the safety population who had at least one double-blind follow-up visit. Tabular of the safety population in the context of MITT population are shown in Table 33 below.

Table 33. Phase 3 Safety Populations: Core and Extension Studies

Population	BMT-301			BMT-302			Total BMT-301/BMT-302
	BMT N	PBO N	Total N	BMT N	PBO N	Total N	
Safety	324	319	643	303	301	604	1247

Population	Study BMT-301E			Study BMT-302E			Total BMT-301E/BMT-302E
	BMT N	Prev. on PBO N	Total N	BMT N	Prev. on PBO N	Total N	
Safety	124	239	363	130	191	321	684

Abbreviations: BMT bremelanotide, PBO placebo, prev. previously
Source: Confirmed with Applicant's datasets

Adequacy of Safety Database

The safety database is adequate. There were three PBO-controlled studies in premenopausal women with HSDD with or without FSAD. There were two main pooling strategies. The main pooling group (A1A) was limited to the two phase 3 core studies and open label extension

phases for HSDD/FSAD who received BMT 1.75 mg SC. Pooling (A1) included all phase 2/3 double-blind and open label extensions for HSDD with or without FSAD who received BMT 1.75 mg SC. In the core periods, there were 620 subjects who received PBO and 627 subjects who received BMT. Of these subjects, 254 subjects who received BMT during the core period and 430 subjects who received PBO during the core period continued into the open-label extension (OLE) period, totaling of 684 subjects. Subjects who received BMT in both the core and extension phases (n=254) were only counted once, resulting in 1,057 unique subjects (627 in core, plus 684 in OLE, minus 254) who received BMT in both phases.

Study design for the phase 2 study (Study 54) was somewhat similar to the phase 3 studies and included a single-blind 4-week PBO run in period, followed by double-blind period that lasted 12 weeks in contrast to the 24-week period studied in phase 3. Study 54 was a dose-finding study and included other BMT doses (0.75, 1.25 mg SC) in addition to the 1.75 mg SC dose group that included 98 subjects. The 12-month extension studies provided safety data up to a total of 18 months of exposure.

The Applicant included other safety poolings, including Group C that included all 23 studies.

The review strategy assessed the combined phase 3 data and the individual studies to determine if there were differences. Data from two additional phase 3 studies in both pre and postmenopausal women with FSAD were considered supportive safety studies (PT-141-2004-52FB and PT-141-2004-53FB) as they used different doses (BMT 10 and 20 mg) and a different formulation and route of administration (intranasal).

See Other Baseline Characteristics subsection in Section 8.1.2 for discussion regarding disease characteristics and generalizability to the U.S. target population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no major quality or integrity concerns discovered during the review. Several Information Requests were issued to clarify clinical issues regarding blood pressure assessment/effects, total BMT exposure, frequency of drug use, misuse, etc. as well as other discipline-related questions. The Applicant was able to address these requests in a timely fashion.

Inspection was conducted of four clinical sites and the Applicant's location. A protocol violation was reported where staff without clinical degrees were approved by the clinical research associate to conduct HSDD assessments at one of the sites. However, this violation was on the part of the clinical investigator (CI) not the Applicant. The CI was ultimately responsible to ensure that the protocol was followed at the site as well as that all site staff were adequately

trained on the protocol and qualified by background/training to performed delegated tasks. In terms of data reliability, it is reassuring that the CI reviewed all HSDD assessments made by the psychometricians and approved the final diagnosis.

No other inconsistencies were reported. Additional information was received from the Office of Scientific Investigations regarding the delayed reporting of the hepatic injury case to the FDA (Study 301-extension). In review of the Establishment Inspection Report, it was determined that the AE was recognized and handled in a timely manner at the study site, with numerous follow up visits and laboratory analyses as well as a hepatology consult. Discussions between the CI and the medical monitor regarding this AE were documented, as were communications between the CI and the consulting hepatologist.

Categorization of Adverse Events

The definitions of serious adverse events (SAEs) were acceptable and consistent with CFR 312.32. TEAEs were identified as events with an onset date on or after the date of the first dose of double-blind study drug and is acceptable. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 for phase 3 and extension studies, and MedDRA version 14 for phase 2 Study PT-141-54. For the ISS, the Applicant has confirmed (response to 1Nov2018 Information Request) that all nonphase 3 studies in the ISS, including Study PT-141-54, were recoded using MedDRA 18.1. AEs were classified using standard terminology (i.e., primary system organ class (SOC) and preferred term) from the verbatim description (investigator term) according to MedDRA 18.1. AE assessments were performed at each scheduled visit (see Table 18 in Section 8.1.1.) and on planned between-visit telephone calls (conducted 10 days after previous visit). We requested a script of the telephone call to ensure the call did not influence data capture and, in turn, bias trial outcome. The script could not be located in the NDA submission. The Applicant provided the telephone script on 22Feb2019, in response to an Information Request. No bias was noted upon review.

Subjects who were discontinued due to AEs were to be monitored for 4 weeks after the final visit, until resolution of the AE, or until the AE became medically stable in the investigator's opinion. Subjects who were discontinued due to an SAE were to be monitored until resolution of the SAE, or until the SAE became medically stable in the investigator's opinion. It does not appear that all AEs were followed until resolution initially. In the second amendment the Applicant continued BP assessment of subjects with elevated readings until the BP returned to an acceptable level.

Reported injection-site reactions were coded across various MedDRA preferred terms, such as pain, erythema and pruritis and were not initially grouped together in the analyses. The occurrence of all injection-site reactions combined (pain, reaction, erythema, hematoma, pruritus, hemorrhage, bruising, paresthesias) elevated the AE rate to 13.2% with BMT versus 8.4% with PBO. As a result, injection-site reactions were added to the most common AEs.

Allergic type reactions were split between rash, hypersensitivity, and urticaria. When grouped together, the difference between groups was small, 12 subjects (1.9%) receiving BMT versus eight subjects (1.3%) receiving PBO. Anaphylaxis was not reported.

The severity categorization was adequate and included:

- Mild: An event that was easily tolerated by the subject, caused minimal discomfort, and did not interfere with everyday activities.
- Moderate: An event that was sufficiently discomforting to interfere with normal everyday activities, and
- Severe: An event that prevented normal everyday activities.

AEs were reported as subject incidence with the AE of interest. The Applicant did not identify any specific AEs of special interest but highlighted hepatic events and pregnancy events.

Routine Clinical Tests

Laboratory assessments in the phase 3 trials included serum chemistry, hematology, and urinalysis conducted at Week 1 (screening), Week 9 (randomization), Week 13 (4 weeks after randomization), and Week 32 (24 weeks after randomization (end of study/early termination)) and was adequate. See Table 18 in Section 8.1.1.

Laboratory testing including chemistry, hematology, hormones (ACTH, sex hormone binding globulin, α-MSH, prolactin, cortisol, oxytocin, FSH, estradiol), HIV, biomarkers (not further specified for possible future testing), urinalysis, serum pregnancy, and urine screen for drugs/alcohol were sent to a centralized facility. Urine pregnancy testing was conducted at a local lab. It is unclear if the chemistry was performed in the fasting state. The Applicant stated that fasting was not required per protocol. The Applicant's convention was to use the first value if the laboratory test was measured twice within a given postdose visit month interval.

Vital signs were assessed up to 1-hour predose and at 1.0, 1.5, and 2.0 hours postdose following the two in-clinic single dosing at Week 5 (single-blind PBO) and Week 9 (randomization). Orthostatic blood pressures were not obtained. Out of range results were categorized as either clinically significant or not clinically significant. Amendment 1 stated that continued BP assessment of subjects with elevated readings should occur until the BP returned to an acceptable level (5Jan2015).

Overall, the safety assessment methods and time points appeared reasonable for this population; however, blood pressures obtained at the routine clinic visits occurred at a distance in time from the actual drug/PBO intake which did not allow for useful capture of blood pressure data.

8.2.4. Safety Results

Deaths

There was one death in the global clinical program, a 42-year-old male receiving PBO in the Thorough QT study who was struck and killed by a motor vehicle while jogging. This event was considered unrelated to the study drug.

Serious Adverse Events

There was a limited number of treatment-emergent SAEs occurring in 11 subjects in the clinical program and the events occurred twofold higher in the BMT group compared to PBO in the two core studies (1.1% versus 0.5%, respectively). All events occurred once. The greatest number of events occurred in the gastrointestinal disorders SOC, although the incidence was low (four BMT subjects versus one PBO subject). The Applicant's numbers were confirmed for the phase 3 core, extension and phase 2/3 databases using AE tabulation (ae.xpt). Summaries of the submitted narratives are listed in Table 34 below.

Table 34. Serious Adverse Events by System Organ Class and Preferred Term in SC BMT Phase 2/3 Core and Extension Studies in HSDD/FSAD, Safety Population, Analysis Groups A1 and A1A

	Core Studies		EXT Studies	Core/EXT Studies Combined	Phase 2/3 SC Studies (Analysis Group A1)
System Organ Class Preferred Term	PBO (N=620) n (%)	BMT 1.75 mg (N=627) n (%)	BMT 1.75 mg (N=684) n (%)	BMT 1.75 mg (N=1057) n (%)	BMT 1.75 mg (N=1155) n (%)
Any SAE	3 (0.5)	7 (1.1)	3 (0.4)	10 (0.9)	11 (1.0)
Gastrointestinal disorders	1 (0.2)	4 (0.6)	0	4 (0.4)	4 (0.3)
Abdominal hernia obstructive	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Abdominal pain	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Gastrointestinal inflammation	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Peritoneal hemorrhage	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Vomiting	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Colitis	1 (0.2)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	2 (0.3)	0	2 (0.2)	2 (0.2)
Invasive ductal breast carcinoma	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Uterine leiomyoma	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Colon cancer	1 (0.2)	0	0	0	0
Nervous system disorders	0	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Cerebrovascular accident	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Headache	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Reproductive system and breast disorders	0	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Endometriosis	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)

System Organ Class Preferred Term	Core Studies PBO (N=620) n (%)	Core Studies BMT 1.75 mg (N=627) n (%)	EXT Studies BMT 1.75 mg (N=684) n (%)	Core/EXT Studies Combined BMT 1.75 mg (N=1057) n (%)	Phase 2/3 SC Studies (Analysis Group A1) BMT 1.75 mg (N=1155) n (%)
Ovarian cyst ruptured	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	0	0	0	0	1 (<0.1)
Chest pain	0	0	0	0	1 (<0.1)
Hepatobiliary disorders	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Cholecystitis	0	0	1 (0.1)	1 (<0.1)	1 (<0.1)
Infections and infestations	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Pneumonia	0	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Blood and lymphatic system disorders	1 (0.2)	0	0	0	0
Anemia	1 (0.2)	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0	0	0	0
Pregnancy	1 (0.2)	0	0	0	0

Abbreviations: BMT bremelanotide, PBO placebo, HSDD hypoactive sexual desire disorder, FSAD female sexual arousal disorder, SAE serious adverse events, SC subcutaneous, EXT extension
Source: Table 14 SCS, page 40

Selected Narratives on Subjects with Exposure to BMT

The distribution of events across studies is shown in Table 35 below. Although there was a twofold increase in events in the BMT group, no trends were seen in the nature of the events. Only headache and vomiting appeared related to study drug administration.

Table 35. Treatment-Emergent Adverse Events by Study and Treatment Group

BMT-301		BMT-302		BMT-301E/302E	Phase 2 Study 54
PBO 1 event/ 1 subject	BMT 6 events/ 4 subjects	PBO 3 events/ 2 subjects	BMT 4 events/ 3 subjects	BMT 3 events/ 3 subjects	BMT 1.75 1 event/ 1 subject
Colitis	Abdominal hernia obstructive	Pregnancy	Pneumonia	Cholecystitis	Chest pain
	Ovarian cyst ruptured/ peritoneal hemorrhage	Anemia/ colon cancer	Abdominal pain/ gastrointestinal inflammation	Endometriosis	
	Invasive ductal breast carcinoma		Uterine leiomyoma	Cerebrovascular accident	
	Headache/ vomiting				

Abbreviations: PBO placebo, BMT bremelanotide
Source: adae.xpt

Ovarian cyst ruptured/peritoneal hemorrhage (b) (6)

A 35-year-old white female randomized to BMT 1.75 mg in the core phase and used eight total doses between (b) (6) Three days after her most recent study drug she experienced ruptured ovarian cyst and peritoneal hemorrhage. On (b) (6) she had pelvic pain, nausea and vomiting. On the following day, she self-administered her eighth and final dose. On (b) (6) she saw her gynecologist for the same complaints. An ultrasound showed a 6 cm left adnexal mass with hemoperitoneum and she underwent laparoscopy with cauterization of a corpus luteum cyst, lysis of adhesion and evacuation of hemoperitoneum. She was discharged on (b) (6) with the event "resolved." She did not take any additional doses and was withdrawn from the trial on (b) (6) It is unlikely this event is related to study drug.

Invasive ductal breast carcinoma (b) (6)

A 48-year-old white female with history of breast implants 5 years prior, who was randomized to BMT 1.75 mg SC in the core phase and received 6 doses over 6 weeks. After finding a breast lump (1 month after study onset), she underwent biopsy of the 10 mm mass that was adjacent to a breast implant and was subsequently diagnosed with invasive ductal carcinoma of the left breast (estrogen and progesterone receptor positive). She had a mastectomy with no evidence of lymph node involvement. The event was reported as severe and occurred 10 days after her most recent study drug administration. Subject was withdrawn. This is event was not related to study drug.

Headache/vomiting (b) (6) *(also discussed in Section 8.2.6)*

A 35-year-old white/Hispanic female with history of headaches randomized to BMT 1.75 mg in a core study and received two BMT doses 3 weeks apart. Immediately following her second dose, she experienced severe, intractable headache as well as nausea, vomiting, flushing, dizziness, and abdominal pain. It was noted that she had tachycardia, elevated diastolic blood pressure, and presented to an urgent care facility where she was treated symptomatically. After the symptoms had not abated and the outpatient facility was closing, she was admitted to the hospital. Laboratory tests were normal, including D-dimer. Her diastolic blood pressure on the day of event (b) (6) was not provided, but it had been 79 mm Hg at screening. On (b) (6) her diastolic blood pressure was 79 mm Hg. She was treated symptomatically and was discharged the following day with a residual headache. She was withdrawn from the study. This event was attributed to study drug.

Abdominal hernia obstructive (b) (6)

A 36-year-old white female with history of multiple surgeries (C-section X2, cholecystectomy, oophorectomy, gastric banding and gastrectomy) randomized to BMT on (b) (6) and received 11 doses through (b) (6) On (b) (6), 23 days after randomization (and after three BMT doses) who presented to the emergency room with severe umbilical pain and

vomiting. Computed tomography (CT) scan showed strangulated ventral hernia with bowel obstruction. She was referred to a surgeon and underwent laparoscopic ventral hernia repair with mesh on (b) (6) Fourteen days after her last dose she was diagnosed with obstructive abdominal hernia. Liver enzymes were elevated, with AST 130 U/L, ALT 200 U/L and alkaline phosphatase of 365 U/L. An ultrasound showed choledocholithiasis but no complications. The hernia event was considered resolved on (b) (6) and the LFT elevation resolved on (b) (6) She continued in the study. It seems unlikely that this is drug related.

Abdominal pain/gastrointestinal inflammation (b) (6)

A 47-year-old white female with history of celiac disease, obesity, cholecystectomy, cholelithiasis, gastric bypass, adenomyosis, hysterectomy/unilateral salpingo-oophorectomy randomized to BMT on (b) (6) and used 18 doses through (b) (6) On (b) (6) (15 days after most recent drug administration) she was admitted to the hospital for epigastric pain. CT scan of abdomen showed marked circumferential mucosal thickening/edema of jejunum in left upper quadrant, and dilated loops of small bowels likely consistent with ileus. She underwent laparoscopy that showed proximal jejunum inflammation. Labs showed elevated neutrophils. Following an esophagogastroduodenoscopy on (b) (6) showing normal jejunum, she was discharged on probiotics (b) (6) The subject completed the core study. The cause of the jejunal inflammation is unclear.

Chest pain (b) (6)

A 41-year-old black female with FSAD and HSDD with history of noncardiac chest pain (since 2010), anxiety, and obesity who was randomized to BMT 1.75 mg SC on (b) (6) and received her take home kit on (b) (6) She took a dose of BMT at 11:00 a.m. on (b) (6) At 2:30 a.m. on (b) (6) she was admitted to the hospital with a provisional diagnosis of anxiety related chest pain. She missed her (b) (6) clinic visit and was lost to follow up. It is unknown how many doses of the eight-syringe kit were administered because she did not return the kit. There were two additional SAEs in Study 54 in the 0.75 mg (asthma) and 1.25 mg (incisional hernia) groups.

Dropouts and/or Discontinuations Due to Adverse Effects

The rates of discontinuations leading to withdrawal across the clinical program are shown in Table 36. In the pooled double-blind period (core) from the two phase 3 trials, there were more discontinuations in the BMT group compared to PBO (17.5% versus 2.3%). The rate of discontinuation due to AEs in the BMT group was slightly higher in Study 301 (18.3% versus 0.9%) compared to Study 302 (16.5% versus 3.3%). Table 37 shows the frequency of AEs leading to discontinuation. Nausea, headache, vomiting, flushing, injection-site reaction, and fatigue were the most common events in the BMT group leading to discontinuation with very few events in the PBO group. The incidence of these AEs leading to discontinuation increased in the extension period.

Table 36. Summary of Adverse Events and AEs Leading to Withdrawal, Safety Population

	Core Studies		EXT Studies	Core/EXT Studies Combined	Group A1 Phase 2/3 SC	Group C Phase 1–3 SC/IN/IV
AE category	PBO (N=620) N (%)	BMT 1.75mg (N=627) N (%)	BMT 1.75mg (N=684) N (%)	BMT 1.75mg (N=1057) N (%)	BMT 1.75mg (N=1155) N (%)	BMT (N 1941) N (%)
Any AE	361 (58.2)	480 (76.6)	534 (78.1)	867 (82.0)	937 (81.1)	1495 (77.0)
Any SAE	3 (0.5)	7 (1.1)	3 (0.4)	10 (0.9)	11 (1.0)	15 (0.8)
AE leading to withdrawal	14 (2.3)	110 (17.5)	139 (20.3)	249 (23.6)	259 (22.4)	323 (16.6)
Any severe AE	18 (2.9)	34 (5.4)	44 (6.4)	75 (7.1)	80 (6.9)	134 (6.9)

Abbreviations: AE adverse event, BMT bremelanotide, PBO placebo, EXT extension, IN intranasal, IV intravenous, SAE serious adverse event, SC subcutaneous
Source: SCS Table 8, page 29

Table 37. Adverse Events Leading to Discontinuation, Occurring at Least Once

	Core Studies		EXT Studies	Core/EXT Studies Combined	Phase 2/3 SC Studies[1]
Preferred Term	PBO (N=620) n (%)	BMT 1.75 mg (N=627) n (%)	BMT 1.75 mg (N=684) n (%)	BMT 1.75 mg (N=1057) n (%)	BMT 1.75 mg (N 1155) n (%)
Any AE leading to study drug discontinuation	14 (2.3)	110 (17.5)	139 (20.3)	249 (23.6)	259 (22.4)
Nausea	0	51 (8.1)	75 (11.0)	126 (11.9)	129 (11.2)
Headache	0	11 (1.8)	14 (2.0)	25 (2.4)	26 (2.3)
Vomiting	0	7 (1.1)	6 (0.9)	13 (1.2)	16 (1.4)
Flushing	0	6 (1.0)	15 (2.2)	21 (2.0)	22 (1.9)
Injection-site reaction	0	5 (0.8)	2 (0.3)	7 (0.7)	7 (0.6)
Fatigue	0	4 (0.6)	5 (0.7)	9 (0.9)	9 (0.8)
Pain	0	3 (0.5)	1 (0.1)	4 (0.4)	4 (0.3)
Influenza-like illness	0	3 (0.5)	0	3 (0.3)	3 (0.3)
Dyspepsia	0	3 (0.5)	0	3 (0.3)	3 (0.3)
Myalgia	0	3 (0.5)	2 (0.3)	5 (0.5)	5 (0.4)
Paresthesia	0	3 (0.5)	0	3 (0.3)	3 (0.3)
Restless legs syndrome	0	3 (0.5)	0	3 (0.3)	3 (0.3)
Insomnia	1 (0.2)	3 (0.5)	0	3 (0.3)	3 (0.3)
Dizziness	0	2 (0.3)	0	2 (0.2)	2 (0.2)
Back pain	0	2 (0.3)	0	2 (0.2)	2 (0.2)
Pain in extremity	0	2 (0.3)	0	2 (0.2)	2 (0.2)
Nasal congestion	0	2 (0.3)	1 (0.1)	3 (0.3)	3 (0.3)
Injection-site pain	0	2 (0.3)	1 (0.1)	3 (0.3)	4 (0.3)
Abdominal pain	0	2 (0.3)	2 (0.3)	4 (0.4)	4 (0.3)
Hypertension	1 (0.2)	2 (0.3)	1 (0.1)	3 (0.3)	4 (0.3)
Hot flush	0	2 (0.3)	0	2 (0.2)	2 (0.2)
Skin hyperpigmentation	0	2 (0.3)	1 (0.1)	3 (0.3)	3 (0.3)
Urticaria	0	2 (0.3)	0	2 (0.2)	2 (0.2)

Abbreviation: BMT bremelanotide, PBO placebo, EXT extension, AE adverse event
[1] Analysis Group A1
Source: adapted from ISS, Table 24, page 72

The table below shows the specific AEs leading to discontinuation separately for Study 301 and 302. For Study 301, nausea led to the most discontinuations (9% with BMT vs. 0% with PBO) followed by flushing (3% with BMT vs. 0% with PBO). Elevated blood pressure led to three discontinuations including one event of "hypertensive urgency" (although there was not adequate documentation of this event, see Table 57.) For Study 302, nausea was the most prevalent reason for discontinuation (7% with BMT vs. 0% with PBO). There were two events of elevated BP with BMT and one event with PBO. In Study 302, more discontinuations due to injection-site reactions were seen; flushing was a less prominent reason for discontinuation.

Table 38. Subjects Who Discontinued Due to Adverse Events by AE Category

	Study 301		Study 302	
	BMT N=324	PBO N=319	BMT N=303	PBO N=301
AE Leading to Discontinuation[1]	**60**	**3**	**54**	**9**
Nausea	32 (10%)	0	20 (7%)	0
Flushing	6 (2%)	0	0 (0%)	0
Headache	7 (2%)	0	4 (1%)	0
Vomiting	5 (2%)	0	2 (1%)	0
Elevated blood pressure[2]	3 (1%)	0	2 (1%)	1 (0.3%)
Body/muscle aches/spasm	1 (1%)	0	0 (0%)	0
Flu-like symptoms	2 (1%)	0	1 (1%)	0
Injection-site reactions	2 (1)%	0	7 (2%)	0
Increased syncope	1 (0%)	0	0	0
Vasovagal	1 (0%)	0	0	0
Overstimulation due to increased desire	1 (0%)	0	0	0
Hyperpigmentation	1 (0%)	0	1 (0%)	0
Suicidal thoughts	1 (0%)	0	0	0
Anxiety	0	0	0	1 (0.3%)
Depressed mood/depression	0	0	0	2(1%)
Unknown	0	0	1 (0%)	1 (0.3%)

[1] Many subjects experienced more than one symptom leading to study discontinuation. The numbers for each AE category above represent the number of unique subjects for each event, but the subcategories may be more than the total number of subjects discontinued due to multiple AEs per subject.
[2] Includes an event each of hypertensive urgency (Study 301)
Abbreviations: AE adverse event, BMT bremelanotide, PBO placebo
Source: Reviewer compiled from adae.xpt datasets (Studies 301 and 302)

Events Leading to Discontinuation

The types of events leading to discontinuation are consistent with the AEs reported during the trials. Selected narratives and/or additional details are presented below.

Suicidal thoughts

Subject (b) (6), a 41-year-old white female who was randomized to BMT on (b) (6) and remained in the double-blind phase through (b) (6) reported an AE of thoughts of self-harm on Day 113 (Week 24). Per the investigator, the patient reported no thoughts of harming

herself “at this time,” but “over the past few weeks” had been having thoughts of self-harm. The investigator asked subject to return study drug and exit from study.

Hyperpigmentation

Two subjects discontinued due to focal hyperpigmentation. Subjects [redacted] a 37-year-old black female who was randomized to BMT on [redacted] and continued treatment through [redacted] She discontinued due to facial hyperpigmentation at Week 20 with subsequent resolution. Subject [redacted] a 30-year-old black female who was randomized to BMT on [redacted] and discontinued [redacted] due to skin hyperpigmentation (not otherwise specified). Resolution was not documented.

Allergic reactions

There were two allergic reactions (not further specified) that were associated with BMT use: Subject [redacted], a 47-year-old black female randomized to BMT on [redacted]. The adds.xpt dataset shows treatment end date also listed as [redacted], although [redacted] is listed as the AE/disposition date (corresponding to Week 4). Subject [redacted], a 43-year-old white female who was randomized to BMT on [redacted] and discontinued due to “allergic reaction that made her not want to dose with study drug anymore” on [redacted]

Elevated BP/hypertension/hypertensive urgency

Five subjects were discontinued due to blood pressure AEs [redacted]. These events are further discussed in section 8.2.6 Blood Pressure Elevation (see Table 57).

There appears to be an imbalance in injection-site reactions with greater numbers in Study 302. The Applicant split injection-site events into groups including: reactions, pain, erythema, etc. A detailed discussion of injection site reactions is provided in the Safety Section of this review (see Categorization of Adverse Events in Section 8.2.3 for detailed summary).

Nausea

Nausea was the most common AE leading to withdrawal. It led to withdrawal in 8% (n=51) of subjects in the BMT group in the core studies and 11% (n=75) in the OLE. In review of the narratives, withdrawal from the study due to nausea occurred anywhere from the first dose up to 11th dose; severe nausea occurred in two subjects [redacted]; however, nausea was reported as moderate in severity in the majority of subjects and generally resolved on the same day. Similar events were seen in the extension phase in those previously on PBO.

Headache

Headache led to withdrawal in 1.8% to 2.0% of subjects exposed to BMT. Headache occurred

within the first few (one to three) doses, was generally of mild to moderate intensity, and was sometimes associated with other symptoms such as nausea, flushing and/or vomiting. Few events had delayed onset beginning one day after the first or second drug treatment. There was one additional "head discomfort" not coded as headache by the Applicant and occurred in the extension phase in a subject previously randomized to PBO in the core (b) (6). She experienced moderate symptoms after her first dose which lasted 2 hours. There were three other subjects with severe headaches:

- (b) (6): A 35-year-old white female with history of "headaches" who was withdrawn following severe headache for 6 days associated with vomiting following her second dose. She was seen at urgent care and admitted to the hospital for intractable headache.
- (b) (6): A 43-year-old white female with no prior history, with severe headache 1 day after second dose lasting 24 hours.
- (b) (6): A 37-year-old white female with no prior history, with severe headache after third dose, which resolved the same day.

Vomiting

Vomiting led to withdrawal in approximately 1% of subjects exposed to BMT. Vomiting was associated with nausea, with the exception of two cases:

- (b) (6): A 35-year-old white female with headache and vomiting in the core phase following the second BMT dose (see headache section, above).
- (b) (6): A 35-year-old white female with moderate vomiting in the core phase following the sixth dose with resolution the same day.

The remaining AEs leading to discontinuation occurred at a rate of <1%. Additional AEs of interest follow.

Elevated blood pressure

The blood pressure criteria for withdrawal was BP >140/90 mm Hg; four subjects met the criteria:

- (b) (6): A 44-year-old black female without history of HTN with moderate "hypertension" 5 days after the last BMT dose (after eight total doses) in the core phase. The subject's BP on (b) (6) (screening) was 129/79 mm Hg. On (b) (6), her BP, taken a few minutes apart, was 136/92 mm Hg and 136/91 mm Hg. On (b) (6) (the last day BP values were reported), her BP, taken a few minutes apart, was 146/91 mm Hg, 142/91 mm Hg, and 145/88 mm Hg. Study drug was withdrawn.

- [redacted]: A 26-year-old black female with mild HTN 1 day after fourth BMT dose in the core phase. The event had not resolved at the time of reporting. The subject's BP, taken a few minutes apart on [redacted] (screening), was 126/91 mm Hg and 130/85 mm Hg. On [redacted], her BP, taken a few minutes apart, was 146/103 mm Hg and 136/91 mm Hg. On 2 [redacted] (early termination visit), her BP, taken a few minutes apart, was 140/93 mm Hg and 142/92 mm Hg.
- [redacted]: A 28-year-old white female with history of HTN with "hypertensive crisis/hypertensive urgency" in the core phase. The subject's BP on [redacted] (screening) was 125/86 mm Hg. Her BP on the date of the first "hypertensive crisis" of [redacted] was 133/80 mm Hg (predose) and 132/88 mm Hg at 1-hour postdose, 136/98 mm Hg at 1.5 hours postdose, 119/86 mm Hg a few minutes after that, and 111/82 mm Hg 2 hours after dosing. No specific treatment for this event was reported. She went home after the "hypertensive crisis" abated. The subject's BP on the dates of the second hypertensive crisis, which lasted from [redacted] was not reported. The next available reported value was on [redacted](early termination visit) when her BP was 111/69 mm Hg. No specific treatment for this event and the event of injection-site reaction was reported; however, it was reported she fell asleep, and the hypertensive crisis abated. There are not enough data to assess the second event, but the first event is unlikely to be hypertensive crisis even though it was reported as such, given the modest change in BP.
- [redacted]: A 40-year-old white female with HTN 19 days after the last BMT dose in the extension phase. She received PBO in the core phase and 16 doses in extension.

Presyncope

[redacted]: A 34-year-old white female with a vasovagal episode that was coded as presyncope after her first dose of BMT in clinic. She had no prior history of syncopal episodes. The event lasted 10 hours and was of "moderate" intensity. At predose, the subject's BP, taken a few minutes apart, was 105/71 mm Hg and 156/135 mm Hg; her pulse rate, taken a few minutes apart, was 51 bpm and 45 bpm. At 9:06 a.m., the subject self-administered study drug. At 9:32 a.m., she complained of "feeling bad" and stated that she felt "hot, shaky, and nauseated." She was assisted to the exam table to lie down and was given a snack and Sprite. Postdose, her BP, taken approximately 10 minutes to 25 minutes apart, was 141/127 mm Hg, 124/81 mm Hg, 94/69 mm Hg, and 123/77 mm Hg; her accompanying pulse rate was 72 beats/min, 58 beats/min, 64 beats/min, and 60 beats/min. She continued to complain of alternating episodes of hotness, coldness, shaking, and nausea. She was treated with ondansetron. No shortness of breath or arrhythmia was noted. At 10:45 a.m., she reported that her symptoms were improving and that she felt better. She refused any further bloodwork and was released from the office in stable condition. Study drug was withdrawn.

Significant Adverse Events

Cardiovascular events

A search for major adverse cardiovascular events was conducted using the following search terms: coronary heart disease, coronary death, myocardial infarction, coronary insufficiency, angina, heart failure, cerebrovascular events, cerebrovascular events including ischemic stroke, hemorrhagic stroke, transient ischemic attack, intermittent claudication, and peripheral artery disease.

There was one myocardial infarction occurring in a 46-year-old black female randomized to PBO (b) (6).

In the pooled phase 3 double-blind treatment period, cardiac disorders were infrequent, occurring in 0.8% of BMT-treated subjects (n=5) and 0.3% of PBO-treated subjects (n=2). Single events of palpitations, first-degree atrioventricular block, bradycardia, sinus arrhythmia, and tachycardia occurred in the BMT group.

Major Adverse Cardiovascular Events Summary

There were no major adverse cardiovascular events[49] in the phase 3 double-blind period core studies among subjects taking BMT. There was one event of myocardial infarction in the PBO group (b) (6), as above). There was one cerebrovascular event in the extension study (301-extension) and one event of angina (302-extension). The full listing of the cardiac disorders SOC is shown in Table 39. In the broader integrated summary of safety database, there were six treatment-emergent occurrences of chest/cardiac discomfort or chest pain following BMT exposure. Additional information on these cases was received from the Applicant in a response to Information Request submitted 21Sep2018 (SD29).

[49] Coronary heart disease (coronary death, myocardial infarction, coronary insufficiency, and angina), heart failure, cerebrovascular events (including ischemic stroke, hemorrhagic stroke, and transient ischemic attack), intermittent claudication (Peripheral Artery Disease).

Table 39. Cardiac Disorders System Organ Class Adverse Events

	Core Studies		EXT Studies	Core/EXT Studies Combined
System Organ Class Preferred Term	PBO (N=620) N (%)	BMT 1.75 mg (N=627) N (%)	BMT 1.75 mg (N=684) N (%)	BMT 1.75 mg (N=1057) N (%)
Any adverse event	361 (58.2)	480 (76.6)	534 (78.1)	867 (82.0)
Cardiac disorders	2 (0.3)	5 (0.8)	5 (0.7)	10 (0.9)
Palpitations	0	1 (0.2)	3 (0.4)	4 (0.4)
Angina pectoris	0	0	1 (0.1)	1 (<0.1)
Atrioventricular block first degree	0	1 (0.2)	0	1 (<0.1)
Bradycardia	0	1 (0.2)	0	1 (<0.1)
Sinus arrhythmia	0	1 (0.2)	0	1 (<0.1)
Sinus tachycardia	0	0	1 (0.1)	1 (<0.1)
Tachycardia	0	1 (0.2)	0	1 (<0.1)
Bundle branch block right	1 (0.2)	0	0	0
Myocardial infarction	1 (0.2)	0	0	0
Nodal rhythm	1 (0.2)	0	0	0
Supraventricular extrasystoles	1 (0.2)	0	0	0

Abbreviation: BMT bremelanotide, PBO placebo, EXT extension
Source: ISS, Table 34, page 98

A query of adverse events from clinical trials was conducted for indications other than hypoactive sexual desire disorder. These events were of interest due to the elevation in blood pressure seen during development.

In conclusion, there were few cardiac-related events in the safety database. No conclusions on BMT-related cardiovascular risk can be made based on review of the narratives.

Severe Adverse Events

Severe AEs were those that prevented normal everyday activities. A tabulation of subjects with severe AEs by treatment group (and greater in the BMT group) as defined by the investigator is shown in Table 40 for the pooled phase 3 double-blind period. Nausea, headache, abdominal pain/gastrointestinal pain, vomiting, and myalgia were the most common severe events with BMT use.

Table 40. Subjects With Severe Adverse Events by Treatment Group in the Pooled Phase 3 Double-Blind Period

Severe Adverse Event	BMT 1.75 mg N Subjects	PBO N Subjects
Nausea	13	1
Headache	5	1
Abdominal pain	3	0
Vomiting	3	0
Myalgia	2	0
Abdominal hernia obstructive	1	0
Abdominal pain upper	1	0
Akathisia	1	0
Back pain	1	0
Bronchitis	1	0
Constipation	1	0
Cough	1	0
Dizziness	1	0
Fatigue	1	0
Flushing	1	0
Gastrointestinal inflammation	1	0
Gastrointestinal pain	1	0
Genital hyperesthesia	1	0
Hot flush	1	0
Influenza-like illness	1	0
Invasive ductal breast carcinoma	1	0
Menorrhagia	1	0
Menstruation irregular	1	0
Ovarian cyst	1	0
Ovarian cyst ruptured	1	0
Pain	1	0
Peritoneal hemorrhage	1	0
Pruritus generalized	1	0
Rhinorrhea	1	0
Somnolence	1	0
Urticaria	1	1
Vaginal hemorrhage	1	0

Abbreviations: BMT bremelanotide, PBO placebo
Source: ae.xpt

Treatment-Emergent Adverse Events and Adverse Reactions

There was a greater number of TEAEs in the BMT group compared to PBO in the pooled 3 double-blind period with similar rates in both pivotal studies (301 and 302). There were also a greater number of moderate (40% versus 26%) and severe (5.4% versus 2.9%) AEs in the BMT group compared to PBO, respectively. Similar trends were seen in the extension studies and combined phase 2/3 safety populations.

The Applicant split the injection-site adverse reactions into individual events of injection-site pain, injection-site reaction, injection-site erythema, injection-site hematoma, injection-site pruritus, injection-site hemorrhage, injection-site bruising, and injection-site paresthesias. All injection-site AEs will be labeled as a group and these figures are represented in Table 41.

Table 41. Treatment-Emergent Adverse Events (≥2%)

TEAE	BMT N=627		PBO N=620		OLE N 1057	
Subjects with any TEAE	480	76.6%	361	58.2%	534	78.1%
Nausea	250	39.9%	7	1.1%	178	26.3%
Flushing	127	20.3%	3	0.5%	141	13.3%
Injection-site reaction (any)[a]	118	13.2%	61	8.4%	88	8.3%
Headache	70	11.2%	13	2.1%	83	7.9%
Vomiting	30	4.8%	1	0.2%	30	2.8%
Cough	21	3.3%	8	1.3%	22	2.1%
Fatigue	21	3.3%	3	0.5%	31	2.9%
Hot flush	17	2.7%	1	0.2%	17	1.6%
Paresthesia	16	2.6%	0	0%	10	0.9%
Dizziness	14	2.2%	0	0%	15	1.4%
Nasal congestion	13	2.1%	3	0.5%	5	0.5%

[a] Combined injection site: pain, reaction, erythema, hematoma, pruritus, hemorrhage, bruising, paresthesias
Abbreviations: BMT bremelanotide, PBO placebo, OLE open-label extension, TEAE treatment-emergent adverse event
Source: Compiled by reviewer using adae.xpt

The most common SOCs were GI disorders, infections and infestations, vascular disorders, and nervous system disorders. The most common TEAEs (≥2% and occurring more in the BMT group) were nausea, flushing, injection-site reactions (any), headache, vomiting, cough, fatigue, hotflushes, paresthesias, and nasal congestion.

The following TEAEs were related to BMT use and were notable:

- Nausea was experienced by 39.9% of subjects across Studies 301 and 302 compared to 1.1% in the PBO groups. Events of nausea led to the most discontinuations due to the AEs, but none were considered serious. Fourteen subjects had events coded as severe. In those experiencing nausea, the average number of events was six over the 18-month period. The mean time to onset was 1.0 hour after injection with median duration of 2.0 hours. Anti-emetic therapy was administered in 12.7% of events. Data from the population PK/PD study showed that nausea and its intensity was related to C_{max} and that the incidence increased with dose and decreased with higher body weight. The odds of nausea in an average person decreased by 14% for every 10 kg increase in weight.
- Hyperpigmentation/skin discoloration and incomplete reversibility. An imbalance in hyperpigmentation/skin discoloration was noted in the clinical program with a sevenfold increased incidence in black subjects. Reversibility was documented in half of all subjects with no apparent predilection for skin type. A Warning and Precaution will be added for the hyperpigmentation and skin discoloration involving skin darkening to educate subjects on the risk of hyperpigmentation and the potential irreversibility (see Section 8.2.8 for a detailed discussion of this finding).

Laboratory Findings

The Applicant conducted laboratory assessments that included chemistry, hematology, and urinalysis at screening/baseline (Week 1), at randomization/Visit 3 (Week 9), Visit 6 (Week 21)

and Visit 9 (Week 32) during the core phase and at Weeks 13, 29, 45, and 52 of the extension phase.

Additional screening tests were conducted at baseline only and include HIV, serum human chorionic gonadotropin, FSH, estradiol, and a drug/alcohol screen. Hormone testing was conducted at the randomization visit (Week 9) and included sex hormone-binding globulin and testosterone (collected predose); ACTH (collected predose and >90 minutes postdose, relative to the first dose only). Prolactin, cortisol, and oxytocin were also collected predose.

The Applicant submitted summary statistics and shift analyses for the chemistry and hematology results. Review showed no clinically significant mean changes or shifts from baseline in chemistry or hematology at end of core (24 weeks) or end of extension (52 weeks). In the PBO-controlled phase, there were small changes in ALT (mean change from baseline to end of extension of 4.6 U/L (BMT) versus -0.7 U/L (PBO) with no significant shifts); AST (mean change from baseline to end of extension of 4.4 BMT versus -1.6 PBO U/L with no significant shifts); creatinine kinase, mean increase in creatinine kinase at end of core in BMT (4 versus -53.7 in PBO) (attributed to high baseline PBO value); potassium, shift imbalance in low readings six BMT subjects versus three PBO subjects at 24 weeks but no mean changes; and triglycerides, shift imbalance from normal to high (42 BMT subjects versus 36 PBO subjects) at end of the core phase.

Clinical Laboratory Results of Interest

The clinical findings of hyperpigmentation prompted a search for evidence that BMT could have an endocrine target. The following labs were further assessed: ACTH, glucose, and cholesterol.

ACTH

ACTH was assessed at predose and at least 90 minutes after the first in-clinic dose. No additional assessments were conducted during the study. Change from predose to >90 readings (in pmol/L) were presented by the Applicant. The normal range in this study was 0 to 10.2 (pmol/L); however, normal values change as ACTH secretion is circadian. The time of lab draw was not denoted in the dataset (lb.xpt), therefore the time of collection across subjects cannot be assumed to the consistent. Data from the exposure dataset (ex.xpt) shows injection times at clinic visits ranging from 8:30 a.m. through 5:30 p.m. making comparisons across the study population unreliable.

Table 42. ACTH Mean Values and Change From Predose

Time Point	BMT-301		BMT-302	
Statistic	PBO	BMT	PBO	BMT
Predose				
n	312	315	286	289
Mean	3.9	4.1	4.2	4.2
Min, max	1, 90	1, 33	1, 72	1, 52
>90 min., postdose				
n	286	286	258	262
Mean	3.9	4.7	3.7	4.6
Min, max	1, 26	1, 58	1, 23	1, 46
Change				
n	280	282	254	256
Mean	-0.1	0.6	-0.4	0.4
Min, max	-82, 24	-28, 46	-70, 3	-49, 41

Abbreviations: ACTH adrenocorticotropic hormone, BMT bremelanotide, PBO placebo
Source: Table 14.3.2.8 CSR 301, page 1091 and CSR 302, page 1060

The mean change in ACTH from pre- to postdose was slightly greater in the BMT group than PBO for Studies 301 and 302 (0.6 versus -0.1 and 0.4 versus -0.4, respectively), but values were still within the normal range. As no additional ACTH levels were obtained in the study, the effect of multiple doses of BMT on ACTH is unknown. It is unclear whether circadian changes in ACTH levels was factored into the collection times.

Serum glucose

Both glucose and nonfasting glucose values were reported by the Applicant, but it is unclear from the study report if subjects were fasting at any point during the study. Confirmation from the Applicant (in response to our 1Nov2018 Information Request) stated that study protocols did not specifically require that blood draws for standard clinical chemistry laboratory testing be performed on fasting subjects. Protocol clarification letters were issued for Studies 301 and 302 and encouraged fasting samples where possible. Glucose values are shown in the tables below; however, these readings do not inform on the incidence of hyperglycemia.

Mean and maximum change from baseline glucose values are shown in Table 43 below.

Table 43. Glucose: Mean and Maximum Change From Baseline in BMT Studies 301 and 302

		BMT-301				BMT-302			
Time		PBO		BMT		PBO		BMT	
Point	Stat.	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL	mmol/L	mg/dL
Baseline	N	262		273		272		267	
	Mean	4.9	88	4.9	88	4.8	86	4.8	86
	Min, max	(2.7, 20)	(49, 359)	(3.11, 9.49)	(56, 171)	(1.8, 8.7)	(32, 157)	(1.9, 8.7)	(34, 156)
Mean at end of study	N	226		223		212		206	
	Mean	4.9	88	5.0	90	5.0	90	4.9	88
	Min, max	(3.5, 8.3)	(63, 149)	(3.5, 12.27)	(63, 221)	(3.2, 8.6)	(58, 155)	(3.3, 7.6)	(60, 137)

Change from baseline	N	226		223		212		206	
	Mean	0.02	0.4	0.1	2.3	0.21	3.8	0.1	2.2
	Min, max	(-12.4, 2.8)	(-223, 50.4)	(-6.0, 4.6)	(-108, 83)	(-1.7, 3.9)	(30, 70)	(-3.6, 2.4)	(-65, 43)

Abbreviations: BMT bremelanotide, PBO placebo

There were similar baseline values across Studies 301 and 302. There were small but inconsistent results in the change from baseline between studies, with greater changes in the BMT group over PBO group in Study 301 but not in Study 302.

The number of outliers based on various upper limits are shown in Table 44. The differences were small and do not appear to be clinically meaningful (and fasting status is unknown and therefore interpretation is not possible).

Table 44. Glucose Outliers in BMT Studies 301 and 302

	BMT-301		BMT-302	
Outlier Threshold	**PBO**	**BMT**	**PBO**	**BMT**
mg/mL (mmol/L)	326	327	306	308
>116 (6.38)	5	10	6	8
>126 (7)	3	4	4	3
>200 (11.1)	0	1	1	0

Abbreviations: BMT bremelanotide, PBO placebo

Elevation in creatinine phosphokinase

Table 45 shows no imbalance in the number of subjects with CPK elevation outside of the normal range between treatment groups in the phase 3 studies.

Table 45. Creatinine Kinase Outliers in Phase 3 (Values >ULN)

	BMT		PBO	
Study	**# of Subjects**	**Range (U/L)**	**# of Subjects**	**Range (U/L)**
301	33	170–4153	39	170–1276
302	40	171–14497	36	173–1139
301E	57	170–5897	—	—
302E	51	170–801	—	—

There was an imbalance in reports of TEAEs of creatinine phosphokinase (CPK) elevation (n=14 cases) in the phase 3 HSDD program (core and extension phases). All subjects had exposure to BMT 1.75 mg at the time of the event. Review of a published literature report[50] for a similar investigational product (melanotan II, BMT is the free acid form with no amide at the carboxyl terminus) of a 39-year-old Caucasian male who injected 6 mg of melanotan II. The product was

[50] Nelson M et al., 2012. Melanotan II Injection Resulting in Systemic Toxicity and Rhabdomyolysis. Clin Toxicol, 50:1169–1173.

purchased over the internet for the purpose of sunless tanning and the amount was six times the recommended starting dose. The subject presented to the emergency room with elevated BP (151/85 mm Hg), tachycardia (maximum HR 146), diaphoresis and muscle tremors. Initial creatinine kinase was 1760 U/L. Urinalysis showed 3+ blood but 0 to 2 red blood cells/high-power field. Rhabdomyolysis was treated with fluids and ICU admission. CPK peaked to 17,000 U/L during admission.

A review of the cases in phase 3 showed most instances of the CPK elevation occurred within 1 to 4 days of the most recent BMT injection but after >3 to 6 months of total exposure. With the exception of one case whose peak value was 14,000 (narrative provided below), the CPK elevations were modest in size and returned to baseline without treatment or drug discontinuation (follow-up CPK not reported for one subject, (b) (6)). There was one repeat CPK elevation with re-exposure. No subjects were symptomatic.

CPK Elevation Narrative -Subject (b) (6)

A 20-year-old white female who was randomized to BMT in the core study with screening and baseline CPK of 106 and 128 U/L, respectively (normal range 24 to 169 U/L). The subject received 10 doses of BMT over an approximate 6-month period (b) (6). At Visit 9 scheduled visit (b) (6) and 1 day after the last dose, the CPK was 14497 U/L (86x ULN). On the same day, other laboratory results were also elevated, lactate dehydrogenase (LDH) 539 U/L, AST 151 U/L, ALT 53 U/L, with normal BUN and creatinine, 5 mg/dL and 0.6 mg/dL respectively. Urinalysis was normal including negative for blood. Follow-up laboratory results on (b) (6) included LDH 163 U/L, AST 25 U/L, ALT 24 U/L, BUN 10 mg/dL, and creatinine 0.6 mg/dL. Per the Applicant, subsequent follow-up with the study site has raised the possibility that the elevated CPK may be due to the fact that the subject was in EMT and fire-fighter training for 2 days during the week of her (b) (6) visit. The event was improved on (b) (6) (CPK 372 U/L) and the subject completed the core phase. No further labs were reported. No symptoms were reported. While a possible explanation exists related to the subject's strenuous physical training, the elevation in CPK seen was impressive.

In summary, there was an imbalance in CPK elevations when reported as an AE, but no imbalance was seen when all available CPK laboratory data was considered. Laboratory data are more useful in this setting as investigators may have different thresholds for reporting a CPK elevation.

Vital Signs

Changes in systolic and diastolic BP and pulse were safety issues of interest. Cuff blood pressures were assessed in the core and extension studies at each clinic visit. Also 24-hour ambulatory blood pressure readings were captured in phase 2 (Study 54). (b) (4) An additional ABPM study was conducted

during the review cycle. Detailed summary of BP and HR findings are discussed in Section 8.2.6. No significant changes in temperature or respiratory rate were noted.

Electrocardiograms

Twelve-lead ECGs (reviewed centrally by a cardiologist), (b) (4) (b) (4)

Phase 3

ECGs were obtained at screening, randomization and at the EOS visit (Week 32) in the supine position after the subject had been at rest for at least 2 minutes.

In subjects exposed to BMT, no subjects had a clinically significant ECG abnormality at screening. At the end of study, there were three subjects with a clinically significant ECG abnormality; Subject (b) (6) with QT prolongation of 423 msec at EOS (Screening value 378msec and baseline 419 at baseline); Subject (b) (6) first degree AV block; Subject (b) (6) bradycardia. One subject (b) (6) had QT prolongation of 556 ms at screening, 462 ms at baseline, and 527 ms on Day 87 (EOS). None of these TEAEs led to subject discontinuation. There were no significant outliers in maximum absolute QT/QTc and maximum QTc changes from baseline between treatment groups.

Study 54 (phase 2b study)

Subject (b) (6) (on BMT 1.75 mg) had sinus rhythm with LVH and ventricular HR 66 beats/min at screening. Visit 7 ECG showed sinus bradycardia with ventricular HR of 37 beats/min and QTc of 388 ms and the subject withdrew from the study. The following day the ECG showed sinus bradycardial with ventricular HR of 48 beats/min and QTc 404 ms. Three additional subjects had abnormal ECGs: (b) (6) (BMT 1.75 mg) sinus bradycardia with ventricular HR 59 beats/min, QT 459 (not clinically significant); (b) (6) (BMT 1.25 mg) sinus bradycardia with prolonged QT (QTc 461 ms), with AE reported as “QT prolonged.” End-of-

study ECG was normal with HR 63 beats/min and QT 433; (b) (6) Visit 7 AE of PR prolongation (ECG showing HR 82 beats/min and QTc 404). AE resolved the following day.

QT

The thorough QT study, PT-141-2005-28, was a single-center, single-dose, randomized, double-blind (except for moxifloxacin positive control), PBO- and moxifloxacin-controlled thorough electrocardiographic study in 264 subjects. Subjects were randomized to intranasal (IN) PBO, IN BMT 5 mg, IN BMT 20 mg (supratherapeutic dose), or oral moxifloxacin 400 mg. Time-matched results demonstrated that "the upper bound of the one-sided 95% confidence interval was <10 ms for both doses of BMT at time points through 24 hours after dosing," compared to moxifloxacin, which demonstrated a PBO-corrected change >5 ms from baseline (from 1 to 12 hours) with upper confidence intervals ranging from 12.4 to 16.9 ms. Hence, in Study PT-141-2005-28, BMT had no effect on "HR, atrial-ventricular conduction, ventricular depolarization, or cardiac repolarization" and no concentration corrected QT interval (QTcI) relationship was identified. The conducted TQT study using intranasal BMT is deemed adequate to support the SC route proposed in the NDA.

Immunogenicity

Despite being a small peptide, BMT shares sequence homology (four amino acids) with endogenous α-MSH and there was concern whether anti-BMT antibodies could cross react and become immunogenic. An immunogenicity assessment of BMT was not performed; however, as requested, the Applicant submitted a risk assessment to address potential cross reactivity to α-MSH. Review of the assessment, including a competitive binding assay, demonstrated that BMT most likely does not bind human leukocyte antigen class II alleles which is required to drive an anti-drug antibody response. Consistent with these findings, pharmacokinetic and clinical efficacy responses do not appear to be impacted by anti-drug antibody responses. Per a review dated 28Sep2018, the Office of Biotechnology Products concluded that clinical data are consistent with a lack of BMT immunogenicity.

In summary, the laboratory and vital sign data did not identify any signals or trends that would translate into labeling requiring patient testing during BMT treatment. However, the effects on the ACTH cortisol axis may need to be further elucidated if more frequent dosing is sought based on both the nonclinical and clinical adverse event profile reported in this application.

8.2.5. Analysis of Submission-Specific Safety Issues

Several safety issues required more specific evaluation:

- BP elevation: Clinically significant increases in systolic and diastolic BPs were noted after single-dose administration in several studies. The duration and magnitude of effect in real world situations was unknown and the impact of PRN usage was also

uncharacterized. A definitive ambulatory BP study was requested/conducted to define the risk more adequately.

- Gastrointestinal disorders: nausea was the most common AE in the clinical program and the Gastrointestinal SOC was the most prevalent SOC.
- Skin disorders: Focal hyperpigmentation that appeared associated with increased dosing frequency and an increase in nevi in two subjects were noted in the clinical program.
- The Beck Scale for Suicidal Ideation was also assessed because BMT is centrally acting. No change from baseline was reported at the end-of-study. There were four subjects in the BMT group, five subjects in the PBO group, and three subjects in the extension phase reporting TEAEs of depression and suicide.
- Hepatic enzyme elevation: A single case of liver injury was reported in the clinical program.

8.2.6. Blood Pressure Elevations

Regulatory History

Due to BP elevations seen in the early clinical development program, ambulatory BP assessments were requested for phase 2, Study PT-141-54 (Study 54) conducted in premenopausal women with FSAD, HSDD or mixed FSAD/HSDD. One day of PBO and 2 days of on-treatment 24-hour ABPM assessments were captured.

On review of the Study 54 clinical study report (submitted to IND 64119 on 18May2015, protocol dated 22Dec2014), we raised concerns over the adequacy of the BP data to inform on BP/HR excursions in the target population. Based on the review of the data, the ranges of BP and HR excursions associated with BMT 1.75 mg were large and may be clinically relevant: SBP (-28 to +27 mm Hg), DBP (-28 to +21 mm Hg), and HR (-33 to +23 bpm). We also had concerns that the safety data from the phase 3 trials (Studies 301 and 302), where use of BMT was primarily sporadic, would not adequately characterize the effect of BMT on BP and the potential interaction between BMT and antihypertensives was unclear. In conjunction with the Division of Cardiovascular and Renal Products (DCaRP), we requested a new ABPM study to definitively address the BP effects of BMT in the target population (advice letter dated 3March 2017).

At the Pre-NDA meeting (minutes dated 18Sep2017), the Applicant was again advised that an ABPM study was strongly recommended. However, the Applicant proposed that (b) (4)

(b) (4)

(b) (4) The ABPM data will be presented first followed by cuff BPs obtained in phase 3.

Ambulatory Blood Pressure Monitoring Data

ABPM was used to evaluate the effect of BMT on BP and its magnitude. ABPM provides more precise measurement of an individual's BP compared to cuff BP measurements; and provides a more precise assessment of average change and greater ability to describe individual variation. Ambulatory BP monitoring was not conducted in the phase 3 trials.

Ambulatory BP data from early studies used the intranasal form of BMT and were conducted in a cohort of subjects with controlled essential HTN, stage 1 or 2, (Study 2006-32) and a separate study was conducted in healthy volunteers administered intranasal BMT with nitroglycerin (Study 2005-23). Study 2006-32 evaluated up to 4 days of consecutive days of 5 mg and 10 mg IN BMT; Study 2005-23 evaluated single doses of IN BMT (5 mg and 10 mg). These latter two studies did not include PK assessment or PK/PD modeling. More relevant ABPM data using SC BMT were conducted in Study PT-141-54 (Study 54) (b) (4)

Study PT-141-54

Study PT-141-54 was a phase 2 dose-finding study in premenopausal women with HSDD with or without FSAD. The study consisted of a 4-week no treatment period, a single dose in-clinic single-blind PBO (followed by 24-hour ABPM), a 4-week single-blind outpatient period (baseline), a 2-week period with two single in-clinic doses (followed by 24-hour ABPM after each dose), and a 12-week double-blind period in which subjects were randomized in a 1:1:1:1 fashion to one of four treatment groups: PBO or SC BMT 0.75, 1.25, or 1.75 mg. Three ABPMs (as above) were conducted following a single dose of PBO and two single doses of BMT, respectively. Repeat ABPM at the end of the 12-week double-blind treatment period was not performed. Manual BPs were obtained for approximately 4 hours (reduced to 2 hours by Amendment 4). Subjects were removed if manual predose BP was ≥140/90 mm Hg on two consecutive measurements; or if manual or ABPM resting BP met the following criteria shown in Table 46 below.

Table 46. Study 54 Blood Pressure Measurement Criteria for Subject Discontinuation

Absolute Measurement			Change From Baseline		
SBP (mm Hg)	DBP (mm Hg)	Consec. (Every 15 Min.)	SBP (mm Hg)	DBP (mm Hg)	Consec. (Every 15 Min.)
≥170 or	≥105	2 readings	≥40 or	≥20	2 readings
≥160 or	≥100	3 readings	≥30 or	≥15	4 readings
≥150 or	≥90	4 readings	—	—	—

Abbreviations: DBP diastolic blood pressure, SBP systolic blood pressure, consec. consecutive

The criteria were further modified in Amendments 3 and 4 following review of data from four subjects who completed Visit 7:

- Subjects who met one BP shift criterion must also have had two readings (consecutive or nonconsecutive) above 150 mm Hg systolic *and* 95 mm Hg diastolic during the 24-hour period for withdrawal
- Subjects who met two BP shift criteria must also have had two readings (consecutive or nonconsecutive) above 150 mm Hg systolic *or* 95 mm Hg diastolic during the 24-hour period for withdrawal

A clinical expert team in cardiovascular disorders (DCaRP) reviewed the BP values and made a recommendation to the Applicant on whether the subject should have been withdrawn.

Subjects who met the withdrawal criteria via manual BP measurement during the 2 hours after in-clinic dosing were followed in the clinic (e.g., BP measured every 15 minutes) until the investigator considered it safe for the subject to be discharged. The subject was asked to continue wearing the ABPM through 24 hours before a final decision was made about withdrawing the subject from the study.

Ambulatory BP monitoring results (PBO-subtracted) are shown in Table 47 using each subject as her own control. Note that only BMT 1.75 mg SC is intended for marketing (see Trial Design in Section 8.1.1).

Table 47. Treatment Group Difference From PBO in Mean Change in Blood Pressure From Corresponding Period, Safety Population

		SBP (mm Hg)		DBP (mm Hg)		HR (Pulse) (bpm)		HR-BP Product (mm Hg bpm)	
Dose	Time (Hrs)	V5	V7	V5	V7	V5	V7	V5	V7
BMT 0.75	0–4	1.8	1.1	1.5	0.6	-5.2*	-4.8*	-492.8*	-491.9*
	>4–8	0.9	1.6	1.3	1.7	-6.2*	-5.5*	-676.5*	-503.3*
	>8–24	0.9	1.6	1.0	1.3*	-0.4	0.1	5.2	114.9
	0–24	1.1	1.5	1.1*	1.3*	-2.2*	-1.6	-187.7	-82.3
BMT 1.25	0–4	2.4*	2.1*	3.0*	2.2*	-5.2*	-6.1*	-436.4*	-583.3*
	>4–8	1.4	1.3*	2.2*	0.9	-6.1*	-6.5*	-621.0*	-669.7*
	>8–24	0.7	1.5*	1.4*	1.7*	-1.5	-0.7	-127.4	4.2
	0–24	1.1	1.6*	1.9*	1.7*	-2.9*	-2.6*	-265.9	-206.5
BMT 1.75	0–4	3.1*	2.5*	3.2*	2.6*	-4.6*	-4.7*	-305.9	-375.4*
	>4–8	2.1	2.2	2.3*	2.2*	-6.6*	-6.6*	-608.1*	-624.5*
	>8–24	0.9	0.6	1.4*	1.4	-0.8	-0.5	-23.7	-31.3
	0–24	1.6	1.3	1.9*	1.8*	-2.2*	-2.2*	-139.1	-184.1

*Nominal P≤0.05; 95% confidence interval for difference excluded 0
Abbreviations: BP blood pressure, bpm beats per minute, BMT bremelanotide, PBO placebo, DBP diastolic blood pressure, HR heart rate, Hrs hours, SBP systolic blood pressure, V visit
Source: Study 54 CSR, Table 12–12, page 198

Mean change with 95% confidence intervals for the BMT 1.75 mg SC dose are shown in Table 48.

There was an increase in BP following BMT administration relative to the PBO arm in all BMT treatment arms. The increase, relative to the PBO arm, was greatest at the 0 to 4-hour time point and there appeared to be a dose-response relationship during this time period. At the 8 to 24-hour time point, there still appeared to be an increase in BP relative to PBO, but the effect was smaller (0.6 mm Hg to 1.6 mm Hg for SBP and 1.0 mm Hg to 1.7 mm Hg for DBP). These increases in BP were associated with corresponding decreases in HR (+0.1 to -6.6 bpm), compared to PBO. These data show that the BP and HR effect persist for at least 24 hours. Given a T_{max} of 60 minutes and a $t_{1/2}$ of 2 hours for SC BMT administration, one would expect the concentration of BMT to be negligible at 24 hours, but the PD effects persist (DCaRP consult, dated 3Sep2017).

Table 48. Study 54: Treatment Group Difference From PBO in Mean Change in Blood Pressure From Corresponding Period, Safety Population, Updated With 95% CI, and Submitted to IND 64119

			Visit 5			Visit 7		
Dose	Parameter	Time (Hrs)	Diff.	Lower 95% CI	Upper 95% CI	Diff.	Lower 95% CI	Upper 95% CI
BMT 1.75 mg	SBP (mm Hg)	0–4	3.1	0.89	5.36	2.5	0.29	4.75
		>4–8	2.1	-0.28	4.54	2.2	-0.26	4.62
		>8–24	0.9	-0.95	2.80	0.6	-1.18	2.40
		0–24	1.6	-0.17	3.32	1.3	-0.40	2.91
BMT 1.75 mg	DBP (mm Hg)	0–4	3.2	1.48	4.94	2.6	0.76	4.44
		>4–8	2.3	0.12	4.43	2.2	0.00	4.36
		>8–24	1.4	0.00	2.73	1.4	-0.03	2.78
		0–24	1.9	0.65	3.13	1.8	0.50	3.02
BMT 1.75 mg	HR (bpm)	0–4	-4.6	-6.88	-2.34	-4.7	-6.79	-2.55
		>4–8	-6.6	-9.26	-3.87	-6.6	-9.31	-3.93
		>8–24	-0.8	-2.59	1.06	-0.5	-2.34	1.43
		0–24	-2.2	-3.89	-0.53	-2.2	-3.84	-0.58
BMT 1.75 mg	HR-BP product (Hg*bpm)	0–4	-305.9	-656.30	44.48	-375.4	-703.88	-46.90
		>4–8	-608.1	-1019.64	-196.55	-624.5	-1026.11	-222.92
		>8–24	-23.7	-299.08	251.71	-31.3	-296.70	234.01
		0–24	-139.1	-395.39	117.13	-184.1	-415.58	47.31

Abbreviations: BMT bremelanotide, PBO placebo, Diff difference, CI confidence interval, BP blood pressure, SBP systolic blood pressure, DBP diastolic blood pressure, HR heart rate, bpm beats per minute

Outlier analyses show more BMT-treated subjects (including BMT 1.75 mg) experienced SBP>160 mm Hg in combination with peak change from baseline >25 mm Hg compared to PBO. See Table 49 and Table 50.

There were no SBP elevations >180 mm Hg lasting longer than 15 minutes. Only five BMT subjects had SBP values >150 mm Hg (one with SBP >160 mm Hg) for >30 minutes. The one subject with SBP >150 mm Hg for >45 minutes had a history of uncontrolled HTN and had recently discontinued her medication. No numeric trends were seen in DBP or HR outliers.

Table 49. Outlier Analysis: Incidence (%) of Blood Pressure Changes Above Clinically Relevant Threshold Values, Safety Population

Blood Pressure Parameter	PBO (N=97) n (%)	BMT 0.75 mg (N=100) n (%)	BMT 1.25 mg (N=99) n (%)	BMT 1.75 mg (N=98) n (%)
SBP				
SBP >160 mm Hg	8 (8)	6 (6)	9 (9)	15 (15)
Peak change from baseline >25 mm Hg	4 (4)	6 (6)	9 (9)	8 (8)
SBP>160 mm Hg + peak change from baseline >25 mm Hg	0	3 (3)	4 (4)	3 (3)
DBP				
DBP >95 mm Hg	41 (42)	55 (55)	55 (55)	62 (63)
Peak change from baseline >25 mm Hg	5 (5)	2 (2)	6 (6)	5 (5)
DBP >95 mm Hg + peak change from baseline >25 mm Hg	5 (5)	2 (2)	6 (6)	5 (5)
MAP				
MAP >110 mm Hg	31 (32)	44 (44)	45 (45)	52 (53)
Peak change from baseline >25 mm Hg	4 (4)	3 (3)	5 (5)	6 (6)
MAP >110 mm Hg + peak change from baseline >25 mm Hg	2 (2)	3 (3)	5 (5)	6 (6)
HR				
HR >110 bpm	73 (75)	65 (65)	70 (71)	67(68)
Peak change from baseline >25 bpm	19 (20)	27 (27)	20 (20)	13 (13)
HR >110 bpm + peak change from baseline >25 bpm	19 (20)	23 (23)	19 (19)	13 (13)

Abbreviations: BMT bremelanotide, PBO placebo, DBP diastolic blood pressure, HR heart rate, MAP mean arterial pressure, SBP systolic blood pressure
Source: Study 54 CSR, Table 12–13, page 200

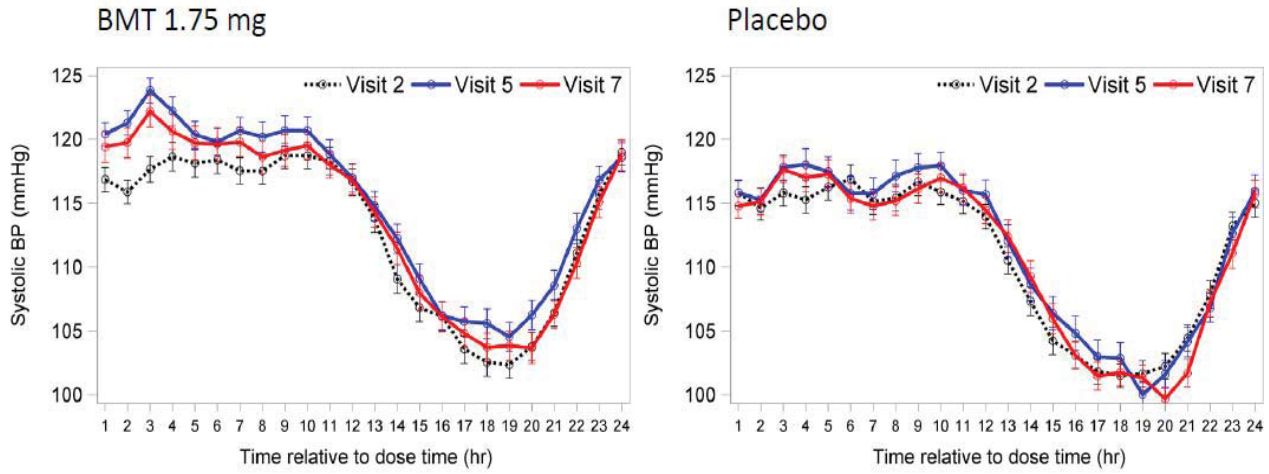
Table 50. Outlier Analysis: Incidence of Maximal Systolic and Diastolic Blood Pressure by Duration for Visits 5 and 7, Safety Population

Blood Pressure Parameter	Duration (minutes)	PBO (N=97) n (%)	BMT 0.75 mg (N=100) n (%)	BMT 1.25 mg (N=99) n (%)	BMT 1.75 mg (N=98) n (%)
SBP >150 and ≤160 mm Hg	≤15	11 (11)	22 (22)	14 (14)	17 (17)
	>15 and ≤30	2 (2)	1 (1)	2 (2)	0
	>30 and ≤45	0	0	2 (2)	1 (1)
	>45	0	0	1 (1)	0
SBP >160 and ≤170 mm Hg	<15	7 (7)	3 (3)	6 (6)	12 (12)
	>15 and ≤30	0	0	0	1 (1)
	>30 and ≤45	0	0	0	0
	>45	0	0	0	0
SBP >170 and ≤180 mm Hg	<15	2 (2)	2 (2)	2 (2)	0
	>15 and ≤30	0	1 (1)	0	1 (1)
	>30 and ≤45	0	0	0	1 (1)
	>45	0	0	0	0
SBP >180 mm Hg	<15	0	1 (1)	1 (1)	0
	>15 and ≤30	0	0	0	0
	>30 and ≤45	0	0	0	0
	>45	0	0	0	0
DBP >95 and ≤100 mm Hg	<15	13 (13)	22 (22)	18 (18)	18 (18)
	>15 and ≤30	5 (5)	4 (4)	2 (2)	1 (1)
	>30 and ≤45	0	0	0	2 (2)
	>45	0	0	1 (1)	1 (1)
DBP >100 mm Hg	<15	23 (24)	32 (32)	35 (35)	42 (43)
	>15 and ≤30	2 (2)	2 (2)	2 (2)	1 (1)
	>30 and ≤45	0	2 (2)	1 (1)	1 (1)
	>45	1 (1)	1 (1)	1 (1)	1 (1)

Abbreviations: BMT bremelanotide, DBP diastolic blood pressure, SBP systolic blood pressure, PBO placebo
Source: Study 54 CSR, Table 12-14, page 201

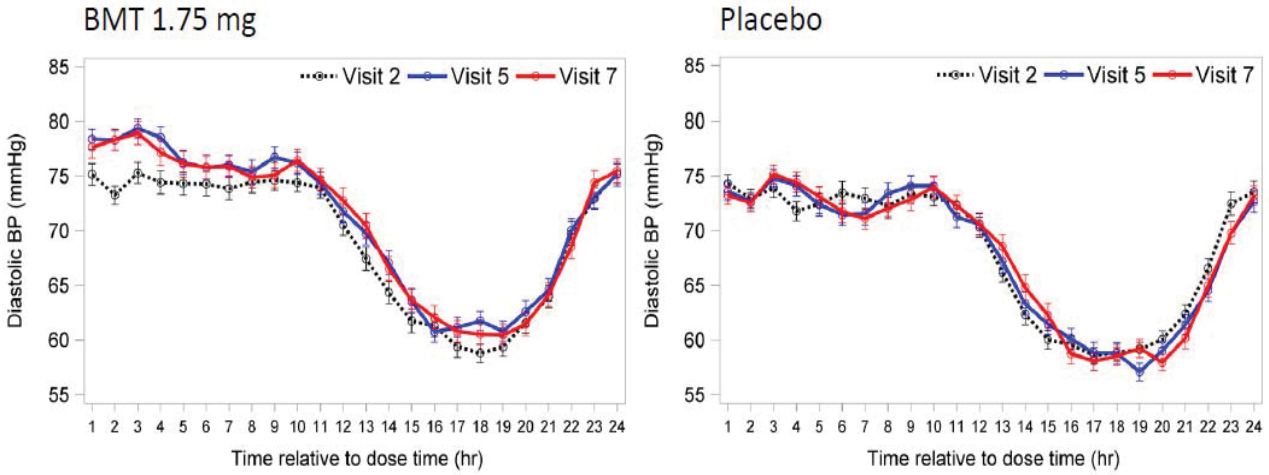
Figure 24, Figure 25, and Figure 26 (below) show a separation in SBP and DBP within the first few hours after dosing in the BMT group compared to PBO. This separation was also seen during nighttime readings. Decreases in HR were most pronounced in the daytime reading (Figure 27).

Figure 24. Study 54: Hourly ABPM Average—Systolic Blood Pressure



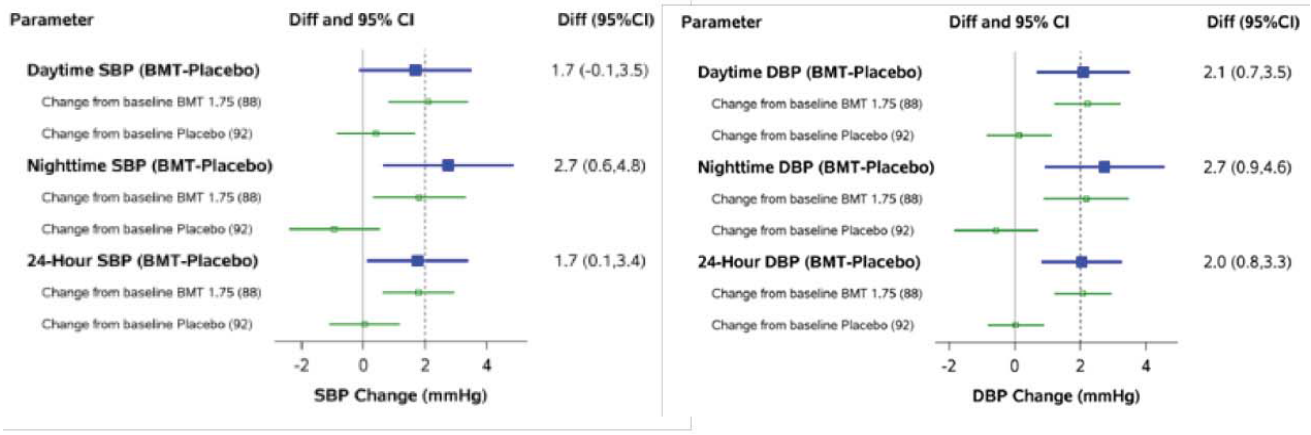
Abbreviations: ABPM ambulatory blood pressure monitoring, BP blood pressure, BMT bremelanotide, hr hour

Figure 25. Study 54 Hourly ABPM Average—Diastolic Blood Pressure



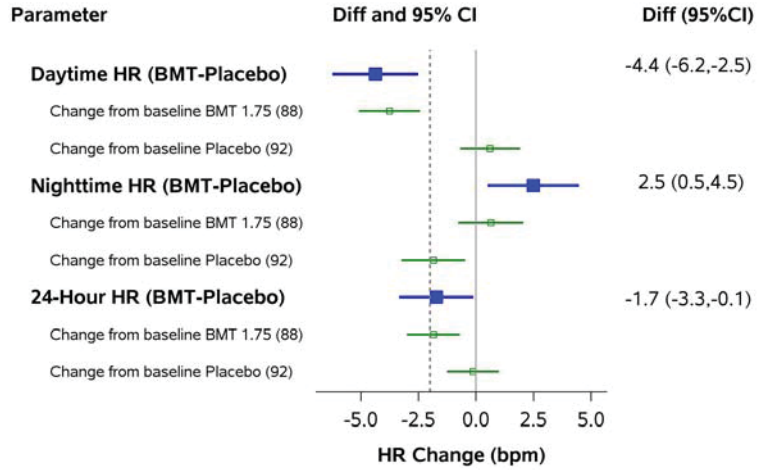
Abbreviation: BP blood pressure, BMT bremelanotide, hr hour

Figure 26. Study 54 BMT 1.75 mg vs. PBO—Systolic Blood Pressure and Diastolic Blood Pressure Change From Baseline to Visit 7, Similar Results Seen for Visit 5 From Baseline



Abbreviations: BMT bremelanotide, PBO placebo, CI confidence interval, DBP diastolic blood pressure, SBP systolic blood pressure
Source: DCaRP analysis, P. Dunnmon

Figure 27. Study 54 Heart Rate BMT 1.75 mg vs. PBO: Change From Baseline to Visit 7, Similar Results Seen for Visit 5 From Baseline



Abbreviations: BMT bremelanotide, PBO placebo, CI confidence interval, HR heart rate
Source: DCaRP analysis, P. Dunnmon

Outlier data for Study 54, both the 4-hour postdose and hourly average, show a numerical increase in outliers for SBP and DBP for the 1.75 mg BMT group compared to PBO.

Table 51. Study 54 Outlier Within 4 Hours Postdose

	SBP >180 mmHg or ≥ 20 mmHg change from baseline				DBP > 105 mmHg or ≥ 15 mmHg change from baseline			
4-h post dose average	0.75 mg	1.25 mg	1.75mg	Placebo	0.75 mg	1.25 mg	1.75mg	Placebo
Visit 5	1/100	1/97	5/98	1/95	2/100	6/97	6/97	2/95
Visit 7	2/90	1/86	2/88	0/92	1/90	2/86	7/88	2/92

Abbreviations: DBP diastolic blood pressure, SBP systolic blood pressure
Source: 2 DCaRP analysis, P. Dunnmon

Table 52. Study 54 Outlier Analysis Using Hourly Average ABPM at Visit 2 as Baseline

	SBP >180 mmHg or ≥ 20 mmHg change from baseline				DBP > 105 mmHg or ≥ 15 mmHg change from baseline			
Hourly average	0.75 mg	1.25 mg	1.75mg	Placebo	0.75 mg	1.25 mg	1.75mg	Placebo
Visit 5	44/100 (44%)	48/97 (49%)	44/98 (45%)	34/95 (36%)	62/100 (62%)	71/97 (73%)	63/98 (64%)	45/95 (47%)
Visit 7	35/90 (39%)	43/86 (50%)	43/88 (49%)	34/92 (37%)	58/90 (64%)	64/86 (74%)	63/88 (72%)	58/92 (63%)

Abbreviations: ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, SBP systolic blood pressure
Source: DCaRP analysis, P. Dunnmon

(b) (4)

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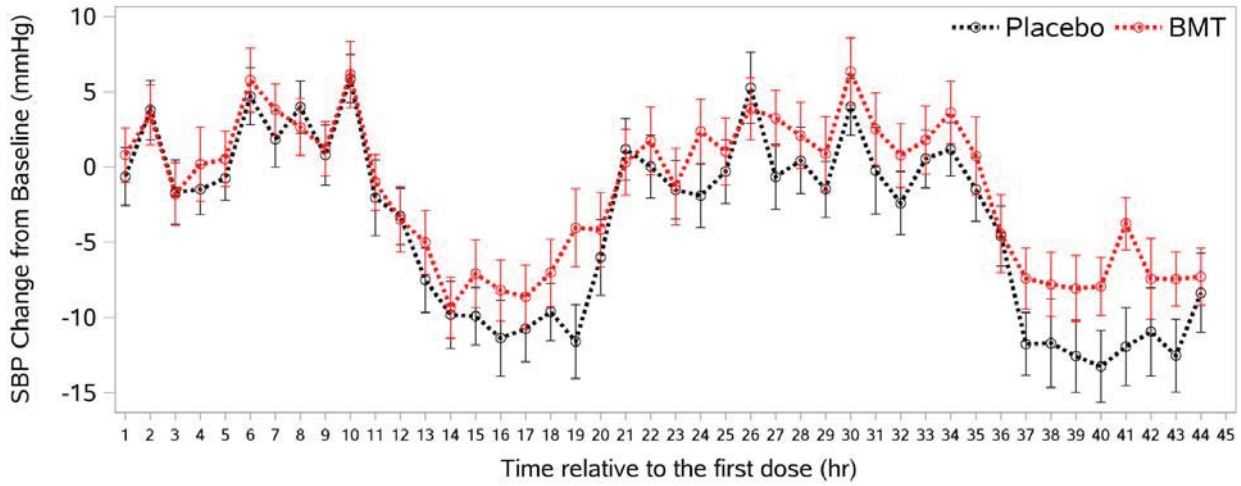
nausea, withdrawal of consent; and two subjects in the PBO group due to nausea and withdrawal of consent.

Subject 027 was withdrawn from the study due to an AE of HTN after receiving 10 doses of BMT. BP was 131/83 mm Hg with a pulse of 99 bpm prior to the first dose of BMT, though it is noted that this subject's DBP on Day -1 at 1:05 p.m. was elevated (135/100 mm Hg). Upward trending of SBP began on Day 2 at 9:15 p.m. (141/101 mm Hg), and on Day 3 at 8:07 p.m. (146/100 mm Hg) and 9:17 p.m. (145/100 mm Hg). On Day 4, BP was 145/94 mm Hg at the assessment prior to the first daily dose of study medication but increased to 152/102 mm Hg and 151/108 mm Hg approximately 1 and 4 hours postdose, respectively. Subsequent Day 4 assessments were elevated, but stable. By the first assessment on Day 5, BP showed improvement and remained stable through Day 5. Study medication was discontinued following the morning dose on Day 4, but the subject remained in the clinic for monitoring until the morning of Day 6.

Figure 28 shows the hourly ABPM change with confidence intervals comparing Day 2 to Day 1. BP at 1-hour predose was used as baseline as there were no 24-hour ABPM baseline data. Table 53 shows the increase from baseline in the delta-delta (change from pre-dose baseline, adjusted by time-matched 24-hour value) nighttime average for SBP of 5.2 mm Hg SBP that was greater than the daytime average (1.9 mm Hg) on Day 2. More pronounced increases from baseline in daytime averages (5.4 mm Hg) along with nighttime averages (5.9 mm Hg) were seen in diastolic BP (Figure 29) on Day 2 as shown in the figures below and Table 54. These results show the differential change from baseline starting the night following the first TID dose (1.25 mg/1 mg/1 mg) which became more pronounced into Day 2 TID dosing with the full dose (2.5 mg/2 mg/2 mg). Only Days 1 and 2 ABPMs were assessed, so it unknown if this effect continues to amplify on Days 3 to 15 of dosing. A decrease in daytime HR (-3.2 bpm) was also noted (see Table 55).

Figure 28. Study 38 Hourly ABPM Change From Day 1 to Day 2, Systolic Blood Pressure



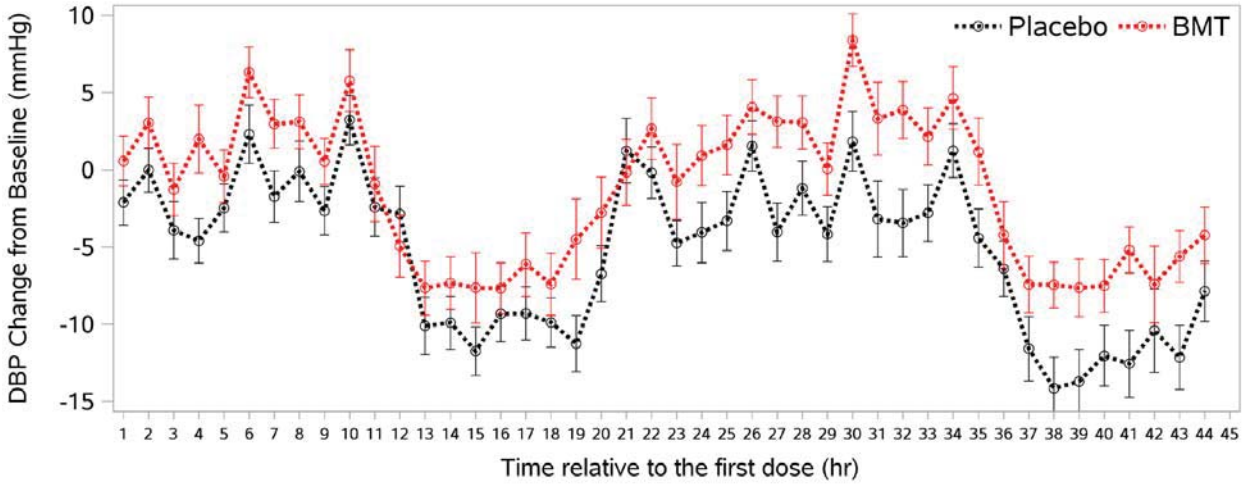
Abbreviations: ABPM ambulatory blood pressure monitoring, SBP systolic blood pressure, hr hour
SBP at 1-hour predose was used as baseline SBP
Source: DCaRP analysis, P. Dunnmon

Table 53. Study 38: Systolic Blood Pressure ABPM BMT vs. PBO

Systolic BP	DAY 1			DAY 2		
Chang from pre-dose baseline*	BMT	Placebo	ΔΔ	BMT	Placebo	ΔΔ
Day-Time Average	1.9 (-1.1, 5.0)	0.9 (-2.4, 4.2)	1.0 (-3.5, 5.5)	2.5 (-1.0, 6.0)	0.6 (-3.1, 4.3)	1.9 (-3.1, 7.0)
Night-Time Average	-7.4 (-11.0, -3.9)	-10.5 (-14.3, -6.7)	3.1 (-2.1, 8.2)	-6.7 (-10.5, -3.0)	-12.0 (-16.0, -8.0)	5.2 (-0.2, 10.7)
24-hour Average	-1.3 (-4.3, 1.7)	-2.8 (-6.1, 0.4)	1.6 (-2.9, 6.0)	-1.6 (-4.9, 1.7)	-4.3 (-7.9, -0.8)	2.8 (-2.1, 7.6)

*There was no 24-hour ABPM baseline data. Baseline SBP was average SBP within 1 hour prior to the first dose on Day 1
Abbreviations: ABPM ambulatory blood pressure monitoring, BMT bremelanotide, PBO placebo
Source: DCaRP analysis, P. Dunnmon.

Figure 29. Study 38 Hourly ABPM Change (Day 1 to Day 2) Diastolic Blood Pressure



Abbreviations: ABPM ambulatory blood pressure monitoring, DBP diastolic blood pressure, hr hour
DBP at 1-hour predose was used as baseline DBP
Source: DCaRP analysis, P. Dunnmon

Table 54. Study 38 Diastolic Blood Pressure—Change From Predose Baseline in ABPM BMT vs. PBO

Diastolic BP	DAY 1			DAY 2		
Chang from pre-dose baseline*	BMT	Placebo	ΔΔ	BMT	Placebo	ΔΔ
Day-Time Average	1.9 (-0.7, 4.5)	-1.6 (-4.4, 1.1)	3.5 (-0.3, 7.3)	3.3 (0.4, 6.2)	-2.0 (-5.1, 1.1)	5.4 (1.1, 9.6)
Night-Time Average	-6.9 (-9.9, -4.0)	-10.6 (-13.8, -7.4)	3.7 (-0.7, 8.1)	-6.5 (-9.7, -3.4)	-12.4 (-15.8, -9.0)	5.9 (1.2, 10.6)
24-hour Average	-1.2 (-3.8, 1.4)	-4.4 (-7.2, -1.6)	3.2 (-0.7, 7.0)	-0.9 (-3.6, 1.9)	-6.0 (-9.0, -3.0)	5.1 (1.1, 9.2)

Abbreviations: ABPM ambulatory blood pressure monitoring, BMT bremelanotide, PBO placebo
Source: DCaRP analysis, P. Dunnmon

Table 55. Study 38: Heart Rate—Change From Predose Baseline in ABPM BMT vs. PBO

HR	DAY 1			DAY 2		
Chang from pre-dose baseline*	BMT	Placebo	ΔΔ	BMT	Placebo	ΔΔ
Day-Time Average	-4.7 (-8.3, -1.1)	-0.9 (-4.7, 3.0)	-3.8 (-9.1, 1.5)	-2.7 (-6.5, 1.0)	0.5 (-3.5, 4.5)	-3.2 (-8.7, 2.2)
Night-Time Average	-8.8 (-12.8, -4.8)	-7.6 (-11.9, -3.3)	-1.2 (-7.0, 4.7)	-7.9 (-11.7, -4.2)	-8.4 (-12.5, -4.4)	0.5 (-5.0, 6.0)
24-hour Average	-5.8 (-9.4, -2.3)	-3.2 (-7.0, 0.6)	-2.7 (-7.9, 2.6)	-5.0 (-8.6, -1.4)	-3.1 (-7.0, 0.8)	-1.9 (-7.2, 3.4)

Abbreviations: ABPM ambulatory blood pressure monitoring, BMT bremelanotide, PBO placebo
Source: DCaRP analysis, P. Dunnmon

(b) (4)

Rationale for Requiring Another ABPM Study

The BP data from the phase 3 trials (Studies 301 and 302) are discussed later in this review. These data are limited because they did not evaluate BP effects with daily BMT use and did not include ABPM, and withdrew subjects from therapy with elevated BP.

Study 54 was limited by (1) the relatively selective population, without significant CV risk factors; (2) evidence that the BP effect had not resolved by 24 hours and may, therefore, persist longer than 24 hours; and (3) absence of data following long-term repeat use of BMT.

(b) (4)

Therefore, we informed the Applicant that another ABPM study will be needed to adequately characterize the BP effects of BMT for the proposed indication. This new study is described below.

AMAG-BMT-HSDD-101

After submission of the NDA, we requested another ABPM study with a randomized-withdrawal phase to reflect what would be expected following long-term daily use and determine how long the BP and HR effects of BMT persist. At the midcycle communication, the Applicant was informed that results of this ABPM study would be needed for review in the premarket phase. The Applicant submitted a study protocol on 20Nov2018; DBRUP and DCaRP jointly reviewed the study protocol and provided feedback. Enrollment began on 12Dec2018. The Applicant

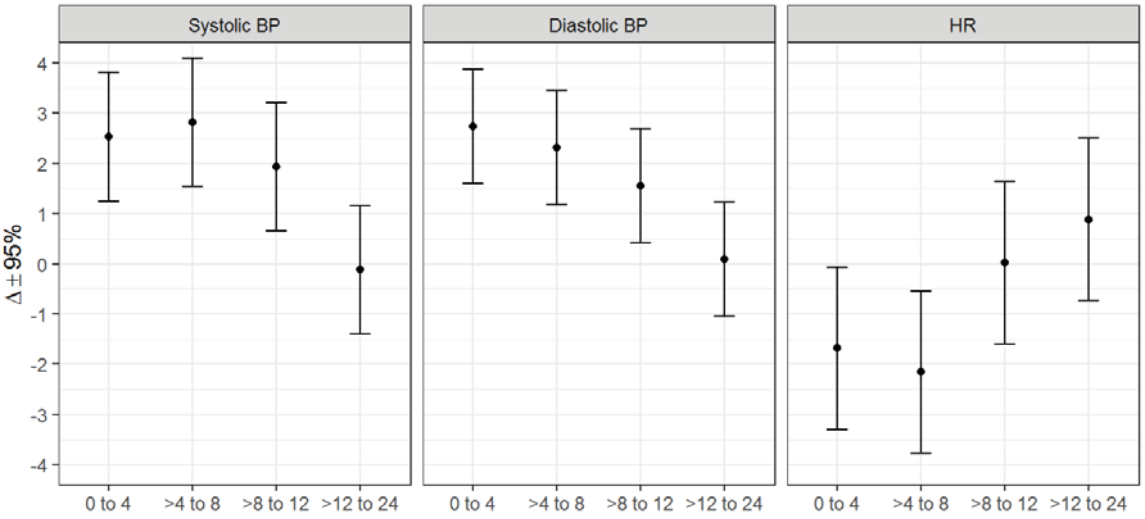
submitted the final study report during the review cycle, which was considered a major amendment that extended the PDUFA date by three months.

Study AMAG-BMT-HSDD-101 was an open-label, phase 1, PBO-controlled, double-blind, parallel-arm, randomized-withdrawal ABPM study in premenopausal women. The study evaluated daily administration of BMT 1.75 mg SC for 8 days (open-label), followed by randomized (1:1), PBO-controlled withdrawal, stratified by hypertensive status for an additional 8 days. We requested that at least 20% of the subjects have controlled HTN (defined as having two or fewer antihypertensive medications). Subjects with diabetes could also be enrolled. ABPM (24 hour) was conducted at baseline (Day -1) and at the end of the open-label (Day 8) and randomized withdraw (Day 16) periods. The primary endpoint was the intra-subject mean change in SBP from baseline (Day -1) during the daytime period (6:00 a.m. to 10:00 p.m.) on Day 8. The study was designed to exclude a 4 mm Hg increase, assuming an increase of 2 mm Hg and standard deviation of 9 mm Hg.

Results of AMAG-BMT-HSDD-101 were submitted on 23Apr2019. Eligible subjects were premenopausal, nonpregnant females in good general health, between 18 to 55 years of age (inclusive). There were 266 subjects screened, of whom 146 were enrolled and dosed on Day -1. A total of 136 subjects entered the open-label period and the 127 who completed this period of study entered the randomized withdrawal period (64 taking BMT versus 63 taking PBO). A total of 122 subjects completed the randomized withdrawal portion of the study; only two subjects (one BMT and one PBO) had controlled HTN.

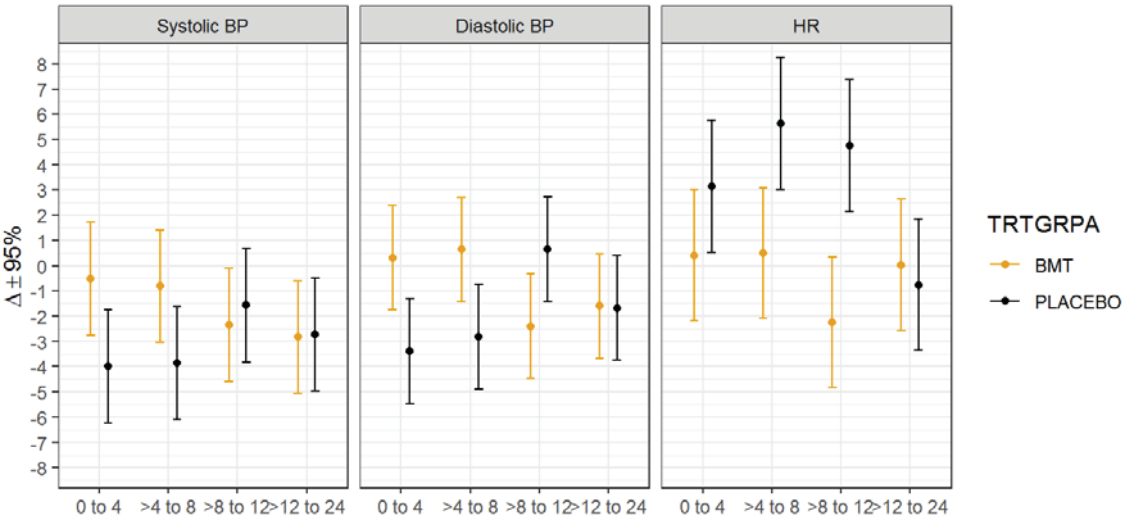
DCaRP evaluated the changes from baseline in the mean SBP, DBP, and HR on Day 8 for the ABPM population; the assessment was consistent with the Applicant's primary analysis and summarized in a review dated 23May2019. Because the changes are time-dependent, the results are shown, grouped into four post-dose time intervals (0 to 4 hours, >4 to 8 hours, >8 to 12 hours, and >12 to 24 hours) below in Figure 30. The results demonstrate that the increase in BP is largest in the first 8 hours post-dose; the reduction in HR is also greatest in the first 8 hours post-dose. These changes appear consistent with the results from Study 54 discussed above and suggest that the peak mean increase in systolic and diastolic BP is 2 to 3 mm Hg.

Figure 30. Change from Baseline (Day -1) to End of Open-Label Treatment (Day 8) for Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Over Time



A comparison of the changes in BP using the same time windows as described above showed that the increase in BP observed after 8 days of dosing in the open-label period did not increase further with 8 additional days of dosing in the randomized withdrawal period. These findings are shown in Figure 31 below.

Figure 31. Change From Day 8 (End of Open-Label Treatment) to Day 16 (End of Randomized Withdrawal) for Patients Receiving BMT/Placebo and BMT/BMT



Black: placebo; orange: bremelanotide (BMT)

This ABPM study demonstrates that the increase in BP with BMT after 16 days of daily dosing is similar to 8 days of dosing, and that the increase in BP is transient during the day and returns to baseline before the expected next dose.

Phase 3 Studies

The phase 3 studies used standardized automated cuff BP assessments for in-clinic visits and throughout safety follow-up. Measurements were obtained predose, 1.0, 1.5, and 2.0 hours after the first in-clinic dose and then at follow-up visits. BP stopping criteria are listed in Trial Design subsection of Section 8.1.1. Mean PBO-subtracted results following the first in-clinic dose are shown in Table 56 below.

Table 56. Phase 3 Change in Mean Manual Cuff Blood Pressure and Heart Rate Following First Dose in Clinic Visit 3

	Study 301			Study 302		
Timepoint (hours)	PBO	BMT	PBO Subtracted Change	PBO	BMT	PBO Subtracted Change
SBP (mm Hg)						
1.0	1.2 (-23, 32)	6.2 (-32, 81)	5	1.2 (-36, 29)	6.8 (-21, 38)	5.6
1.5	1.5 (-26, 38)	6.1 (-62, 73)	4.6	1.0 (-33, 55)	6.9 (-21, 32)	5.9
2.0	1.4 (-32, 38)	7.8 (-33, 83)	6.4	1.7 (-40, 26)	6.4 (-29, 40)	4.2
DBP (mm Hg)						
1.0	0.7 (-24, 20)	3.8 (-54, 43)	3.1	0.4 (-17, 21)	4.2 (-22, 29)	3.8
1.5	1.3 (-38, 58)	3.9 (-66, 43)	3.2	0.8 (-24, 65)	4.9 (-20, 35)	4.1
2.0	1.1 (-36, 32)	4.4 (-58, 47)	3.3	1.5 (-20, 26)	4.4 (-20, 36)	2.9
Pulse (bpm)						
1.0	0.5 (-19, 24)	-4.5 (-41, 17)	-5	0.4 (-24, 25)	-3.8 (-31, 26)	-4.2
1.5	0.9 (-23, 32)	-3.6 (-37, 19)	-4.5	0.6 (-25, 21)	-3.6 (-29, 22)	-4.2
2.0	0.9 (-20, 22)	-3.3 (-40, 21)	-4.2	1.0 (-25, 30)	-2.9 (-25, 20)	-3.9

Abbreviations: BMT bremelanotide, bp blood pressure; bpm beats per minute; DBP diastolic blood pressure; PBO placebo
Source: 301 and 302 CSR, Table 14.3.3.3, page 1100 and 1069, respectively

The remaining in-clinic cuff readings were not timed according to the injection of BMT; therefore, those later vital sign readings may have been acquired off drug making the BP readings less informative.

Adverse Events of Hypertension/Elevated Blood Pressure (Phase 3)

Twelve subjects receiving BMT had TEAEs coded as “blood pressure increased,” “hypertension” or “hypertensive urgency.” Six of the 12 subjects had elevated BP after the first dose of study drug. The first dose of study drug was self-administered in the clinic (Visit 3, Randomization visit). Onset of BP elevations began between 1 hour (first BP assessment) and 2.5 hours post-dose. One of these six patients reported immediate symptoms of headache and vomiting with elevation of DBP mentioned but BP readings were not reported. The other six patients had elevations at routine visits. The timing of the last dose is unknown in those instances.

Limited narratives for Study 301-162-1001 coded two events of “hypertensive urgency,” although the clinical information does not provide adequate support for the AE. The second event, resulting in urgent care and hospital admission, lacked any BP readings. The Applicant was asked to exercise due diligence in obtaining the information. No additional information was submitted.

Table 57. Blood Pressure Increased Cases

USUBJID	Age Race	AECODE	Severity	Completed DB?	TX Start Date/Time	AE Start Date/Time	Doses Prior to AE	Timing Relative to Dose	BP Data
(b) (6)	46 W	BP increased	Mod	Y		(b) (6)	1	1 hour after first dose	139/84, 177/104
	49 W	BP increased	Mild	Y			5	N/A	No readings at time of event; 2 hours later 141/93; (baseline 126/86)
	40 W	BP increased	Mild	N			1	2.5 hours after first dose	159/100; 150/103
	35 W	DBP increased	Mild	N			2	Immediate	SAEs of vomiting, headache, flushing, tachycardia, and elevated DBP. Seen and admitted at urgent care. BP not provided in the narrative. No reading in VS dataset
	47 W	BP increased "transient elevation"	Mild	N			1	1.5 hours	Moderate flushing. Discrepancy between narrative and dataset; per dataset ADAE: 121/79 at baseline, at 1.5 h 155/90 at 1.5 hours, 150/111 on 6Jan2016
	44 B	HTN	Mod	N			8	N/A	136/92, drug withdrawn
	26 B	HTN	Mild	N			4	N/A	146/103, repeat 136/91
	28 W	Hypertensive urgency	Mod	N			1	1.5 hours	136/98 at 11:55 a.m. *Not c/w HTN urgency
		Hypertensive urgency	Mod	N			2	N/A	No clinic BP readings at that time; subject withdrawn *Not c/w HTN urgency
	31 W	BP increased	Mod	N			9	N/A	144/95 at Week 28 unscheduled visit 22Dec2015 169/104

USUBJID	Age Race	AECODE	Severity	Completed DB?	TX Start Date/Time	AE Start Date/Time	Doses Prior to AE	Timing Relative to Dose	BP Data
(b) (6)	34 W	BP increased	Mild	Y		(b) (6)	4	N/A	146/87, repeat 153/85, P109, 28Sep2015 unscheduled 154/77 P109
	33 W	BP increased	Mild	N			1	1.5 hours	129/104 at 1.5 hours 151/95 at 2 hours
	51 W	HTN	Mild	Y			1	2 hours	171/83 at 2 hours, repeat 172/84
		HTN	Mild	Y			3	N/A	148/82, 101 141/89, 101
		HTN	Mild	Y			5	N/A	153/86 at 2:21 p.m., Week 24; 169/90 4Apr2016 at 2:21 p.m. (unscheduled visit)

Abbreviations: ADAE analysis dataset for adverse events, AE adverse event, B black, BP blood pressure, BMT bremelanotide, DB double-blind, DBP diastolic blood pressure, HTN hypertension, Mod moderate, SAE serious adverse events, TX treatment, W white

8.2.7. Hepatic Adverse Events

A single case of acute hepatitis was reported in Study 301 extension study. A delayed 15-day safety report of acute hepatitis for Subject (b) (6) was submitted on (b) (6). We deemed the case consistent with a potential Hy's law case due to elevated AST (maximum 1163 U/L, 40X ULN), ALT (maximum 1065U/L, 43X ULN), TBili (maximum 7.6 mg/dL, 6X ULN), and a slightly elevated alkaline phosphatase. Subject (b) (6) was a 52-year-old white female (DOB (b) (6) age (b) (6) years at enrollment) with history of obesity and HTN who was taking no medications other than BMT. She was randomized into Study 301 on (b) (6) started the open-label phase on (b) (6), with last dose on (b) (6)

After taking 20 doses, she was seen in clinic for an early withdrawal/EOS visit on (b) (6) (Study Day 386) due to recurrent post-injection rhinorrhea. During the visit, it was discovered, to the best of the Applicant's estimate, that she had been experiencing fatigue beginning mid-to-late July. Mild nausea, loss of appetite, unexpected weight change, and increased fatigue began on or about (b) (6). These latter symptoms started approximately 10 days after her last injection on (b) (6) Physical exam noted scleral icterus and dark urine. No inciting factors were reported. She was not hospitalized. Liver test values were highest at time of diagnosis and declined over time (Table 58 and Table 59). The peak in liver tests could not be established. Liver tests were within the normal range during the core phase.

Table 58. Liver Function Tests: Subject (b) (6)

Laboratory Test (Normal Range)	(b) (6)						
AST (10–35 U/L)	1065	969	595	513	220	149	165
ALT (6–29 U/L)	1163	1084	764	712	376	245	183
TBili (0.2–1.2mg/dL)	6.22	7.6	6.9	4.7	3.2	2.5	2.2
Alkphos (33–130 U/L)	145	164	144	153	119	100	100
GGT	210	—	—v	—	—	—	—

Abbreviations: Alkphos alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT gamma-glutamyl transferase, TBili Total Bilirubin; DOP day of presentation

Table 59. Additional Liver Function Tests: Subject (b) (6)

Laboratory Test (Normal Range)	(b) (6) (V1)	(V3)	(V6)	(V9)	(VE4)	(b) (6)		
LDH U/L (not reported)	187	180	171	165	167	372	--	--
Albumin (3.6–5.1g/d)	4.3	4.5	4.6	4.7	4.7	3.9	--	--
Total protein (6.1–8.1 g/dL)	6.8	7.3	7.4	7.7	7.7	6.9	--	--
Protime (9.0–11.5 s)	—	—	—	—	—	—	12.3H	10.3

Abbreviation: LDH lactate dehydrogenase, Protime prothrombin time; V visit

The subject's weight trended downward with change from baseline of -6.9 kg, but she denied using weight loss supplements or drugs. Lisinopril was listed as a medication, but she had never filled the prescription. No recent travel other than the family cabin in North Carolina.

An extensive evaluation was conducted including clinical course, follow-up laboratory work, radiology results (ultrasound), review of nonclinical and biopharmacological studies, and a mechanistic search on melanocortin receptor and MSH-mediated pathway.

Additional clinical course

The subject was followed for an additional 24 months. During this period, she had a small bump in AST/ALT of 70 and 59 U/L, respectively, on (b) (6) with return to normal range by (b) (6). Repeat labs (b) (6) show normal AST/ALT but an increase in TBili 1.8 mg/dL (previously 1.2 to 1.4 range). The protime was normal. In response to our (b) (6), Information Request for additional information in an attempt to elucidate the cause of her continued LFT abnormalities (e.g., diabetes, nonalcoholic fatty liver disease, alcohol usage, etc.), the following was submitted: magnetic resonance image showing normal liver and mild splenomegaly; normal AST/ALT and normal TBili; normal HbA1c. Additional labs included elevated high sensitivity C-reactive protein (interpreted as high relative CV risk), normal protime, and normal hepatic panel, including Hepatitis E, immunoglobulins, gamma-glutamyl transferase, and iron studies. The subject also had an elevated ferritin of 719 (normal range 15–150 ng/mL) on (b) (6). Repeat ferritin on (b) (6) was normal (98, range 10–232 ng/mL). The subject was followed for a total of 2.4 years.

Table 60. Follow-Up Laboratory Data: Subject (b) (6)

Laboratory Test (Normal Range)	(b) (6)				No Interval Readings	(b) (6)		
AST (10–35 U/L)	34	59	49	24		30	41	23
ALT (6–29 U/L)	27	70	63	21		28	44	21
TBili (0.2–1.2mg/dL)	1.4	1.4	1.2	1.2		1.8	1.5	1.1
Alkphos (33–130 U/L)	88	95	91	80		78	87	85

Abbreviations: ALT alanine aminotransferase, Alkphos alkaline phosphatase, AST aspartate aminotransferase, TBili Total Bilirubin

The subject was confirmed to have been premenopausal at the time of the study. Current menopausal status is unknown. She continues to deny acetaminophen use/abuse, alcohol intake or use of herbal preparations. At a follow up liver consultation on (b) (6), the subject was given a diagnosis of Gilbert's syndrome and "resolved DILI;" no further workup was deemed necessary.

Result of the global database search for additional cases revealed one additional occurrence of LFT elevation not deemed a Hy's law case occurring in alcohol study PT-141-2002-11 (Subject (b) (6) using intranasal BMT+ethanol, described below.

Subject (b) (6)

A 40-year-old Hispanic female who had an ALT of 31 U/L at screening and 39 U/L at baseline (normal range <40 U/L). At discharge, approximately 12 hours after receiving BMT+ethanol, the subject had an ALT of 124 U/L, with follow up level of 45 U/L, 6 days later. AST was 28 U/L at the screening and baseline visits (normal range <37 U/L); with increase to 71 U/L at discharge with return to baseline (28 U/L) 6 days. This event was labeled an adverse event.

Table 61. Subject (b) (6) Liver Function Tests and Dosing History

	Screening	Baseline	Day 1	Day 4	Day 7	Discharge	Follow-up
	(b) (6)						(b) (6)
ALT (<40 u/L)	31	39	BMT	Ethanol	BMT+ Ethanol	124	45
AST (<37 u/L)	28	28				71	28

Abbreviations: BMT bremelanotide, ALT alanine aminotransferase, AST aspartate aminotransferase

During the IND phase, DBRUP consulted with DILI experts in the Agency. We concluded (letter dated 12Jul2017) that the etiology of the index case of acute liver injury had not been determined. The expert opinion was that DILI was not a probable cause and this assessment was shared by the Applicant's two independent reviews; however, DILI remained "possible" per Roussel Uclaf Causality Assessment Method and Drug-Induced Liver Injury Network scoring methodology.

The ISS reports one case of acute hepatitis (index case discussed above, Subject (b) (4) in Study 301 OLE). At the time of the index case, all subjects had completed the core study, but the OLE was ongoing. The Applicant analyzed AEs in the clinical program using the Hepatic Disorders Standardised MedDRA Query to search for additional cases (see Table 62 below). One subject was found with a GGT elevation (rated "severe") who was randomized to placebo. There was one additional elevation of transaminase between 3X and 5X ULN, Subject (b) (6), a 20-year-old female with maximum AST of 151 U/L at Week 32 of core phase (ALT of 53 and normal range TBili). Baseline values were within normal range.

Table 62. Adverse Events of SMQ Hepatic Disorder in SC BMT Phase 3 Core and Extension Studies in HSDD, Safety Population, Analysis Group A1A

	Core Studies		EXT Studies	Core/EXT Studies Combined*
System Organ Class Preferred Term	PBO (N=620) n (%)	BMT 1.75 mg (N=627) n (%)	BMT 1.75 mg (N=684) n (%)	BMT 1.75 mg (N 1057) n (%)
Any adverse event	6 (1.0)	6 (1.0)	8 (1.2)	14 (1.3)
Investigations	6 (1.0)	4 (0.6)	7 (1.0)	11 (1.0)
Blood bilirubin increased	0	2 (0.3)	2 (0.3)	4 (0.4)
Aspartate aminotransferase increased	1 (0.2)	0	3 (0.4)	3 (0.3)
Liver function test abnormal	2 (0.3)	1 (0.2)	1 (0.1)	2 (0.2)
Alanine aminotransferase increased	2 (0.3)	0	2 (0.3)	2 (0.2)
Gamma-glutamyltransferase increased	3 (0.5)	1 (0.2)	0	1 (<0.1)
Hepatic enzyme increased	0	0	1 (0.1)	1 (<0.1)
Congenital, familial, and genetic disorders	0	1 (0.2)	0	1 (<0.1)
Hereditary haemochromatosis	0	1 (0.2)	0	1 (<0.1)
Hepatobiliary disorders	0	0	1 (0.1)	1 (<0.1)
Hepatitis acute	0	0	1 (0.1)	1 (<0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2)	0	1 (<0.1)
Hepatic adenoma	0	1 (0.2)	0	1 (<0.1)

Abbreviations: BMT bremelanotide, PBO placebo, HSDD hypoactive sexual desire disorder, SC subcutaneous, SMQ standardised MedDRA query, EXT extension
* All subjects exposed to BMT in both core and extension
Source: Applicant Table 25, ISS page 79

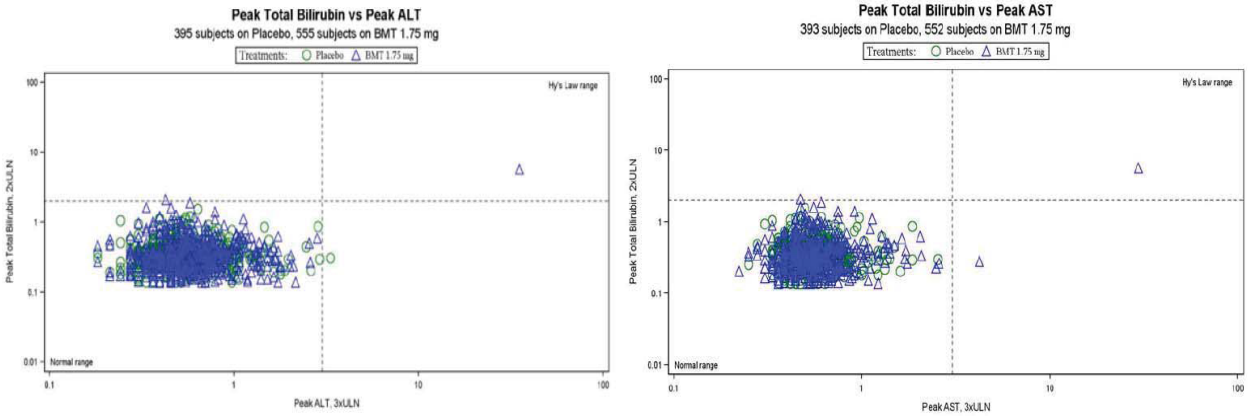
Other than the index case with elevated AST/ALT (>40X ULN) and TBili (6X ULN), there were few outliers in these markers (see Table 63 below). The greatest number of occurrences involved TBili >1.5X to 2X ULN. Evaluation of drug-induced serious hepatotoxicity plots of the available data in phase 3 shows the two subjects already discussed above (b) (6) (see Figure 32 below). FDA confirmed these plots. No worrisome trends were identified in the laboratory data although the single case of hepatitis will be included in labeling.

Table 63. Post-Baseline Outlier Liver Function Test Results in SC BMT Phase 3 Core and Extension Studies, Safety Population, Analysis Group A1A

	Liver Function Test Values		
Variable Category	BMT in Core/EXT Studies (N=627)	BMT in EXT Study Only (N=430)	Total BMT (N=1057)
ALT			
>3–5X ULN	0	1 (0.3)	1 (0.1)
>5–10X ULN	0	0	0
>10–20X ULN	0	0	0
>20X ULN	1 (0.2)	0	1 (0.1)
AST			
>3–5X ULN	1 (0.2)	0	1 (0.1)
>5–10X ULN	0	0	0
>10–20X ULN	0	0	0
>20X ULN	1 (0.2)	0	1 (0.1)
Elevated ALT or AST levels			
ALT or AST Elevation >3X ULN	1 (0.2)	1 (0.3)	2 (0.2)
ALT or AST Elevation >5X ULN	1 (0.2)	0	1 (0.1)
Total Bilirubin			
>1.5–2X ULN	6 (1.1)	1 (0.3)	7 (0.7)
>2–5X ULN	1 (0.2)	0	1 (0.1)
>5X ULN	1 (0.2)	0	1 (0.1)
Potential Hy's Law			
ALT or AST >3X ULN and total bilirubin >2X ULN	1 (0.2)	0	1 (0.1)

Abbreviations: BMT bremelanotide, ALT alanine aminotransferase, AST aspartate aminotransferase, SC subcutaneous, ULN upper limit of normal, EXT extension
Source: Applicant Table 45, ISS page 118

Figure 32. Evaluation of Drug-Induced Serious Hepatotoxicity Plots for Phase 3 Combined



Abbreviations: ALT alanine aminotransferase, AST aspartate aminotransferase, BMT bremelanotide, ULN upper limit of normal
Source: ISS, Figure 5, pages 120–121

8.2.8. Skin Disorders

Nonclinical data indicate that BMT stimulates MCR-1 and an imbalance in hyperpigmentation/ skin discoloration was noted in the clinical program. The mechanism leading to this focal hyperpigmentation in women is unknown.

Skin Lesions/Neoplasms

During development of BMT, reports on melanocytic nevi and cutaneous malignancy were as follows:

- No subject experienced a cutaneous malignancy.
- One subject (b) (6) experienced changing mole with pigment and shape change that was mild, not related to study drug, recovered/resolved, and did not lead to dose change. Per ae.xpt dataset, the onset of the event began within the first month of treatment and resolved between the 10th and 11th doses. No excision was reported.
- One subject (b) (6) experienced "melanocytic nevus, compound with moderate atypia" that was mild, possibly related to study drug, recovered/resolved, and did not lead to dose change.

Focal Hyperpigmentation/Skin Discoloration

(See also Treatment-Emergent Adverse Events subsection in Section 8.2.4)

Following our request, the Applicant provided MedDRA mapping of verbatim terms ("AEDECOD" = skin discoloration, pigmentation disorders, and hyperpigmentation), narratives/case report forms for affected subjects, and an analysis of pigmentation-related AEs (response to 1Nov2018 Information Request). Table 64 shows the skin AEs by race and duration of exposure to 1.75 mg BMT. Of note, no photographs were taken as part of the development program.

Per the Applicant's reporting, 20 (1.9%) of 1057 subjects had a TEAE of hyperpigmentation/ discoloration in the phase 3 and extension studies. Events included skin hyperpigmentation, skin discoloration, gingival hyperpigmentation, lip discoloration, melanocytic nevus, pigmentation disorder, scleral pigmentation, seborrheic keratosis, and skin lesion. With intermittent use in phase 3, the onset of events did not appear to be related to duration of exposure; BMT exposure >15 months (five subjects [3.5%]), BMT exposure >12 to 15 months (four subjects [1.8%]), and BMT exposure >3 to 6 months (five subjects [2.5%]). However, when BMT was dosed daily (TID for 15 days, max dose 6.5 mg) the incidence of hyperpigmentation was 63% with onset as early as Day 1; or following once daily administration (1.75 mg SQ) for 8 days the incidence was 38%. A higher incidence of events was seen in black subjects (8.5%) versus white subjects (1.1%). No difference in exposure intervals was noted. No hyperpigmentation disorders were reported in subjects with race recorded as "other."

Table 64. Treatment-Emergent Adverse Events of Hyperpigmentation/Discoloration (Pigmentation Disorders) by Race and Duration of BMT Exposure in BMT Phase 3 Core and Extension Studies, Safety Population

	Subject Groups with Duration of BMT 1.75 mg SC Exposure											
	>0 - 3 Months (N=223) n (%)			>3 - 6 Months (N=199) n (%)			>6 - 9 Months (N=206) n (%)			>9 - 12 Months (N=63) n (%)		
Preferred term	White N=202 n (%)	Black N=15 n (%)	Other N=6 n (%)	White N=167 n (%)	Black N=25 n (%)	Other N=7 n (%)	White N=181 n (%)	Black N=21 n (%)	Other N=4 n (%)	White N=48 n (%)	Black N=12 n (%)	Other N=3 n (%)
Any AE of pigmentation disorder	**1 (0.5)**	**2 (1.3)**	**0**	**2 (1.2)**	**3 (12.0)**	**0**	**2 (1.1)**	**0**	**0**	**0**	**1 (8.3)**	**0**
Skin hyperpigmentation	0	1 (6.7)	0	1 (0.6)	3 (12.0)	0	1 (0.6)	0	0	0	0	0
Skin discolouration	0	0	0	1 (0.6)	0	0	0	0	0	0	1 (8.3)	0
Gingival hyperpigmentation	0	0	0	0	1 (4.0)	0	0	0	0	0	0	0
Lip discolouration	0	1 (6.7)	0	0	0	0	0	0	0	0	1 (8.3)	0
Melanocytic naevus	0	0	0	0	0	0	0	0	0	0	0	0
Pigmentation disorder	1 (0.5)	0	0	0	0	0	1 (0.6)	0	0	0	0	0
Scleral pigmentation	0	0	0	0	0	0	0	0	0	0	0	0
Seborrhoeic keratosis	0	0	0	0	0	0	0	0	0	0	0	0
Skin lesion	0	0	0	0	0	0	0	0	0	0	0	0

	Subject Groups with Duration of BMT 1.75 mg SC Exposure						Total			
	>12 – 15 Months (N=222) n (%)			>15 Months (N=144) n (%)			Any BMT Exposure (N=1057) n (%)			
Preferred term	White N=190 n (%)	Black N=24 n (%)	Other N=8 n (%)	White N=123 n (%)	Black N=20 n (%)	Other N=1 n (%)	White N=911 n (%)	Black N=117 n (%)	Other N=29 n (%)	Total N=1057 n (%)
Any AE of pigmentation disorder	**2 (1.1)**	**2 (8.3)**	**0**	**3 (2.4)**	**2 (10.0)**	**0**	**10 (1.1)**	**10 (8.5)**	**0**	**20 (1.9)**
Skin hyperpigmentation	0	1 (4.2)	0	0	1 (5.0)	0	2 (0.2)	6 (5.1)	0	8 (0.8)
Skin discolouration	0	1 (4.2)	0	2 (1.6)	1 (5.0)	0	3 (0.3)	3 (2.6)	0	6 (0.6)
Gingival hyperpigmentation	0	0	0	0	1 (5.0)	0	0	2 (1.7)	0	2 (0.2)
Lip discolouration	0	0	0	0	0	0	0	2 (1.7)	0	2 (0.2)
Melanocytic naevus	2 (1.1)	0	0	0	0	0	2 (0.2)	0	0	2 (0.2)
Pigmentation disorder	0	0	0	0	0	0	2 (0.2)	0	0	2 (0.2)
Scleral pigmentation	0	0	0	0	1 (5.0)	0	0	1 (0.9)	0	1 (<0.1)
Seborrhoeic keratosis	1 (0.5)	0	0	0	0	0	1 (0.1)	0	0	1 (<0.1)
Skin lesion	0	0	0	1 (0.8)	0	0	1 (0.1)	0	0	1 (<0.1)

Abbreviations: AE adverse event, BMT bremelanotide, AE adverse event
Source: Applicant Table 2, response to 1Nov2018 Information Request, page 7

The Applicant did not address reversibility of the focal hyperpigmentation. Using our query, 18 of the 20 subjects had qualifying hyperpigmentation/skin discoloration, excluding melanocytic nevi and seborrheic dermatosis. Using this subset of 18 subjects, nine subjects had unresolved hyperpigmentation at the time of reporting. There was no difference between black and white

subjects: four subjects in the core phase (two black, two white), and five subjects in extension (two black, three white) did not experience resolution of hyperpigmentation/skin discoloration.

A consultative review conducted by the Division of Dermatology and Dental Products (DDDP) identified 13 total subjects with hyperpigmentation related AEs. The analysis was limited to those subjects whose verbatim terms clearly described increased pigmentation (i.e., "darkening," "darkened") and excluded subjects with verbatim terms that did not clearly describe increased pigmentation (i.e., "discoloration"). The primary safety population included query of the two phase 3 studies and Study 54 (those exposed to 1.75 mg) where the study population, dosing, formulation, and dosing regimen were similar.

Further limiting the analysis to phase 3, no subjects on PBO experienced a hyperpigmented-related AE, while six (1%) subjects on BMT experienced eight hyperpigmented-related AEs. Of the eight reported hyperpigmentation AEs, four had resolved at the time of reporting. Three of these subjects continued into the open-label period. During the open-label period, an additional seven (1%) subjects experienced hyperpigmented-related AEs; six of these seven subjects had previously received PBO while one subject received BMT in the double-blind phase. No events were included from the phase 2 study based on the criteria.

Table 65. Subjects Experiencing Hyperpigmentation During Trials BMT-301 and BMT-302

	Randomization at Baseline	
	PBO	BMT
Double-blind treatment[1]	0/620 (0%)	6/627 (1%)
Open-label extension[2]	6/684	1/684

Abbreviation: BMT bremelanotide, PBO placebo
[1] Double-blind treatment period was 24 weeks in the phase 3 trials and 12 weeks in the phase 2b study.
[2] Open-label extension (up to 52 weeks long) and includes only subjects from phase 3 trials BMT-301 and -302.
Source: Dermatology Consult, compiled by statistical reviewer P. Imbriano

Table 66. Subjects Reporting Their First Hyperpigmentation-Related AE[1] by Race

	PBO-Controlled Period Subjects with AE/Subjects (%)		OLE Period[2] Subjects with AE/Subjects (%)
	BMT (N=627)	PBO (N=620)	N=680
African American	3/73 (4.1)	0/71 (0.0)	4/70 (5.7)
Caucasian	3/536 (0.6)	0/531 (0.0)	3/590 (0.5)
Other	0/18 (0.0)	0/18 (0.0)	0/20 (0.0)

Abbreviations: BMT bremelanotide, AE adverse event, PBO placebo, OLE open-label extension
[1] Hyperpigmentation-related AE terms included: skin spot discoloration right cheek; darkened pigmented spot on face; dark spots on face and ear; darkened areolas, bilateral breasts; facial skin darkening; skin darkening; darkening of facial skin; darkening of skin; hyperpigmentation (6); hyperpigmented areas of face; increased pigmentation; and darkening of hyperpigmented areas of skin on face.
[2] Open-label extension includes only subjects from phase 3 trials BMT-301 and -302
Source: Dermatology Consult, compiled by statistical reviewer P. Imbriano

A higher proportion of black subjects (approximately 7-fold) compared to white subjects experienced BMT-related hyperpigmentation in the PBO-controlled phase (4.1% black versus 0.6% white) and in open-label extension periods (5.7% black versus 0.5% white).

In a consultative review dated 4Jan2019, DDDP concluded the following:

- During the development program for BMT, approximately 1% of subjects reported AEs of hyperpigmentation. All subjects who reported these AEs were treated with BMT. Therefore, it is reasonable to conclude that an AE of hyperpigmentation is due to the study drug. Of subjects who experienced hyperpigmentation during the PBO-controlled period, half (four subjects) reported resolution of this AE. Additionally, of subjects who experienced hyperpigmentation, a higher proportion were black. Most subjects developed hyperpigmentation during the first 6 months of exposure to BMT. The most frequently reported anatomical locations of pigmentary changes were on the face, breasts, and gingiva.
- No malignant melanomas or other cutaneous malignancies were reported during the development of BMT.

Given the greater proportion of black subjects experiencing a hyperpigmentation-related AE compared to Caucasian subjects (4.1% versus 0.6% in the PBO-controlled period and 5.1% versus 0.5% in the open-label period, respectively), DDDP recommended inclusion of the following statement in Section 5 Warnings and Precautions of labeling because the pigmentary changes reported were noted in aesthetically important anatomical locations (face and gingiva):

> *Focal Hyperpigmentation: In controlled clinical trials hyperpigmentation, including face, gingiva, and breasts, were reported in subjects who received BMT. Patients with dark skin were more likely to develop hyperpigmentation. Complete resolution of hyperpigmentation did not occur in some subjects.*

DDDP recommended that routine skin examination would be adequate to monitor cutaneous malignancies in a pro-melanogenic state. DDDP did not recommend additional postmarketing evaluation for skin malignancy.

8.2.9. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable. All COA analyses that pertained to safety/tolerability were exploratory and were not informative for labeling purposes.

8.2.10. Safety Analyses by Demographic Subgroups

Only premenopausal women were enrolled in the phase 2/3 studies. Safety assessment by sex or menopausal status is not applicable.

The majority of subjects enrolled in the double-blind portion of phase 3 were white (83%), with black subjects making up 12% of the enrolled population. The remaining populations were too small for making comparisons. There were greater rates of AEs in the BMT group in the white population (e.g., nausea, flushing, headache, vomiting, etc.). However, there were greater rates of specific events, such as injection-site reactions and skin pigmentation (see Treatment-Emergent Adverse Events and Adverse Reactions) in the black population.

Table 67. Subjects With Treatment-Emergent Adverse Events by Race (>2% Difference)

	White				Black			
AECODE	**BMT**		**PBO**		**BMT**		**PBO**	
Adverse Events	514 (81%)		538 (85%)		76 (12%)		76 (12%)	
Nausea	236	46%	7	1%	10	13%	0	0%
Flushing	122	24%	3	1%	2	3%	0	0%
Injection site (all)	110	21%	55	10%	32	42%	7	9%
Headache	64	12%	10	2%	2	3%	3	4%
URTI	31	6%	37	7%	1	1%	1	1%
Vomiting	30	6%	1	0%	0	0%	0	0%
Fatigue	20	4%	2	0%	1	1%	0	0%
Cough	19	4%	8	1%	1	1%	0	0%
Hot flush	17	3%	1	0%	0	0%	0	0%
Dizziness	13	3%	3	1%	0	0%	0	0%
Nasal congestion	13	3%	3	1%	0	0%	0	0%
Abdominal pain (all)	20	4%	8	1%	0	0%	0	0%
Hypertension	2	0%	2	0%	2	3%	1	1%
CK increased	0	0%	0	0%	3	4%	0	0%
Skin hyperpigmentation	1	0%	0	0%	3	4%	0	0%

Abbreviation: BMT bremelanotide, PBO placebo, URTI upper respiratory tract infection
Source: Compiled from ADAE.xpt and dm.xpt

With respect to ethnicity, the majority of subjects were non-Hispanic or non-Latino (n=1141) compared to 106 subjects of Hispanic or Latino descent. Nausea, flushing, upper respiratory infection, dizziness, and fatigue were the most common AEs among Hispanics/Latinos, and the incidences were similar to the population, overall.

In terms of country of origin, enrolled subjects were primarily from the United States (97%), rendering adequate comparison by country (United States versus Canada) not feasible.

8.2.11. Specific Safety Studies/Clinical Trials

Alcohol Interaction Study (PT-141-2002-11)

Study design: This is a phase 1, three-way crossover, evaluating the effect of a single 20 mg intranasal (IN) dose of BMT (or PBO) with 0.6 g/kg ethanol equivalent to 4 oz. vodka, or two glasses of wine, or three beers (or PBO drink) in healthy men and women. The 20 mg IN dose produces a mean BMT C_{max} value approximately 2.5-fold the mean C_{max} of 1.75 mg SC. Subjects were randomized to receive all three study treatments (A-C) in one of six different sequences (1

through 6). There was a 2-day washout between doses. Dosing was to occur at the same time for each individual and was to be between 0800 and 1000 hours. Consumption of ethanol was followed by nasal spray administration 10 minutes after completion of the ethanol drink. The primary objectives were hemodynamic effects, PK, safety, and tolerability.

Table 68. Treatment Groups

Treatment A: BMT	Treatment B: BMT+Ethanol	Treatment C: Ethanol
20 mg IN BMT	20 mg IN BMT	PBO spray
PBO drink	0.6 g/kg ethanol	0.6 g/kg ethanol

Abbreviation: BMT bremelanotide, PBO placebo, IN intranasal

The study randomized 24 healthy male (n=12) and female (n=12) subjects, ages 21 to 45, weight 50 kg to 100 kg. Men were included to assess safety, tolerability, and potential pharmacokinetic and pharmacodynamic interactions. Baseline alcohol usage was limited to ≤3 drinks per day/21 drinks per week. Nondrinkers were excluded.

Safety Results

There were no deaths, serious AEs, or discontinuation due to AEs. Numerically, there were more subjects with AEs in the BMT+ethanol (treatment B) (75%) compared to either BMT alone (treatment A) (66%) or ethanol alone (treatment C) (58%). There were few hemodynamic AEs (see Table 69). The incidence of flushing was higher with bremelanotide plus ethanol compared to alcohol alone, but similar to the incidence with bremelanotide alone. The incidence of headache was higher with bremelanotide plus ethanol compared to bremelanotide alone, but similar to the incidence with ethanol alone. The incidence of other adverse reactions was similar across treatment groups. The incidence of abnormal orthostatic blood pressure reductions was comparable between the bremelanotide plus ethanol group and the ethanol alone group.

Table 69. Hemodynamic Adverse Events by Treatment Group

Adverse Event	BMT+Ethanol	BMT	Ethanol
SBP decreased	1 (4%)	0	0
Dizziness	2 (8%)	1 (4%)	1 (4%)
Dizziness postural	0	1 (4%)	1 (4%)
Syncope	1 (4%)	0	0

Abbreviations: BMT bremelanotide, SBP systolic blood pressure
Source: Compiled from AE.xpt

Of note, there was one event of decreased SBP in the BMT+ethanol group (Subject (b) (6), two subjects with postural dizziness (one each in BMT (Subject (b) (6)) and ethanol (Subject (b) (6)) groups), and one syncope in BMT+ethanol group (Subject (b) (4). See narratives below. There were also four events of dizziness across the treatment groups.

Narratives

Decreased SBP (Subject (b) (6)

A 27-year-old Hispanic female subject had an AE of an asymptomatic decrease in SBP after receiving BMT+ethanol; the decrease in BP was reported as mild in intensity and related to treatment. This subject was found to have a sitting BP of 80/60 mm Hg at 10:00 a.m. (approximately 2 hours after the start of the ethanol drink). However, this subject had a predose BP of 94/70 mm Hg and had relatively low BP values throughout the day and on other dosing days as well (BP averaged approximately 90/60 mm Hg during the study).

This subject also reported mild flushing beginning at 8:28 a.m., which resolved at 9:30 a.m. on this same day. This sitting SBP of 80 mm Hg was reported as an AE because it was <85 mm Hg, which met the protocol-specified criteria for vital signs of potential clinical concern.

Postural hypotension (Subject (b) (6)

A 40-year-old Hispanic female subject experienced postural hypotension (reported by the investigator as orthostatic lightheadedness) after BMT IN. This AE was reported at 10:16 p.m. at the time the subject arose from the sitting to immediate standing positions for the 2-hour postdose vital signs check and was considered mild and possibly related to treatment. The subject's sitting vital signs at this time point were BP 124/88 mm Hg and pulse rate of 70 bpm, immediate standing BP 130/92 mm Hg and pulse rate of 80 bpm, and 2-minute standing BP 126/84 mm Hg and pulse rate of 84 bpm. Thus, although the subject reported feeling lightheaded upon position change, this could not be corroborated with orthostatic vital signs changes. The subject was noted to have a normal glucose value at this time point (83 mg/dL; normal range 65-139 mg/dL for a random, nonfasting specimen).

Syncope (Subject (b) (6)

A 36-year-old black male subject who experienced a 15-second syncopal episode after receiving BMT+ethanol (BP 114/80 mm Hg at the time of episode). This episode occurred approximately 2 hours and 30 minutes after the start of the ethanol/orange juice drink. Analysis of serial plasma glucose levels for this subject demonstrated a substantial drop to 51 mg/dL after a temporary orange juice induced increase. Normal nonfasting plasma glucose levels range from 65 mg/dL to 139 mg/dL. The glucose load in the 532 mL of orange juice, which was ingested after an overnight fast, likely accounted for the reactive hypoglycemia observed in this subject. This pattern of reactive hypoglycemia was observed in this subject across all three treatments. This finding prompted the Principal Investigator and Applicant to examine serial glucose levels in all subjects using back-up PK plasma samples. With the exception of this subject, there was no evidence in any subject during any treatment of an effect of BMT and/or ethanol on serial glucose levels, notwithstanding the modest and transient increase in serum glucose after orange juice ingestion. Therefore, the post-treatment reactive hypoglycemia that is correlated with the syncopal episode in one subject appears to be an isolated occurrence.

This event led to the Applicant adding serial glucose measurements at predose and 15, 30, 45 minutes and at 1, 2, 3, 4, 8, and 12 hours using the backup PK plasma samples. See Laboratory results section.

The most common events (occurring at a higher incidence in the BMT+ethanol group than BMT alone with comparison to ethanol alone) were headache (20% versus 4% versus 17%), somnolence (29% versus 13% versus 38%), hiccups (8% versus 0% versus 0%), feeling hot (8% versus 4% versus 0%), dizziness (8% versus 4% versus 4%) and nasal congestion (8% versus 4% versus 0%).

As the study enrolled both males and females, female subjects were analyzed separately. A total of 92% of women in BMT+ethanol group compared to 58% in the BMT group had at least one AE (compared to 75% of the ethanol group, suggesting the increased effect is partly due to ethanol intake). The most frequent AEs seen in the BMT+ethanol group (compared to BMT group) were headache (42% versus 8%), dizziness (16.7% versus 8.3%, compared to 8.3% with ethanol alone), hiccups, nasal congestion, and flushing. The rates of headache and dizziness were 2-fold greater in women than in the male/female population combined. The incidence of nausea in the BMT+ethanol group was equal to that in the BMT alone group, and somnolence was greatest in the ethanol group. The decreased BP event (BMT+ethanol group) and one of the postural dizziness events (BMT) occurred in female subjects, as described above.

One subject had documented symptomatic hypoglycemia (see Subject (b) (6) above). Blood glucose was 51 mg/dL with a syncopal episode. For all other subjects, there was a transient increase in glucose followed by a return to baseline.

There was an increase in the mean ALT and AST values attributable to the ethanol with an approximate 1.5- to 3-fold reversible increase in serum transaminases in some subjects. Subject (b) (6) had an AE of ALT elevation. An increased alanine aminotransferase (increased ALT or SGPT) of moderate intensity was reported after receiving BMT+ethanol. Subject (b) (6) also had a 3-fold increase in ALT (see Section 8.2.7).

Vital Sign Assessment

Vital signs were recorded in three different positions (sitting, immediate standing, and 2-minutes standing). Over the 12-hour postdose period there were generally small mean increases or decreases in blood pressure across treatment groups. HR increased across the entire postdose period. The BP changes in the BMT+ethanol group were generally comparable to or favorable to changes seen with BMT alone or ethanol alone except at a few timepoints, but even at those timepoints, mean changes between groups were small.

There were more outliers with SBP increases >20 mmHg in the BMT alone group compared to BMT+ETOH group (8 versus 3) (compared to 3 in ethanol alone group). Similar trends were seen

in outliers in DBP increases >20 mmHg, 19 in BMT alone versus 10 in BMT +ETOH and 9 in ETOH alone. There was one subject with orthostatic BP change <90 mmHg (Subject (b) (6) discussed above.)

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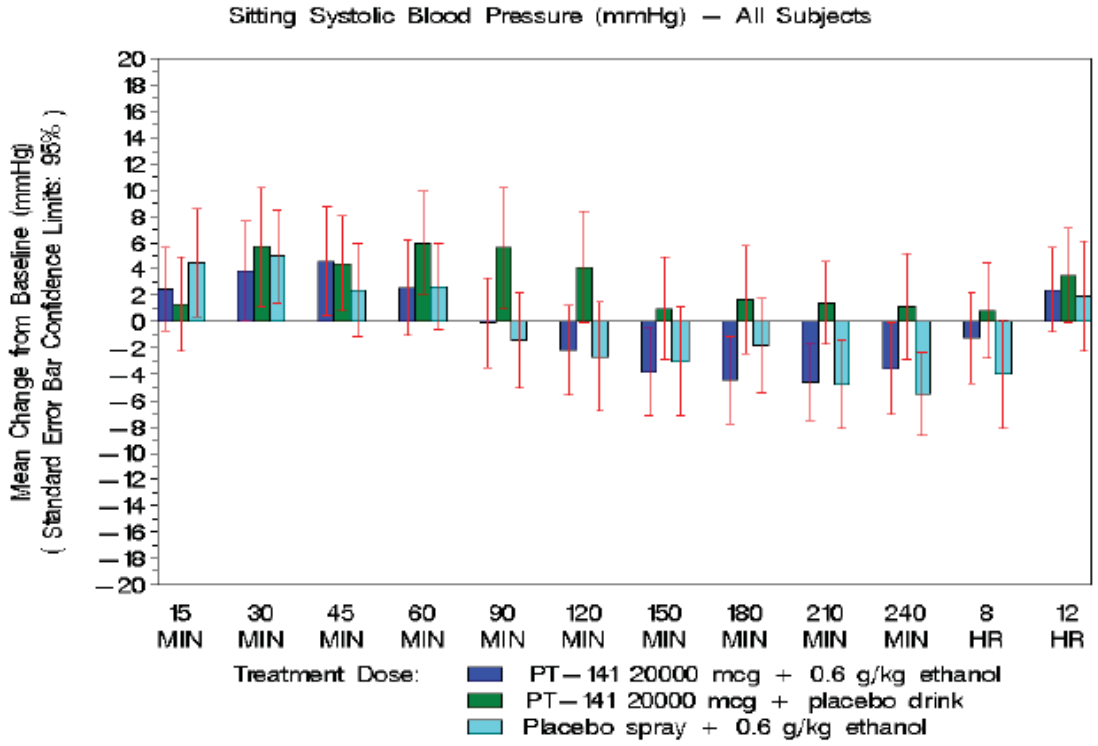
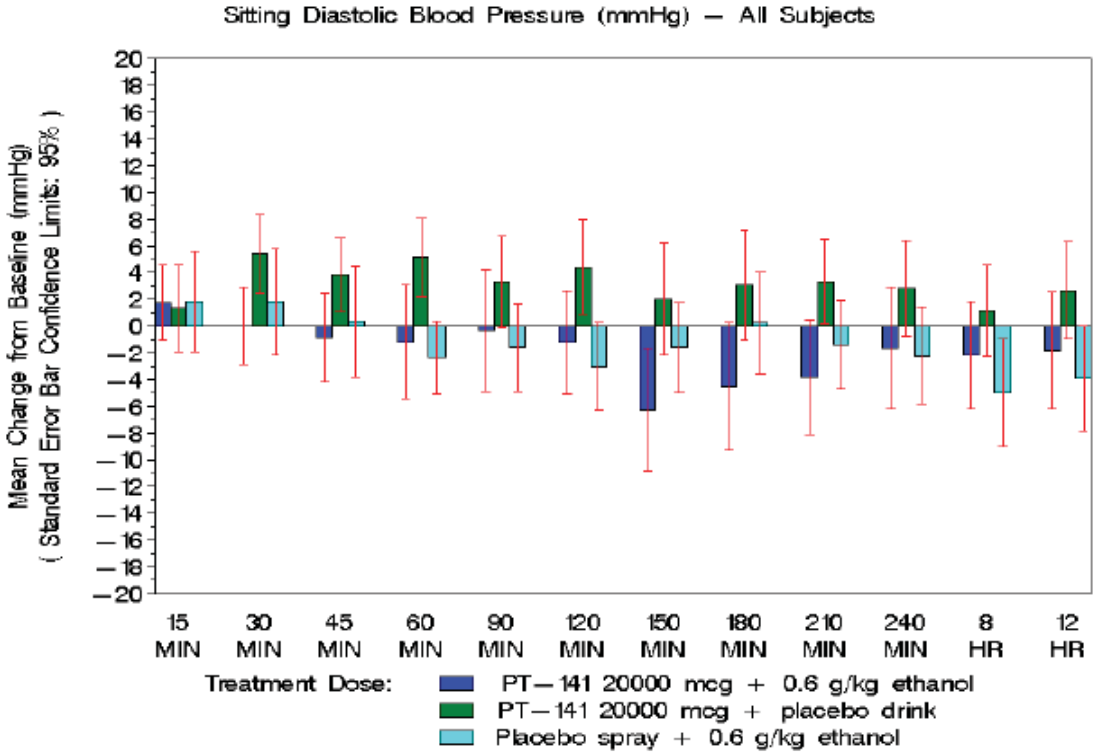
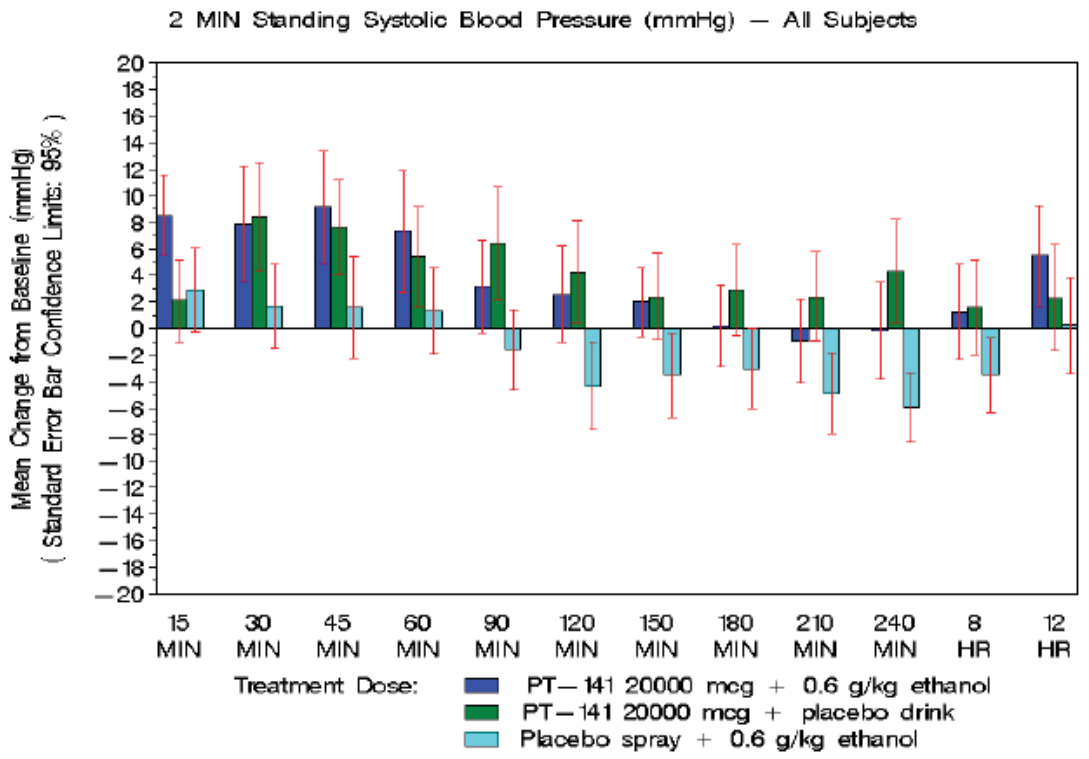
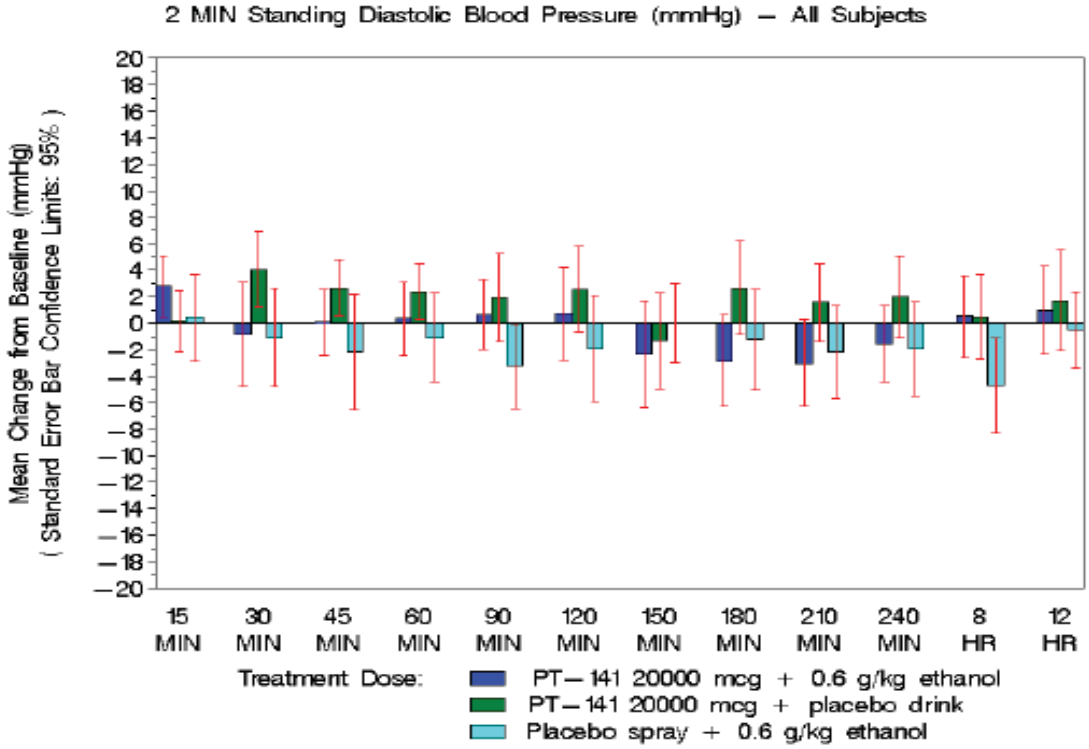
Figure 33. Mean Changes Systolic Blood Pressure and Diastolic Blood Pressure: Sitting and 2 Minutes Standing, All Subjects





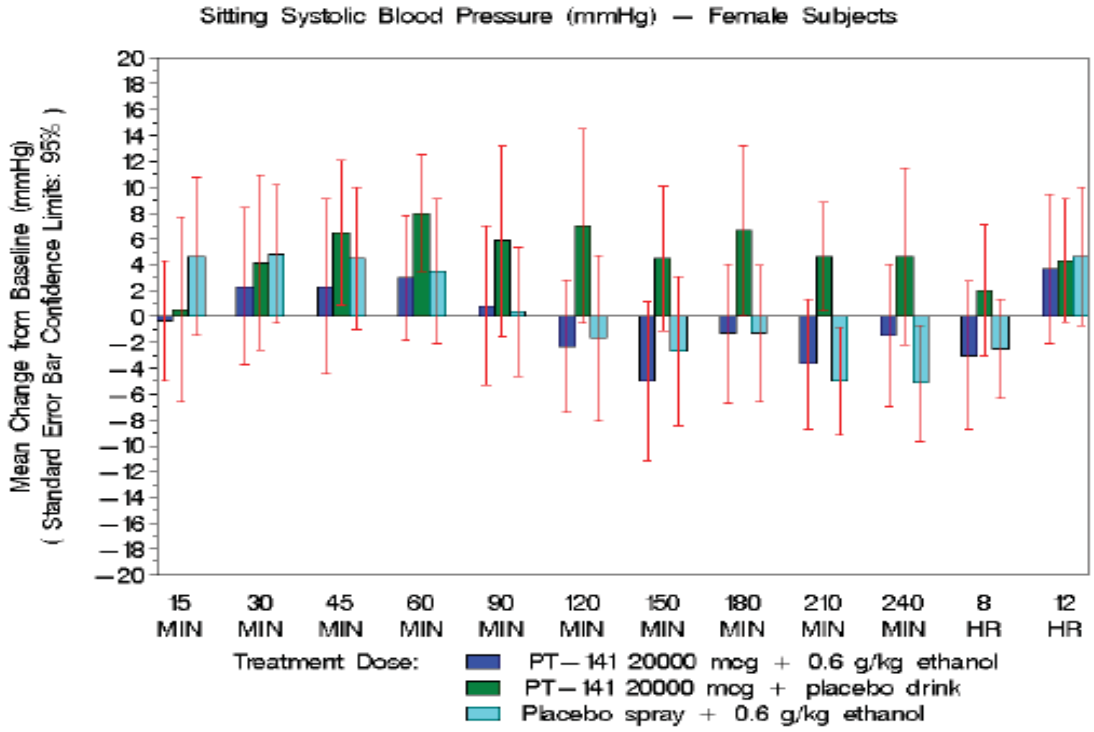


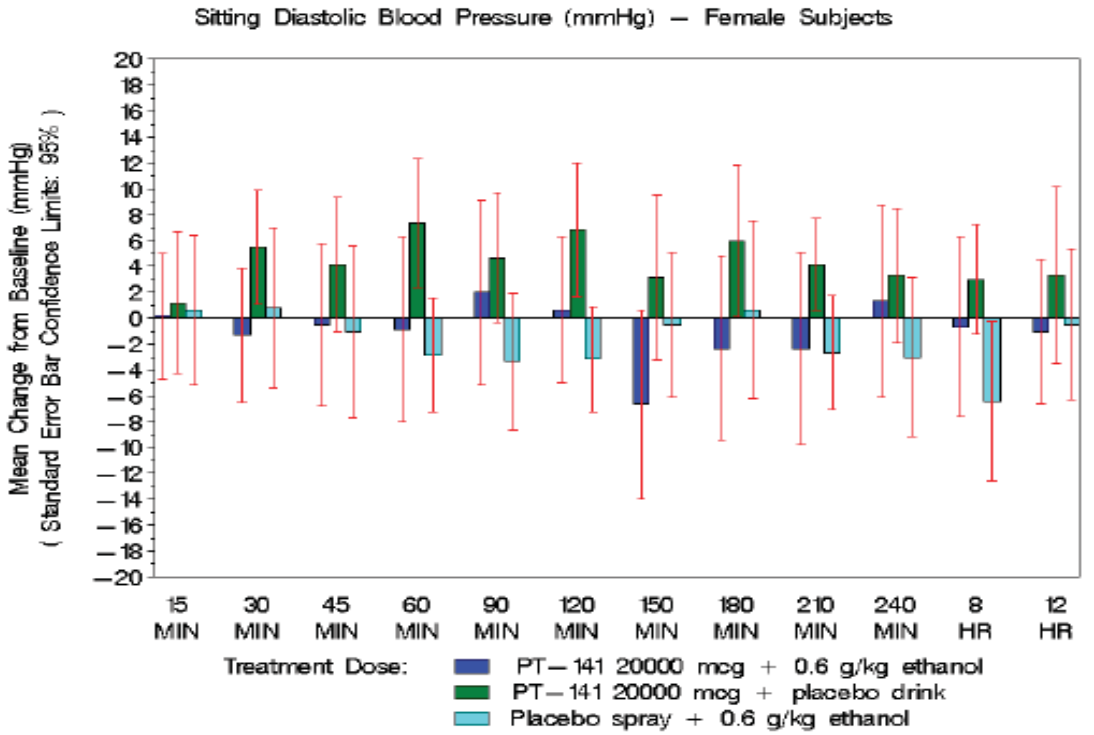


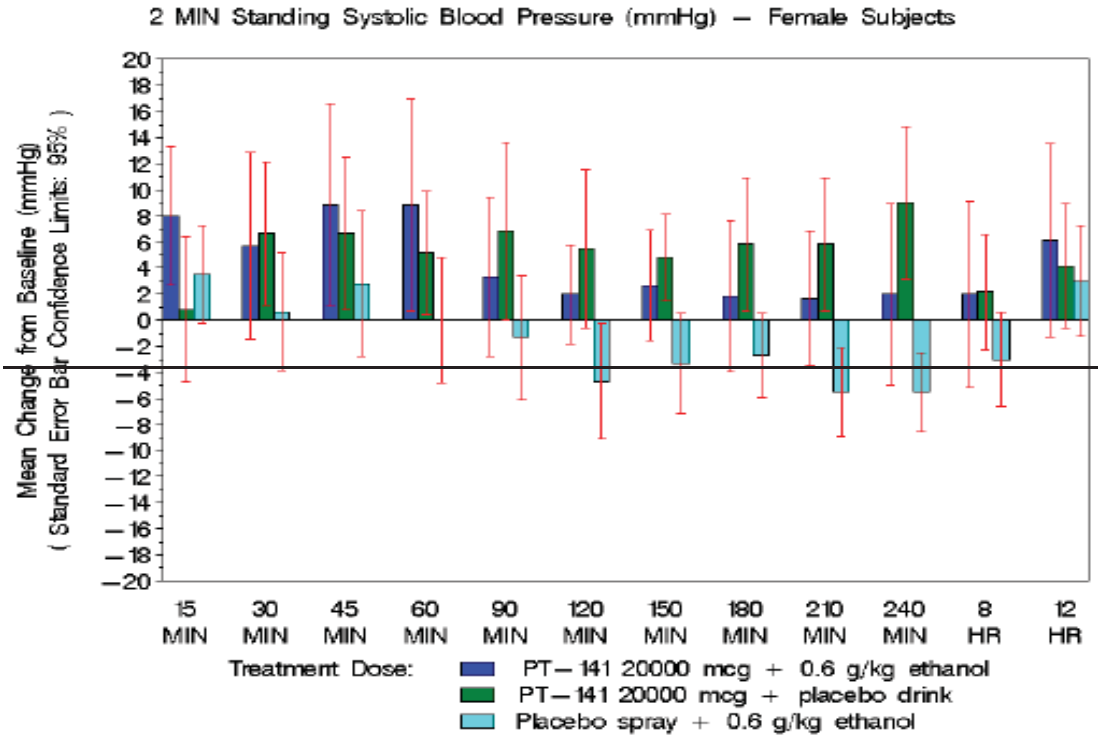
Abbreviation: MIN minutes

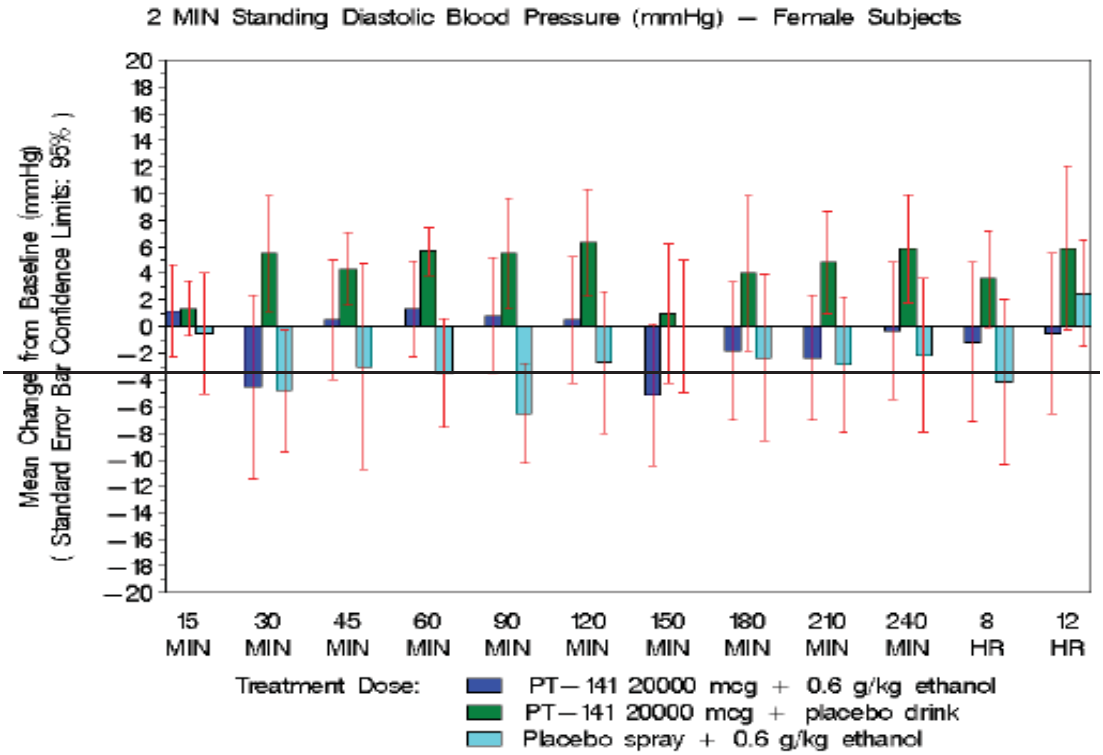
Mean change from baseline in SBP and DBP for the female population are shown below, sitting and 2 minutes standing.

Figure 34. Mean Changes Systolic Blood Pressure and Diastolic Blood Pressure: Sitting and 2 Minutes Standing, Female Subjects









Abbreviation: MIN minutes

Drug-Drug Interaction Studies

Renal safety

A renal pharmacokinetic study was conducted and reviewed by the clinical pharmacology review team to assess dosing in renal impairment for labeling purposes. From a clinical perspective, there appeared to be an increased incidence of nausea and vomiting in the severe renal insufficiency group compared to normal subjects, and increased incidence of headache in the moderate and severe renal insufficiency groups, respectively. However, the sample sizes are very small, limiting conclusions. No trends were seen in laboratory values.

Hepatic safety: BMT-116

A hepatic safety study was conducted and reviewed by the clinical pharmacology team to assess labeling in patients with hepatic impairment. Most of the subjects with impaired function were positive for Hepatitis C and no data from patients with severe hepatic insufficiency subjects were submitted.

Data for mild and moderate hepatic impairment and normal hepatic function show the following key findings:

- There were no deaths, SAEs, or discontinuations due to TEAEs. No severe or life-threatening TEAEs were reported and no events of concern (such as gastrointestinal events) occurred more frequently in the moderate hepatic insufficiency group and no increase in frequently-reported symptoms (e.g., nausea, vomiting, headache, injection site) were identified.
- There were no Hy's Law cases. Three subjects (13%) with moderate hepatic impairment had elevations in AST>3 to 5X ULN on Day 3, and two subjects (8%) with moderate hepatic impairment had elevations in TBili >1.5 to 2X ULN on Day 3. One subject (b) (6), a 55-year-old white male with mild hepatic impairment, experienced a moderate TEAE of hepatic enzyme increased on Day 3 (elevated AST of 77 U/L and ALT 105 U/L). AST peaked on Day 7 (136 U/L) and ALT peaked on Day 14 (247 U/L). The event resolved after 25 days.

Human abuse potential: BMT-117

A randomized, double-blind, crossover study was conducted in 56 recreational stimulant users (38 males, 18 females) to evaluate the abuse potential of single doses of BMT (1.75 mg, 3.5 mg, and 5.25 mg) compared to single doses of phentermine (45 mg and 90 mg) and PBO.

Based on this study and other abuse-related animal and human data, it was concluded that BMT does not have abuse potential and is reviewed separately (see Overdose, Drug Abuse Potential, Withdrawal, and Rebound subsection in Section 8.2.12).

Safety assessments included laboratories, vital signs, 12-lead ECG, physical examination, Columbia Suicide Severity Rating, and pregnancy testing.

No deaths were reported. Two subjects taking BMT had study drug withdrawn due to an AE. An additional subject had cardiac discomfort while taking BMT but was not withdrawn until a subsequent TEAE. These narratives are summarized below.

- Subject (b) (6): 30-year-old white female with mild headache and moderate nausea 1.5 hours after BMT 5.25 mg lasting 21 hours. Study drug discontinued.
- Subject (b) (6): 26-year-old white female, withdrawn due to upper respiratory infection following BMT 3.5 mg. Study drug discontinued.
- Subject (b) (6) A 31-year-old white male with momentary heart pressure/cardiac discomfort "like my heart was constricted" 2.5 hours after BMT 5.25 mg on Day 46. The event lasted 5 seconds. The subjects continued into the study, but study drug later discontinued on Day 53 due to hypertension, 160/111 mm Hg and 180/112 mm Hg, 1.25 hours and 1.5 hours following phentermine 90 mg.

During the treatment phase, 54 of 56 (96.4%) subjects had at least one TEAE. Dose dependent TEAEs that occurred at rates greater in the BMT group compared to the phentermine or PBO groups were nausea, vomiting, feeling hot, injection-site pain, upper respiratory infection, restlessness, increased erection (in male participants), flushing/hot flush. Hypertension was only reported in the phentermine 90 mg group. Three subjects had euphoria-like events identified as potential abuse-related signals.

The Controlled Substance Staff conducted an abuse potential assessment of BMT. Based on their evaluation of the clinical and nonclinical abuse-related data, it does not appear that BMT has abuse potential. However, misuse was identified in the clinical trial (i.e., use more frequently than every 24 hours). The consequences of misuse, including hypertension and focal hyperpigmentation have been discussed previously in this safety section. These concerns will be captured in the Overdose section of labeling.

Antihypertensives: BMT-101

A double-blind, PBO-controlled, 2-period crossover study was conducted in healthy pre- and postmenopausal women (ages 18 to 69 years) to assess the effect of single doses of BMT coadministered with antihypertensive medication or diuretics. PK parameters and hemodynamic effects were assessed. The chosen medications included cohort 1 (HCTZ, metoprolol, amlodipine, lisinopril, losartan), cohort 2 (BMT versus PBO) and cohort 3 (furosemide) with a run-in period to achieve steady state. Baseline and time-matched ABPM post-BMT were conducted for 24 hours.

The most common events per treatment group are shown below in Table 70.

Table 70. Treatment-Emergent Adverse Events: Any TEAE and Most Common TEAEs

Panel System Organ Class Preferred Term	Anti-HTN Alone N (%)	Anti-HTN+BMT N (%)	Anti-HTN PBO N (%)	EOS After BMT Dosing N (%)	EOS After PBO Dosing N (%)
Panel A (HCTZ)	22	20	20	10	10
Subjects with any TEAE	6 (27.3)	11 (55.0)	1 (5.0)	0 (0.0	0 (0.0
Nausea	1 (4.5)	6 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	1 (4.5)	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	2 (9.1)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel B (metoprolol)	22	21	21	11	10
Subjects with any TEAE	2 (9.1)	6 (28.6)	1 (4.8)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	0 (0.0)	2 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Vulvovaginal discomfort	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Panel C (amlodipine)	20	20	20	8	12
Subjects with any TEAE	3 (15.0)	8 (40.0)	3 (15.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	3 (15.0)	2 (10.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vulvovaginal discomfort	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Panel D (lisinopril)	21	20	20	9	11
Subjects with any TEAE	5 (23.8)	6 (30.0)	2 (10.0)	0 (0.0)	0 (0.0)
Nausea	1 (4.8)	6 (30.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	1 (4.8)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	0 (0.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)
Panel E (losartan)	27	23	25	12	14
Subjects with any TEAE	4 (14.8)	6 (26.1)	4 (16.0)	0 (0.0)	0 (0.0)
Flushing	0 (0.0)	4 (17.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (7.4)	3 (13.0)	1 (4.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	2 (8.7)	1 (4.0)	0 (0.0)	0 (0.0)
Abdominal discomfort	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia oral	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia oral	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Restlessness	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Genital paresthesia	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMT bremelanotide, EOS end of study, HTN hypertension, PBO placebo; TEAE treatment-emergent adverse event
Source: BMT-101 CSR, Tables 54 to 56, pages173–178

Two subjects had elevations in liver tests:

- In cohort 1, Subject (b) (6) had ALT elevation>3X ULN to 5X ULN on Day 13 and Day 14 (amlodipine+BMT was given on Day 12). The subject had received amlodipine doses on Day 1 through Day 9, amlodipine and PBO dose on Day 10, amlodipine on Day 11, and amlodipine and BMT on Day 12. On Day 20, ALT values reduced to <3X ULN and

normalized by Day 32. Corresponding AST remained <2X ULN, and corresponding bilirubin values were within the normal range.

- In cohort 2, Subject (b) (6) showed TBili elevation that was >1.5X ULN to 2X ULN on Day -21 to Day -3, on Day -2, and on Day 2. This subject received BMT on Day 1 and PBO on Day 3, following the reported bilirubin elevation. Bilirubin values normalized to 1.2 mg/dL by Day 5. Corresponding AST and ALT values were within the normal range.

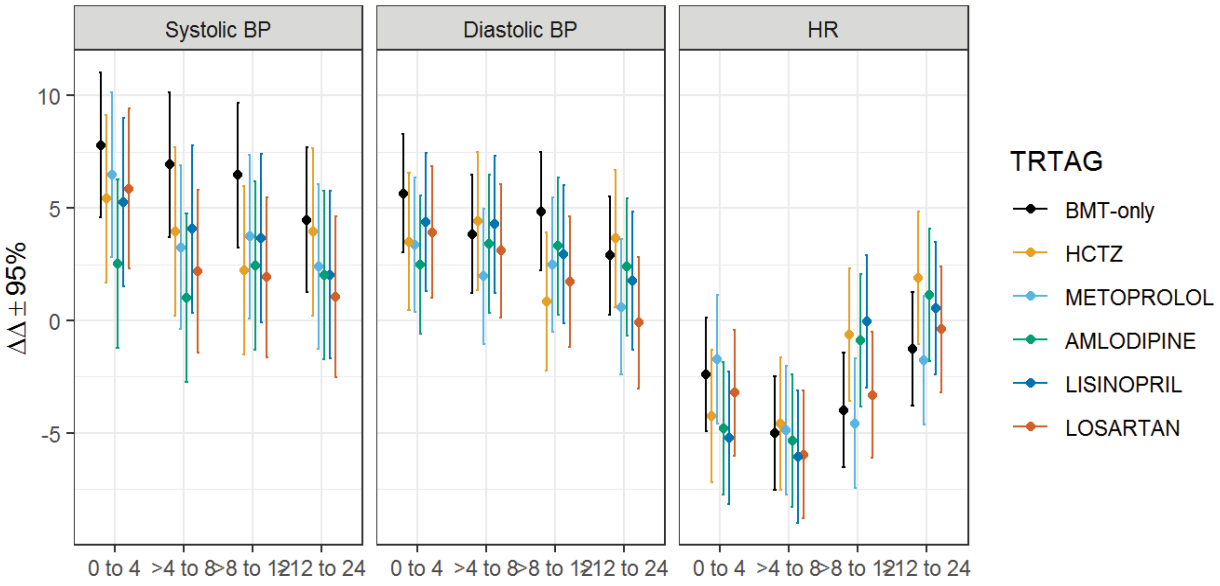
Blood pressure

DCaRP also evaluated this study and discussed the findings in their consultative review dated 23May2019. Overall, the trends seen in the hourly ABPM readings (anti-HTN with BMT compared to anti-HTN alone) (b) (4). Increases in SBP and DBP and decreases in HR were observed following a single dose of BMT, peaking within several hours postdose. The increases in BP observed in this study were higher than that of the dedicated ABPM study (AMAG-BMT-HSDD-101) discussed in Section 8.2.6.

The reason for the larger increase in BP observed in this study is unclear; however, it is possible that it could be partially explained by differences in patient demographics as the BMT-alone cohort in BMT-101 only included postmenopausal women whereas the dedicated ABPM study included only premenopausal women.

Comparison of the change from baseline in BP and HR between the BMT+antihypertensives vs. PBO+antihypertensives groups is shown in Figure 35 below. DCaRP's analysis showed a numerically smaller increase in SBP and DBP for BMT+antihypertensives compared to BMT alone. This suggests that antihypertensives could mitigate the BMT-induced BP elevations. Because very few patients with controlled hypertension are included in the clinical program, the effects of BMT on blood pressure in patients maintained on antihypertensives have not been well characterized.

Figure 35. Change From Baseline and BMT-PBO for Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate



Abbreviations: BMT bremelanotide, PBO placebo, BP blood pressure, HR heart rate
Source: DCaRP review

The Applicant also submitted a study in subjects with controlled HTN (PT-141-2006-35). This study was conducted in men with ED and not relevant to this patient population. Further, by definition, subjects with ED have CV disease and are different from the baseline CV risk of the target population.

8.2.12. Additional Safety Explorations

Human Reproduction and Pregnancy

Pregnant women were excluded during the clinical development program, however, if approved, pregnancies in women using BMT are anticipated in the postmarketing setting given the indication and indicated population. There was a total of 13 pregnancies in the phase 2/phase 3 program (including three pregnancies occurring in the single-blind PBO period, and three who received PBO in the core phase. The remaining seven pregnancies (see Table 71 below) occurred during exposure to BMT in the core (n=3) and/or extension phases (n=4).

In the BMT group, there was one spontaneous abortion, one premature infant, four full-term live births, and one outcome was unknown due to lost to follow-up. No birth defects were reported in either group. The exposure and outcomes for those exposed to BMT are shown below. Only two events were considered SAEs, [redacted] (b) (6) premature termination (PBO group) and [redacted] (b) (6) spontaneous abortion (BMT). There were no exposures in lactating women.

Table 71. Pregnancy Outcomes: BMT Core/Extension Studies

USUBJID	Age/Race	Exposure Period	Outcome
(b) (6)	27 BF	(b) (6)	Last information pregnancy ongoing. Subject declined further follow-up
	37 WF		Spontaneous abortion 56 days after last dose (b) (6). SAE
	27 WF		Full-term male infant born at 37 weeks; baby had hyperbilirubinemia and received light therapy for a week
	29WF		Healthy full-term infant born at 41 weeks
	34 BF		Healthy full-term infant born at 39 weeks
	40 BF		Healthy full-term infant born at 41 weeks
	35 BF		Healthy full-term infant born at 38 weeks

Abbreviations: USUBJID unique subject identification, BF black female, BMT bremelanotide, SAE serious adverse events, WF white female, EXT extension

The number of BMT-exposed pregnancies were small across the clinical program and phase 3 program. Pregnancies occurred anywhere from 2 days to 51 days following the last known injection. Due to the large number of premenopausal women of childbearing potential who would be exposed if approved, the Division of Pediatric and Maternal Health and Division of Epidemiology was consulted. Two pregnancy-related studies (one registry-based and one retrospective cohort observational study) and one lactation study will be postmarketing requirements (see Section 13).

Pediatrics and Assessment of Effects on Growth

HSDD does not exist in the pediatric population and the clinical program enrolled adult women 18 years of age or older.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Drug abuse potential

The Applicant proposes that BMT not be scheduled under the Controlled Substances Act, based on a lack of abuse-related signals in preclinical and clinical studies with BMT.

In a review dated 22Mar2019, the Controlled Substance Staff (CSS) concluded that BMT has negligible abuse potential and does not appear to produce physical dependence. Thus, CSS

concluded that BMT should not be recommended for scheduling under the Controlled Substances Act and recommends that Section 9 (Drug Abuse and Dependence) be omitted from labeling.

Overdose/Misuse summary from phase 3 clinical program

Despite the instruction to phase 2/3 patients not to take two BMT doses within a 24-hour period, the ISS stated that 129 subjects self-administered BMT doses 20-24 hours apart and 85 subjects dosed <20 hours apart. In response to an Information Request (dated 21Sep2018), the Applicant updated these numbers to report that 16.8% (178/1057) of subjects self-administered BMT doses <24 hours apart, 12.9% (136/1057) of subjects administered BMT doses 20 to <24 hours apart; 4.4% (46/1057) of subjects administered BMT doses 12 to <20 hours apart, and 3.9% (41/1057) of subjects administered BMT doses <12 hours apart. The Applicant provided a listing of these subjects and AEs potentially related with overdose. The window for this analysis of postdose events was defined as:

- Within 14 days of the second consecutive dose administered <24 hours of a previous dose, or
- Up to an additional 5 days after any subsequent injection in the postdose window, whichever was greater.

The Applicant's listing does not include any AEs outside of this window. The discrepancy in the reported numbers per the Applicant was due to manual tabulation versus specific programming used in the 21Sep2018 response. Table 72 below provides a summary of TEAEs following consecutive BMT injections based on timing of dosing.

In response to our request, the Applicant stated (response to Information Request 30Nov2018) that the underlying reason for subjects to take more than one dose could not be determined from the electronic case report forms as the datapoint was not collected and the limited amount of information did not provide a reason for the majority of subjects.

Table 72. Overall Summary of TEAEs Following Two Consecutive BMT 1.75 mg-Injections Administered Less Than 24 Hours Apart

Category	20 to < 24 hours n (%)	12 to < 20 hours n (%)	< 12 hours n (%)
Total number of subjects with BMT administered in dosing interval	136 (12.9)	46 (4.4)	41 (3.9)
Any adverse event	49 (4.6)	9 (0.9)	5 (0.5)
Any serious adverse event	0	0	0
Any adverse event leading to study withdrawal	4 (0.4)	1 (<0.1)	0
Any SAE	3 (0.3)	0	0

Abbreviations: BMT=bremelanotide, SAE=serious adverse event
Source: Response to IR, 21Sep2018

Overall, there were no deaths or SAEs related to dosing <24 hours apart. There appears to be an error, where the last row of the table was categorized "Any SAE" instead of "any severe AE." There were three (0.3%) subjects with a severe AE [Subjects (b) (6) – constipation (occurring 7 days after consecutive dosing); (b) (6) – back pain (with the next dose after consecutive dosing, no resolution date, subject not withdrawn); and (b) (6) – hypertriglyceridemia (occurring 3 days after consecutive dosing [11th total injection]).

Five subjects had an AE following consecutive dosing <24 hours apart leading to withdrawal:

- (b) (6): 37-year-old black female with consecutive dosing 20 hours apart on (b) (4) (sixth injection) and (b) (6) (seventh injection) with AE of skin hyperpigmentation (moderate) following seventh injection. The event lasted 2 months.
- (b) (6): 38-year-old white female with consecutive dosing 23 hours and 30 minutes apart on (b) (6) (25th injection) and (b) (6) (26th injection) with AE of intermittent breast tenderness in (b) (6) (day not given). Event resolved (b) (6)
- (b) (6): 31-year-old female of multiple ethnicities randomized to PBO in the core study. Upon entering the extension study, she used the first two BMT doses within 22 hours and 15 minutes of each other and experienced nausea (moderate). Nausea occurred with each subsequent injection and she withdrew following the fifth injection (2 weeks later). No increased AE intensity was documented.
- (b) (6): 49-year-old white female previously on BMT in the core study. She used BMT 12 hours apart on (b) (6) (seventh injection) and (b) (6) (eighth injection) during the extension phase. Nausea and vomiting occurred 2.5 hours after the eighth injection leading to withdrawal.
- (b) (6): 38-year-old white female previously on PBO in the core study with consecutive BMT dosing 23 hours apart on (b) (6) (fourth injection) and (b) (6) (fifth injection) during the extension. AE of leg stiffness and genital pain reported

following the fifth injection on 19Jul2016. Her next dose on 20Jul2016 was followed by nausea and recurrence of leg stiffness and genital pain.

Study BMT-301

In Study 301 core phase, 41 subjects used consecutive doses of BMT <24 hours apart. The majority of subjects who reported AEs had the same AE for the first and the second dose without any change in intensity. There were several new onset AEs with the second consecutive doses: severe constipation, hyperpigmentation, night sweats, melanocytic nevus and dysesthesias at injection site. The majority of the AEs were mild or moderate in intensity. Considerable shorter spans between doses were seen in several subjects: 5 minutes (b) (6) [and took next dose 3 days later], 12 minutes (b) (6), 2 hours and 8 minutes (b) (6); no AEs were reported around the administration time of interest for these subjects. Sixteen subjects in Study 301 core phase had consecutive dosing more than once (maximum, four times) during the study.

Study BMT-302

In Study 302 core phase, 29 subjects used consecutive doses <24 hours apart. There were more instances in Study 302 (compared to 301) of consecutive dosing in shorter time frames, such as the 4- to 14-hour time window. There were also more instances of repeat dosing within the first hours after the previous dose, as follows: 5 minutes, 19 minutes, 47 minutes (b) (6), 9 minutes (b) (6), 17 minutes (b) (6), 51 minutes (b) (4), 1 hour and 15 minutes (b) (6) 2 hours (b) (6) and 4 hours and 27 minutes (b) (6). Review of the AEs showed new events of injection site reaction, darkened areolas/face, increased salivation, ear/sinus infection following the second consecutive dose. Seven subjects had more than one instance of consecutive dosing, with Subject (b) (6) having seven instances (ranging from 17 minutes to 23 hours and 3 minutes) and (b) (6) having nine instances (ranging 5 minutes to 21 hours and 48 minutes). Review of AEs for these subjects did not show any events coincident with increased timing of dosing.

Study BMT-301 Extension

There were 70 subjects in Extension Study 301 with consecutive dosing within the 24-hour window. There were new events of insomnia, gastroesophageal reflux disease, and melanocytic nevus after the second dose. The intensity of events was largely consistent between the first and second consecutive doses. One subject (b) (6) 49-year-old white female) reported new onset of nausea and vomiting after her eighth dose (administered 12 hours after the seventh), leading to withdrawal. Seventeen subjects used more than one consecutive dose. Subject (b) (6) (25-year-old black female) had 21 consecutive injections (ranging from less than two hours to 23 hours after the previous dose). Subject (b) (6) (38-year-old white female) reported five consecutive injections; Subjects (b) (6) (45-year-old white female) and (b) (6) (48-year-old black female) each reported six consecutive doses less than 24 hours apart. The extreme outliers include 5 minutes (b) (6) 10

minutes (b) (6); 39 minutes (b) (6)); 1 hour and 13 minutes (b) (6); 2 hours (b) (6); and 4 hours and 13 minutes (b) (6)).

Study BMT-302 Extension

There were 56 subjects in Extension Study 302 who repeated the next BMT dose in less than the 24-hour window. After the consecutive doses, there were events of worsening hypertriglyceridemia (after 11th dose), sunburn (after fifth dose), and flushing. One subject reported dark spots on her skin following four doses, the first two doses were less than 24 hours apart. Twenty-one subjects used consecutive doses less than 24 hours apart more than once during the study period. Five subjects used consecutive doses >5 times (b) (6); the last subject (b) (6) used consecutive dosing 11 times during the study period.

Additional AEs were not seen with shorter times between dosing. As study drug was taken at home, no clinical BP readings following consecutive dosing are available. Review of clinic blood pressure data looking for trends in BP over the duration of the study showed one subject with elevated BP after a total of 11 consecutive doses, described below.

Subject (b) (6)

A 29-year-old white female who was randomized to BMT in the core phase in Study 302. Review of data in the AE dataset (advs.xpt) showed baseline BP in core of 130/85 mm Hg and the maximum BP after the first dose was 129/97 mmHg (1.5 hours postdose). Baseline BP in the extension phase was 140/81 mm Hg. During the first clinic visit in the extension phase, her maximum BPs were 147/92, 118/98, and 126/78 mm Hg at 1 hour, 1.5 hours, and 2 hours postdose, respectively. Her in-clinic BPs in the extension were the following: Week 12: 146/129 mm Hg (pulse 81 and same day repeat of 120/84), Week 20: 107/75 mm Hg, Week 36: 132/117 mm Hg (114/77 mm Hg same day repeat) at, and Week 52 (EOS) 129/93 mm Hg The Applicant confirmed these readings stating repeats on the same day were within normal. As the timing of dosing was variable, no conclusions or hypotheses can be made.

The event of worsening hypertriglyceridemia (severe) was noted with second consecutive dosing within 24 hours but elevation in triglycerides is not consistent with the known safety profile of the drug and is possibly an isolated finding. There were several events of new onset flushing after consecutive dosing.

Generally, the same AEs were experienced following the first and second consecutive doses; and dosing history does not suggest that consecutive dosing affected the time to next dose. However, there were some new onset events with second dosing. Several events of concern are notable including one episode of nausea and vomiting after second dosing leading to drug withdrawal, elevated BP after multiple instances of second dosing, and melanocytic nevi after second dosing. BMT causing melanocytic nevi after two doses is unlikely.

Further review of advs.xpt showed no increased BP at scheduled visits following the consecutive dosing <24 hours apart, with the exception of (b) (6) (discussed above). However, this assessment is limited to in-clinic assessments with no BPs recorded around the actual time of intake.

In the midcycle communication, we identified the concern of misuse as a major safety issue, as a significant number of subjects dosed BMT <24 hours apart. The majority of subjects also continued using BMT after the overdose/misuse. Most instances of the consecutive dosing occurred close to the 24-hour period on the following day suggesting that overdose/misuse may not have been intentional. However, there remain many subjects with whom the time interval of the repeat dose was considerably shorter, with 3.9% (41/1057) of subjects administering BMT doses <12 hours apart, and some repeated the next dose as quickly as 5 minutes later. We reiterated this concern for misuse as a significant safety issue during a teleconference with the Applicant on 7Nov2018. To mitigate this concern, the Applicant proposed to limit the use of BMT to no more than 8 doses per month (revised labeling submitted on 21Dec2018). Of note, few patients used more than eight doses per month in the phase 3 trials.

8.2.13. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. BMT has not been approved in any other country and there is no postmarketing experience to date.

Expectations on Safety in Postmarket Setting

BMT is not indicated for postmenopausal women. During early drug development, variable drug exposure and elevated blood pressure were seen. The applicant subsequently focused further drug development for premenopausal women. It is conceivable that postmenopausal women may seek treatment and BMT will be prescribed. To the extent possible, this risk will be addressed in labeling; however, data are not available to support a contraindication. Other off-label uses could also include sexual performance/erectile dysfunction and use as a self-tanning aid. This latter use was published for a related product obtained over the Internet. The subjects experienced rhabdomyolysis with supratherapeutic doses.[51] As with another product approved for the treatment of HSDD in premenopausal women, the labeling will include Limitations of Use, specifying that BMT is not indicated for the treatment of HSDD in postmenopausal women or in men and that it is not indicated to enhance sexual performance. Furthermore, the label

[51] Nelson M et al., 2012. Melanotan II Injection Resulting in Systemic Toxicity and Rhabdomyolysis. Clin Toxicol, 50(10): 1169–1173.

will emphasize that the hyperpigmentation is focal and therefore, the product is not suitable for a tanning agent.

8.2.14. Integrated Assessment of Safety

The overall safety profile of BMT is derived from 1247 women with HSDD participating in the two 24-week, phase 3, randomized, PBO-controlled trials (BMT-301 and BMT 302). Additional safety information is obtained from 684 women from these two trials who completed BMT treatment for 6 more months in open-label, safety extension studies. There were 1057 unique subjects who received BMT in both the core and extension phases (627 in core phase, plus 684 in extension phase, minus 254 who were counted twice). Key safety issues identified in the clinical program are highlighted below.

Blood Pressure

MCR-4 agonists are known to cause blood pressure elevations in nonclinical studies. Elevations in blood pressure and decreases in pulse with BMT use were seen during ambulatory blood pressure assessment in the phase 2 study (PT-141-54) following a single BMT dose. In phase 3 trials, there was a maximal increase of 6 mm Hg systolic blood pressure and 3 mm Hg in diastolic blood pressure that peaked between 2 to 4 hours post dose. There was a corresponding reduction in HR up to 5 bpm.

We required a premarket, dedicated ABPM study (8 days of open-label treatment with daily BMT followed by 8 additional days of randomized withdrawal with BMT vs. PBO), which was completed during the current review cycle. Results showed that the increase in SBP and DBP was transient, with a peak effect in mean SBP of 2.8 mm Hg between 4 to 8 hours post-dose and 2.7 mm Hg for mean DBP at 0 to 4 hours post-dose. These changes returned to baseline before the next scheduled BMT dosing. This transient increase with a PRN drug in a population that is generally at low cardiovascular risk can be adequately managed with a Warning and Precaution.

BMT should not be used in patients with uncontrolled hypertension or those with known cardiovascular disease. Because few subjects with controlled hypertension were enrolled in the clinical program, the effects of BMT on blood pressure in these women are not well characterized to inform use.

Potential for Misuse

In clinical trials, BMT was used, on average, one time per week and two to three times per month. Few subjects in the Phase 3 trials used more than 8 doses per month, even though the protocol allowed up to 12 doses per month. Given the elevations in blood pressure, the identification of some subjects who administered BMT more frequently than the recommended

interval of 24 hours raised concerns. A total of 16.8% of subjects in the phase 3 studies misused the study medication by taking more than one dose within a 24-hour period; 3.9% (41/1057) self-administered BMT doses less than 12 hours apart and as close together as 5 minutes apart. While the number of AEs did not appear to increase with earlier dosing than recommended, the effect on blood pressure was not captured and the full effect remains unknown. To mitigate this concern, the Applicant proposed recommending no more than eight doses per month, which was consistent with the conduct in phase 3 trials. Considering the transient elevations in blood pressure, the recommended dosing regimen adequately addresses the concern for potential misuse.

Focal Hyperpigmentation

BMT stimulates MCR-1 and caused focal hyperpigmentation/skin discoloration in 13 (1%) BMT-treated subjects (compared to 0 events in subjects receiving PBO). The effects were more common in black individuals (4.1%) compared to white individuals (0.6%) in the double-blind phase. The pigmentary changes occurred most frequently on the face, gingiva and breasts. Half of all the subjects affected did not report resolution by the end of study visit. No additional follow-up period was specified in the protocol. No increased risk of skin malignancy was noted. However, because unresolved hyperpigmentation was observed in cosmetically important areas, inclusion in the Warning and Precaution section of labeling is appropriate.

Liver Injury

A single case of acute hepatitis was reported in the clinical program. The event involved elevation of AST and ALT>40X ULN and TBili 7X ULN along with nausea, loss of appetite, unexpected weight change, and increased fatigue that occurred following 20 doses over 1 year of drug treatment. An etiology for the event was not found despite an extensive search, including imaging, laboratory assessment, and consultation with hepatologists. The expert opinion was that DILI was not a probable cause but was considered “possible” per Roussel Uclaf Causality Assessment Method and Drug-Induced Liver Injury Network scoring methodology. No additional notable liver events were seen nor are there imbalance in outliers of serum transaminases across the phase 3 program between BMT and PBO. This potential risk will be addressed in labeling.

Use in Women of Childbearing Potential/Pregnancy/Lactation

Due to the target population and the expected treatment effect, BMT exposure in pregnancy is anticipated. There were few BMT-exposed pregnancies in the phase 2/3 studies (seven total cases), and no birth defects were reported. The nonclinical data provides inconclusive evidence regarding the effect of BMT on fetal harm. As a NOAEL could not be determined in the developmental toxicity studies, labeling will recommend effective contraceptive use during treatment with BMT to reduce the risk of pregnancy and inadvertent exposure to a fetus. The Applicant has agreed to three postmarketing requirements for pregnancy (observational

pregnancy registry and retrospective epidemiology) and lactation to evaluate pregnancy, maternal, and fetal/neonatal outcomes.

Nausea

BMT was shown to be emetogenic in nonclinical studies. Nausea was the most common symptom experienced with BMT use, occurring in 40% of patients and leading to withdrawal in 8% of patients in the double-blind phase. The onset of nausea occurred within 1 to 3 hours and coincided with C_{max}. The majority of events were reported as moderate in severity and resolved the same day. Severe nausea occurred in two subjects. This tolerability issue can be adequately handled in labeling.

8.3. Statistical Issues

The co-primary endpoints for both phase 3 trials were measured as the change from baseline to end of study. The end of study visit occurred after 24 weeks of double-blind treatment for patients who completed the double-blind treatment period, but could have occurred any time after baseline for patients that discontinued treatment. This was especially problematic because a much higher percentage of BMT patients failed to complete the double-blind treatment period compared to placebo patients. Further analyses were performed to determine if efficacy results for the co-primary endpoints were driven by patients who discontinued treatment early. Analyses examining efficacy in completers and dropouts, along with a 50% trimmed mean analysis and responder- based analyses for patients who completed and reached the end of the double-blind treatment period, favored BMT over placebo, consistent with the primary efficacy analysis.

Additionally, BMT is administered PRN and its effects only last for hours; however, both coprimary endpoints for the phase 3 trials used a monthly recall. The monthly recall has potential for recall bias and might not accurately capture the effect of the drug, especially because most patients only had a few injections per month. However, this would be expected to bias the trial towards the null hypothesis of no difference between treatment groups because patients would presumably be factoring in most days when they had not received BMT during the one- month recall. Analysis of the exploratory EDQ daily diary suggests that daily scores related to sexual desire are moderately correlated with monthly recall values; however, this analysis is limited due to the daily diary only being administered for 7 days instead of the entire month. The EDQ also did not include questions directly related to distress. Regardless, the results for the coprimary endpoints across two studies would be highly unlikely if BMT had no effect on desire and distress, even if a monthly recall is not ideal for measuring the effect of BMT.

8.4. Conclusions and Recommendations

Based on the totality of the efficacy and safety data presented in this application, we conclude that subcutaneous BMT shows statistically significant efficacy for the treatment of acquired, generalized HSDD in premenopausal women. Exploratory analyses of clinical meaningfulness appear to support the treatment benefit. All the safety concerns identified during this review can be adequately mitigated through labeling or evaluated via postmarketing requirements. Availability of BMT will provide a new treatment option to premenopausal women with HSDD. The as-needed dosing regimen confers an additional advantage without requiring daily dosing. The benefit-risk profile of BMT is favorable and the product should be approved.

9 Advisory Committee Meeting and Other External Consultations

We determined that this application did not raise issues requiring external expert advice. Therefore, an advisory committee meeting was not convened to discuss the application.

10 Pediatrics

The Applicant requested a full waiver from pediatric studies required under the Pediatric Research Equity Act, based on the rationale that HSDD has no relevant pediatric sub-population. We agree with the Applicant's rationale that pediatric studies would be impossible or highly impractical because the condition does not occur in the pediatric age group. The Applicant submitted an agreed-upon, initial Pediatric Study Plan under IND 064119 on 14Dec2016.

The Pediatric Review Committee met on 25Jul2018 to discuss the waiver request; the Committee concurred with our plan to grant a full waiver in pediatric patients. The final Pediatric Review Committee decision is documented in the Meeting Minutes dated 27Aug2018.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 73. Summary of Significant Labeling Changes[1]

Section	Proposed Labeling	Approved Labeling
2 Dosage and Administration	Not to exceed one dose within 24 hours.	Not to exceed 1 dose within 24 hours. Patients can administer up to eight doses per month
4 Contraindications	None	Women with uncontrolled hypertension or known cardiovascular disease
5.1 Warnings and Precautions	None	Transient increases in blood pressure: (b) (4) BMT use may increase blood pressure
5.2 Warnings and Precautions	None	Focal hyperpigmentation: In clinical trials, focal hyperpigmentation was reported and occurred in greater proportions in black subjects. Hyperpigmentation may not be reversible.
5.3 Nausea	None	Nausea: In controlled clinical trials, nausea was reported by 40% of patients and most commonly with the (b) (4). In 13% of patients, anti-emetics were required for symptom relief.
6 Adverse Reactions		Further characterized nausea; added headache, flushing, acute hepatitis
7 Drugs Interactions		Substantial edits added
8.1 Pregnancy		Substantial edits made
8.3 Females of Reproductive Potential	None	Added recommendation to use effective contraception
12.2 Clinical Pharmacology		Added description of ABPM study results and other substantive edits
14 Clinical Studies		Deleted (b) (4) not agreed-to by DBRUP
17 Patient Counseling Information		Substantial edits added

[1] High-level changes and not direct quotations

The Patient Package Insert is deemed acceptable by DBRUP, Office of Prescription Drug Promotion, and the Division of Medical Policy Programs.

The Instructions for Use is deemed acceptable by both DBRUP and the Division of Medication Error Prevention and Analysis (DMEPA).

The carton and container labeling is also deemed acceptable by DMEPA.

12 Risk Evaluation and Mitigation Strategies

The review team determined that a REMS is not necessary to ensure the benefits outweigh the risks of this product. Labeling alone is adequate to inform providers and patients of the risks. Additional measures to assure safe use are not necessary. See the June 14, 2019 review by the Division of Risk Management, Office of Medication Error Prevention and Risk Management.

13 Postmarketing Requirements and Commitment

As the indicated population is of reproductive age and data on pregnancy and neonatal outcomes are lacking, the following pregnancy-related and lactation postmarketing requirements will be requested:

Pregnancy Registry

A prospective, registry-based, observational cohort study that compares maternal, fetal, and infant outcomes in women exposed to BMT during pregnancy to an internal, unexposed comparison cohort of pregnant women. The registry will identify major and minor congenital malformations, spontaneous abortions, elective terminations, small for gestational age, pre-term births, and any other adverse pregnancy outcomes. These outcomes will be adjudicated with medical chart review. Infant outcomes including effect on postnatal growth and development will be assessed through at least the first year of life.

Epidemiology Study

A retrospective cohort study using electronic claims data that compares maternal, fetal, and infant outcomes in women exposed to BMT during pregnancy to an internal, unexposed comparison cohort of pregnant women. Maternal, fetal, and infant outcomes, (b) (4) , and any other adverse pregnancy outcomes will be adjudicated with medical chart review. Pregnant women exposed and unexposed to (b) (4) are to be matched by age at pregnancy and gestational age at cohort entry.

This study will complement the postmarketing pregnancy registry study. To assess the extent of misclassification for (b) (4) exposure in claims data, we will require the Applicant to conduct an evaluation of the validity of claims exposure data, compared to patient self-reported data. The Applicant may utilize either a (b) (4) We are requiring the Applicant to collect information to include, but not limited to, the following data elements (to the extent possible):

- Age, demographics, body mass index
- Exposure to smoking, alcohol, drugs
- Medical history, concomitant medications, prenatal vitamins, obstetrical history
- Current pregnancy: date of last menstrual period/gestational dating, prenatal tests and ultrasound results, pregnancy status
- BMT exposure data (timing of exposure in pregnancy, dose, duration)

Lactation Study

We are requiring a lactation study (b) (4)

14 Appendices

14.1. References

See footnotes throughout this document.

14.2. Financial Disclosure

The Applicant disclosed financial interests/arrangements with clinical investigators for covered Studies 301 and 302 as recommended in the guidance for industry, *Financial Disclosure by Clinical Investigators*. No investigators disclosed any interests/arrangements. In the 74-day letter, the Applicant was asked to further clarify whether any investigators received cumulative compensation that exceeds $25,000. In response (submitted 3Aug2018), the Applicant states, "In accordance with 21 CFR, Part 54, all principal investigators and sub-investigators listed on the signed Forms FDA 1572 for Palatin-Applicant clinical trials referenced in this new drug application (NDA) have submitted signed Financial Disclosure statements indicating the extent to which, if any, they received compensation from the study Applicant in any of the following disclosable financial interests and arrangements. Upon review of these disclosures there were no investigators or subinvestigators with information to disclose and therefore FDA Form 3455 does not apply." The submitted information is adequate.

Table 74. Covered Clinical Study: BMT-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 103		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) Not needed due to no disclosable financial interests/arrangements
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) Not applicable

Table 75. Covered Clinical Study: BMT-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 96		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant) Not needed due to no disclosable financial interests/arrangements
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant) Not applicable

14.3. Analysis of EDQ

Both coprimary endpoints used a 4-week recall. There was concern that the 4-week recall period might not accurately capture the effect of a drug that was only taken a few times a month on an as-needed-basis. Although the EDQ was not used as a primary endpoint, it contains multiple questions related to sexual desire and was administered as both a daily diary and 4-week recall. Exploratory analyses were performed to determine how well responses from the daily diary version matched those from the 4-week recall. A subject's average value from the daily diaries in the week preceding a clinical visit was compared to the subject's 4-week recall score at the clinical visit.

There are several caveats with this analysis. The daily diary only covers a fraction of the 4-week recall period, as it was only administered during the last 7 days before study Visits 2, 3, 6, and 9. Also, both questions 5 and 7 and their response options differ by version. In the monthly recall version, both questions are asked in terms of how frequently something occurred ("How often

did you want to have sexual activity?," "How often did you initiate a sexual activity?"). Response options are on an integer scale from 1 to 5 for the 4-week recall version, where 1 represents never and 5 always. For the daily diary, the questions are asked in terms of whether something occurred in the past 24 hours ("Did you want to have sexual activity?," "Did you initiate a sexual activity?"). Responses are a binary yes/no. This makes direct comparison between the two versions for questions 5 and 7 difficult. Furthermore, there were large amounts of missing data for the daily diary version. Among subjects with data from at least one daily diary in the 7 days preceding study Visit 3 (baseline), over 31% had only 3 or fewer days of data in Study 301 and over 36% had 3 or fewer days in Study 302. As the average daily diary score for the week is likely to be less accurate for those with a large amount of missing data, we excluded any average score with less than four observations.

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Table 76**Error! Reference source not found.** displays the correlations between the average daily score and the 4-week recall score during the placebo lead-in period. Despite the daily diary not covering the entire 4-week recall period, the correlation between the average daily score and the 4-week recall score is moderately strong for most items. Only three items have a correlation that is consistently well below 0.6 in both trials. Two of those items (Did you Initiate a Sexual Activity and How Often Did You Want to Have Sexual Activity) are from the two questions with different response scales between versions, as discussed earlier. In addition to those two questions, Receptivity to Partner's Requests is also not well correlated between versions. The questions related to desire appear to be moderately well correlated between versions, providing some support that the treatment effect of the drug on desire is properly captured by the primary endpoint for desire. Unfortunately, none of the EDQ questions relate to distress, making it difficult to evaluate whether the 4-week recall period is appropriate for measuring distress.

Table 76. Correlation Between 4-Week Recall and Average Daily Score for Elements of Desire Questionnaire

Question	BMT-301	BMT-302
1. How often sexual desire or interest	0.64	0.60
2. Intensity of sexual desire or interest	0.64	0.58
3. Sexual thoughts or fantasies	0.64	0.61
4. Interest in engaging in sex	0.60	0.60
5. How often did you want to have sexual activity	0.51	0.45
6. Receptivity to partner's request	0.41	0.38
7. How often you initiate sex	0.37	0.45
8. Interest in initiating sex	0.60	0.55
9. Satisfaction with desire or interest	0.66	0.62

Abbreviations: BMT bremelanotide

The weekly individual item scores and EDQ total score were also examined. The EDQ weekly total score was calculated as the mean of questions 1, 2, 3, 4, 6, 8, 9 shown in the table above. Scores ranged from 1 (lowest desire) to 5 (highest desire). The mean was calculated for each day and then for the week. The results were similar across studies. Combined data (Study

301/Study 302) are shown below in Table 77**Error! Reference source not found.**. The total scores show a separation between treatment groups at Months 3 and 6 of the double-blind treatment period. Smaller changes were seen in questions 5 and 7 dealing with how often subjects initiate sex or are receptive to partners' invitation for sex. Larger changes were seen with desire-related questions. At Week 21, 217 BMT patients and 246 PBO patients had an injection on the same day an entry was made in the EDQ daily diary. At Week 32, 129 BMT patients and 193 PBO patients had an injection on the same day an entry was made in the EDQ daily diary.

Table 77. Elements of Desire Questionnaire Weekly Scores (Calculated From Daily Scores): BMT-301/BMT-302 Combined

EDQ Score	Screening Visit 2 (Mean,SD)		Baseline Visite 3 (Mean,SD)		DB Month 3 Visit 6 (Mean,SD)		DB Month 6 Visit 9 (Mean,SD)	
	BMT	Placebo	BMT	Placebo	BMT	Placebo	BMT	Placebo
Item Scores								
Q1.How Often Sexual Desire or Interest	1.51(0.443)	1.48(0.433)	1.66(0.528)	1.68(0.567)	2.08(0.798)	1.76(0.681)	2.16(0.830)	1.71(0.703)
Q2.Intensity of Sexual Desire or Interest	1.39(0.372)	1.37(0.363)	1.54(0.472)	1.54(0.497)	1.91(0.750)	1.64(0.614)	2.03(0.800)	1.59(0.633)
Q3.How Often Sexual Thoughts or Fantasies	1.45(0.450)	1.45(0.420)	1.61(0.524)	1.59(0.532)	1.98(0.765)	1.68(0.667)	2.09(0.802)	1.68(0.677)
Q4.Interest in Engaging in Sex	1.42(0.384)	1.43(0.391)	1.59(0.508)	1.59(0.497)	1.97(0.753)	1.69(0.656)	2.06(0.812)	1.65(0.662)
Q5.How Often Want to Have Sex	0.15(0.188)	0.15(0.191)	0.20(0.244)	0.23(0.255)	0.34(0.306)	0.25(0.282)	0.32(0.303)	0.21(0.272)
Q6.Receptivity to Partner's Requests	0.89(0.588)	0.92(0.635)	0.86(0.694)	0.96(0.744)	1.22(1.055)	1.09(0.906)	1.27(1.056)	0.98(0.882)
Q7.How Often You Initiate Sex	0.05(0.106)	0.05(0.098)	0.07(0.123)	0.08(0.128)	0.14(0.183)	0.10(0.151)	0.13(0.186)	0.09(0.149)
Q8.Interest in Initiating Sex	1.33(0.347)	1.32(0.382)	1.50(0.504)	1.50(0.481)	1.89(0.775)	1.61(0.639)	1.96(0.801)	1.57(0.639)
Q9.Satisfaction with Desire or Interest	1.51(0.616)	1.56(0.645)	1.75(0.783)	1.71(0.764)	2.39(0.957)	1.99(0.908)	2.54(0.981)	1.92(0.932)
Total Scores[1]	**1.45(0.356)**	**1.45(0.371)**	**1.61(0.489)**	**1.61(0.497)**	**2.04(0.748)**	**1.74(0.640)**	**2.14(0.791)**	**1.69(0.664)**

Abbreviations: BMT bremelanotide, EDQ Elements of Desire Questionnaire, DB double-blind, SD standard deviation

The monthly recall (not shown) showed a numeric increase in BMT values over the 6-month trial duration with steady PBO values. The Applicant presented statistical analyses of the results but the EDQ was deemed exploratory prospectively. It is unclear if the daily or weekly differences on the EDQ are clinically meaningful.

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CHRISTINA Y CHANG
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AUDREY L GASSMAN
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06/21/2019 04:07:06 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW

Application number:	210557
Supporting document/s:	2
Applicant's letter date:	03-28-2018
CDER stamp date:	03-28-2018
Product:	Bremelanotide Vyleesi ©
Indication:	Hypoactive sexual desire disorder (HSDD)
Applicant:	Amag Pharmaceuticals, Inc
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

MEMO TO FILE SDN 57 6-17-19

The purpose of this memo is to discuss an issue regarding impurities that arose late in the review cycle. When the Unireview was being finalized, we became aware that the sponsor had submitted information to the CMC section of the review (3.2.P.5) regarding the characterization of an impurity that they designated (b) (4) This impurity was not identified or discussed in the PharmTox section of the submission and was not included in the nonclinical review of impurities.

During discussions with the CMC reviewers, it became apparent that Impurity (b) (4) had been identified following implementation of a new HPLC method that led to slightly different resolution of peaks in the drug product. Characterization of Impurity (b) (4) occurred *after* completion of the nonclinical program.

We also discovered that, in the sponsor's description of different batches of the drug product (Figure 3.2.P.5.5-16), they had mislabeled two of the chromatograms, which led to confusion about the characterization of the impurities in the nonclinical and clinical lots.

An RFI was sent to the sponsor, requesting correction of the chromatogram figures, correction of the labels on the figures describing the method of heat treatment for generating degradants, and clarification of the calculations that were made to determine human exposure to the (b) (4) degradant.

We found the submitted information acceptable and concurred with the sponsor's determination of the specification limits for impurity (b) (4).

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LESLIE C MCKINNEY
06/24/2019 04:17:21 PM

MUKESH SUMMAN
06/24/2019 06:56:45 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA LABELING REVIEW

Application number:	210557
Supporting document/s:	2
Applicant's letter date:	03-28-2018
CDER stamp date:	03-28-2018
Product:	Bremelanotide Vyleesi ©
Indication:	Hypoactive sexual desire disorder (HSDD)
Applicant:	Amag Pharmaceuticals, Inc
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

1 Executive Summary

1.1 Recommendations

The final text for the PharmTox sections of the label as submitted by the sponsor below is acceptable.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Reviewer's comment: Pharmacological class: melanocortin receptor agonist. Vyleesi© is the first product of this pharmacological class to be approved.

INDICATIONS AND USAGE:

VYLEESI is a melanocortin receptor agonist indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:

- A co-existing medical or psychiatric condition,
- Problems with the relationship, or
- The effects of a medication or drug substance

Based on nonclinical data (see Section 8) the following advice was place in the highlights:

USE IN SPECIFIC POPULATIONS

- Pregnancy: Advise patients to discontinue VYLEESI if pregnancy is suspected (8.1)
- Females of Reproductive Potential: Advise patients to use effective contraception while taking VYLEESI (8.3)

Reviewer's comment: There was considerable discussion with the clinical team and with the nonclinical AD (Ron Wange) as to whether use of bremelanotide should be contraindicated for use during pregnancy. Because there is no evidence for teratogenicity of bremelanotide, a contraindication was not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to VYLEESI during pregnancy. Pregnant women exposed to VYLEESI and healthcare providers are encouraged to (b) (4) calling the [insert pregnancy registry name] at [insert contact information].

Risk Summary

The few pregnancies in women exposed to VYLEESI in clinical trials are insufficient for determining whether there is a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.

Based on findings in animal studies, the use of VYLEESI in pregnant women may be associated with the potential for fetal harm. In animal reproduction and development studies, daily subcutaneous administration of bremelanotide to pregnant dogs during the period of organogenesis at exposures greater than or equal to 16 times the maximum recommended dose (based on area under the concentration-time curve or AUC) produced fetal harm. In mice subcutaneously dosed with bremelanotide during pregnancy and lactation, developmental effects were observed in the offspring at greater than or equal to 125-times the maximum recommended dose (based on AUC) [see Data]. However, the lowest bremelanotide dose associated with fetal harm has not been identified for either species. For this reason, women should use effective contraception while taking VYLEESI and discontinue VYLEESI if pregnancy is suspected.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

There were 7 pregnancies reported in the clinical trials of more than 1057 women treated with VYLEESI for up to 12 months. Among these 7 pregnancies, no major congenital anomalies were reported. There was one spontaneous abortion (miscarriage), five full-term live births, and one outcome was unknown due to loss to follow-up.

Animal Data

An embryofetal development study was conducted in the dog and a pre- and postnatal development study was conducted in the mouse to inform developmental risk. These two species are not routinely used for reproductive toxicity assessment but were the only two species that could be successfully dosed by the subcutaneous route during gestation.

> *Reviewer's comment: We believe that this label is the first to allow the use of reprotox data from the dog to support risk assessment. The PharmTox AD, Ron Wange, was consulted for his opinion on whether reprotox data from the dog was sufficient for use in risk assessment. He concurred that the data from the dog, while limited by low numbers of litters, provided useful information for risk assessment.*

Bremelanotide was administered subcutaneously to pregnant dogs (8/dose) at 2, 8, or 20 mg/kg from gestation day (GD) 18-35, corresponding to the period from implantation to late embryogenesis in the dog. Embryofetal toxicity, as measured by post-implantation loss, was elevated approximately 3 to 8-fold compared to controls across all treated groups but was not dose-dependent. A developmental no-observed-effect level (NOEL) was not set. At the low dose of 2 mg/kg/day in the dog, exposure was approximately 16 times the human exposure based on AUC.

In a pre- and postnatal development study, female mice (30/dose) were dosed subcutaneously at 0, 30, 75, and 150 mg/kg/day from GD 6 through lactation day (LD) 28, and two generations of offspring were assessed (F1 and F2). There were no effects on reproductive parameters in parental (F0) or F1 generation animals at doses up to 150 mg/kg/day (approximately 760 times the human AUC). However, developmental delays were observed in the F1 generation mice at ≥ 30 mg/kg/day (approximately 125 times the human AUC). For that reason, a developmental NOEL was not set. There were no significant effects on the growth and development of F2 generation pups.

8.2 Lactation

Risk Summary

There is no information on the presence of bremelanotide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VYLEESI and any potential adverse effects on the breastfed child from VYLEESI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of VYLEESI during pregnancy is not recommended [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception while taking VYLEESI, and to discontinue VYLEESI if pregnancy is suspected.

Reviewer's comment: The recommendation to use contraception and to discontinue use during pregnancy is based on nonclinical data demonstrating early fetal loss in the dog. Reprotox studies in the rabbit also demonstrated early fetal loss, but these studies could not be cited in the label because of confounding factors in those studies.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bremelanotide is a melanocortin receptor (MCR) agonist that nonselectively activates several receptor subtypes with the following order of potency: MC1R, MC4R, MC3R, MC5R, MC2R. At therapeutic dose levels, binding to MC1R and MC4R is most relevant. Neurons expressing MC4R are present in many areas of the central nervous system (CNS). The mechanism by which VYLEESI improves HSDD in women is unknown. The MC1R is expressed on melanocytes; binding at this receptor leads to melanin expression and increased pigmentation.

Reviewer's comment: Section 12.1 required considerable editing. The sponsor's text, which originally stated that stated that (b) (4)

(b) (4)

Lastly, the ability of bremelanotide to increase pigmentation in the skin is a direct result of its binding to MCR1. This statement was included to explain one of the primary side effects of the drug.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There were no significant increases in tumor incidence in two-year carcinogenicity studies with intranasal administration (0.5, 2.5, and 5 mg/animal/day) of bremelanotide to male and female rats, and subcutaneous administration (3, 9, and 15 mg/kg/day) to male and female mice. Multiples of exposure were calculated based on average Cmax at the high dose over the course of the study and were 1.1-fold and 111-fold the human Cmax for rats and mice, respectively.

Reviewer's comment: We negotiated with the sponsor to recalculate the multiples of exposure based on the fact that exposure in the rat declined significantly over the course of the study.

Mutagenesis

Bremelanotide was not genotoxic or mutagenic in a battery of tests, including the in vitro bacterial reverse mutation assay, the in vitro chromosomal aberration test in Chinese Hamster Ovary cells, and the in vivo mouse micronucleus assay.

Impairment of Fertility

There were no effects on fertility in male (75 mg/kg/day, approximately 375 times the human AUC) or female (150 mg/kg/day, approximately 760 times the human AUC) mice following subcutaneous administration.

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/s/

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MUKESH SUMMAN
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Office of Clinical Pharmacology Review-

Appendices

NDA or BLA Number	210557
Link to EDR	\\CDSESUB1\evsprod\NDA210557
Submission Date	03/23/2018(SDN2); 05/03/2018(SDN4); 08/03/2018 (SDN18); 08/29/2018(SDN24); 10/19/2018(SDN31); 12/14/2018 (SDN39); 01/25/2019 (SDN43); 03/29/2019 (SDN49)
Submission Type	Standard
Brand Name	Vyleesi™
Generic Name	Bremelanotide (BMT)
Dosage Form and Strength	Solution; 1.75 mg
Route of Administration	Subcutanous Injection
Proposed Indication	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD)
Applicant	AMAG Pharmaceuticals INC
Associated IND	IND 064119
OCP Review Team	Li Li, Ph.D.; Doanh Tran, Ph.D.; Fang Li, Ph.D.; Jerry Yu, Ph.D.
OCP Final Signatory	Shirley K. Seo, Ph.D. Director of Division of Clinical Pharmacology III Office of Clinical Pharmacology

Table of Contents

Note: This document contains the appendices to the Clinical Pharmacology review.

APPENDICES

1 Summary of Bioanalytical Method Validation and Performance

Five high performance liquid chromatography tandem mass spectrometry (LC-MS/MS) methods were developed and validated for the quantitative determination of BMT in human plasma. The lower limit of quantification (LLOQ) for BMT was 0.5 ng/mL. The detailed method and validation parameters are described below. The linearity of standard curve, selectivity/specificity, assay accuracy and precision, extraction efficiency and dilution fulfilled the standard acceptance criteria. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period.

Table 1 Validation Parameters for Method 48354

Bioanalytical Method	48354
Studies	PT-141-56, (b) (4) PT-141-54
Methodology	LC-MS/MS
Biological matrix	Na_2EDTA Human Plasma
Extraction method	Protein Precipitation
Internal Standard	(b) (4)
Calibration curve range	0.5 -250 ng/mL
Standards: Precision & Accuracy:	 Inter-run: 4.1% to 10.0% & 95.8% to 104.5%
QCs: Precision & Accuracy:	Intra-run: 3.4% to 15.5% & 89% to103.0% Inter-run: 6.2% to 12.9% & 98.4% to 102.3%
LLOQ: Precision & Accuracy:	 Inter-run: 13.2% & 97.4 %
Long-term stability	367 days at -20°C
Analyte Recovery	39% to 46%
Freeze-thaw stability	Demonstrated for 3 cycles for at ≤ -20ºC

Table 2 Validation Parameters for Method 14116

Bioanalytical Method	14116
Studies	BMT-103, BMT-107, BMT-115, BMT-116, BMT-301, BMT-302
Methodology	LC-MS/MS
Biological matrix	K_3EDTA Human Plasma
Extraction method	Solid Phase Extraction
Internal Standard (IS)	BMT-d_8
Selectivity/Specificity	BMT not detected in the 6 individual samples analyzed
Carry-over	An insignificant amount of carryover was observed after some high standards & QC-H samples
Calibration curve range	0.5 -250 ng/mL
Standards: Precision & Accuracy:	Inter-run: 1.1% to 5.1% & 93.6% to 103.6%
QCs: Precision & Accuracy:	Inter-run: ≤ 2.7% & 98.5% to 101.0% Intra-run: ≤ 2.8% & 97.0% to 103.3%
LLOQ: Precision & Accuracy:	Inter-run: 7.1% & 97.2% Intra-run: 3.64% to 5.5% & 90.2 % to 102.2%

Long-term stability	183 days in human plasma at -20°C.
Analyte Recovery	86.3% to 94.7% for BMT and 86.4% to 87.2% for IS
Freeze-thaw stability	Demonstrated for 3 cycles for at ≤ -20ºC

Table 3 Validation Parameters for Method ZZ50747-01

Bioanalytical Methods	ZZ50747-01
Studies	BMT-101, BMT-104, BMT-105, BMT-117, BMT-118
Methodology	LC-MS/MS
Biological matrix	K_2EDTA Human Plasma
Extraction method	Solid phase extraction
Internal Standard (IS)	BMT-d_8
Selectivity/Specificity	No significant interference at the retention time and mass transition of BMT was observed from endogenous components in any of the 10 aprotinin-treated human plasma (K_2EDTA) lots screened or of d8-BMT(IS) in any of the 10 aprotinin-treated human plasma (K_2EDTA) lots screened
Carry-over	No carryover was observed after some high standards & QC-H samples
Calibration curve range	0.5 to 250 ng/mL
Standards: Precision & Accuracy:	Inter-run: ≤4.1% & 96.9% to 104.4%
QCs: Precision & Accuracy:	Inter-run: 4.8 to 6.7% & 104% to 110.0% Intra-run: 0.9% to 5.6% & 96% to 115.4%
LLOQ: Precision & Accuracy:	Inter-run: 6.6% & 111% Intra-run: 2.4% to 5.6% & 102.4 % to 115.4%
Long-term stability	182 days at -20°C (polypropylene tubes) 188 days at -80°C (polypropylene tubes)
Analyte Recovery	57% to 65% for BMT and 59% for IS
Freeze-thaw stability	Demonstrated for 6 cycles for at ≤ -20ºC or -80°C

Table 4 Validation Parameters for Method 46442

Bioanalytical Methods	46442
Studies	PT-2001-06
Methodology	LC-MS/MS
Biological matrix	K_3EDTA Human Plasma
Extraction method	Protein Precipitation
Internal Standard (IS)	(b) (4)
Selectivity/Specificity	BMT not detected in the 6 individual samples analyzed
Carry-over	An insignificant amount of carryover was observed after some high standards & QC-H samples
Calibration curve range	0.5 to 500 ng/mL
Standards: Precision & Accuracy:	Inter-run: ≤12% & 97.6% to 102.6%
QCs:	Inter-run: ≤ 9.6% & 102.6% to 110.5%

Precision & Accuracy:	Intra-run: ≤ 11.3% & 99.1% to 114.8%
LLOQ: Precision & Accuracy:	Inter-run: 12.6% & 97.1% Intra-run: 14.4% & 91.3 % to 104.8%
Long-term stability	14 months in human plasma and 258 days in human urine at -70°C.
Analyte Recovery	37.3% to 43.5% for BMT and 50.0% to 52.8% for IS
Freeze-thaw stability	Demonstrated for 3 cycles for at ≤ -20ºC

Table 5 Validation Parameters for Method 46581

Bioanalytical Methods	46581
Studies	PT-141-2002-14F
Methodology	LC-MS/MS
Biological matrix	K_3EDTA Human Plasma
Extraction method	Protein Precipitation
Internal Standard (IS)	(b) (4)
Selectivity/Specificity	No significant interfering peaks w/in retention region of BMT on chromatograms
Carry-over	No significant carryover, greater than 20%, was noted
Calibration curve range	0.5 to 100 ng/mL
Standards: Precision & Accuracy:	Inter-run: ≤18.3% & 97.3% to 104.5%
QCs: Precision & Accuracy:	Inter-run: ≤ 9.2% & 97% to 102.1% Intra-run: ≤ 11.2% & 89.8% to 105.3%
LLOQ: Precision & Accuracy:	Inter-run: ≤ 9.7% & 88.9% Intra-run: ≤ 11.7% & 85 % to 107.4%
Long-term stability	12 weeks in human plasma at -70°C. Stability test beyond 12 weeks was not found in the report
Analyte Recovery	92.4% to 104% for BMT and 102% to 104% for IS
Freeze-thaw stability	Demonstrated for 3 cycles for at ≤ -20ºC

Assays for DDI Studies:

LC-MS/MS methods were also developed and validated for the quantitative determination of the plsam concentrations of concomitant medications administered in drug interaction studies. Upon detailed review, these bioanalystical methods are acceptable based on FDA Guidance for Industry on bioanalytical method validation.

2 Clinical BA/BE Assessments

2.1 Study PT-141-56 (BE and Absolute BA Study)

Title: A Phase 1, Double-Blind, Cross-over Study to Evaluate the Safety, Tolerability, Absolute and Relative Bioavailability, and Bioequivalence of Subcutaneously Administered BMT via Prefilled Syringe and Autoinjector in Healthy Female Subjects

Objectives:

- To determine if BMT 1.75 mg subcutaneously (SC) administered via prefilled syringe (PFS) is bioequivalent to the same dose administered via autoinjector (AI) in healthy female subjects.
- To determine the absolute bioavailability of a 1.0 mg dose of BMT administered SC via AI using an intravenous (IV) formulation of BMT.
- To evaluate the initial safety and tolerability of BMT administered SC via a prefilled, single-use AI in healthy female subjects.

Study Design:
This was a single-center, 2-part study to evaluate the PKs, safety, and tolerability of BMT administered SC and IV in 36 healthy female subjects with BMI between 18 and 32 kg/m^2. Part 1 consisted of a double-blind, crossover design to compare SC administration of BMT 1.75 mg delivered via PFS vs. AI. Healthy female subjects each received 2 doses of BMT 1.75 mg, administered SC and delivered as a single dose on each of 2 days, with 1 dose from a PFS and the other dose from an AI. Each single dose (on Days 1 and 3) was followed by a 48 hr washout period in which no drug was administered. On Day 5, subjects in Group 1 received a single 1.0 mg dose of BMT administered SC via AI, and subjects from Group 2 received a single BMT 0.2 mg dose administered as a 5 mL solution over 5 min via IV syringe pump. An overview of study design and BMT dosing is illustrated in **Table 1**.

Table 1: Overview of Study Design and BMT Dosing

<table>
<tr><th rowspan="2">Group</th><th colspan="4">Part 1
(Group: 1, 2, 3, 4)
(36 subjects, double-blind to device)</th><th colspan="2">Part 2
(Group: 1 & 2 Only)
(20 subjects, open-label)</th></tr>
<tr><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th><th>Day 5</th><th>Day 6</th></tr>
<tr><td>1
N = 10</td><td rowspan="3">Dosing[a]:
BMT
1.75 mg SC
via AI or
PFS</td><td rowspan="3">Washout</td><td rowspan="3">Dosing[b]:
BMT
1.75 mg SC
via PFS or
AI</td><td rowspan="2">Washout</td><td>Dosing:
BMT
1.0 mg SC
(AI)</td><td rowspan="2">Washout
and
Discharge</td></tr>
<tr><td>2
N = 10</td><td>Dosing:
BMT
0.2 mg IV</td></tr>
<tr><td>3
N = 8</td><td rowspan="2">Washout
and
Discharge</td><td rowspan="2">NA</td><td rowspan="2">NA</td></tr>
<tr><td>4
N = 8</td></tr>
</table>

Blood samples for PK analysis were collected at the following time points:

- SC Injection: pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs after dosing.
- IV Injection: pre-dose and at 2, 5, 10, 15, 20, and 30 min, and at 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hrs after dosing.

Plasma concentrations of BMT were analyzed by [redacted] (b) (4) using a validated liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) assay with linear analytical range of 0.500 to 250 ng/mL (Bioanalytical Study Report No. 80262 and Bioanalytical Method Validation Report No. 48354).

PK Results:

As shown in **Figure 1**, the mean plasma concentration-time profiles of BMT administered via PFS and AI devices are superimposed (PK parameters in **Table 2**). With PFS as the reference product and AI as the test product, the calculated 90% confidence interval (CI) for ratio of geometric means (GMR) of C_{max} and $AUC_{0-\infty}$fell well within the 80% to 125% range (C_{max}: 100% [96% -105%], $AUC_{0-\infty}$: 98% [96% - 101%]), indicating that 1.75 mg BMT SC administered via PFS is bioequivalent to the same dose administered via AI. C_{max} and AUC for BMT is dose-proportional in the dose range of 1 - 1.75 mg (**Table 3**). The calculated values for the absolute bioavailability were 114% and 116% for AI and PFS, respectively, indicating a complete absorption of BMT into the systemic circulation following SC administration via AI or PFS (**Table 4**).

Figure 1. Mean Plasma Concentration-vs.-Time Curves for BMT 1.75 mg SC via PFS and AI Administration (PK Population)

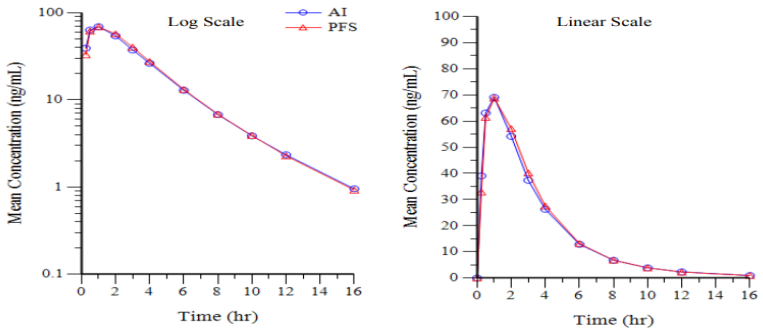


Table 2. Mean PK Parameters of BMT 1.75-mg SC Stratified by Administration Device (Bioequivalence PK Population)

Administration Device	Statistic	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	$\%AUC_{Extrap}$ (%)	λ_z (hr^{-1})	$t_{1/2}$ (hr)	V_z/F (L)	Cl/F (L/hr)
AI	N	36	36	36	36	36	36	36	36	36
	Mean	72.8	NA	272	276	1.5	0.266	2.70	25.0	6.48
	SD	13.5	NA	39	40	0.8	0.046	0.56	5.8	1.00
	Min	50.0	0.50	185	188	0.6	0.148	2.00	17.6	5.01
	Median	72.0	1.01	274	276	1.2	0.273	2.54	24.7	6.33
	Max	113.0	1.04	345	349	3.9	0.347	4.68	49.5	9.32
	CV%	18	NA	14	14	53	17	21	23	16
	Geometric Mean	71.6	NA	269	273	1.3	0.262	2.65	24.5	6.41
PFS	N	36	36	36	36	36	36	36	36	36
	Mean	73.5	NA	278	281	1.3	0.264	2.67	24.4	6.38
	SD	18.8	NA	45	45	0.4	0.035	0.35	3.8	1.06
	Min	45.3	0.50	182	186	0.6	0.203	2.04	17.3	4.29
	Median	70.1	1.01	280	285	1.2	0.259	2.68	24.6	6.14
	Max	137.0	2.03	401	408	2.4	0.340	3.42	32.8	9.42
	CV%	26	NA	16	16	33	13	13	16	17
	Geometric Mean	71.4	NA	274	278	1.2	0.261	2.65	24.1	6.30

Note: t_{lag} was zero-hr for all subjects.

Table 3 PK Parameters for BMT 1.0 mg and 1.75 mg SC via AI Administration (Relative Bioavailability PK Population)

BMT Dose (mg)	Statistic	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	$\%AUC_{Extrap}$ (%)	λ_z (hr^{-1})	$t_{1/2}$ (hr)	V_z/F (L)	Cl/F (L/hr)
1.0	N	10	10	10	10	10	10	10	10	10
	Mean	46.3	NA	160	164	2.2	0.284	2.52	23.1	6.42
	SD	12.1	NA	38	38	1.0	0.052	0.5	5.9	1.52
	Min	29.3	0.5	107	108	1.3	0.205	1.91	14.6	4.18
	Median	44.8	1	159	163	2.0	0.283	2.45	25.4	6.12
	Max	68.2	1.06	236	239	4.5	0.362	3.37	30.3	9.24
	CV%	26	NA	24	23	44	18	19.87	26	24
	Geometric Mean	44.8	NA	156	160	2.1	0.28	2.48	22.4	6.26
1.75	N	10	10	10	10	10	10	10	10	10
	Mean	74	NA	261	266	1.7	0.259	2.87	27.9	6.83
	SD	15.1	NA	51	51	1.1	0.067	0.85	8.9	1.42
	Min	53.8	0.5	185	188	0.6	0.148	2	18.6	5.01
	Median	77	0.51	265	267	1.3	0.251	2.76	27.5	6.56
	Max	93.8	1.04	345	349	3.9	0.347	4.68	49.5	9.32
	CV%	20	NA	19	19	63	26	29.6	32	21
	Geometric Mean	72.6	NA	257	261	1.4	0.25	2.77	26.8	6.7

Table 4 PK Parameters for BMT 0.2 mg via IV Administration (Absolute Bioavailability PK Population)

Statistic	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (hr·ng/mL)	$AUC_{0-\infty}$ (hr·ng/mL)	$\%AUC_{Extrap}$ (%)	λ_z (hr^{-1})	$t_{1/2}$ (hr)	V_{ss} (L)	Cl (L/hr)
N	9	9	9	9	9	9	9	9	9
Mean	26.2	NA	25.1	27.0	7.2	0.369	1.91	15.8	7.56
SD	4.7	NA	4.3	3.9	3.3	0.047	0.23	1.9	1.17
Min	19.1	0.12	17.8	20.6	1.1	0.317	1.50	13.4	6.34
Median	25.3	0.12	24.7	26.4	7.0	0.344	2.02	15.3	7.58
Max	33.0	0.14	30.3	31.5	13.2	0.463	2.18	19.7	9.73
CV%	18	NA	17	15	46	13	12	12	15
Geometric Mean	25.8	NA	25.0	26.7	6.2	0.366	1.89	15.7	7.48

Safety Results

When administered at the SC doses of 1.75 mg by both PFS and AI devices, and 1.0 mg by AI, as well as at the IV dose of 0.2 mg, BMT was safe and well-tolerated. No serious or severe AEs occurred during the study. The most frequent TEAEs reported were GI and injection site disorders.

Conclusions

- At a dose of 1.75 mg, the SC administration of BMT administered via the AI device was bioequivalent to the PFS device.
- When administered SC via AI, the PK parameters of the 1.0 mg dose of BMT decreased in a dose-proportional manner from the PK parameters of the 1.75 mg dose.
- The bioavailability of the 1.75-mg dose for both AI and PFS SC administration demonstrated that BMT was completely available to the systemic circulation following SC administration.

Reviewer's Comments:

- *The safety and efficacy assessments of BMT for HSDD treatment are mainly based on Phase 3 studies (BMT-301 and BMT-302) where AI was used. The purpose of this BE study was to support the Phase 2 dose-finding study (Study PT-141-54), which was conducted with PFS.*

- *BMT plasma concentrations were determined using a validated LC/MS/MS method (see details in Appendix 1). BMT plasma samples were analyzed within the demonstrated stability window (received in July ~ August 2013, analyzed by September 2013). Two-Thirds (124) samples were chosen for Incurred Sample Reanalysis, 95 out of 124 reanalyzed samples (77%) met acceptance criteria. Overall, the bioanalytical method used in this study is acceptable.*

- *BE study is adequately powered and BE result is consistent with the analysis conducted by this reviewer.*

3 Clinical PK and/or PD

3.1 Study BMT-107 (Mass Balance Study)

Title: An Open-label, Single Center, Single Subcutaneous Dose Study to Investigate PK, Absorption, Metabolism, and Excretion of [^{14}C]-Labeled BMT in Healthy Females and Males

Objectives:

- To assess the absorption, metabolism, and excretion (AME), including mass balance, of BMT in healthy females and males using [^{14}C]-labeled BMT
- To assess the metabolite profile and identify any unknown metabolites, if possible, of BMT in healthy females and males using [^{14}C]-labeled BMT

Study Design:
This study was an open-label, non-randomized, AME study in 8 healthy subjects (3 females, 5 males). On Day 1 of the study, each subject received a single subcutaneous (SC) dose of 1.75 mg [^{14}C]-labeled BMT (approximately 75 µCi). Blood, urine, and fecal samples were obtained through at least 96 hours after dosing for PK evaluation, and through at least 72 hours after dosing for identification of metabolites. Particularly, blood samples for PK were collected at 0 (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose. Additional blood samples were collected every 24 hours until Discharge. Blood samples for metabolite profiling and identification in plasma were collected at 0 (predose) and 0.5, 1, 2, 4, 8, 12, 24, 48, and 96 hours postdose. Urine samples were collected at -12 to 0 (predose, the last void within 1 hour prior to dosing) and 0 to 6, 6 to 12, 12 to 16, 16 to 24, 24 to 48, 48 to 72, and 72 to 96 hours postdose. Additional urine samples were collected at 24-hour intervals until Discharge. Fecal samples were collected daily (24-hour intervals) from Day 1 until Discharge.

Plasma concentrations of BMT were determined by (b) (4). using a validated LC/MS/MS method (Bioanalytical study report (b) (4) 17087; validation report 46442). Total radioactivity concentrations were determined by (b) (4). using (b) (4) Profiling and characterization of metabolites in plasma, urine, and feces were conducted by (b) (4) using standard laboratory procedures. Quantitation of the metabolites present in plasma, urine, and feces was based on the profiles of radioactivity. Metabolites were identified and/or characterized by liquid chromatography-mass spectrometry.

PK Results:
AME
Following SC administration, BMT was rapidly absorbed and eliminated, with a median t_{max} of approximately 0.50 hours and an mean $t_{1/2}$ of approximately 2.7 hours (**Figure 1**). The geometric mean $AUC_{0\text{-}192h}$ ratio of plasma BMT to plasma total radioactivity was 0.150 (CV% = 16.9%), suggesting that BMT plays a minor role in contributing toward the circulating total radioactivity in plasma.

Over 192-hour sample collection period, 88% of the administered radioactive dose was recovered in all excreta (urine and feces) with 23% in the feces and 65% in urine, indicating BMT is primarily excreted via the kidney. In addition, 36.5% of the administered dose was excreted in urine as unchanged BMT, with most (31.9%) excreted within 6 hours postdose (**Figure 2**).

The geometric mean $AUC_{0\text{-}192h}$ ratio of total radioactivity in whole blood to total radioactivity in plasma (blood/plasma ratio) was 0.733 (CV% =7.8%), indicating minimal partitioning of total radioactivity into red blood cells. The overall distribution and excretion profiles for total radioactivity in plasma and whole blood were similar between male and female subjects. The recovery of total radioactivity in excreta (urine

and feces) over 192-hour postdose sample collection period was slightly lower for male subjects than for female subjects (mean recoveries: 92.5% and 84.8% for females and males, respectively).

Figure 1 Mean Concentration- Time Profiles of BMT in Plasma, Total Radioactivity in Plasma, and Total Radioactivity in Whole Blood

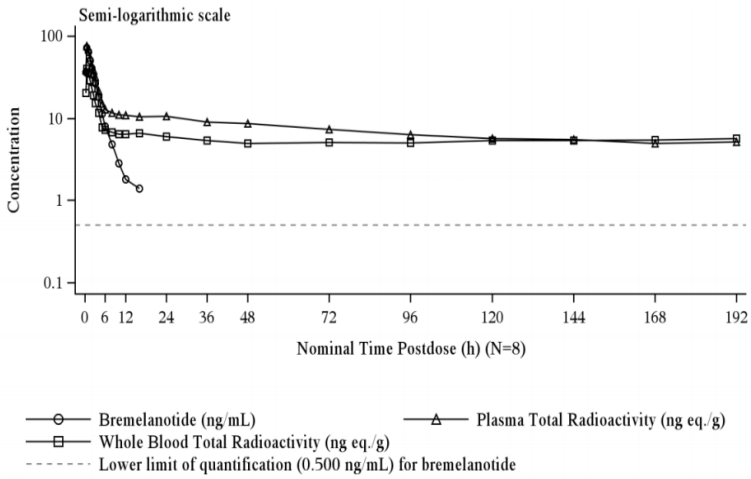
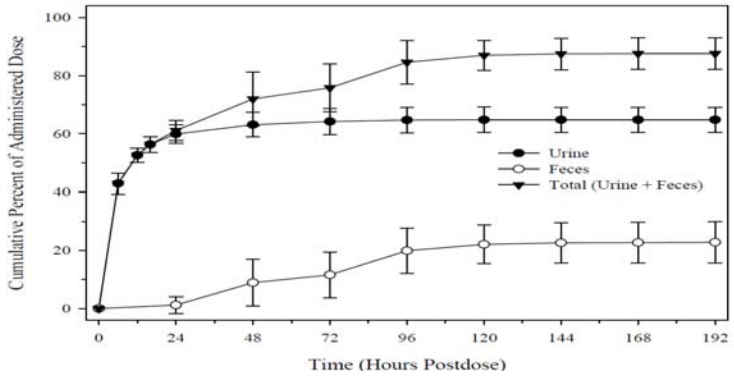


Figure 2 Mean (±SD) Cumulative Percent Recovery of Total Radioactivity in Urine and Feces



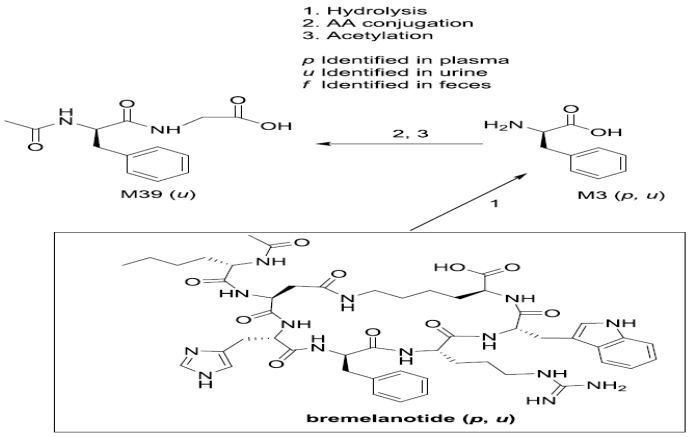
Metabolite Profiling

- Plasma: After a single SC 1.75-mg dose of [^{14}C]-BMT to healthy human subjects, BMT, M3 (the single amino acid D-phenylalanine), and three impurities were detected in timepoint pooled plasma samples (0.5 to 96 hours postdose). Across 8 study subjects, metabolite M3 was detected in the 8-, 12-, and 24-hour post-dose plasma samples. Three impurities were detected only in 0.5- and 1-hour post-dose plasma samples. Using the calculated $AUC_{0\text{-}96h}$, BMT accounted for approximately 74% of the radioactivity and M3 accounted for approximately 24% of the radioactivity. Three impurities accounted for less than (b)(4)% of the radioactivity each.
- Urine: BMT and ten components (metabolites, degradants and/or impurities) were detected in pooled 0- to 72-hour postdose urine samples.BMT accounted for approximately 42% of the recovered radioactive dose in urine. Metabolite M3 accounted for approximately 10% of the radioactive dose. In addition, M39, a metabolite formed via acetylation and glycine conjugation of M3, accounted for approximately 6% of the radioactive dose. Other metabolites, degradants, and impurities accounted for less than (b)(4)% of the radioactive dose each.

- Feces: A total of 12 metabolites were detected in pooled feces samples, 0- to 144-hour post-dose. No BMT was detected. M51 accounted for approximately 8% of the radioactive dose. Other metabolites accounted for less than 2% of the radioactive dose each.

Proposed Metabolic Pathway of BMT in Human

The primary metabolic pathway involved the multiple hydrolysis of the amide bond of the cyclic peptide and eventually the formation of the major metabolite M3 in both plasma and urine samples. In addition, M3 underwent acetylation and glycine conjugation reactions to form M39.



Safety Results:

BMT was well tolerated in healthy male and female subjects when administered as a single SC injection of 1.75 mg (approximately 75 μCi) of [^{14}C]-BMT. No serious adverse events or severe TEAEs were reported during the study and no subjects withdrew from the study due to a TEAE. There were no clinically significant findings or trends noted in vital signs measurements, ECG parameters, or physical examinations during the study.

Conclusions:

- Once absorbed into the systemic circulation, BMT is rapidly hydrolyzed and plays a minor role in contributing toward the circulating total radioactivity in plasma after 12 hours postdose.
- Renal is the primary route of elimination of total radioactivity following BMT administration.
- Urinary excretion of unchanged BMT accounted for 36.5% of the administered dose, with most (~31.9%) excreted within 6 hours post-dose.
- M3, the single amino acid D-phenylalanine, is the major metabolite in both plasma and urine samples.

Reviewer's Comments:

- *The mass balance study shows that renal is the major elimination pathway for BMT clearance, as 64.8% of radioactive dose was found in urine and BMT accounted for 42% of the recovered radioactive dose.*
- *Following SC administration, 26% recovered radioactive dose was found in feces, suggesting a significant contribution of biliary excretion. However, it should be also noted that all the radioactivities in feces were not associated with parent drug of BMT, but inactive metabolites. In addition, in vitro study (Study 8349337) using human hepatocytes suggested that BMT has minimal hepatic metabolism with 85.2% of dose remaining after 240 minutes incubation. Therefore, it is not clear if hepatic clearance play a significant role in BMT PK.*

3.2 Study PT-141-2001-06 (Single Ascending Dose in Men)

Title: A Phase 1, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Maximum Tolerated Dose to Evaluate the Safety, Tolerability, PK and PD Effect of Subcutaneously Administered BMT in Healthy Male Subjects

Objectives:

- To assess the safety and tolerability of single SC doses of BMT administered to healthy male subjects
- To assess the PK profile of BMT; and assess the PD effect (b) (4) using a plethysmographic device, the RigiScan® Plus Rigidity Assessment System

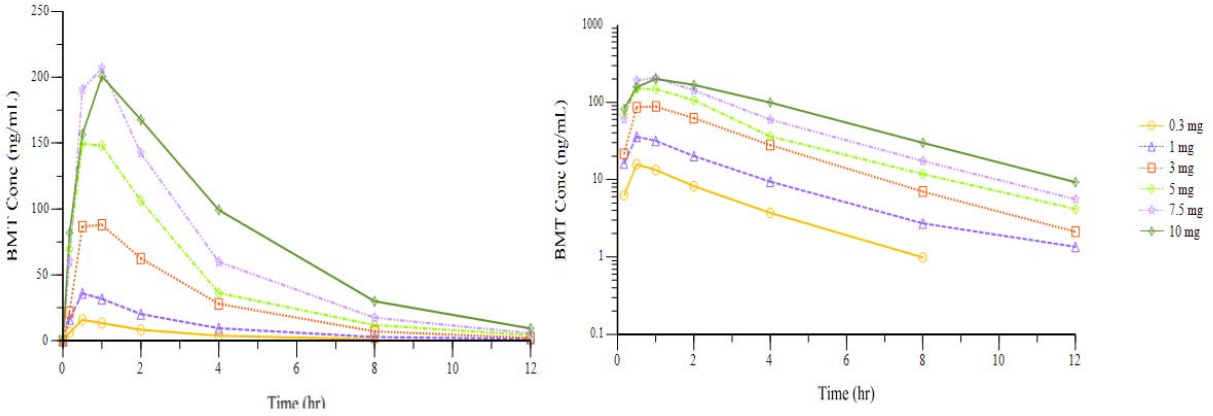
Study Design:

This was a randomized, double blind, placebo-controlled, parallel group, single administration, dose escalation study to maximum tolerated dose (MTD) in 56 healthy adult male subjects. Seven BMT dose levels were studied: 0.1, 0.3, 1, 3, 5, 7.5 and 10 mg. In each dose group of 8 subjects, 6 subjects received BMT and 2 subjects received placebo. Blood samples (approximately 7.5 mL) for the analysis of plasma concentrations of BMT were drawn at pre-dose, 10, 30 minutes, 1, 2, 4, 8 and 12 hours post-dose. Plasma concentrations of BMT were analyzed using a validated LC/MS/MS assay with linear analytical range of 0.500 to 500 ng/mL (Bioanalytical Method Validation Report (b) (4) Study No. 46442).

PK Results

Mean C_{max} and AUC_{0-t} increased with escalating doses of BMT in a less than dose proportional manner (**Figure 1**). Particularly, C_{max} appeared to reach a plateau at the 7.5 mg dose level as mean C_{max} values were similar for the 7.5 and 10.0 mg doses. When BMT doses increased from 0.3 mg to 10 mg (33-fold), mean C_{max} values increased from 16.37 ng/mL to 208.17 ng/mL (13-fold) and mean AUC_{0-t} increased from 41.61 to 878.22 ng·h/mL (21-fold). Mean half-lives ($t_{1/2}$) appear to be similar cross the studied doses, ranging from 1.92 hours to 2.68 hours. PK samples for the 0.1 mg dose group were not analyzed because this group was dosed in error.

Figure 1 Mean BMT Plasma Concentration - Time Profile After SC Administration of 0.3 mg, 1 mg, 3 mg, 5 mg, 7.5 mg and 10 mg of BMT



PD Results: Not reviewed (b) (4)

Safety Results:
No serious AE were reported in this study. The most common AEs were somnolence (38.1%), flushing (31.0%), vomiting (11.9%), nausea (9.5%) and pruritus at the injection site (7.1%). Vomiting was mild to moderate in intensity and was noted in 1 (17%), 1 (17%) and 3 (50%) subjects receiving the 5, 7.5 and 10 mg doses, respectively. The onset of vomiting was delayed (6 to 10 hours for the 5 and 7.5 mg doses and 6 to 15 hours for the 10 mg dose) and responded to ondansetron when given. No clinically significant laboratory test, physical examination or ECG abnormalities attributable to treatment were observed following SC BMT administration.

Conclusions:

- Mean C_{max} and AUC_{0-t} values increased with escalating doses of BMT from 0.3 mg to 10 mg in a less than dose proportional manner.
- Single SC BMT doses ranging from 0.3 to 10 mg in healthy adult male subjects were safely administered and were well tolerated by the majority of healthy adult male subjects. The 10 mg BMT dose was designated the maximum tolerated dose.

Reviewer's Comments:

- *The maximum study dose of 10 mg is 5.7-fold of the proposed therapeutic dose of 1.75 mg, representing the highest SC BMT dose studied in human.*

- *In Phase 3 Study BMT-301 where 1.75 mg SC BMT was administered, the onset of vomiting were 1.75 hours (SD: 2h) post-dose. It is interesting that in this study, the onset of vomiting was delayed, i.e., 6 to 10 hours for the 5 mg and 7.5 mg doses and 6 to 15 hours for the 10 mg dose.*

3.3 Study BMT-2002-14F (Single Ascending Dose in Women)

Title: A Phase 1, Double-Blind, Placebo-Controlled, Dose Escalation Study to Maximum Tolerated Dose to Evaluate the Safety, Tolerability and PD Effect of Subcutaneously Administered BMT in Healthy Female Subjects

Objectives:

- To assess the safety and tolerability of single subcutaneous (SC) doses of BMT administered to healthy female subjects
- To assess the PD effect of BMT, defined by vaginal blood flow (measured using vaginal photoplethysmography) to assess arousal, and a Video Assessment Questionnaire (VAQ) to assess desire

Study Design:
This was a double-blind, placebo-controlled, single dose, dose escalation study in 32 healthy adult female subjects. Four BMT doses were studied, i.e., 0.3 mg (Group I), 1 mg (Group II), 3 mg (Group III) and 5 mg (Group IV). Each dose group had 8 subjects with 6 subjects received BMT and 2 subjects received placebo. Blood samples for plasma BMT concentration determination were obtained at 0 hour (pre-dose) and at 30 minutes post-dose. Plasma concentrations of BMT were analyzed using validated LC/MS/MS assays by (b) (4) with LLOQ of 0.500 ng/mL (Bioanalytical Report 47409, Validation Report 46581).

PK Results
The mean plasma BMT concentrations at 30 minutes post-dose increased in a somewhat greater than dose proportional manner over the SC BMT dose range of 0.3 to 5 mg (i.e., an approximately 25-fold increase in mean plasma BMT concentrations was noted for a 17-fold increase in BMT dose). Within the dose range of 1 – 5 mg, BMT PK seems to be dose proportional (**Table 1**).

Table 1. Summary Plasma BMT Concentration at 30 Minutes Post-Dose Following SC Administration to Healthy Female Subjects

	0.3 mg (N=6)	1 mg (N=6)	3 mg (N=6)	5 mg (N=5)
Mean	9.38	50.08	149.35	237.20
SD	3.14	16.96	41.21	87.46
Median	9.14	45.05	162.50	231.00
Minimum	4.33	35.00	91.10	152.00
Maximum	13.00	83.00	194.00	379.00

PD Results: Defer to Clinical Reviewer.

Safety Results
Single SC BMT doses, ranging from 0.3 to 5 mg, were safely administered and generally well tolerated by these healthy adult female subjects. The most common AEs were nausea (16.7%), headache (12.5%), vomiting (8.3%) and somnolence (8.3%). Vomiting was noted in 1 subject receiving BMT 3 mg and 1 subject receiving BMT 5 mg. The onset of vomiting was delayed, i.e., approximately 4 hours post-dose. AEs were predominantly mild in nature, except two subjects in the BMT 3 mg group reported moderate somnolence and two subjects in the BMT 5 mg group reported nausea and headache, respectively, which were moderate in intensity. No clinically significant laboratory tests, vital signs, physical or pelvic

examination findings, or ECG abnormalities attributable to treatment were observed following SC BMT administration.

Reviewer's Comment

The current study only measured BMT concentrations at 30 minutes post-dose, a timepoint that is quite close to the Tmax of BMT. As a result, BMT concentrations are quite variable (as demonstrated by >30% CV) and may not provide an accurate prediction on the dose proportionality of BMT cross the dose range of 0.3 – 5 mg.

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3.5 Study BMT-115 (Renal impairment)

Title: A Phase I, Multicenter, Open-Label, Parallel-Group Adaptive Pharmacokinetic Single Dose Study of Subcutaneous Bremelanotide in Subjects with Normal and Impaired Renal Function

Objective: To evaluate the pharmacokinetic (PK) profile of bremelanotide following a 1.75 mg single subcutaneous (SC) dose of BMT in subjects with impaired renal function relative to demographically matched, controls with normal renal function.

Study Design:
This was a multi-center, open-label, non-randomized, parallel-group, adaptive single dose study to evaluate the PK profile of BMT following a single SC 1.75 mg dose in subjects with impaired renal function relative to matched, controls with normal renal function. A total of 32 subjects were included in this study and received a single 1.75 mg SC dose of bremelanotide The subjects were enrolled and assigned to four groups: 8 subjects in group with normal renal function (eGFR $\geq$ 90 mL/min/1.73m^2, Group 1), 8 subjects in group with severe renal impairment (eGFR < 30 mL/min/1.73m^2, Group 2); 8 subjects in group with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2, Group 3), 8 subjects in group with mild renal impairment (eGFR 60-89 mL/min/1.73m^2, Group 4). A fixed dose of 1.75 mg bremelanotide was administered subcutaneously via autoinjector in the abdomen by qualified study staff. Blood samples for PK measurements were collected prior to drug administration and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours postdose for PK blood sampling and 0-4, 4-8, 8-12,12-24, and 24-48 hours postdose for urine PK collection.

PK Results:
The mean values of C_{max} of bremelanotide in subjects with normal renal function, mild , moderate, severe renal impairment were comparable (**Figure 1** and **Table 1)**. BMT AUC values were higher in subjects with mild to severe renal impairment compared to subjects with normal renal function. Subjects with severe renal impairment had mean AUC that was 2-fold of that in subjects with normal renal function.

Figure 1. **Mean Plasma Concentration-Time Profiles of BMT stratified by Renal Function Group (Study BMT-115)**

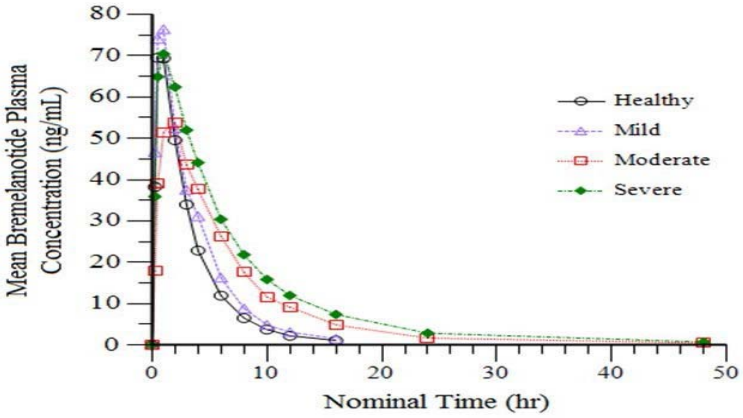


Table 1. **Mean ± SD PK Parameters of BMT (Study BMT-115)**

	Treatment Group			
PK Parameters	**Normal Function N = 8**	**Mild N = 8**	**Moderate N = 8**	**Severe N = 8**
C_{max} (ng/mL)	76.5 ± 24.6	81.6 ± 8.69	56.4 ± 14.5	74.8 ± 29.6

3.5 Study BMT-115 (Renal impairment)

Title: A Phase I, Multicenter, Open-Label, Parallel-Group Adaptive Pharmacokinetic Single Dose Study of Subcutaneous Bremelanotide in Subjects with Normal and Impaired Renal Function

Objective: To evaluate the pharmacokinetic (PK) profile of bremelanotide following a 1.75 mg single subcutaneous (SC) dose of BMT in subjects with impaired renal function relative to demographically matched, controls with normal renal function.

Study Design:
This was a multi-center, open-label, non-randomized, parallel-group, adaptive single dose study to evaluate the PK profile of BMT following a single SC 1.75 mg dose in subjects with impaired renal function relative to matched, controls with normal renal function. A total of 32 subjects were included in this study and received a single 1.75 mg SC dose of bremelanotide The subjects were enrolled and assigned to four groups: 8 subjects in group with normal renal function (eGFR $\geq$ 90 mL/min/1.73m^2, Group 1), 8 subjects in group with severe renal impairment (eGFR < 30 mL/min/1.73m^2, Group 2); 8 subjects in group with moderate renal impairment (eGFR 30-59 mL/min/1.73m^2, Group 3), 8 subjects in group with mild renal impairment (eGFR 60-89 mL/min/1.73m^2, Group 4). A fixed dose of 1.75 mg bremelanotide was administered subcutaneously via autoinjector in the abdomen by qualified study staff. Blood samples for PK measurements were collected prior to drug administration and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours postdose for PK blood sampling and 0-4, 4-8, 8-12,12-24, and 24-48 hours postdose for urine PK collection.

PK Results:
The mean values of C_{max} of bremelanotide in subjects with normal renal function, mild , moderate, severe renal impairment were comparable (**Figure 1** and **Table 1)**. BMT AUC values were higher in subjects with mild to severe renal impairment compared to subjects with normal renal function. Subjects with severe renal impairment had mean AUC that was 2-fold of that in subjects with normal renal function.

Figure 1. **Mean Plasma Concentration-Time Profiles of BMT stratified by Renal Function Group (Study BMT-115)**

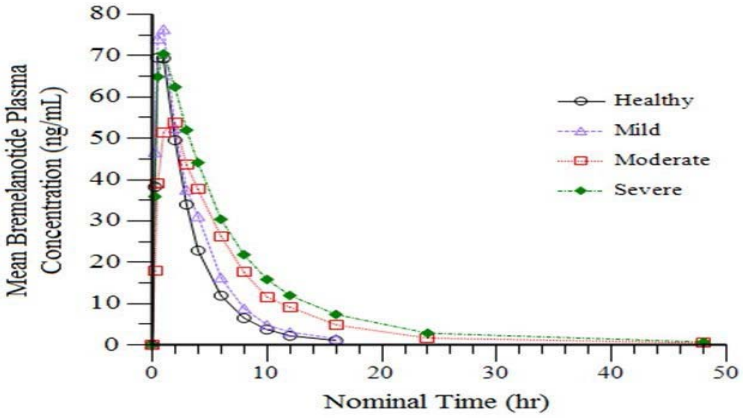


Table 1. **Mean ± SD PK Parameters of BMT (Study BMT-115)**

	Treatment Group			
PK Parameters	**Normal Function N = 8**	**Mild N = 8**	**Moderate N = 8**	**Severe N = 8**
C_{max} (ng/mL)	76.5 ± 24.6	81.6 ± 8.69	56.4 ± 14.5	74.8 ± 29.6

T_{max} (h) median(range)	1.0 (0.5-1.0)	0.75(0.50-1.00)	2.0(0.5-2.0)	1.0 (1.0-3.0)
AUC_{0-t} (ng*h/mL)	258 ± 60.0	306 ± 54.9	388 ± 134	517 ± 152
AUC_{0-inf} (ng*h/mL)	263 ± 62.3	313 ± 55.4	399 ± 140	528 ± 154
$T_{1/2}$ (h)	2.85 ± 0.58	3.20 ± 0.82	4.88± 1.37	5.42 ± 1.61
CL/F (L/h)	7.04 ± 1.98	5.74 ± 1.00	4.94 ± 1.92	3.55 ± 0.95

Safety Results:
Overall, subjects with severe renal impairment had TEAE profile differences compared to subjects with normal renal function that were notable. Intensity of TEAEs was greater in subjects with severe renal impairment (Normal: mild 50%, moderate 25%, severe 0%; Severe renal impairment: mild 0%, moderate 88%, severe 13%). The incidence of nausea and vomiting was higher in subjects with severe renal impairment (Normal: nausea 25%, vomiting 13%; Severe renal impairment: Nausea 50%, vomiting 25%).

Based on these results, BMT should be used with caution in patients with severe renalimpairment. No dosage adjustments are recommended for patients with mild to moderate renal impairment.

***Reviewer's Comment*:**
BMT exposure (AUC0-inf) increased 2-fold in subjects with severe renal impairment, 1.5-fold in subjects with moderate renal impairment, and 1.2-fold in patients with mild renal impairment. There was an increase in the frequency and severity of adverse events that are commonly associated with BMT in subjects with severe renal impairment compared to those with normal renal function. No dosing adjustments are recommended for patients with mild to moderate renal impairment. BMT should be used with caution (i.e., as it relates to a potential increase in frequency and severity of adverse events that are commonly related to bremelanotide, e.g., nausea and vomiting) in patients with severe renal impairment.

3.6 Study BMT-116 (Hepatic Impairment)

Title: A Phase I, Multicenter, Open-Label, Parallel-Group, Pharmacokinetic Single Dose Study of Subcutaneous Bremelanotide in Male and Female Subjects with Normal and Impaired Hepatic Function

Objective: To evaluate the PK profile of BMT following a 1.75 mg single subcutaneous (SC) dose of BMT in subjects with impaired hepatic function relative to demographically matched, controls with normal hepatic function.

Study Design:
This was a multi-center, open-label, non-randomized, parallel-group, single dose study to evaluate the PK profile of BMT following a single SC 1.75 mg dose in subjects with impaired hepatic function relative to matched, controls with normal hepatic function.

A single dose of BMT 1.75 mg SC was administered to 16 subjects with mild (Child-Pugh Class A: 5 to 6 points) or moderate (Child-Pugh Class B: 7 to 9 points) hepatic function impairment and 8 subjects with normal hepatic function. Subjects with severe (Child-Pugh Class C; 10-15 points) hepatic impairment were not evaluated in this study. Subjects with normal hepatic function were matched by gender, age (± 10 years) and weight (± 20%) to the pooled mean values of all subjects with hepatic impairment, to the extent possible. Demographic characteristics of the subjects are summarized in Table 1. Hepatic-impaired subjects were permitted to continue taking any prescription or OTC medication necessary for the management of their hepatic disease or other concurrent illness.
BMT was administered at a dose of 1.75 mg subcutaneously via autoinjector in the abdomen by a qualified study staff. Blood samples for PK measurements were collected prior to drug administration and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours following drug administration.

Table 1: Demographic Characteristics of Subjects in Study BMT-116

		Healthy N=8	**Mild N=8**	**Moderate N=8**	**Overall N=24**
Age (years)	Mean (SD)	49.6 (4.57)	53.6 (5.07)	55.5 (6.65)	52.9 (5.82)
	Min, Max	45, 56	46, 61	43, 64	43, 64
Gender (%)]	Male	6 (75)	7 (88)	7 (88)	20 (83)
	Female	2 (25)	1 (13)	1 (13)	4 (17)
Ethnicity [n(%)]	Hispanic/Latino	4 (50)	1 (13)	0	5 (21)
	Not	4 (50)	7 (88)	8 (100)	19 (79)
Race [n(%)]	White	8 (100)	6 (75)	7 (88)	21 (88)
	Asian	0	1 (13)	0	1 (4)
	Black or African American	0	1 (13)	1 (13)	2 (8)
Weight (kg)	Mean (SD)	99.38 (9.014)	101.46 (24.921)	89.33 (20.975)	96.72 (19.415)
	Min, Max	89.4, 111.2	66.9, 146.7	62.4, 125.7	62.4, 146.7
BMI (kg/m^2)	Mean (SD)	32.40 (1.778)	33.09 (5.525)	29.51 (6.877)	31.67 (5.210)
	Min, Max	29.3, 34.5	25.8, 41.7	19.3, 41.9	19.3, 41.9
Child-Pugh Score	Mean (SD)	0	5.1 (0.35)	7.5 (0.53)	6.3 (1.30)
	Min, Max	0	5, 6	7, 8	5, 8

PK Results:
As shown in **Figure 1** and **Table 1**, exposure of BMT (C_{max} and AUCs) was comparable between subjects with normal hepatic function and subjects with mild hepatic impairment. BMT mean C_{max} and AUC values were slightly higher for subjects with moderate hepatic impairment compared to subjects with normal hepatic function. Compared to healthy subjects, the PK parameters showed statistically significant

differences only with the moderate hepatic impairment group but not the mildly impaired group, The relative bioavailability analysis showed that BMT C_{max} and AUC for subjects with moderate hepatic impairment were approximately 1.3- to 1.7-fold higher, respectively, than those for subjects with normal hepatic function.

Figure 1. **Mean BMT Plasma Concentration-Time Profiles in Subjects with Normal or Impaired Hepatic Function (Study BMT-116)**

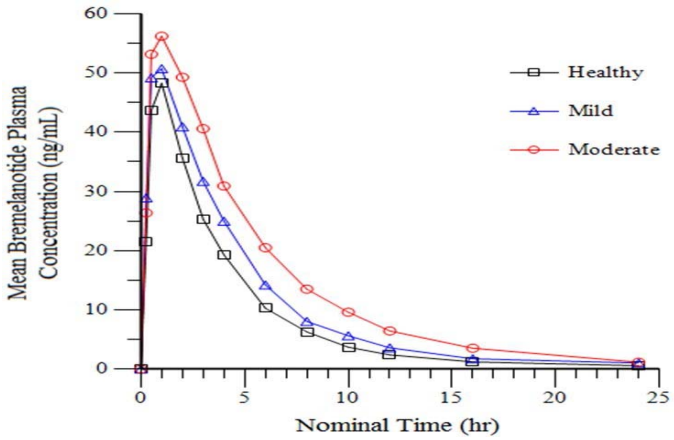


Table 1. Mean ± SD PK Parameters of BMT in Subjects with Normal Hepatic Function, Mild, or Moderate Hepatic Impairment (Study BMT-116)

	Treatment Group		
PK Parameters	**Normal Function N = 8**	**Mild N = 8**	**Moderate N = 8**
C_{max} (ng/mL)	48.4 ± 10.9	53.3 ± 11.5	61.1 ± 15.0
T_{max} (h) median(range)	1.0 (0.5-1.08)	0.75(0.50-1.00)	0.5(1.0-2.0)
AUC_{0-t} (ng*h/mL)	198 ± 40.8	248 ± 71.5	336 ± 90.1
AUC_{0-inf} (ng*h/mL)	204 ± 42.4	254 ± 72.6	344 ± 93.3
$T_{1/2}$ (h)	3.46 ± 0.67	3.53 ± 0.73	4.33± 0.61
CL/F (L/h)	8.88± 1.59	7.38 ± 2.04	5.34 ± 1.06

***Reviewer's Comments*:**

- *Compared to subjects with normal hepatic function, the exposures of bremelanotide did not increase in subjects with mild hepatic impairment. No dose adjustment in subjects with mild hepatic impairment is required.*
- *Compared to subjects with normal hepatic function, the Cmax and AUC values of bremelanotide in subjects with moderate hepatic impairment increased 1.3-fold and 1.7-fold, respectively. Overall, the slightly increased exposure of bremelanotide is unlikely to have a clinically significant impact on efficacy or safety. Bremelanotide can be used in subjects with moderate hepatic impairment.*
- *No PK information was available in subjects with severe hepatic impairment. However, bremelanotide exposure is expected to be higher in subjects with severe hepatic impairment than moderate impairment as there is a trend that bremelanotide clearance decreases with declining hepatic function. Bremelanotide should be used with caution in subjects with severe hepatic impairment.*

4 Clinical Drug Interaction Assessments

4.1 Study BMT-101 (DDI Study)

Title: A Double-blind, Randomized, Placebo-controlled, 2-period, Single-dose Crossover Study of the PK, PD, Safety, and Tolerability of BMT Coadministered with Anti-hypertensive Medications in Healthy Women

Objectives:

- To assess the PK parameters of the coadministered anti-hypertensive (HTN) medications (Cohort 1) or diuretics (Cohort 3) after a single dose of BMT

- To assess the hemodynamic effects (systolic blood pressure, diastolic blood pressure, and heart rate) of a single subcutaneous dose of BMT or Placebo in healthy female subjects with or without coadministration of anti-HTN medications (Cohort 1 and Cohort 2).

Study Design:
This was a single-center, randomized, placebo-controlled, 2-period, single-dose crossover study to assess the PK, PD, safety and tolerability of BMT and coadministered anti-HTN medications in 157 healthy female subjects. The following 3 cohorts were studied:

- Cohort 1 (N=107; 20 subjects/anti-HTN medication): Healthy pre-menopausal and post-menopausal women coadministered a single dose of 1.75 mg BMT or placebo with their respective anti-HTN medication at steady-state (hydrochlorothiazide [HCTZ], metoprolol, amlodipine, lisinopril, or losartan);
- Cohort 2 (N=27): Healthy post-menopausal women administered a single dose of 1.75 mg BMT or placebo;
- Cohort 3 (N=23): Healthy pre-menopausal and post-menopausal women coadministered a single dose of furosemide with a single dose of 1.75 mg BMT or placebo.

BMT or placebo was administered in a double-blind manner as a single SC injection, separated by 48 hours of washout period. The dose and mode of administration of study drugs are summarized in table below. All anti-HTN medications were administered in the morning after an overnight fast.

Study Drug	**Dose and Mode of Administration**
BMT Injection	SC injection via autoinjector pen containing 1.75 mg in 0.3 mL volume
Placebo Injection	Sterile aqueous solution for SC injection identical to BMT without the active ingredient; autoinjector pen containing 0.3 mL volume
HCTZ (Microzide®)	12.5 mg oral capsule; once daily
Metoprolol (Lopressor®)	100 mg oral tablet; once daily
Amlodipine (Norvasc®)	5 mg oral tablet; once daily
Lisinopril (Prinivil®)	10 mg oral tablet; once daily
Losartan (Cozaar®)	50 mg oral tablet; once daily
Furosemide (Lasix®)	20 mg oral tablet; single dose

To confirm the achievement of steady-state condition for anti-HTN medications, plasma samples for the analysis of C_{trough} were collected in the morning prior to drug administration on Days 3, 4, 5, and 6 (HCTZ, metoprolol, lisinopril, and losartan panels only) and on Days 7, 8, 9, and 10 (amlodipine panel only). On the day of BMT or placebo dosing, plasma samples for the PK analysis of anti-HTN medications, BMT and furosemide were collected at pre-dose, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.

Plasma concentrations of BMT were analyzed using a validated LC/MS/MS assay with linear analytical range of 0.500 to 250 ng/mL in a bioanalytical laboratory of [redacted] (b) (4) (Bioanalytical Report No. CA22301-01 and Bioanalytical Method Validation Report ZZ50747-01). Plasma concentrations of anti-HTN medications (parent drug or metabolite) were determined using validated bioanalytical methods as described in the table below.

	Methods	Bioanalytical Report	Validation Report
HCZ	LC-MS/MS	CA22301-02	19822-04
Metoprolol	LC-MS/MS	CA-22301-03	ZZ24817-01
Amlodipine	LC-MS/MS	CA22301-04	AA25708-01
Lisinopril	LC-MS/MS	CA22301-05	ZZ50826-01
Losartan and losartan acid	LC-MS/MS	CA22301-06	ZZ21772-01
Furosemide	LC-MS/MS	CA22301-07	ZZ26130-03

PK Results:

Cohort 1: Effect of a Single-Dose of BMT or Placebo on the PK of Anti-HTN medications

Steady-state condition was confirmed with all 5 Anti-HTN drugs. HCTZ $C_{max,ss}$ was 27% lower and occurred 2 hours later when taken with BMT compared to placebo (**Figure 1 1**). There was no significant change in HCTZ $AUC_{tau,ss}$. Similar trend, i.e., decreased $C_{max,ss}$ and delayed T_{max} with minimum impact on $AUC_{tau,ss}$, was observed with metoprolol, losartan and its main metabolite losartan acid (**Figure ; Figure 33**). PK profiles of amlodipine and lisinopril are similar when co-administered with BMT or placebo. The Geometric Mean Ratios (BMT/Placebo) and 90% CI of C_{max} and $AUC_{tau,ss}$ for anti-HTN medications are summarized in Error! Reference source not found..

Figure 1. Mean Plasma HCTZ Concentration-Time Profiles Following HCTZ + BMT and HCTZ + Placebo

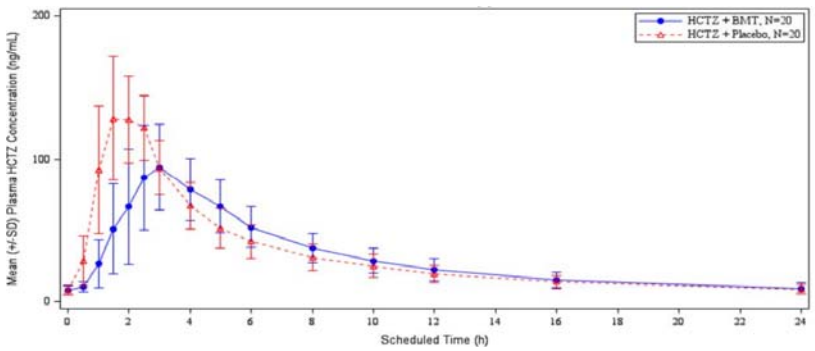


Figure 2. Mean Plasma Metoprolol Concentration-Time Profiles Following Metoprolol + BMT and Metoprolol + Placebo

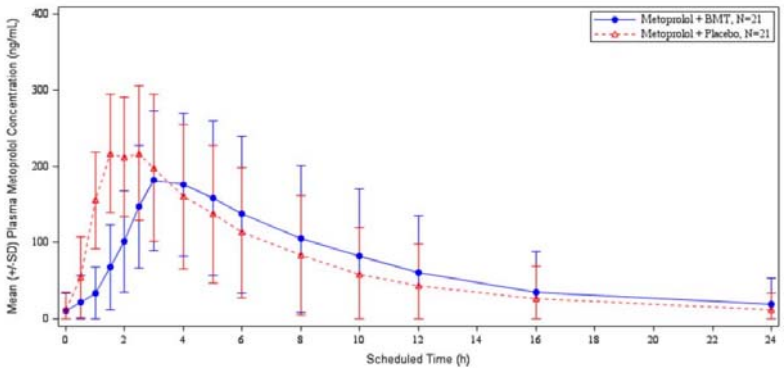


Figure 3. Mean Plasma Losartan and Losartan Acid Concentration-Time Profiles Following Losartan + BMT and Losartan + Placebo

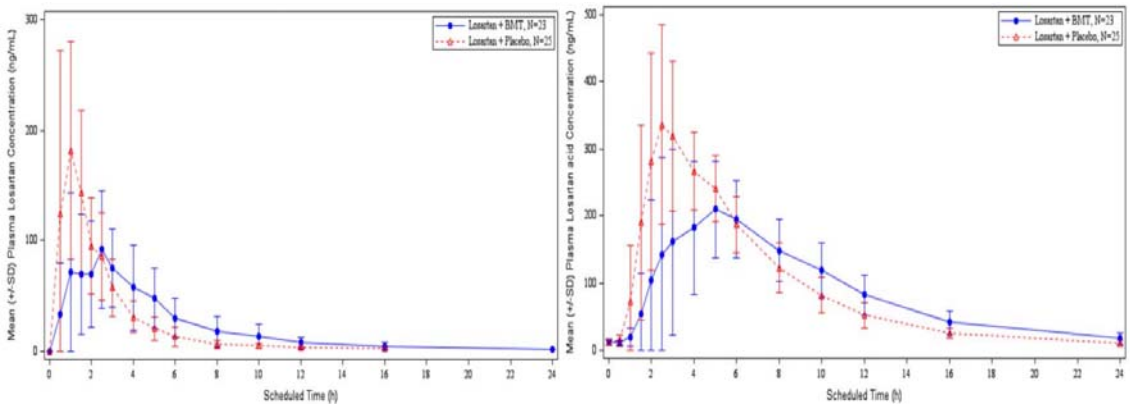


Table 1. Effect of BMT on the PK of anti-HTN medications

Study	Parent Drug or Active metabolites	Geometric Mean Ratio (%) [90% CI]	
		Cmax	AUCt
BMT- 101	Amlodipine	93.54 [89.47-97.79]	97.55 [94.94-100.23]
	Lisinopril	92.34 [81.01-105.25]	95.22 [84.43-107.38]
	HCTZ	73.20 [66.05-81.12]	94.20 [87.51-101.39]
	Metoprolol	78.38 [71.56-85.84]	95.57 [91.36-99.97]
	Losartan	49.15 [41.40-58.35]	98.95 [92.81-105.49]
	Furosemide	32.25 [25.42-40.91]	84.50 [76.50-93.35]

Cohort 1: Effect of Anti-HNT medications on the PK of BMT

Mean plasma concentration-time profiles of BMT coadministered with the 5 anti-HTN medications were similar cross treatment groups.

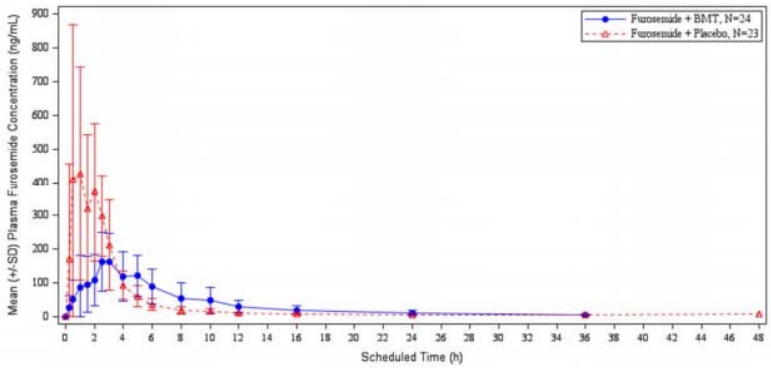
Cohort 2: BMT

Subjects in Cohort 2 were administered a single SC dose of BMT 1.75 mg or placebo alone on Day 1 and Day 3. All subjects in this cohort were post-menopausal women. Peak BMT concentration occurred at 1.0

hour (median) after BMT administration. Mean BMT C_{max} was 82.51 ng/mL, AUC_{0-t} was 311.7 h*ng/mL, and $t_{½}$ was approximately 3.4 hours.

Cohort 3: Effect of a Single-Dose of BMT or Placebo on the PK of a Single-Dose of Furosemide
After coadministration with BMT, furosemide C_{max} was substantially lower (~213 ng/mL versus ~699 ng/mL), while AUC_{0-inf} was modestly lower (~1267 h*ng/mL versus ~1445 h*ng/mL) compared to coadministration with placebo. T_{max} was delayed by about 1.5 hours after coadministration with BMT than with placebo (median, 3.0 hours versus 1.5 hours). Mean furosemide t½ was slightly less following furosemide + BMT than following furosemide + placebo (~5.8 hours versus ~6.7 hours; **Figure** and Error! Reference source not found.). APPEARS THIS WAY ON ORIGINAL

Figure 4. Mean Plasma Furosemide Concentration-Time Profiles Following Furosemide + BMT and Furosemide + Placebo



Cohort 3: Effect of a Single-Dose of Furosemide on the PK of a Single-Dose of BMT
A single dose of furosemide did not affect the PK of BMT.

PD Results: Defer to the clinical reviewer.

Safety Results: All TEAEs, including drug-related TEAEs, were mild or moderate in severity. No subject had a severe TEAE. There were no clinically significant changes from baseline in chemistry, hematology and coagulation, or urinalysis. Aside from the ABPM changes, which are reviewed by the clinical reviewer, no clinically meaningful changes in vital signs or physical examination findings were observed.

Conclusion:

- For the 6 anti-HTN medications studied, concomitant administration of a single SC dose of BMT 1.75 mg resulted in no change in the bioavailability of steady-state amlodipine and lisinopril; a significantly decreased rate, but not extent, of absorption for steady-state HCTZ, metoprolol, and losartan; and decreased bioavailability for single-dose furosemide in adult women.
- BMT PK parameters are similar with and without the concomitant administration of medications mentioned above based on cross-cohort comparison.
- Overall, a single SC dose of BMT was well tolerated when administered with therapeutic doses of HCTZ, metoprolol, amlodipine, lisinopril, losartan, and furosemide.

Reviewer's Comments:

- *The overall study design is adequate to assess the PK interaction between BMT and commonly used anti-HTN medications. The dose and dosing regimen of anti-HTN medications are consistent with the labeling recommendation and reflect the real-life scenario.*
- *The assessment of PD (BP) effect may not add much value on the clinical relevance of the potential drug interactions between BMT and Anti-HTN, as the study was conducted in healthy subjects and it is not clear whether the study results (BP effect) can be extrapolated to women with hypertension taking BMT.*
- *It appears that BMT affects the PK of other drugs by slowing gastric motility leading to delayed T_{max}, reduced C_{max}, and minimum decrease in the AUC of concomitant medications. Given the magnitude of interactions regarding AUC change is relatively small, the review team believes these interactions are not clinical significant and thus no special labeling instruction (i.e., dose or dosing regimen adjustment) is needed when these anti-HTN medications are co-administered with BMT.*

4.2 Study BMT-103 (DDI Study)

Title: A Phase 1, Double-blind, Randomized, Placebo-controlled, 2-sequence, 2-period, Crossover Study of BMT 1.75 mg Coadministered as a Single-dose Injection with Oral Venlafaxine (a Serotonin-norepinephrine Reuptake Inhibitor [SNRI]), Sertraline (a Selective Serotonin Reuptake Inhibitor [SSRI]), or Naltrexone/Bupropion in Healthy Female Subjects

Objectives:

- To investigate a possible PK interaction between of a single SC dose of BMT and selected concomitant antidepressant medications (venlafaxine HCl and sertraline HCl), and anti-obesity medication (naltrexone HCl/bupropion HCl) at steady-state therapeutic doses in healthy female subjects
- To assess and compare the possible effect on BP resulting from a single SC dose of BMT or placebo (PBO) coadministered with venlafaxine HCl, sertraline HCl, or naltrexone HCl/bupropion HCl in healthy female subjects

Study Design
This was a single-center, randomized, placebo-controlled, single-dose (1.75 mg of BMT), double-blind (to BMT), 3-panel (A, B, and C), 2-sequence, 2-period, crossover study in 127 healthy female subjects to assess the effect on BP, the potential PK interaction, and the safety and tolerability of BMT coadministered venlafaxine HCl, sertraline HCl, and naltrexone HCl/bupropion HCl. After fulfilling the screening requirements, all subjects were randomized (1:1:1) to 1 of the 3 treatment panels (A, B, or C), which were conducted in parallel fashion. Each panel was a 2-period crossover design based upon the sequence of BMT or PBO, coadministered with the selected DDI medication. After suitable washout periods, the subjects were administered the opposite treatment (BMT or PBO).

BMT/PBO was administered in a double-blind fashion, as a single SC injection, with BMT at the intended therapeutic dose (1.75 mg). After the Up-titration Period and attainment of steady-state concentrations, venlafaxine HCl (225 mg) and sertraline HCl (200 mg) were each administered once daily (QD), and naltrexone HCl/bupropion HCl (2 tablets, each containing 8 mg naltrexone HCl/90 mg bupropion HCl) was administered twice per day with doses approximately 12 hours apart (BID). With the exception of the evening dose of naltrexone HCl/bupropion HCl, all study medications were administered with food, in the morning, within 10 minutes after subjects had finished a standard breakfast. The evening dose of naltrexone HCl/bupropion HCl was administered within 10 minutes after a snack.

Plasma concentrations of BMT were analyzed using a validated LC/MS/MS assay with linear analytical range of 0.500 to 250 ng/mL by [redacted] (b) (4) (Bioanalytical Report No. RPT04505/17086 and Bioanalytical Method Validation Report RPT03473/14116).

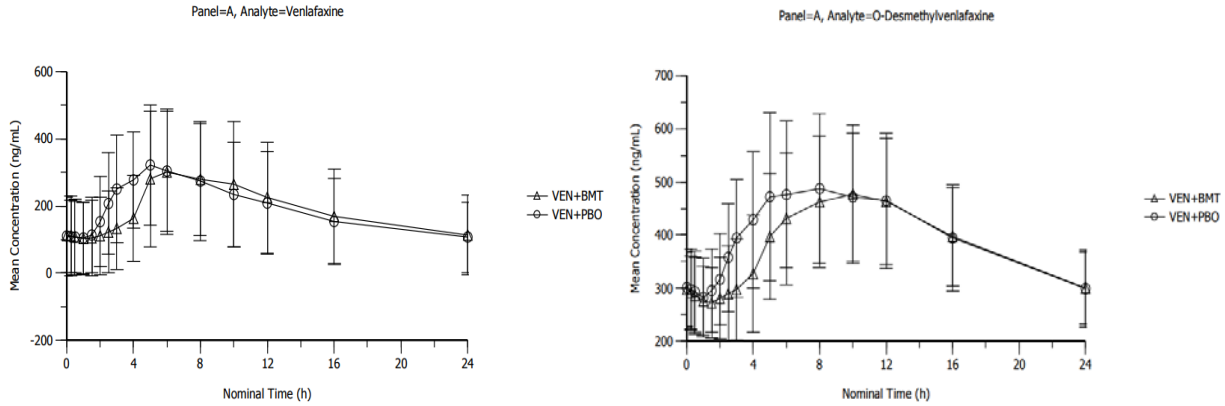
Plasma concentrations of concomitant medications (parent drug or metabolite) were determined using validated bioanalytical methods described in the table below.

	Methods	**Bioanalytical Report**	**Validation Report**
Naltrexone and metabolites Bupropion and metabolites	LC-MS/MS	RPT04505/17086	RPT04589/17081
Sertraline Velafaxine	LC-MS/MS	RPT04505/17086	RPT04590/17080

PK Results
<u>Panel A: Effect of a Single Dose of BMT or Placebo on the PK of Venlafaxine</u>

Administration of Venlafaxine HCl + BMT resulted in similar $C_{max,ss}$ for venlafaxine and its active metabolite O-Desmethylvenlafaxine (ODV), but there was a 1-2 hours delay in their t_{max} values, compared to administration with Placebo. There were no apparent differences in overall systemic exposure (AUC) for venlafaxine and ODV during the 24-hour dosing interval (**Figure 1,** Error! Reference source not found.). APPEARS THIS WAY ON ORIG NAL

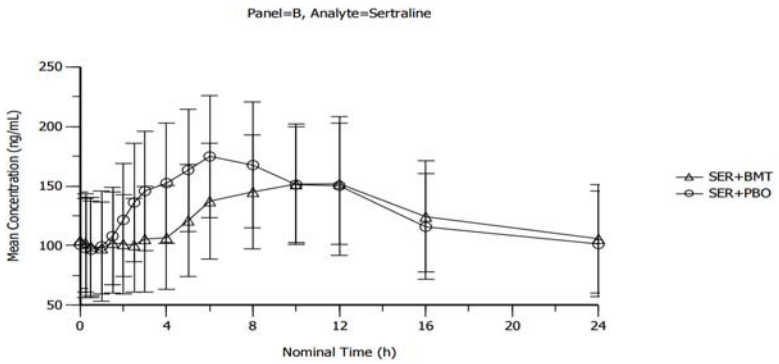
Figure 1 Mean (SD) Plasma Venlafaxine and ODV Concentration-Time Profiles after Administration of Venlafaxine HCl + BMT and Venlafaxine HCl + Placebo (Panel A) – PK Population



Panel B: Effect of a Single Dose of BMT or Placebo on the PK of Sertraline HCl

Administration of Sertraline HCl + BMT resulted in 14% decrease in sertraline $C_{max,ss}$ and a 4-hour delay in t_{max}, compared to administration of Sertraline HCl + Placebo. However, there were no apparent differences in overall systemic exposure for sertraline during the 24-hour dosing interval (**Figure 2,** Error! Reference source not found.).

Figure 2 Mean (SD) Plasma Sertraline Concentration-Time Profiles after Administration of Sertraline HCl + BMT and Sertraline HCl + Placebo (Panel B) – PK Population



Panel C: Effect of a Single Dose of BMT or Placebo on the PK of Naltrexone and Bupropion

$C_{max,ss}$ and $AUC_{tau,ss}$ for both naltrexone and bupropion were significantly reduced (approximately 14%-63% reduction) when coadministered with BMT compared to with Placebo (Error! Reference source not found.**, Figure 3 and Figure 4**). Median $t_{max,ss}$ occurred 3 hours later for both naltrexone and buproprion after coadministration with BMT compared to with Placebo. However, mean $t_{1/2}$ was similar across treatments (3.07±0.91 h vs 2.85±1.09 h for naltrexone and 7.62 ± 3.45 vs 5.59 ±1.58h for bupropion). Additionally, coadministration with BMT significantly decreased the $C_{max,ss}$ and $AUC_{tau,ss}$ of 6β-naltrexol APPEARS THIS WAY ON ORIGINAL

and the $AUC_{tau,ss}$ of erythrohydrobupropion. Significant differences were also suggested by the 90% CIs for $AUC_{tau,ss}$ of hydroxybupropion and threohydrobupropion; however, the wide CI (i.e., 90% CI of GMR ratio contains 100%) for these metabolites could be due to PK variability and the relatively small number of subjects with $AUC_{tau,ss}$ reported.

Table 2 Effect of BMT on the PK of Venlafaxine, Sertraline, Naltrexone, Bupropion and their active metabolites

Parent Drug or Active metabolites	Geometric Mean Ratio (%) [90% CI]	
	$C_{max,ss}$	$AUC_{t,ss}$
Venlafaxine	96.30 [91.55-101.29]	95.19 [92.75-97.69]
O-Desmethylvenlafaxine	98.86 [95.9 – 101.91]	96.23 [93.84-98.68]
Sertraline	86.01 [82.88-89.27]	94.05 [91.35-96.84]
Naltrexone	36.93 [31.07-43.90]	59.82 [48.97-73.09]
6β -naltrexol[a]	63.97 [59.79-73.06]	79.19 [72.63-86.33]
Bupropion	66.10 [59.79-73.06]	86.04 [78.78-93.97]
hydroxybupropion[b]	87.74 [84.65-90.94]	86.50 [66.85-111.92]
threo-hydrobupropion[b]	85.98 [82.14-90.01]	95.66 [71.49-128.00]
erythro-hydrobupropion[b]	94.93 [89.55-100.62]	79.19 [72.63-86.33]

Figure 3 Mean (SD) Plasma Naltrexone and 6β-Naltrexol Concentration-Time Profiles after Administration of Naltrexone HCl/Bupropion HCl + BMT and Naltrexone HCl/Bupropion HCl + Placebo (Panel C) – PK Population

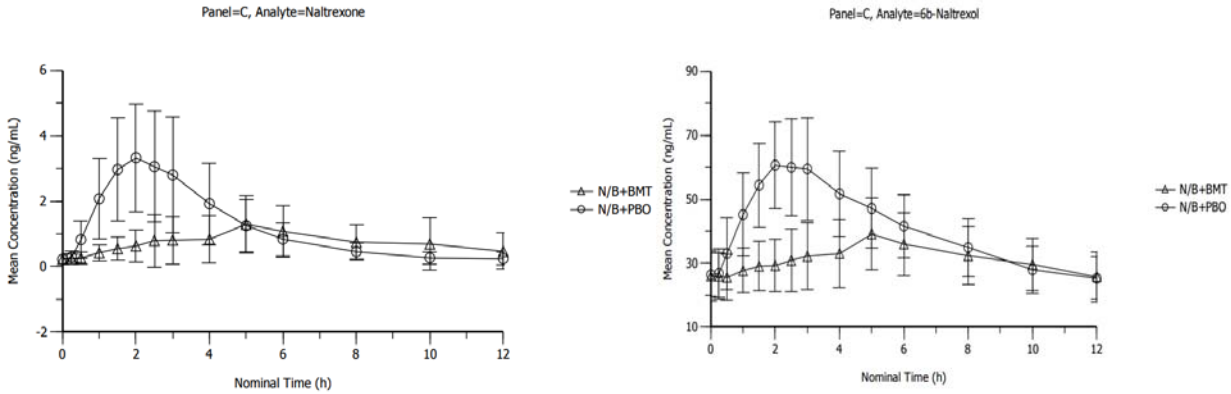
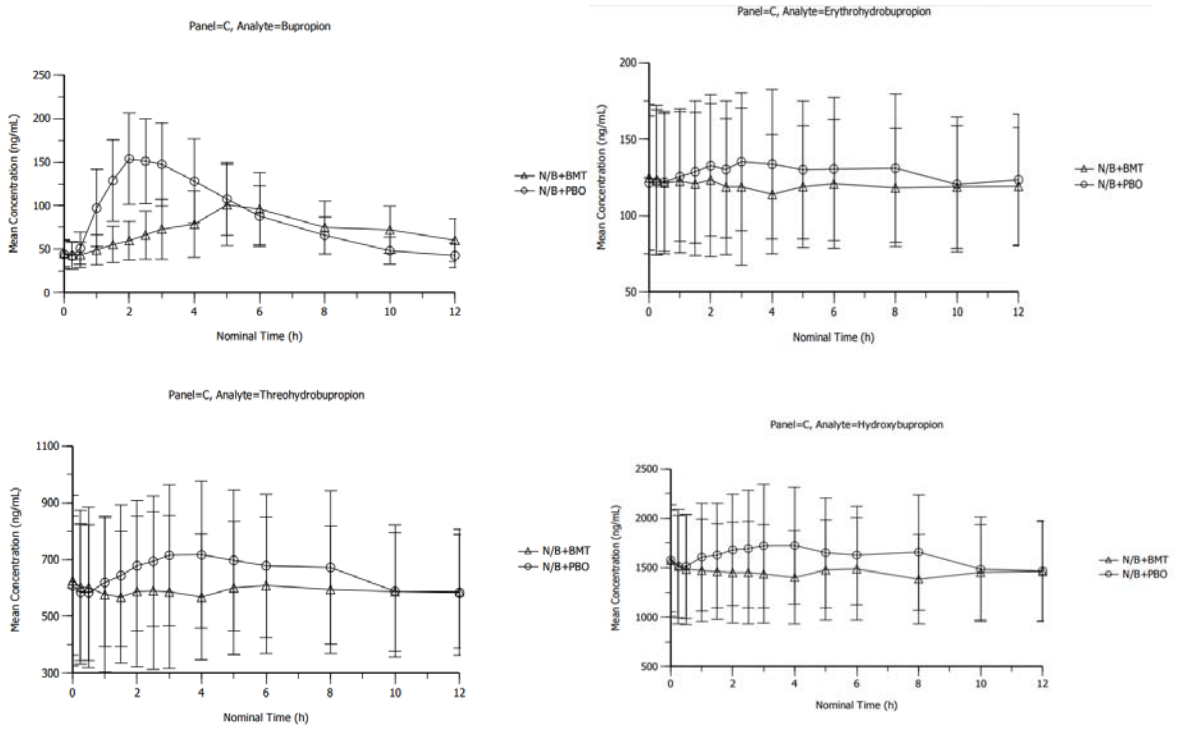


Figure 4 Mean (SD) Plasma Bupropion, Erythrohydrobupropion and Threohydrobupropion Concentration-Time Profiles after Administration of Naltrexone HCl /Bupropion HCl + BMT and Naltrexone HCl /Bupropion HCl + Placebo (Panel C) – PK Population



PK of BMT in Panels A, B, and C

The mean BMT concentration-time profiles were superimposable for all treatments.

PD Results: PD results are reviewed by the clinical reviewer.

Safety Results

There were no deaths or severe AEs reported during the study in any cohort, except in Panel B where one SAE was reported as serotonin syndrome related to sertraline HCl. Most AEs during this study were mild in severity and related to the DDI medications. There were no significant increases from baseline observed in creatinine, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransaminase (AST), creatinine clearance, or estimated glomerular filtration rate (eGFR) during this study. There were no unusual or unexpected AEs related to the BMT.

Conclusions

- When venlafaxine and sertraline were taken with BMT, T_{max} was delayed. Systemic exposure ($C_{max,ss}$ and $AUC_{tau,ss}$) of venlafaxine and sertraline were not significantly changed.
- Relative bioavailability of naltrexone and bupropion were significantly decreased, and peak concentrations of both drugs occurred approximately 3 hours later after naltrexone HCl/bupropion HCl coadministration with BMT than with placebo. Additionally, coadministration with BMT significantly decreased $C_{max,ss}$ and $AUC_{tau,ss}$ for 6-β-naltrexol and $AUC_{tau,ss}$ for erythrohydrobupropion.
- The PK parameters of BMT were similar across treatments and no apparent differences were observed.

Reviewer's Comments:

*This study examined the PK interaction between BMT and a weight loss drug Contrave® (*naltrexone HCl/bupropion HCl*). The results showed co-administration of BMT led to 64% decrease in naltrexone $C_{max,ss}$ and 40% decrease in its $AUC_{tau,ss}$. In addition, bupropion $C_{max,ss}$ decreased by 36% and $AUC_{tau,ss}$ decreased by 20% in the presence of BMT. Considering that BMT is only taken as needed and Phase 3 studies showed low frequency of use (2-3 times/month) in the study subjects, the review team believes that occasionally decreased concentrations of naltrexone may not have major effect on the overall efficacy of Contrave®, i.e., long term weight loss.*

Naltrexone is also indicated for the treatment of alcohol and opioid dependence. There are two available forms of naltrexone for this indication: 1) Vivitrol® is an extended-release naltrexone product, administered once per month via intramuscular injection. Considering the mechanism of interaction is slowing gastric motility and Vivitrol® is a sustained release product, it is unlikely that BMT can affect the PK and efficacy of Vivitrol®; 2) The other and most commonly used form of naltrexone for the treatment of alcohol and opioid dependence is Revia®, oral tablet (50 mg), taken once daily for 12 weeks. Although no dedicated DDI study is conducted with naltrexone alone oral formulation, co-administration with BMT may result in a marked decrease in naltrexone exposure. Therefore, patients should avoid using BMT with an orally administered naltrexone containing product that is intended to treat alcohol and opioid addiction due to severe consequence of treatment failure.

4.3 Study BMT-104 (DDI Study)

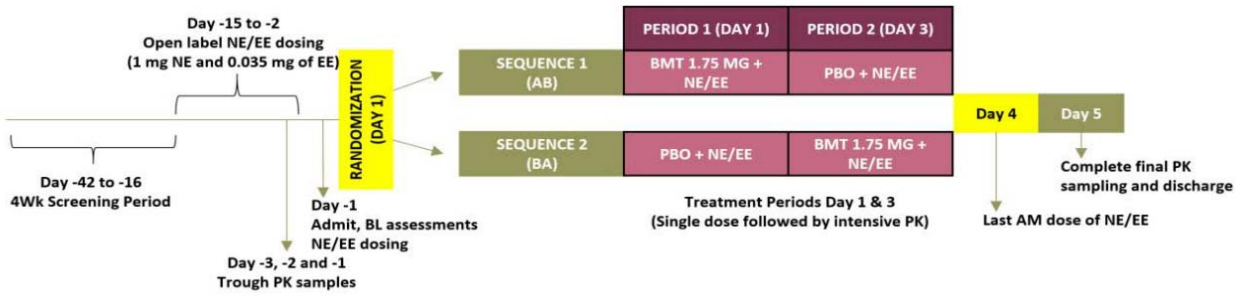
Title: A Randomized, Placebo-controlled, Double-blind Study to Evaluate the PK Effects of Coadministration of BMT with Norethindrone/Ethinyl Estradiol Oral Contraceptive Tablets in Healthy Female Subjects

Objectives: To investigate if there was a PK interaction between BMT and norethindrone (NE)/ethinyl estradiol (EE) in healthy female subject and to evaluate the safety and tolerability of coadministration of BMT with NE/EE in healthy female subjects.

Study Design

This was a single-center, randomized, 2-way crossover, double-blind, placebo-controlled, drug-drug interaction (DDI) study to assess the PK, safety, and tolerability of BMT (single 1.75 mg subcutaneous [SC] dose) when coadministered with an oral contraceptive, NE/EE (1 mg of NE and 0.035 mg of EE, once daily with a standard breakfast) in 45 healthy female subjects. This study consisted of a Screening Phase, a pre-treatment Phase (15 days of supervised oral dosing of NE/EE 1 mg/0.035 mg), and a Treatment Phase (Days 1 through 4). On Day 1, subjects began the 4-day Treatment Phase consisting of 4 additional days of open-label NE/EE dosing coadministered on Days 1 and 3 with a single dose of BMT 1.75 mg SC or matching placebo in a double-blind, 2-period crossover manner. The BMT and placebo doses were separated by a 48-hour washout period (**Figure 1**).

Figure 1. Overview of Study Design, Dosing Schedule, and PK Sampling Schedule



Plasma concentrations of BMT, NE and EE were analyzed using a validated LC/MS/MS assays in a bioanalytical laboratory of (b) (4).

	Methods	Bioanalytical Report	Validation Report
BMT	LC-MS/MS	CA21575-01	ZZ50747-01
NE	LC-MS/MS	CA21575-02	ZZ33943-01
EE	LC-MS/MS	CA21575-03	21704-4

PK Results

NE and EE concentrations were at steady-state before BMT or placebo co-administration on Day 1. Mean NE $C_{max,ss}$ and $AUC_{\tau,ss}$ were approximately 13% and 4% lower, respectively, for NE/EE + BMT than for NE/EE + Placebo (**Figure 2, Table 1**). T_{max} values of NE were comparable between BMT and placebo. Mean EE $C_{max,ss}$ and $AUC_{\tau,ss}$ were approximately 13% and 4% lower, respectively, for NE/EE + BMT than for NE/EE + Placebo (**Figure 3, Table 1**). Peak EE concentration occurred slightly later after coadministration of NE/EE with BMT than with placebo (median, ~3.5 versus ~ 2.5 hours).

Table 1. Effect of BMT on the PK of NE and EE

Parent Drug	Geometric Mean Ratio (%) [90% CI]	
	$C_{max,ss}$	$AUC_{t,ss}$
NE	87.00 [80.75-93.73]	95.68 [93.49-97.92]
EE	86.66 [81.93 –91.66]	96.15 [94.45-97.88]

Figure 2 Mean Plasma NE Concentration-time Profile Following the Administration of NE/EE + BMT and NE/EE + Placebo

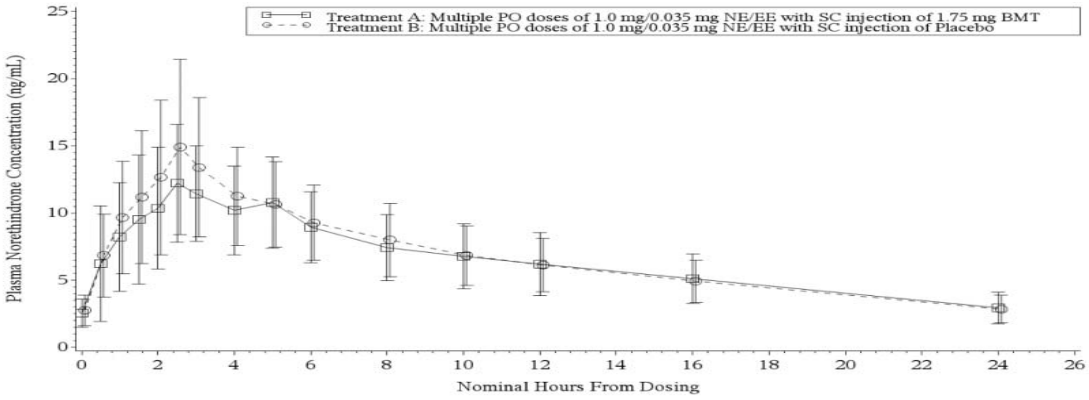
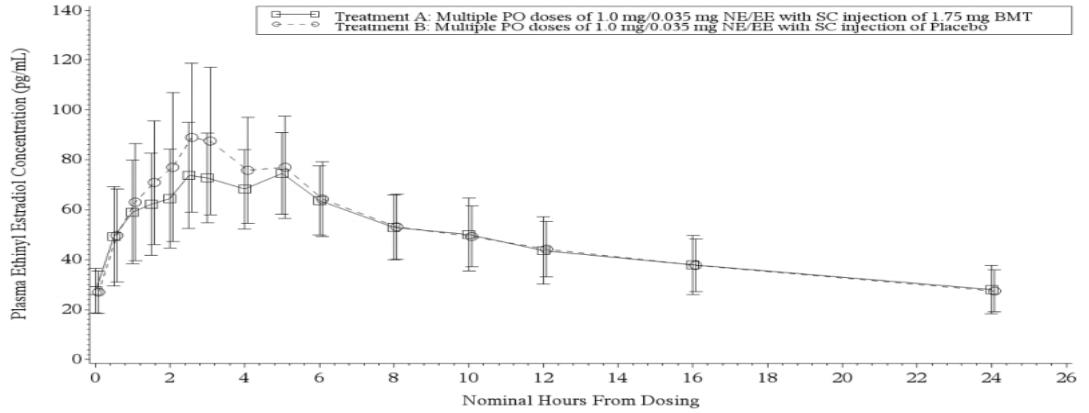


Figure 3. Mean Plasma EE Concentration-time Profile Following the Administration of NE/EE + BMT and NE/EE + Placebo



Safety Results

Coadministration of NE/EE with BMT did not appear to significantly change the incidence of AEs following BMT use observed when compared to those seen in the overall clinical program. The frequent AEs of nausea and flushing are consistent with the known profile of BMT; additionally nausea is a known AE following oral contraceptives, however, there was not an increased level or frequency of nausea with NE/EE + BMT. Flushing occurred exclusively following NE/EE + BMT administration.

Conclusions

- BMT had no statistically significant effect on the bioavailability of NE or EE at steady-state.
- A single dose of SC BMT, coadministered with oral NE/EE, appeared to be generally safe and well tolerated by the healthy female subjects in this study.

4.4 Study BMT-105 (DDI Study)

Title: A Randomized, Placebo-controlled, Double-blind, Multi-panel Study to Evaluate the PK and Blood Pressure Effects of Coadministration of BMT with Selected Concomitant Medications in Healthy Male and Female Subjects

Objectives:

- To evaluate a possible PK interaction between BMT and selected concomitant drug-drug interaction (DDI) medications (pseudoephedrine, phentermine, celecoxib, and indomethacin)
- To explore the potential additive effect of BMT on BP when coadministered with commonly used medications that are associated with increased BP

Study Design

This was a single-center, randomized, 2-way crossover, double-blind, placebo-controlled, multi-panel (A, B, C, and D), drug-drug interaction study to assess the effect on PD (BP), PK, safety and tolerability of BMT (single 1.75 mg SC dose) when coadministered with 4 different concomitant DDI medications (pseudoephedrine, phentermine, celecoxib, and indomethacin). A total of 144 subjects wer enrolled in the study (36/panel). BMT or placebo was administered in a double-blind manner as a single SC injection, separated by 48 hours of washout period. The dose and mode of administration of study drugs are summarized in table below. All DDI medications were administered in the morning after an overnight fast.

Study Drug	Dose and Mode of Administration	Washout Period
BMT Injection	SC injection via autoinjector pen containing 1.75 mg in 0.3 mL volume	/
Placebo Injection	SC injection via autoinjector pen containing 0.3 mL volume without the active ingredient	/
Panel A: Pseudoephedrine	A single dose of 2 × 30 mg oral tablets	2 days
Panel B: Phentermine	A single dose of 37.5 mg oral tablet	6 days
Panel C: Celecoxib	200 mg QD for 10 days (steady-state)	2 days
Panel D: Indomethacin	25 mg TID for 10 days (steady-state)	2 days

Plasma concentrations of BMT, pseudoephedrine, phentermine, celecoxib and indomethacin were analyzed using validated LC/MS/MS assays in a bioanalytical laboratory of (b) (4).

	Methods	LLOQ	Bioanalytical Report	Validation Report
BMT	LC-MS/MS	0.5 ng/mL	CA20882-01	ZZ50747-01
Pseudoephedrine	LC-MS/MS	1.0 ng/mL	CA20882-02	ZZ17456-01
Phentermine	LC-MS/MS	0.25 ng/mL	CA20882-03	ZZ00906-01
Celecoxib	LC-MS/MS	10.0 ng/mL	CA20882-04	ZZ41514-01
Indomethacin	LC-MS/MS	5.0 ng/mL	CA20882-05	ZZ49697-01

PK Results

Co-administration with BMT had no statistically significant effect on the bioavailability of pseudoephedrine and phentermine (**Figure 1; Figure 2; Table 1**). Coadministration with BMT had a statistically significant effect on Cmax but not AUC_t of celecoxib (**Figure 3; Table 1**). Coadministration with BMT statistically significantly reduced the bioavailability of indomethacin with C_{max} and AUC_t reduced by approximately 35% and 19%, respectively, compared to placebo (**Figure 4; Table 1**).

Table 1 Effect of BMT on the PK of Pseudoephedrine, Phentermine, Celecoxib and Indomethacin

Parent Drug	Geometric Mean Ratio (%) [90% CI]	
	C_{max}	AUC_t
Pseudoephedrine	90.26 [86.83-93.83]	107.93 [105.07- 110.86]
Phentermine	91.53 [89.07-94.05]	102.77 [100.38 - 105.23]
Celecoxib	87.32 [77.74-98.08]	113.37 [104.78-122.67]
Indomethacin	65.29 [57.74-73.83]	81.20 [77.60-84.96]

Figure 1. Mean Plasma Pseudoephedrine Concentration-time Profiles Following the Administration of Pseudoephedrine + BMT and Pseudoephedrine + Placebo

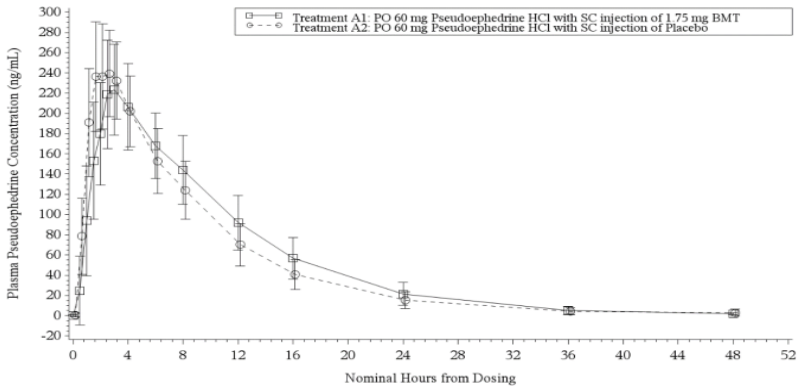


Figure 2. Mean Plasma Phentermine Concentration-time Profiles Following the Administration of Phentermine + BMT and Phentermine + Placebo

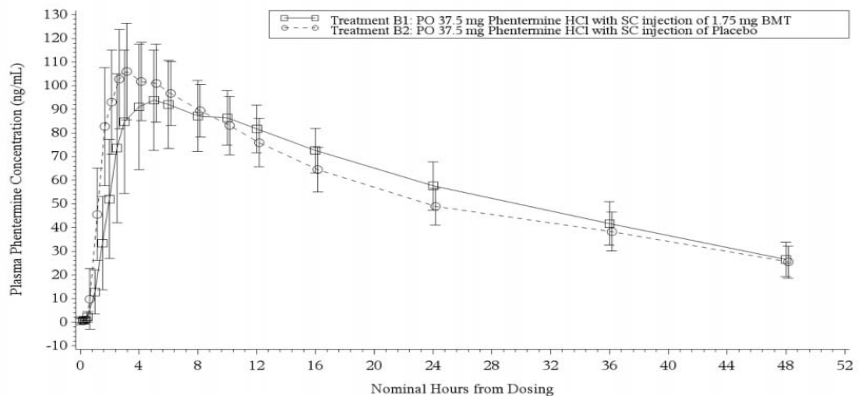


Figure 3. Mean Multiple-dose Plasma Celecoxib Concentration-time Profiles Following the Administration of Celecoxib + BMT and Celecoxib + Placebo

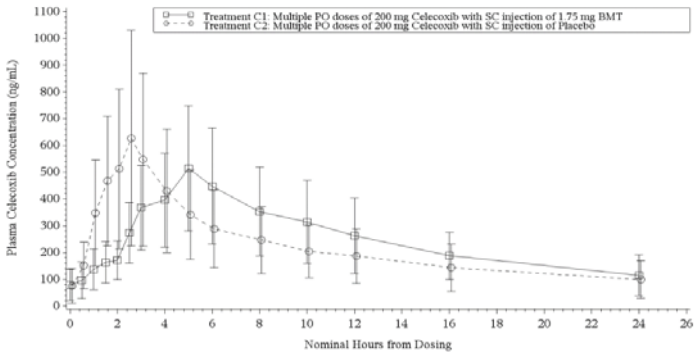
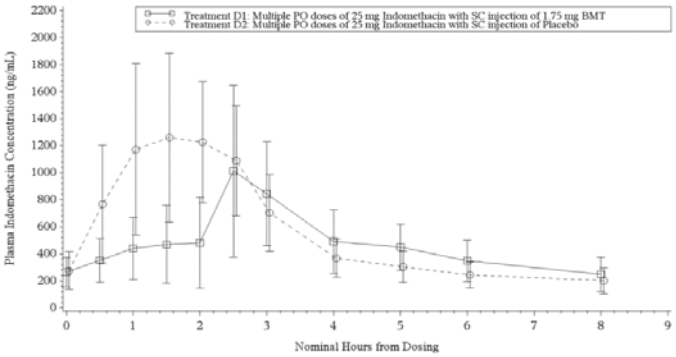


Figure 4. Mean Steady State Plasma Indomethacin Concentration-time Profiles Following Administration of Indomethacin + BMT and Indomethacin + Placebo



BMT PK profiles in all 4 treatment groups are superimposed with mean BMT C_{max} ~70 to ~76 ng/mL occurred ~0.6 to ~1.0 hour (median) after administration. The mean elimination half-life was ~2.7 to ~3 hours.

Safety Results

There were no deaths or serious adverse events (SAEs) in this study. The majority of AEs were mild and the most common AEs reported across all panels included flushing, headache, and nausea. Most AEs in each of the 4 panels were considered probably or possibly related to the study drug. There were no laboratory-related AEs and no subjects in any of the panels with outlier liver function tests at the end of the study.

Conclusions

- The bioavailability of pseudoephedrine and phentermine was unchanged by BMT coadministration.
- Coadministration with subcutaneous BMT significantly reduced the rate (but not extent) of oral celecoxib absorption and reduced the bioavailability of oral indomethacin.
- A single dose of subcutaneous BMT, coadministered with oral pseudoephedrine, phentermine, celecoxib, and indomethacin appeared to be safe and well tolerated in the healthy male and female subjects in this study.

Reviewer's Comments:

- *In the current study, the concomitant medications were dosed to the therapeutic levels to mimic the real-life scenario. The only exception is phentermine, where it was co-administered with BMT/placebo as a single dose rather than multiple dose to the steady-state condition. Data from clinical trials suggest that the long-term effects of phentermine pharmacotherapy may result in a low occurrence of hypertension, or a significant reductions in BP. Therefore, the Applicant studied the single dose of phentermine to reflect the worst-case scenario of BP increase. From the perspective of PK interaction, single-dose of phentermine is also acceptable.*
- *Although the 90% CI of GMR (BMT/Placebo) for celecoxib C_{max} fell outside of 80% to 125% boundary, the magnitude of exposure change (13% decrease) is modest and thus the interaction is not considered as clinically relevant.*
- *Indomethacin is used for acute pain. Therefore, decreased Cmax or delayed Tmax, when taken with BMT, may affect its onset of analgesic action.*

4.5 Study BMT-118 (DDI Study)

Title: A Randomized, Placebo-controlled, Double-blind, Crossover Study to Evaluate the PK of the Coadministration of BMT and Metformin, an Oral Hypoglycemic Agent, in Healthy Male and Female Subjects

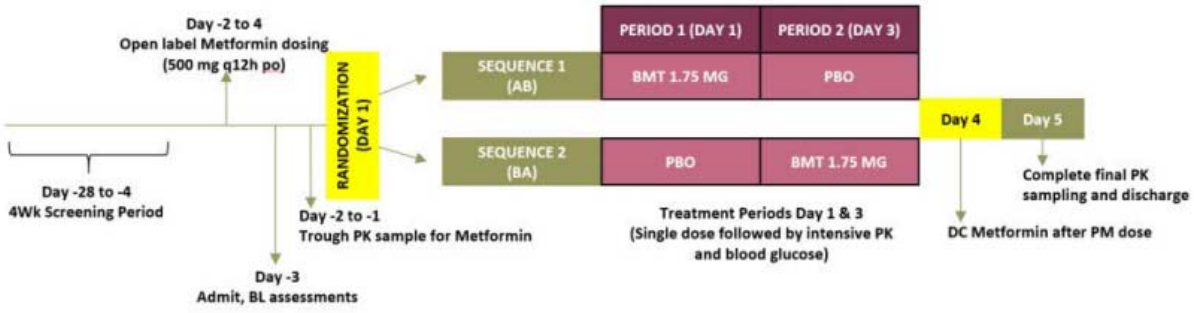
Objectives:

- To evaluate a possible PK interaction between BMT and steady-state concentrations of the oral hypoglycemic agent metformin in healthy male and female subjects
- To evaluate the PD, safety, and tolerability of BMT when coadministered with metformin in healthy male and female subjects.

Study Design

This was a single-center, randomized, 2-way crossover, double-blind, placebo-controlled, drug-drug interaction study in 36 healthy male and female subjects to assess the PK, PD, safety, and tolerability of BMT (single 1.75 mg subcutaneous [SC] dose) when coadministered with metformin (500 mg BID with standard meal to steady state).

Figure 1. Study Schematic



Plasma concentrations of BMT and metformin were analyzed using validated LC/MS/MS assays in a bioanalytical laboratory of (b) (4)

	Methods	LLOQ	Bioanalytical Report	Validation Report
BMT	LC-MS/MS	0.5 ng/mL	CA21574-01	ZZ50747-01
Metformin	LC-MS/MS	30.0 ng/mL	CA21574-02	ZZ00904-01

PK Results

Metformin C_{max} and AUC_{τ} were approximately 18% and 8% lower, respectively, after co-administration with BMT compared to co-administration with placebo; the decrease in C_{max} was statistically significant (90% CI:78.62% - 85.72%). Median metformin t_{max} was approximately 4 hours after metformin coadministration with BMT and with placebo. BMT PK profile was consistent with that observed from other PK studies (**Figure 2; Figure 3**).

Figure 2. Mean Plasma Metformin Concentration-time Profiles Following the Administration of Metformin + BMT and Metformin + Placebo

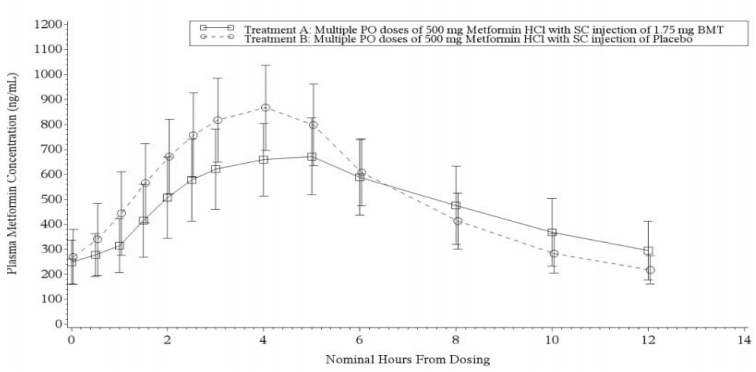
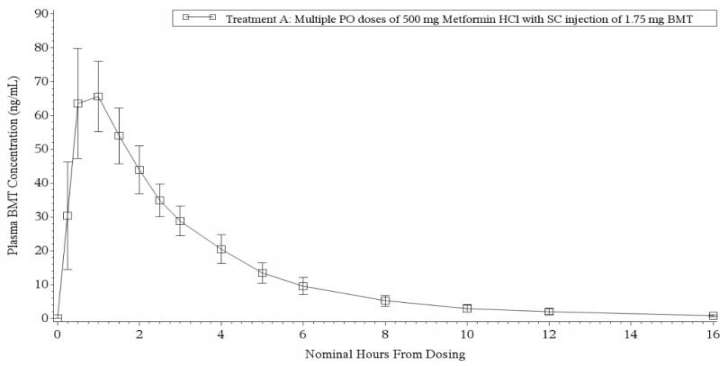


Figure 3. Mean (SD) Plasma Bremelanotide Concentration-time Profile Following the Administration of Metformin +BMT in Healthy Adults



PD effect (glucose levels): Defer to the clinical reviewer.

Safety Results

Overall, the safety profile of BMT administered with metformin was similar to that seen in studies of BMT alone and does not reflect evidence of additional tolerability concerns associated with the coadministration of BMT with metformin. Mean serum chemistry, hematology, coagulation, and urinalysis parameters were within normal range at the postdose time points for all treatments, and changes from baseline were minimal.

Reviewer's Notes and Comments:

- *Metformin is a commonly prescribed agent for treatment of type 2 diabetes. The 500 mg BID was chosen based on information from the metformin US prescribing information.*
- *Co-administration with BMT led to a slight decrease in metformin C_{max} with no impact on AUC values. The DDI is not considered as clinically significant based on minimal exposure change in metformin.*

4.6 Study PT-141-2005-23

Title: A Single-Center, Double-Blind, Randomized, Placebo-Controlled, Three-Period Crossover Study Assessing the Blood Pressure Effects of 2 Doses of BMT Alone and Co-Administered with Sublingual Nitroglycerin in Normal, Healthy Subjects

Objectives:

- To assess the effect on blood pressure (BP) and heart rate (HR) of the co-administration of sublingual nitroglycerin (NTG) and intranasal BMT to healthy, adult male and female subjects
- To assess the PK of PT-141 alone and following co-administration with NTG

Study Design:

This was a Phase 1, single-center, double-blind, randomized, placebo-controlled, 3-period, crossover study in 36 healthy male and female subjects. Each subject received a single dose of BMT 5 mg, BMT 15 mg or placebo via intranasal administration, and co-administered with a 0.4-mg dose of NTG during a dosing period. Subjects were randomized to 1 of 6 treatment sequences. The NTG dose was administered in the fasted state at 08:00 on the days indicated in the table below to minimize the influence of diurnal rhythm on BP and HR measurements. Blood samples for BMT PK analysis were collected immediately before the BMT or placebo doses at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, and 8 hours postdose. BP and HR were measured 1.0, 0.5, and 0.25 hours prior to the NTG dose; and 0.5, 1, 2, 3, 4, 6, 8, 12, and 23 to 24 hours following the NTG dose. 24-hour ABPM was performed 15 to 30 minutes predose through 24 hours postdose. Plasma concentrations of BMT were analyzed using validated LC/MS/MS assays by (b) (4) with LLOQ of 0.500 ng/mL (Validation Report 46581).

PK Results

Administration of BMT 5 mg or 15 mg alone resulted in a stepwise increase in exposure (Cmax, AUC) as the BMT dose was increased; although the increase in exposure was not strictly dose proportional. Co-administration of NTG 30 minutes after administration BMT 5 mg and 15 mg resulted in no significant change in the PK of BMT, as the GMR (+NTG/−NTG) for BMT PK parameters C_{max} and $AUC_{0-\infty}$ were within the 80%-125% acceptance interval (**Table 1**).

Table 1 Mean (%CV) BMT PK Parameters following Intranasal Administration of 5 mg and 15 mg BMT with and without NTG

	PK Parameter	BMT	BMT+ NTG	GMR (90%CI)
BMT 5 mg	AUC_{0-t} (ng·hr/mL)	51.5 (79)	50.4 (85)	92 [66, 128]
	$AUC_{0-\infty}$ (ng·hr/mL)	55.6 (75)	59.7 (74)	99 [75, 130]
	C_{max} (ng/mL)	26.6 (179)	23.5 (139)	102 [70, 149]
	T_{max} (hr)	0.5	0.75	
	$t_{½}$ (hr)	2.1 ± 0.6	2.8 ± 1.5	
BMT 15 mg	AUC_{0-t} (ng·hr/mL)	271 (66)	211 (86)	55 [31, 99]
	$AUC_{0-\infty}$ (ng·hr/mL)	296 (63)	237 (80)	77 [54, 109]
	C_{max} (ng/mL)	139 (68)	105 (83)	56 [33, 95]
	T_{max} (hr)	0.5	0.75	
	$t_{½}$ (hr)	2.1 ± 0.4	2.2 ± 0.4	

Safety Results

The percentage of subjects who experienced treatment-emergent AEs was 56% for subjects who received placebo, 71% for subjects who received PT-141 5 mg, and 81% for subjects who received PT-141 15 mg. The most common (≥10%) treatment-emergent AEs reported by BMT 5-mg subjects were headache, flushing, nausea, abdominal pain upper, dizziness, and feeling hot. The most common (≥10%) treatment-emergent AEs reported by BMT 15-mg subjects were headache, nausea, abdominal pain upper, flushing, dizziness, and feeling hot. Of the most common AEs, the only AE with ≥5% difference in incidence between the BMT doses was abdominal pain upper, reported by 17% of BMT 15-mg subjects and 12% of BMT 5-mg subjects. No clinically significant changes from baseline were observed for clinical laboratory or 12-lead ECG results.

Reviewer's Comments

- *In this DDI study, BMT was administered via intranasal spray, rather than the proposed route of SC injection. Nonetheless, systemic exposure (C_{max} and AUC) of BMT following IN administration 15 mg BMT are higher than the clinical relevant concentrations for the SC route. Therefore, the results of this study can be used to demonstrate the DDI of BMT, 1.75 mg SC with NTG.*
- *The effect of BMT on the PK of NTG was not studied. Nonetheless, it may not be critical as*
    - *BMT is unlikely to affect NTG PK: BMT affects the PK of orally administered drugs by slowing gastric motility. NTG was administered via sublingual.*
    - *The goal of the study is to examine the effect of BMT on the PD (the hemodynamic effect) of NTG. If there is no significant PD effect, it may not be necessary to determine the effect of BMT on NTG PK.*

4.7 Study PT-141-2002-11

Title: A Placebo-Controlled, Randomized, Double-Blind, Three Period, Three-Way Crossover Study to Evaluate the Hemodynamic and Pharmacokinetic Interactions of Intranasally Administered BMT and Ethanol in Healthy Male and Female Subjects

Objectives:

- To assess the hemodynamic effects of IN BMT when taken with ethanol, specifically changes in orthostatic vital signs (SBP, DBP and pulse rate)
- To assess the PK interaction between BMT and ethanol

Study Design:

This was a placebo-controlled, randomized, double-blind, three-period, three-way crossover study to assess the safety of a single IN dose of BMT when co-administered with ethanol in 24 healthy male and female subjects. Subjects were randomly assigned (2 females and 2 males per path) to one of six Treatment Paths, as shown in the table below (BMT is denoted as PT-141):

Treatment Path	N	Day 1	Day 4	Day 7
1	4	20 mg PT-141 + placebo drink	20 mg PT-141 + 0.6 g/kg ethanol	Placebo spray + 0.6 g/kg ethanol
2	4	20 mg PT-141 + placebo drink	Placebo spray + 0.6 g/kg ethanol	20 mg PT-141 + 0.6 g/kg ethanol
3	4	20 mg PT-141 + 0.6 g/kg ethanol	Placebo spray + 0.6 g/kg ethanol	20 mg PT-141 + placebo drink
4	4	20 mg PT-141 + 0.6 g/kg ethanol	20 mg PT-141 + placebo drink	Placebo spray + 0.6 g/kg ethanol
5	4	Placebo spray + 0.6 g/kg ethanol	20 mg PT-141 + placebo drink	20 mg PT-141 + 0.6 g/kg ethanol
6	4	Placebo spray + 0.6 g/kg ethanol	20 mg PT-141 + 0.6 g/kg ethanol	20 mg PT-141 + placebo drink

Blood samples for PK evaluations of BMT and ethanol were drawn pre-dose, and at 15, 30 and 45 minutes, and 1, 2, 3, 4, 8 and 12 hours post-dosing. The hemodynamic effect of coadministration of BMT and ethanol was examined and compared to BMT or ethanol administration alone using orthostatic vital sign checks. Vital signs, including sitting, immediate standing and 2-minute standing SBP, DBP and pulse rate measurements, were obtained approximately 15 minutes pre-dose, 15, 30, 45 and 60 minutes post-dosing and, thereafter, every 30 minutes up until 4 hours post-dosing, and at 8 and 12 hours post-dosing during Study Days 1, 4 and 7.

Plasma BMT concentration were analyzed using to a validated method and HPLC-MS/MS analysis. Full details of the validation of the method are described in the Method Validation Report previously submitted with Study PT-141-2000-03 (IND 61,706). Blood samples for ethanol concentration determination were analyzed by (b) (4) using an enzyme immunoassay method.

PK Results

Plasma BMT concentration-time profiles and mean PK parameters such as C_{max} and $AUC_{(0-t)}$ were generally similar in the BMT+Ethanol and BMT+ Placebo groups for both males and females (**Figure 1**).

No statistically significant differences were observed between males and females for these BMT PK parameters. Mean ethanol C_{max} and $AUC_{(0-t)}$ in the Ethanol + BMT group were slightly lower than Ethanol + Placebo group for both males and females (**Figure 2**). The ethanol exposure differences between treatments were not statistically significant.

Figure 1. Mean Plasma BMT Concentration-Time Profiles By Treatment and Gender

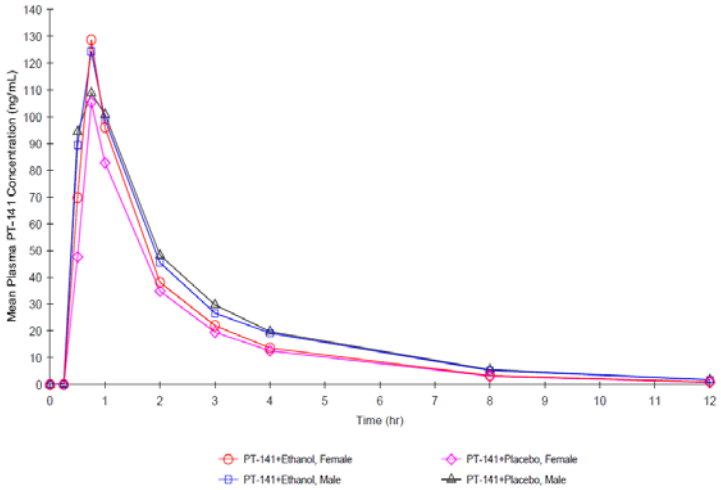
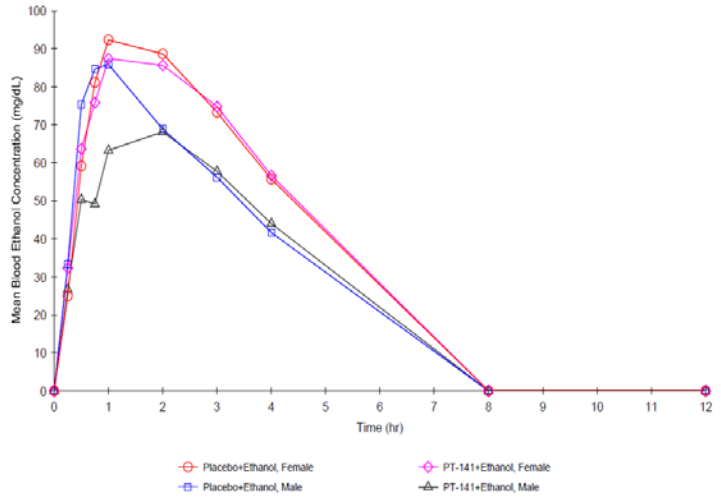


Figure 2. Mean Blood Ethanol Concentration-Time Profiles By Treatment and Gender



PD Results: Defer to the clinical reviewer

Safety Results

Co-administration of BMT +Ethanol did not result in an increased frequency of treatment-emergent AEs. Among all subjects, the most common AEs, reported in at least 5% of subjects in any treatment group, were flushing, somnolence, headache, hiccups, nausea, feeling hot, dizziness (excluding vertigo), taste disturbance and nasal congestion. There were no overall significant differences in the number of subjects with AEs based on the Kruskal-Wallis exact test ($p > 0.05$). Some AEs, such as nausea, headache and flushing, were reported more often in female subjects than in male subjects. Somnolence was reported

more often in male subjects than in female subjects. One subject (male subject (b) (6) experienced a brief 15-second syncopal episode after receiving BMT+Ethanol. This episode occurred approximately 2 hours and 30 minutes after the start of the ethanol drink.

Conclusions

- Ethanol did not have a significant effect on BMT PK, and, conversely, BMT did not have a significant effect on ethanol PK in these subjects.

Reviewer's Comment:

The ethanol dose of 0.6 g/kg is approximately equivalent to 4 ounces of vodka or 2 glasses of wine or 2 beers and was selected as representing a significant and relevant amount of ethanol that might be ingested in close proximity to BMT administration in patients using study medication in the "at-home" setting. Overall, the study design appears to be sufficient to detect the PK interactions between BMT and ethanol.

5 Population PK

The Applicant submitted a population PK/PD report entitled "Population Pharmacokinetics and Pharmacodynamics Analysis for Bremelanotide". Analyses in this report include population PK analysis, FSFI and FSDS analysis, blood pressure analyses, SSE analyses, and nausea/vomiting analyses.

Objectives: The objectives of the report were to characterize bremelanotide population pharmacokinetics and possible effect of demographic factors and concomitant medication on bremelanotide pharmacokinetics in premenopausal women.

Data: The population pharmacokinetic analysis included PK data from two Phase 1 studies (Studies PT-141-2002-14 and PT-141-56), one Phase 2b study (PT-141-54) and two Phase 3 studies (BMT-301 and BMT-302). Details of the included studies are summarized in **Table 1**.

Table 1: Summary of Studies Included in Population PK Analysis

Study #	Population*	Study Design	Active Dose and Dosing Regimen	Blood Sample Collection
PT-141-2002-14	23 healthy female subjects	A Phase 1, randomized, double-blind, placebo-controlled, parallel-group single-dose, dose escalation study	0.3, 1, 3 and 5 mg SC, single dose	Before dosing (0 hr), and at 0.5 hr after dosing
PT-141-54	294 premenopausal women with FSAD and/or HSDD	A Phase 2b, randomized, placebo-controlled, parallel-group, dose-finding study. The run-in period: 4 weeks, single-blind, placebo treatment; the randomization period: 14 weeks, double-blind, placebo or active treatment	Randomization period: 0.75, 1.25, 1.75 mg SC, as needed	Randomization visit and again approximately one week later: before dosing (0 hr), and at 0.5, 1, 2, and 4 hrs after dosing
PT-141-56	36 healthy female subjects	A Phase 1, double-blind, BA/BE study. Part 1: crossover; Part 2: parallel-group	Part 1: 1.75 mg SC, one dose via AI and the other dose via PFS, with 48 hrs washout between doses). Part 2: 1.0 mg SC single dose via AI, or 0.2 mg IV single dose	SC: before dosing (0 hr), and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs after dosing. IV: before dosing (0 hr), and at 2, 5, 10, 15, 20, and 30 min, and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hrs after dosing
BMT-301, BMT-302	319 (for Study BMT-301) and 290 (for Study BMT-302) premenopausal women with HSDD (with or without decreased arousal)	Phase 3, randomized, double-blind, placebo-controlled, parallel-group studies. The run-in period: 4 weeks, single-blind, placebo treatment; the randomization period: 24 weeks, double-blind, placebo or active treatment	Randomization period: 1.75 mg SC, as needed	Randomization visit: 3 time points postdose (15-45, 46-90, and > 90 min)

FSAD: female sexual arousal disorder; HSDD: hypoactive sexual desire disorder; BA/BE: bioavailability/bioequivalence; SC: subcutaneous; IV: intravenous; AI: autoinjector; PFS: prefilled syringe

Source: Table 1 on page 15 of Applicant's population PKPD report PPK1819

A total of 4632 PK samples from 963 subjects from Studies PT-141-2002-14 (n = 23), PT-141-56 (n = 36), PT-141-54 (n = 294), BMT-301 (n = 319), and BMT-302 (n = 290) were included in the population PK analysis. The demographic data for subjects included in the final population PK dataset is summarized in **Table 2.**

Table 2: Summary of Continuous Covariates at Baseline

variable	miss_n	nonmiss_n	min	p.25th	p.50th	p.75th	max	mean	sd
AGE	0	963	19	32	38	43	56	37.4	7.55
WEIGHT	1	962	43.1	64.5	74.5	88.4	193	78.4	19.3
BMI	2	961	17.4	24	27.5	32.5	57.7	28.9	6.83
BSA	2	961	1.39	1.7	1.83	1.97	2.94	1.85	0.209
CRCL	1	962	57.6	104	127	157	444	136	44.7
EGFR	0	963	48	81.4	95.2	111	229	98.9	23.4
ALB	23	940	3.3	4.2	4.4	4.6	5.4	4.43	0.299
BILI	42	921	0.1	0.292	0.4	0.5	2	0.435	0.239
AST	0	963	6	15	18	22	92	19.4	6.61
ALT	0	963	5	13	16	21	91	18.2	8.87

Source: Table on page 134 of Applicant's population PKPD report PPK1819

Population PK Model Development

Base Model: The selected base model was a 2-compartmental model with first-order processes, fixing F1=1 and KA=0.535 /hr, using exponential error models to describe the IIV of CL & V2 and allowing correlation between CL & V2, using an additive plus proportional error model to describe the intra-individual variability, and analyzing the data in original scale.

Final Model: Covariate analysis were conducted with SCM algorithm in PsN for assessing influence of each covariate on bremelanotide pharmacokinetic parameters such as apparent clearance (CL/F) and apparent volume of distribution (V2/F. The final backward model from SCM contained the following PK parameter-covariate relationships: CLWEIGHT-2, CLSITE-1, CLPOP-1 CLEGFR-1, V2WEIGHT-1, V2SITE-1, V2POP-1, with 1: a linear function, and 2: a power function.

The final model was a 2-compartmental model with first-order processes, fixing F1=1 and KA=0.535 /hr, using exponential error models to describe the IIV of CL & V2 and allowing correlation between CL & V2, using an additive plus proportional error model to describe the intra-individual variability, and analyzing the data in original scale. EGFR, GRP and WEIGHT were significant covariates on CL. GRP, INJ and WEIGHT were significant covariates on V2. All the covariate-parameter relationships were via a linear function, except that V2-WEIGHT relationship was via a power function.

The parameter estimates from the final model (Model 157) including covariate effects are summarized in **Table 3**.

Table 3: Parameter Estimates and Covariate Effects for Bremelanotide Population Pharmacokinetic Final Model (Model 157)

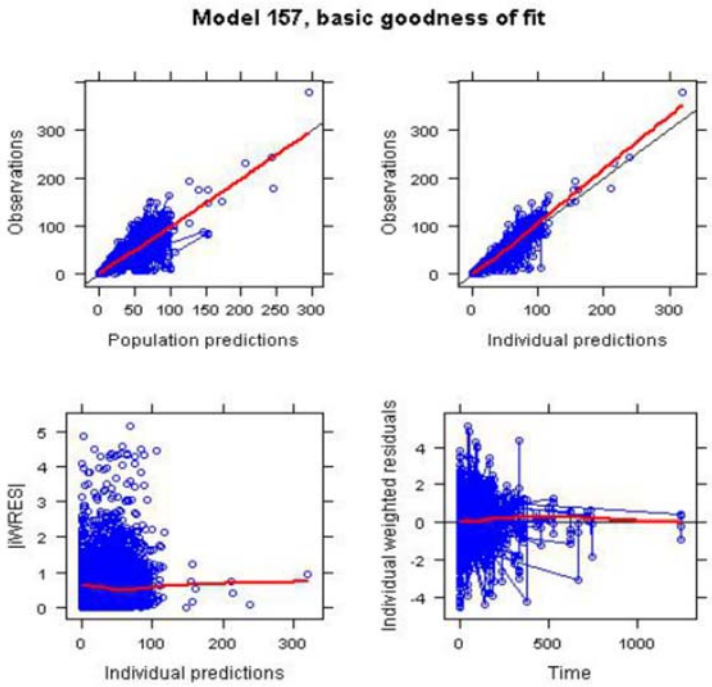
Parameter Description (Unit)	Parameter Estimate (NONMEM)	%RSE (NONMEM)	95% CI[&] (Bootstrap)
CL (L/hr)	**7.11**	1.10	(6.94, 7.26)
	× (1 + 0.00174 × (eGFR -95.22))	15.9	(0.00114, 0.00238)
	× (1 - 0.131) if healthy	16.9	(-0.173, -0.0849)
	× $(WEIGHT/74.5)^{0.528}$	5.80	(0.470, 0.587)
%CV for CL inter-individual variability	16%[#]	6.9*	(14%, 17%)[$]
V2 (L)	**2.19**	2.80	(2.06, 2.31)
	× (1 + 0.559) if healthy	13.6	(0.377, 0.774)
	× (1 + 0.332) if thigh injection	18.3	(0.199, 0.490)
	× (1 + 1.22) if arm or hand injection from IV doses	21.1	(0.735, 1.83)
	× (1 + 0.0222 × (WEIGHT-74.5))	6.7	(0.0190, 0.0252)
%CV for V2 inter-individual variability	36%[#]	11*	(31%, 40%)[$]
Correlation between CL & V2	0.39[#]	22*	--
V3 (L)	**6.04**	4.30	(5.55, 6.57)
Q (L/hr)	**2.02**	5.50	(1.82, 2.25)
F1	**1 FIX**	--	--
KA (1/hr)	**0.535 FIX**	--	--
Additive residual error	0.103	55.6	(0.0272, 0.183)
Proportional residual error	19.8%	3.10	(18.5%, 21.0%)

CL: clearance; V2 and V3: volume of distribution of the central and peripheral compartment, respectively; Q: intercompartmental clearance;
F1: bioavailability; KA: the 1st order absorption rate constant.
RSE: relative standard error of the parameter estimate. %RSE = SE × 100 / Parameter Estimate.

Source: Table 2 on page 32 of Applicant's population PKPD report PPK1819

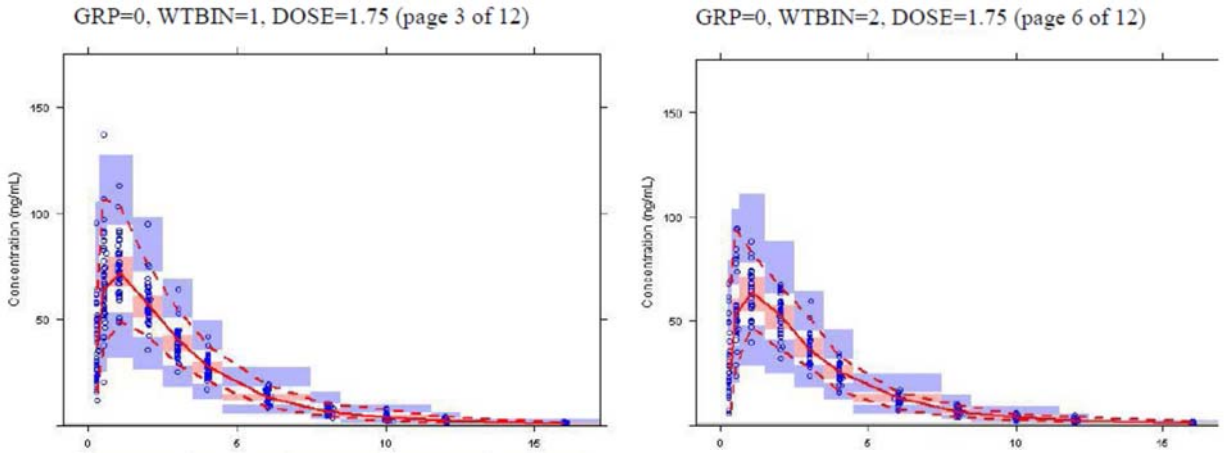
Model Evaluation: The final model was evaluated graphically by goodness-of-fit plots, visual predictive checks (VPCs) as well as bootstrap evaluation. The goodness-of-fit plots for the final model are displayed in **Figure 1** and the VPCs plots are demonstrated in **Figure 2.**

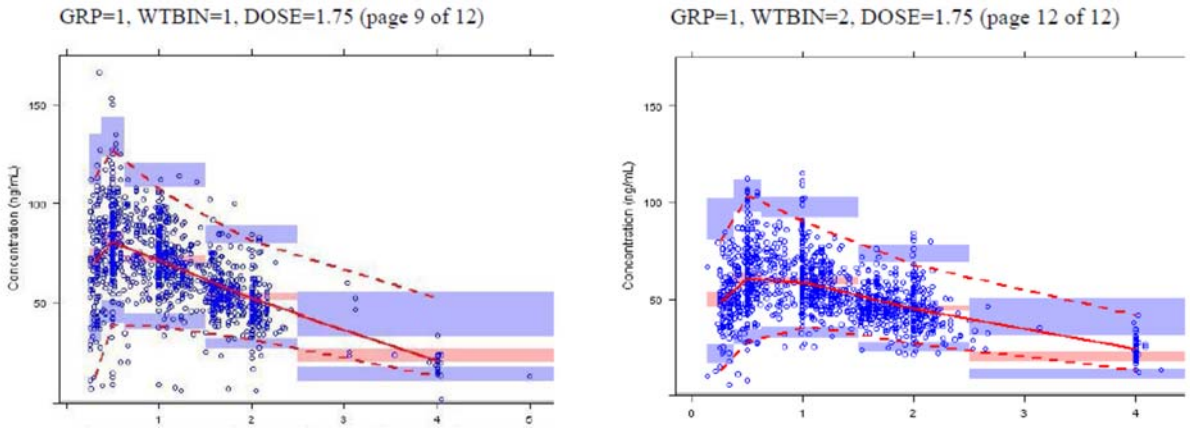
Figure 1: Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figure 5 on page 30 of Applicant's population PKPD report PPK1819

Figure 2: Visual Predictive Checks for 1.75 mg Dose for the Final Population PK Model





In the upper panel, blue cycles: the observed individual data (> LLOQ); dashed and solid red lines: the 2.5th, 50th, and 97.5th percentiles of the observed data (> LLOQ); blue and red shaded areas: model-predicted 95% confidence interval for the 2.5th, 50th, and 97.5th percentiles. In the lower panel, red cycles and red line: the observed concentrations of total < LLOQ;blue shaded areas: model-predicted 95% confidence interval of concentrations. GRP=1: HSDD; FSAD/mixed (most common); GRP=0: healthy.
WTBIN=1: WEIGHT ≤ 74.5 kg; WTBIN=2: WEIGHT>74.5 kg. DOSE unit: mg.

Source: Adapted from Appendix 8.2.15 on page 150-155 of Applicant's population PKPD report PPK1819

Reviewer's comments: The Applicant's population PK analysis is acceptable. The final population PK model appeared to be able to characterize the PK profile of bremelanotide as indicated in the applicant's goodness-of-fit plots and the VPC plots. The reviewer was able to verify the Applicant's analysis.

6 Exposure-Response Analyses

The efficacy data were from Phase 2 study PT-141-54 and Phase 3 studies BMT-301 and BMT-302.

In study PT-141-54 blood samples for PK analysis were collected at predetermined time points before and for up to 4 hrs after in clinic, randomized study drug administration during Visits 5 and 7 (up to 2 hrs post-dosing after Amendment #4). Visit 5 was the randomization visit, and Visit 7 was approximately one week after Visit 5. The concentration data were included in the analysis.

In study BMT-301 and BMT-302, pharmacokinetic plasma samples were obtained at Visit 3 at 3 time points (15-45, 46-90, and > 90 minutes) after an observed dose, and the concentration data were included in the analysis.

Pharmacodynamic Data: The efficacy data from the study included in the analysis:

- The desire domain of the Female Sexual Function Index (FSFI) collected at each visit, every 4 weeks, from baseline to end of study.
- The desire item (Item 13) of the FSDS-DAO collected at each visit, every 4 weeks, from baseline to end of study.
- The number of satisfying sexual events (SSEs) associated with study drug administration (defined as an SSE that occurred within 16 hours of dosing) from baseline to end of study.

For FSFI, FSDS-DAO and SSE data, the baseline referred to the data collected pre-dose at Visit 5. Because FSFI, FSDS-DAO and SSE evaluate patients' sexual desire or sexual events in the last 4 weeks, the pre-dose data at the randomization visit reflected patients' sexual desire or sexual events during the 4-week run-in period.

The safety data included in the analysis were SBP, DBP, nausea and vomiting.

FSFI Data: The FSFI Q1 and Q2 data were pooled from 3 studies. The number of data records and number of subjects from each study that were included in the analysis are shown below:

- 1242 of 1407 total records were used from 363 of 438 total subjects in Study 54.
- 3642 of 3891 total records were used from 626 of 665 total subjects in Study 301.
- 3146 of 3464 total records were used from 566 of 635 total subjects in Study 302

FSFI Q1 Modeling: Because FSFI Q1 scores are discrete categorical data ranging from 1 to 5 with the higher the score, the more sexual desire a subject has, an ordered categorical data model was used, and the codes denoted ordering but not distances between categories. The proportion of subjects having a specific score at a given time was essentially a probability. The probability values are bound between 0 and 1, and can cause numeric problems during modeling. Therefore, logit transformations were used to handle the probability values, and the logit itself has no boundary and can range from $-\infty$ to $+\infty$ (typically from -8 to +8, or from -6 to +6, is sufficient to cover the probability range from 0 to 1). Cumulative logits (LGEs, where GE stands for great than or equal to) were used to capture the logits for score ≥ 2, ≥ 3, ≥ 4, ≥ 5, and then cumulative logits were back transformed into cumulative probabilities (PGEs). And the probability for a specific score was calculated as the difference between two adjacent cumulative probabilities. An additive error model was used to describe the IIV for cumulative logit for score ≥ 2 (LGE2) in all the models.

Some key equations used in the model development are shown below.

;Baseline values
B2 for LGE2
B3 for LGE3-LGE2
B4 for LGE4-LGE3
B5 for LGE5-LGE4
;Logits for score ≥ 2, score ≥ 3, score ≥ 4, score ≥ 5
LGE2 = B2 + TEF2 + DEF2 + ETA(1)
LGE3 = LGE2 + B3 + TEF3
LGE4 = LGE3 + B4 + DEF4
LGE5 = LGE4 + B5
;Probabilities for score ≥ 2, score ≥ 3, score ≥ 4, score ≥ 5
PGE2 = EXP(LGE2)/(1+EXP(LGE2))
PGE3 = EXP(LGE3)/(1+EXP(LGE3))
PGE4 = EXP(LGE4)/(1+EXP(LGE4))
PGE5 = EXP(LGE5)/(1+EXP(LGE5))
;Probabilities for score = 1, score = 2, score = 3, score = 4, score = 5
P1 = (1-PGE2)
P2 = (PGE2-PGE3)
P3 = (PGE3-PGE4)
P4 = (PGE4-PGE5)
P5 = PGE5
where Bs were baseline values, LGEs were cumulative logits, PGEs were cumulative probabilities (note that PGE2 ≥ PGE3 ≥ PGE4 ≥ PGE5), TEFs were time effect, DEFs are drug effect, and ETA(1) was the random-effects parameter for IIV for LGE2.

The drug effect (DEF) was added as a linear function to a placebo model with a slope variable multiplied by a drug exposure variable. A proportional odds model was used for the drug effect.
The average concentration during the active dosing days (CAVDOSE) was used as the drug exposure variable initially during the model development (Model 209 and onwards). Two tolerance terms (TOLEs) and one offset term were added to modify the time effects (TEFs) to further capture the fluctuation in the observed data that could not be explained by the drug effect (Models 214, 216 and 217). The linear drug effect (DEF2) on LGE2 was the main drug effect and it described that the higher the average concentration during the active dosing days, the higher the logit (and thus the probability) of achieving a score ≥ 2, and the higher the probabilities of achieving a score ≥ 3, a score ≥ 4, and a score of 5.

SCM was used for the covariate analysis. The following covariates were found to be significant on LGE2: PLAC, RACE, and WEIGHT, where PLAC was injection site from the previous visit until the current visit (0: always thigh, 1: always abdomen (most common), and 4: combination of sites), RACE was race (0: White [most common], 1: Black, 2: Asian, 3: Native American, 4: Pacific Islander, 5: Other or Multiple), and WEIGHT was weight

Final Model for FSFI Q1
The final model was an ordered categorical data model with logit transformations and back transformation to probabilities to describe the proportion of subjects achieving a specific FSFI Q1 score over time. A linear drug effect (DEF2) on the cumulative logit for scores ≥ 2 (LGE2) and a proportional odds model were used to describe the observed trend of less patients having FSFI Q1 score=1 and more

patients having FSFI Q1 score ≥ 2 with BMT treatment. The model predicted that the higher the average concentration during the active dosing days, the higher the logit (and thus the probability) of achieving a score ≥ 2, and the higher the probabilities of achieving a score ≥ 3, a score ≥ 4, and a score of 5. The covariate effects of injection site, race and weight were mainly on the baseline values of the LGE2. Different exposure metrics provided similar results. The parameter estimates from the final model are shown in
Table 4. The visual predictive check plots for the final model is shown in **Figure 3**.

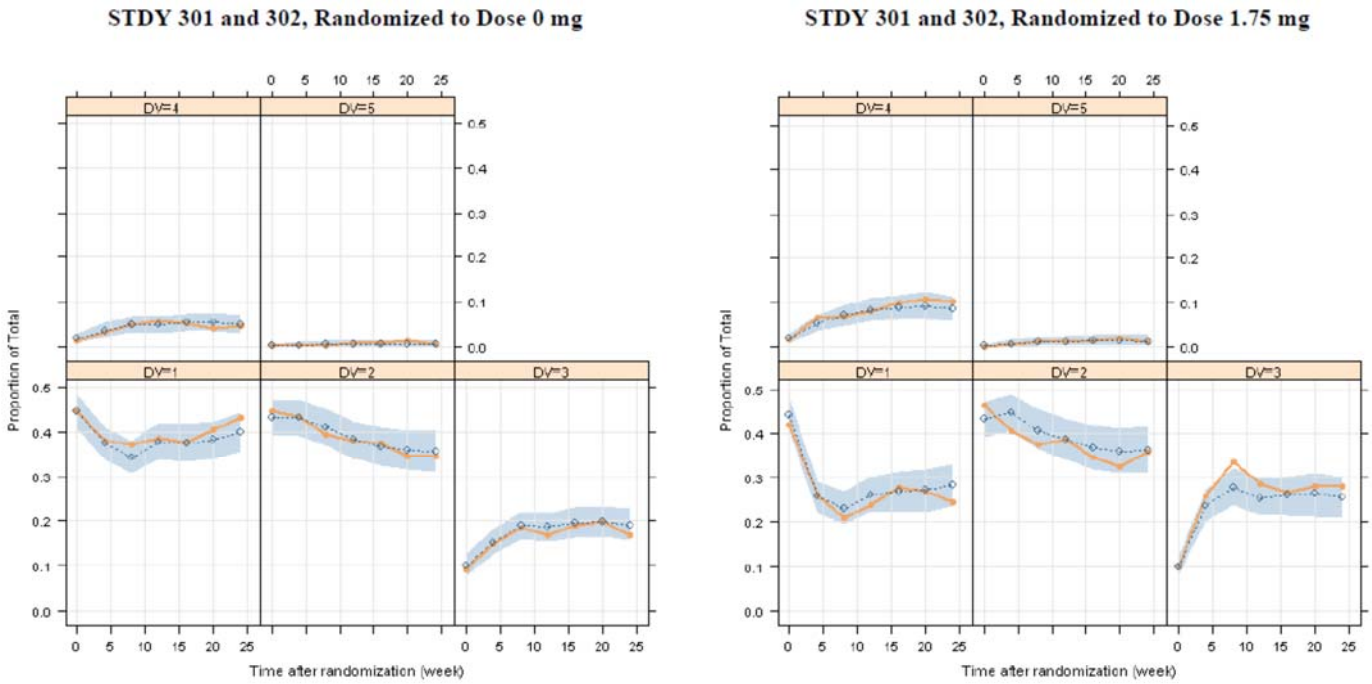
Table 4: Parameter Estimates from the Final Model for FSFI Q1

Parameter Description	Parameter	Unit	Parameter Estimate	%RSE
B2 (baseline value for LGE2) for STY2=300	TH1	--	0.0707	155
B3 (baseline value for LGE3- LGE2)	TH2	--	-3.26	4.20
B4 (baseline value for LGE4- LGE3)	TH3	--	-2.71	2.60
B5 (baseline value for LGE5- LGE4)	TH4	--	-2.87	4.80
Additive diff. in B2 b/w 54 & 300	TH5	--	0.984	21.1
The 1st piece of piece-wise TEF2 on LGE2 for 300	TH6	1/week	0.168	28.0
The 2nd piece of piece-wise TEF2 on LGE2 for 300	TH7	--	0.584	19.7
The 1st piece of piece-wise TEF2 on LGE2 for 54	TH8	--	0.645	24.0
The 2nd piece of piece-wise TEF2 on LGE2 for 54	TH9	--	1.09	16.7
The 1st piece of piece-wise TEF3 on LGE3 for 300	TH10	1/week	0.0837	20.4
Slope for DEF2 on LGE2	TH11	1/(ng/mL)	0.100	10.4
The 3rd piece of piece-wise TEF2 on LGE2 for 300	TH12	--	0.546	23.1
The 4th piece of piece-wise TEF2 on LGE2 for 300	TH13	--	0.434	30.2
Tolerance for the 1st piece of TEF2 on LGE2 for 300	TH14	1/week	-0.0471	42.2
Tolerance for TEF3 on LGE3 for 300	TH15	1/week	-0.0274	20.3
Offset for TEF3 on LGE3 for 300	TH16	week	-7.30	30.8
Slope for DEF4 on LGE4 for 300 and PTAFEWK ≤ 8	TH17	1/(ng/mL)	-0.0411	40.4
Additive diff. in LGE2 comparing PLAC=4 to PLAC=1 or 0	TH18	--	0.366	22.3
Additive diff. in LGE2 comparing RACE=1 to RACE=0 or 5	TH19	--	1.38	13.7
Additive diff. in LGE2 comparing RACE=2 to RACE=0 or 5	TH20	--	2.16	30.3
Additive diff. in LGE2 comparing RACE=3 to RACE=0 or 5	TH21	--	-1.65	50.1
Additive diff. in LGE2 comparing RACE=4 to RACE=0 or 5	TH22	--	5.13	49.3
Linear slope for LGE2_WEIGHT relationship	TH23	1/kg	0.0123	27.5
SD for LGE2 IIV	OM1:1	--	2.30#	5.49*

If STDY=54, then STY2=54; If STDY=301 or 302, then STY2=300.
LGE2, LGE3, LGE4, and LGE5: logit for DV ≥ 2, DV ≥ 3, DV ≥ 4, and DV ≥ 5, respectively.
TEF: time effect. DEF: drug effect. PTAFEWK: protocol time after first event in week (i.e., protocol week after randomization). IIV: inter-individual
PLAC: Injection site from the previous visit until the current visit. 0: always thigh, 1: always abdomen (most common), 4: combination of sites.
RACE=0: White (most common), 1: Black, 2: Asian, 3: Native American, 4: Pacific Islander, 5: Other or Multiple.
RSE: relative standard error of the parameter estimate. %RSE = SE × 100 / Parameter Estimate.
SD: standard deviation. SD = sqrt(OMEGA2). The value is shown in OMEGA - CORR MATRIX FOR RANDOM EFFECTS.
* RSE for OMEGA2, is based on final parameter estimate and standard error of estimate from OMEGA - COV MATRIX FOR RANDOM EFFECTS.

Source: Table 3 on page 45 of Applicant's population PKPD report PPK1819

Figure 3: FSFI Q1 Visual Predictive Check Plots for Studies 301 and 302 (Final FSFI Q1 Model)



Source: Figure 11 on page 49 of Applicant's population PKPD report PPK1819

Exposure-Response Relationship for FSFI Q1: The observed FSFI Q1 maximum change from baseline (baseline defined as the score at the time of randomization) for each subject during the randomization period vs corresponding model-predicted average concentration during dosing days (CAVDOSE) in Studies 54, 301 and 302 are shown in **Figure 4**.

As shown in **Figure 4**, more than 60% of the placebo subjects had no improvement in FSFI Q1 score (i.e., maximum change from baseline = 0), while all the subjects who received active doses had improvement in FSFI Q1 score by at least 1 point compared to the baseline. As the CAVDOSE values increased, there was generally a trend of an increasing percentage of subjects achieving improvement by at least 2 points. However, the trend was weak due to the variability in the data. The overall exposure-response relationship for FSFI Q1 is flat.

Figure 4: Observed FSFI Q1 Maximum Change from Baseline vs Model-Predicted Average Concentration During Dosing Days in Studies 54, 301 and 302

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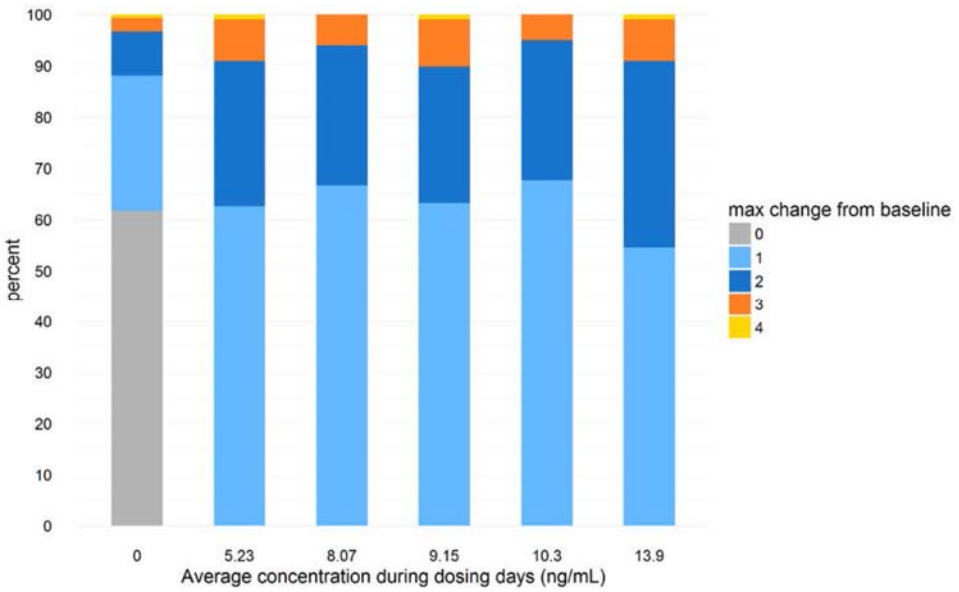

The CAVDOSE values were binned into 6 groups. The group with CAVDOSE=0 was subjects who did not administer any active dose (e.g., placebo subjects). The remaining 5 groups were from subjects who received active doses (0.75, 1.25 and 1.75 mg) and each group had roughly the same number of subjects. The x-axis values were calculated as the (min + max)/2 of each group's CAVDOSE values

Source: Figure 12 on page 50 of Applicant's population PKPD report PPK1819

FSFI Question 2 Modeling: The modeling approach for FSFI Q2 were very similar to FSFI Q1. The final model was an ordered categorical data model with logit transformations and back transformation to probabilities to describe the proportion of subjects achieving a specific FSFI Q2 score over time. A linear drug effect (DEF2) on the cumulative logit for scores ≥ 2 (LGE2) and a proportional odds model were used to describe the observed trend of less patients having FSF2 Q2 score=1 and more patients having FSF2 Q2 score ≥ 2 with BMT treatment. The model predicted that the higher the average concentration during the active dosing days, the higher the logit (and thus the probability) of achieving a score ≥ 2, and the higher the probabilities of achieving a score ≥ 3, a score ≥ 4, and a score of 5. The covariate effects of body mass index (BMI) and race were mainly on the baseline values of the LGE2. Different exposure metrics provided similar results.

The parameter estimates from the final model are shown in **Table** 5. The visual predictive check plots for the final model is shown in **Figure 5**.

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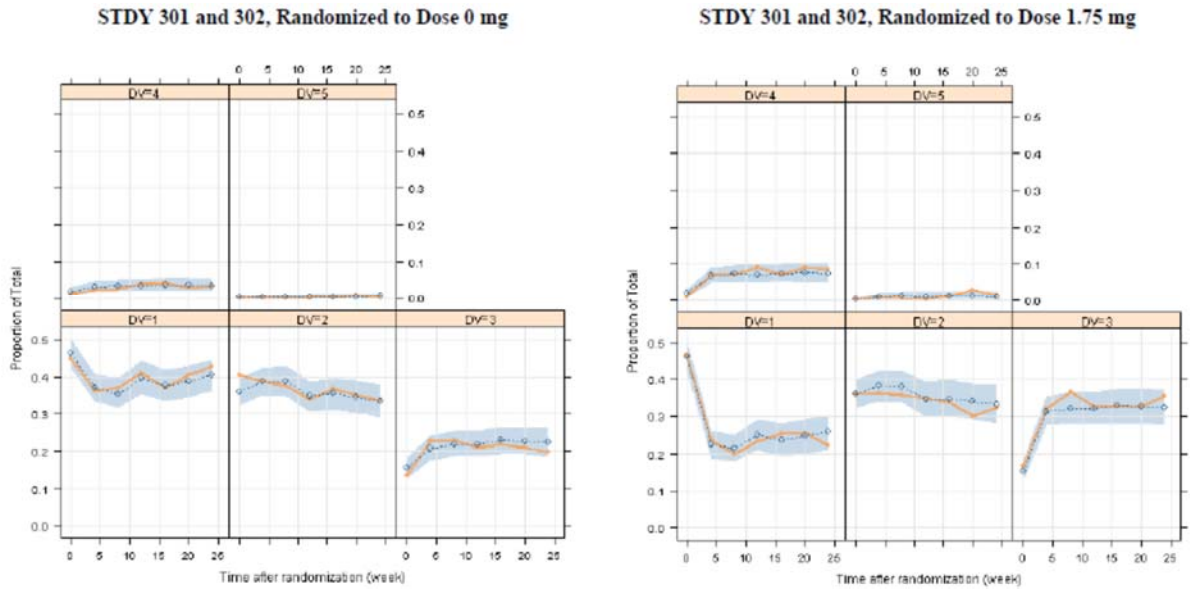
Table 5: Parameter Estimates from the Final Model for FSFI Q2

Parameter Description	Parameter	Unit	Parameter Estimate	%RSE
B2 (baseline value for LGE2) for STY2=300	TH1	--	0.0347	21.3
B3 (baseline value for LGE3-LGE2)	TH2	--	-3.17	2.21
B4 (baseline value for LGE4-LGE3)	TH3	--	-3.54	2.27
B5 (baseline value for LGE5-LGE4)	TH4	--	-2.94	5.48
Fractional diff. in B2 b/w 54 & 300	TH5	--	31.9	21.9
The 1st piece of piece-wise TEF2 on LGE2 for 300	TH6	1/week	0.185	13.4
The 2nd piece of piece-wise TEF2 on LGE2 for 300	TH7	1/week	0.109	11.6
The 3rd piece of piece-wise TEF2 on LGE2 for 300	TH8	1/week	0.0447	14.4
The 4th piece of piece-wise TEF2 on LGE2 for 300	TH9	1/week	0.0311	18.0
The 5th piece of piece-wise TEF2 on LGE2 for 300	TH10	1/week	0.0209	23.4
The 2nd piece of piece-wise TEF3 on LGE3	TH11	1/week	0.0286	32.7
The 3rd piece of piece-wise TEF3 on LGE3	TH12	1/week	0.0189	24.8
The 1st piece of piece-wise TEF2 on LGE2 for 54	TH13	1/week	0.0410	40.2
The 3rd piece of piece-wise TEF3 on LGE3 for 54	TH14	1/week	0.0553	21.7
Slope for DEF2 on LGE2	TH15	1/(ng/mL)	0.134	7.76
Linear slope for LGE2_BMI relationship	TH16	1/(ng/mL)	0.0445	22.7
Fractional diff. in LGE2 comparing RACE ≥ 1 to RACE=0	TH17	--	1.25	14.6
SD for LGE2 IIV	OM1:1	--	2.48#	5.44*

If STDY=54, then STY2=54; If STDY=301 or 302, then STY2=300.
LGE2, LGE3, LGE4, and LGE5: logit for DV ≥ 2, DV ≥ 3, DV ≥ 4, and DV ≥ 5, respectively.
TEF: time effect. DEF: drug effect.
RACE=0: White (most common); RACE ≥ 1: Black, Asian, etc.
IIV: inter-individual variability.
RSE: relative standard error of the parameter estimate. %RSE = SE × 100 / Parameter Estimate.
SD: standard deviation. SD = sqrt(OMEGA2). The value is shown in OMEGA - CORR MATRIX FOR RANDOM EFFECTS.
* RSE for OMEGA2, is based on final parameter estimate and standard error of estimate from OMEGA - COV MATRIX FOR RANDOM EFFECTS.

Source: Table 4 on page 53 of Applicant's population PKPD report PPK1819

Figure 5: FSFI Q2 Visual Predictive Check Plots for Studies 301 and 302 (Final FSFI Q2 Model)

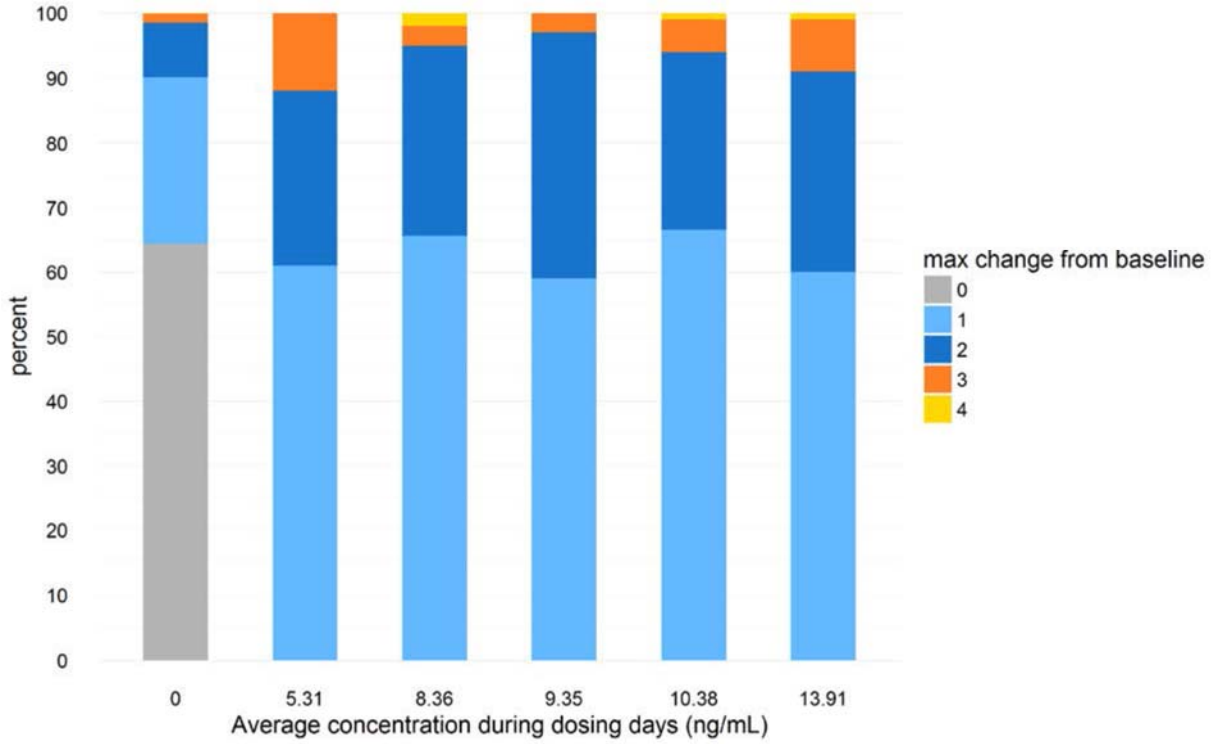


Source: Figure 15 on page 56 of Applicant's population PKPD report PPK1819

Exposure-Response Relationship for FSFI Q2: The observed FSFI Q2 maximum change from baseline (baseline defined as the score at the time of randomization) for each subject during the randomization period vs corresponding model-predicted average concentration during dosing days (CAVDOSE) in Studies 54, 301 and 302 are shown in **Figure 6**.

As shown in **Figure 6**, more than 60% of the placebo subjects had no improvement in FSFI Q2 score (i.e., maximum change from baseline = 0), while all the subjects who received active doses had improvement in FSFI Q2 score by at least 1 point compared to the baseline. Among the subjects who received active dose, the trend between the CAVDOSE values and percentage of subjects achieving improvement was not very clear due to the variability in the data. The overall exposure-response relationship for FSFI Q2 is flat.

Figure 6: Observed FSFI Q2 Maximum Change from Baseline vs Model-Predicted Average Concentration During Dosing Days in Studies 54, 301 and 302



Source: Figure 16 on page 57 of Applicant's population PKPD report PPK1819

FSDA Modeling: The dataset used for FSDA-DAO Item 13 were from Phase 2 study (Study 54) and Phase 3 Studies (Studies 301 and 302). The number of data records and number of subjects from each study are as the following:

- 1240 of 1406 total records were used from 363 of 438 total subjects in Study 54.
- 3642 of 3888 total records were used from 628 of 665 total subjects in Study 301.
- 3142 of 3452 total records were used from 566 of 634 total subjects in Study 302

The scores from FSDS-DAO Item 13 (shortened as FSDS) was set as the DV in the NONMEM control streams for the analysis.

Similar to the models sused for FSFI Q1 and Q2 analyses, an ordered categorical data model was used for FSDS. The final model was an ordered categorical data model with logit transformations and back transformation to probabilities to describe the proportion of subjects achieving a specific FSDS score over time. A linear drug effect (DEF3) on the cumulative logit for scores ≤ 3 (LLE3) and a proportional odds model were used to describe the observed trend of less patients having FSDS score=4 and more patients having FSDS score ≤ 3 with BMT treatment. The model predicted that the higher the average concentration during the active dosing days, the higher the logit (and thus the probability) of achieving a score ≤ 3, and the higher the probabilities of achieving a score ≤ 2, a score ≤ 1, and a score of 0. The drug effect was sensitized over time, so for a given drug exposure, the observed drug effect increased slowly over time. The covariate effect of race was mainly on the baseline values of the LLE3. Different exposure metrics provided similar results.

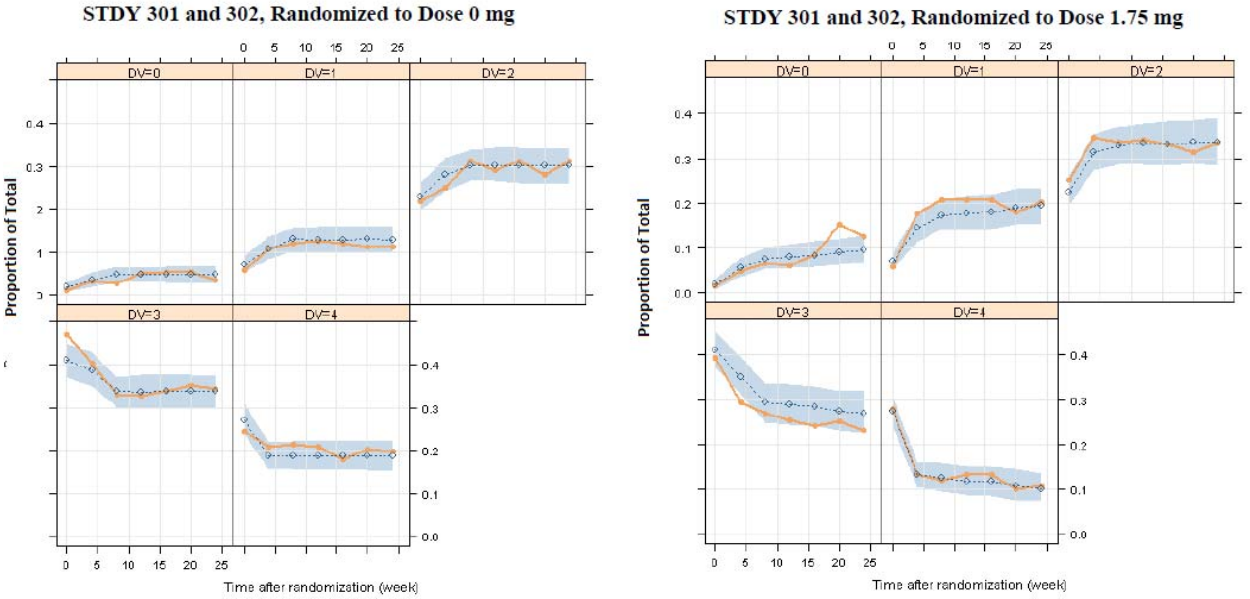
The parameter estimates for the final model are shown in **Table 6**. The VPC plots for the final model are shown in **Figure 7**.

Table 6: Parameter Estimates from the Final Model for FSDS-DAO Item 13

Parameter Description	Parameter	Unit	Parameter Estimate	%RSE
B3 (baseline value for LLE3)	TH1	--	1.70	6.19
B2 (baseline value for LLE2-LLE3)	TH2	--	-3.21	2.27
B1 (baseline value for LLE1-LLE2)	TH3	--	-2.61	2.01
B0 (baseline value for LLE0-LLE1)	TH4	--	-2.28	2.86
Fractional diff. in B3 b/w 54 & 300	TH5	--	0.534	24.2
The 1st piece of piece-wise TEF3 on LLE3 for 300	TH6	1/week	0.834	10.7
The 1st piece of piece-wise TEF3 on LLE3 for 54	TH7	1/week	0.101	16.9
The 2nd piece of piece-wise TEF3 on LLE3 for 54	TH8	1/week	0.0715	30.2
The 2nd piece of piece-wise TEF2 on LLE2 for 300	TH9	1/week	0.391	18.2
The 1st piece of piece-wise TEF2 on LLE2 for 54	TH10	1/week	0.0356	67.3
The 3rd piece of piece-wise TEF2 on LLE2 for 54	TH11	1/week	0.0293	71.8
Slope for DEF3 on LLE3	TH12	1/(ng/mL)	0.0610	20.6
Sensitization for DEF3 on LLE3	TH13	1/week	0.0460	39.6
Additive diff. in LLE3 comparing RACE=1 to RACE=0 or 5	TH14	--	0.879	21.8
Additive diff. in LLE3 comparing RACE=2 to RACE=0 or 5	TH15	--	1.14	59.2
Additive diff. in LLE3 comparing RACE=3 to RACE=0 or 5	TH16	--	-2.20	36.8
Additive diff. in LLE3 comparing RACE=4 to RACE=0 or 5	TH17	--	5.75	48.3
SD for LLE3 IIV	OM1:1	--	2.39#	5.17*

Source: Table 5 on page 62 of Applicant's population PKPD report PPK1819

Figure 7: Visual Predictive Check Plots for Studies 301 and 302 for Final FSDS-DAO Item 13 Model



Source: Figure 19 on page 65 of Applicant's population PKPD report PPK1819

Reviewers Comments: The population pharmacodynamic analysis was able to characterize observed FSFI Q1 or Q2 and FSDS-DAO. The Applicant's analyses were verified by the reviewer. There was no evident exposure-response relationship for the primary efficacy endpoints, and there was no trend of observed FSFI Q1 or Q2 maximum change from baseline vs. body weight in patients dosed with BMT 1.75 mg. Dose adjustment based on body size is not necessary.

Blood Pressure (SBP and DBP) Modeling: SBP and DBP data were pooled from 3 studies. The number of data records and number of subjects from each study that were included in the analysis are shown below:

- 123760 of 124484 total records were used from 393 of 394 total subjects in Study 54.
- 3786 of 5084 total records were used from 635 of 642 total subjects in Study 301.
- 3476 of 4712 total records were used from 590 of 596 total subjects in Study 302.

The Final Model for SBP: The double-delta SBP (ddSBP) and double-delta DBP (ddDBP) values were used in the NONMEM analysis. The double-delta BP was calculated as the change from pre-dose baseline adjusted by the time-matched 1st 24-hr ABPM value or 1st BP manual monitoring within the same subject. The final model for ddSBP contained a BASE model plus a linear drug effect term. The BASE model included typical baseline, plus a device effect (DEVEFF), a 24-hr circadian rhythm, a 12-hr circadian rhythm and inter-occasion variability to describe the difference between Visits 5 and 7 for Study 54. The drug effect was associated with the concentrations in the peripheral compartment. There was no clear relationship between covariates (demographics, concomitant medications, injection site, baseline SBP or DBP values, and lab values) and the drug effect at a given concentration.

The parameter estimates for the final model are shown in **Table 7**. The basic GOF plots for the final ddSBP model are shown in **Figure 8**. The VPC plots for the ddSBP from the final model are shown in **Figure 9**.

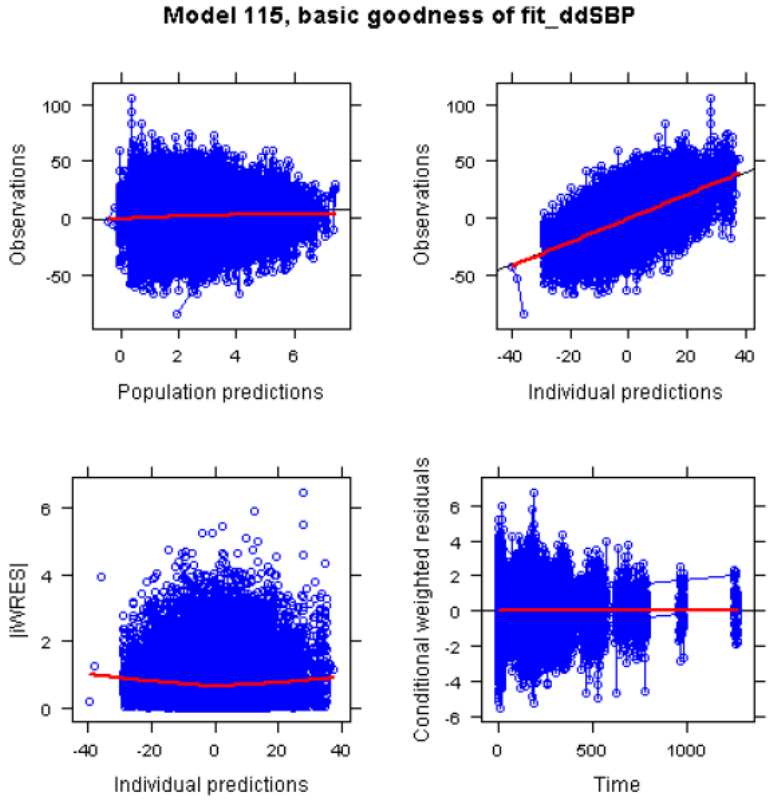
Table 7: Parameter Estimates for the Final ddSBP Model

Parameter Description (Unit)	Parameter	NONMEM (Model 115)		Bootstrap (Model 115)	
		Parameter Estimate (%RSE)	90% CI`	Parameter Estimate[&]	90% CI[&]
ddSBP residual additive error (mmHg)	TH1	12.0 (0.88)	(11.8, 12.2)	12.0	(11.8, 12.2)
TVBASE (typical BASELINE) (mmHg)	TH2	1.31 (42)	(0.400, 2.22)	1.28	(0.242, 2.36)
DEVEFF (device effect) for DEVICE=1 (mmHg)	TH3	-0.851 (72)	(-1.85, 0.152)	-0.832	(-1.90, 0.305)
AMP (amplitude for 24-hr oscillation) (mmHg)	TH4	0.462 (45)	(0.123, 0.801)	0.546	(0.239, 0.884)
TPEAK (peak time for 24-hr oscillation) (clock time in hr)	TH5	20.5 (11)	(16.7, 24.3)	20.3	(16.4, 23.5)
AMP2 (the 2nd amplitude for 12-hr oscillation) (mmHg)	TH6	0.749 (22)	(0.481, 1.02)	0.770	(0.553, 1.04)
TPEAK2 (the 2nd peak time for 12-hr oscillation) (clock time in hr)	TH7	10.4 (4.1)	(9.69, 11.1)	10.5	(9.84, 11.2)
TVSL (typical slope) (mmHg/[ng/mL])	TH8	0.128 (17)	(0.0923, 0.164)	0.126	(0.0976, 0.166)
SD for ddSBP baseline additive IIV	OM1:1	8.1[#] (6.7*)	--	8.1[$]	(7.6, 8.5)[$]
SD for additive IOV when Visit 5 for Study 54, or Visit 3 for Studies 301 & 302	OM2:2	3.2[#] (12*)	--	3.2[$]	(2.9, 3.5)[$]
SD for additive IOV when Visit 7 for Study 54	OM3:3	3.2[#] (--)	--	3.2[$]	(2.9, 3.5)[$]
SD for drug effect slope additive IIV	OM4:4	0.31[#] (11*)	--	0.31[$]	(0.28, 0.33)[$]

IIV: inter-individual variability. IOV: inter-occasion variability.
RSE: relative standard error of the parameter estimate. %RSE = SE*100/Parameter Estimate.

Source: Table 9 on page 76 of Applicant's population PKPD report PPK1819

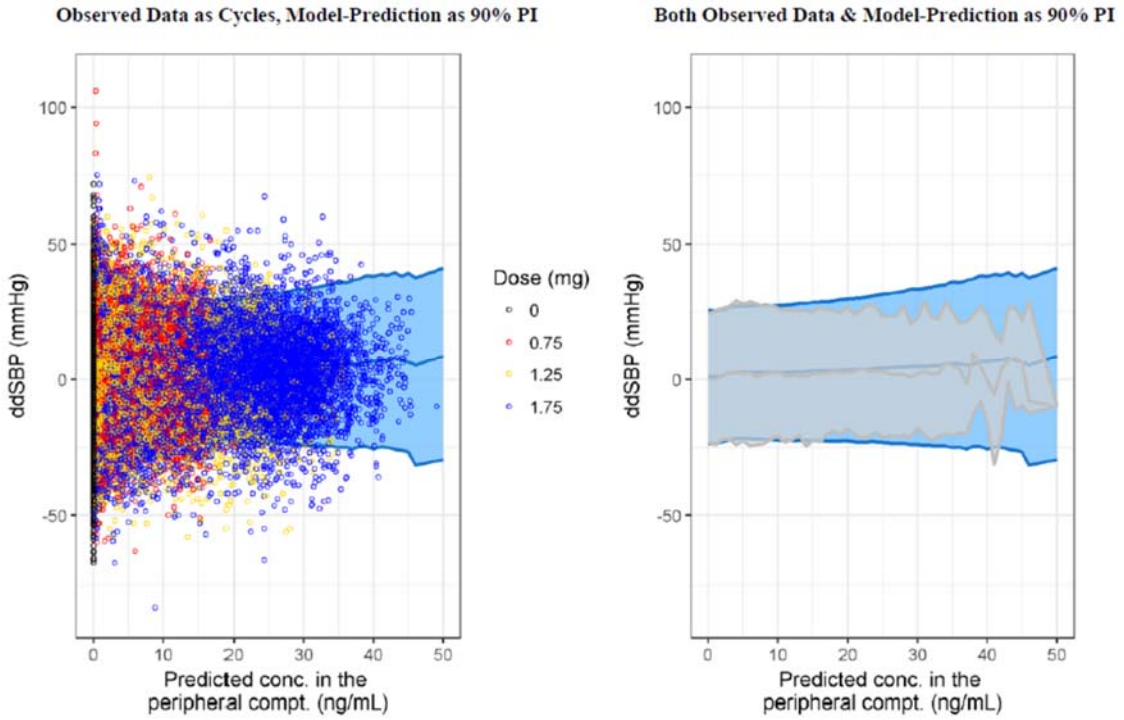
Figure 8: Basic Goodness of Fit Plots of the Final ddSBP Model (Model 115)



Blue circles: observed or model-predicted data points. Black lines: line of unity or horizontal line with y=0. Red lines: smooth lines. |iWRES|: absolute value of individual weighted residuals.
Unit of observations, population predictions and individual predictions: mmHg

Source: Figure 22 on page 74 of Applicant's population PKPD report PPK1819

Figure 9: Visual Predictive Check Plots (Final ddSBP Model)



Cycles: the observed individual data; blue (model-prediction) and gray (observed data) lines: 5th, 50th, and 95th percentiles; blue (model-prediction) and gray (observed data) shaded area: 90% PI. PI: prediction interval.

Source: Figure 2 on page 6 of Applicant's response to Information Request of Aug 15, 2018

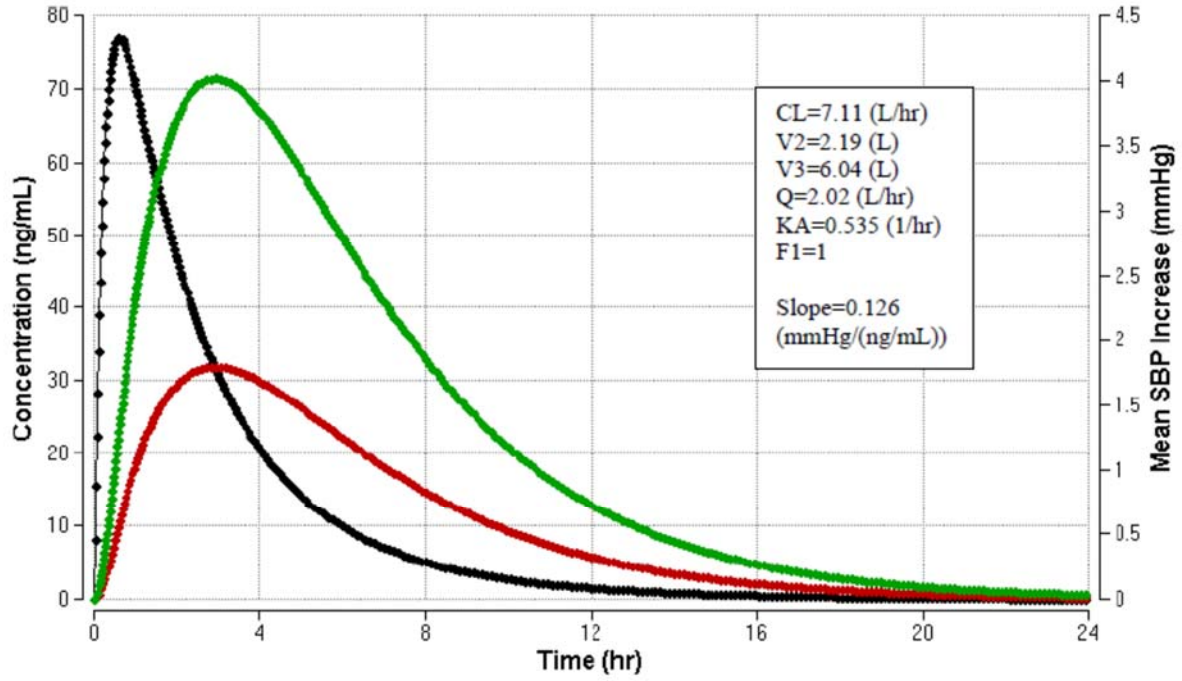
Simulations for ddSBP: A simulation was conducted with the software Berkeley Madonna to demonstrate the typical concentrations in the plasma and peripheral compartment after a single SC dose of 1.75 mg of BMT and the associated SBP increase (**Figure 10**).

The simulation showed that after a SC dose of 1.75 mg BMT, the typical Cmax in the plasma and in the peripheral compartment was 77.1 and 31.9 ng/mL, respectively, and the Tmax in the peripheral compartment was about 2 hrs after the Tmax in the plasma. The mean and upper bound of the 95% one-sided CI of the largest SBP increase were calculated as follows:

- Mean of the largest SBP increase = 31.9 (ng/mL) x 0.126 mmHg/(ng/mL) = 4.02 mmHg
- Upper bound of the 95% one-sided CI of the largest SBP increase = 31.9 (ng/mL) x 0.166 mmHg/(ng/mL) = 5.30 mmHg

where 0.126 and 0.166 mmHg/(ng/mL) were the median and the upper bound of the 90% two-sided CI from the bootstrap results for the typical slope. The upper bound of the 95% one-sided CI = The upper bound of the 90% two-sided CI.

Figure 10: Simulated Typical Concentrations in the Plasma and Peripheral Compartment and Mean SBP Increase after a Single SC Dose of 1.75 mg BMT



Black line: concentrations in the plasma; red line: concentrations in the peripheral compartment; green line: mean SBP increase.

Source: Figure 24 on page 78 of Applicant's population PKPD report PPK1819

Parameter	Plasma	Peripheral
Typical T_{max} (hr)	0.6	2.9
Typical C_{max} (ng/mL)	77.1	31.9

The Final Model for ddDBP: The final model for ddDBP contained a BASE model plus a linear drug effect term. The BASE model included a 24-hr circadian rhythm, a 12-hr circadian rhythm and inter-occasion variability to describe the difference between Visits 5 and 7 for Study 54. The drug effect was associated with the concentrations in the peripheral compartment. There was no clear relationship between covariates (demographics, concomitant medications, injection site, baseline SBP or DBP values, and lab values) and the drug effect at a given concentration

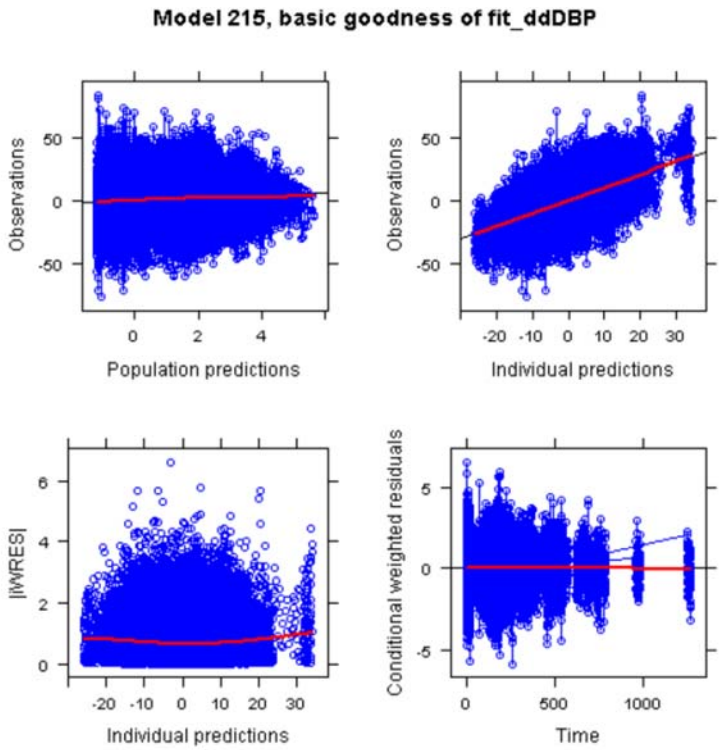
The parameter estimates for the final model are shown in **Table 8.** The basic GOF plots for the final ddSBP model are shown in **Figure 11**. The VPC plots for the ddSBP from the final mode are shown in **Figure 12.**

Table 8: Parameter Estimates for the Final ddDBP Model

Parameter Description (Unit)	Parameter	NONMEM (Model 215)		Bootstrap (Model 215)	
		Parameter Estimate (%RSE)	90% CI^	Parameter Estimate[&]	90% CI[&]
ddDBP residual additive error (mmHg)	TH1	11.2 (0.88)	(11.0, 11.4)	11.2	(11.1, 11.4)
AMP (amplitude for 24-hr oscillation) (mmHg)	TH2	0.653 (28)	(0.357, 0.949)	0.708	(0.420, 1.01)
TPEAK (peak time for 24-hr oscillation) (clock time in hr)	TH3	20.6 (7.4)	(18.1, 23.1)	20.6	(17.6, 22.9)
AMP2 (the 2nd amplitude for 12-hr oscillation) (mmHg)	TH4	0.892 (17)	(0.635, 1.15)	0.911	(0.685, 1.14)
TPEAK2 (the 2nd peak time for 12-hr oscillation) (clock time in hr)	TH5	10.2 (3.4)	(9.64, 10.8)	10.3	(9.72, 10.9)
TVSL (typical slope) (mmHg/[ng/mL])	TH6	0.120 (16)	(0.0894, 0.151)	0.119	(0.0896, 0.149)
SD for ddSBP baseline additive IIV	OM1:1	6.4[#] (7.3*)	--	6.4[$]	(6.0, 6.7) [$]
SD for additive IOV when Visit 5 for Study 54, or Visit 3 for Studies 301 & 302	OM2:2	2.3[#] (12*)	--	2.3[$]	(2.1, 2.5) [$]
SD for additive IOV when Visit 7 for Study 54	OM3:3	2.3[#] (--)	--	2.3[$]	(2.1, 2.5) [$]
SD for drug effect slope additive IIV	OM4:4	0.25[#] (12*)	--	0.25[$]	(0.23, 0.28) [$]

IIV: inter-individual variability. IOV: inter-occasion variability.
RSE: relative standard error of the parameter estimate. %RSE = SE*100/Parameter Estimate.

Figure 11: Basic Goodness of Fit Plots of the Final ddSBP Model (Model 115)

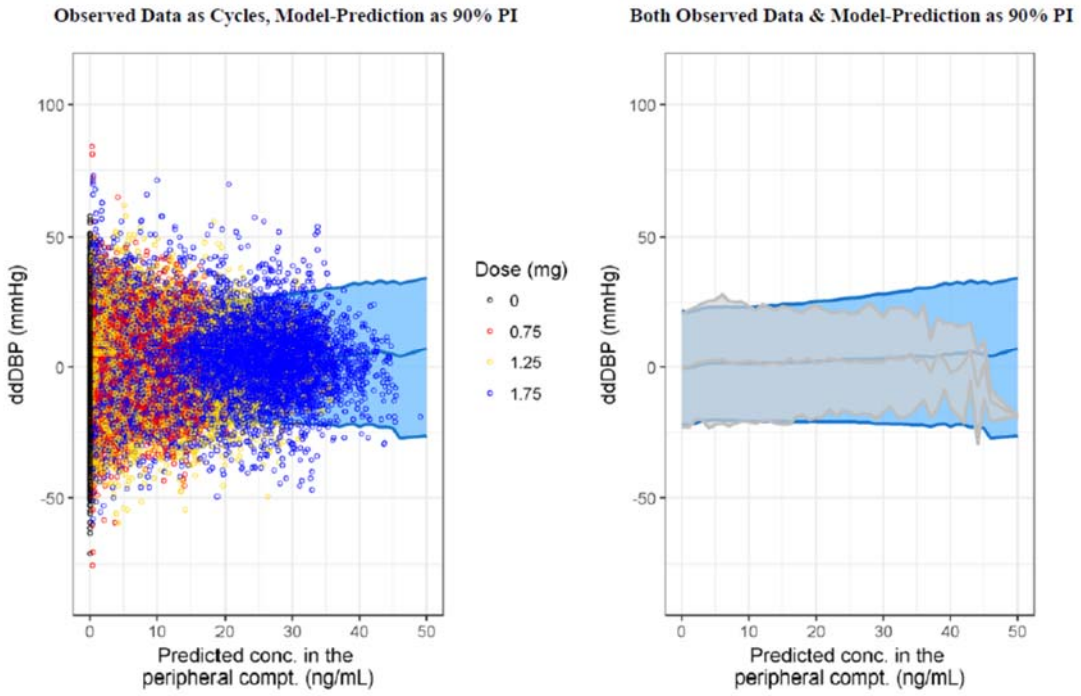


Blue circles: observed or model-predicted data points. Black lines: line of unity or horizontal line with y=0.
Red lines: smooth lines. |iWRES|: absolute value of individual weighted residuals.
Unit of observations, population predictions and individual predictions: mmHg.

Time: actual time after the very 1st dose (hr).

Source: Figure 25 on page 78 of Applicant's population PKPD report PPK1819

Figure 12: Visual Predictive Check Plots (Final ddDBP Model)



Source: Figure 3 on page 7 of Applicant's response to Information Request of Aug 15, 2018

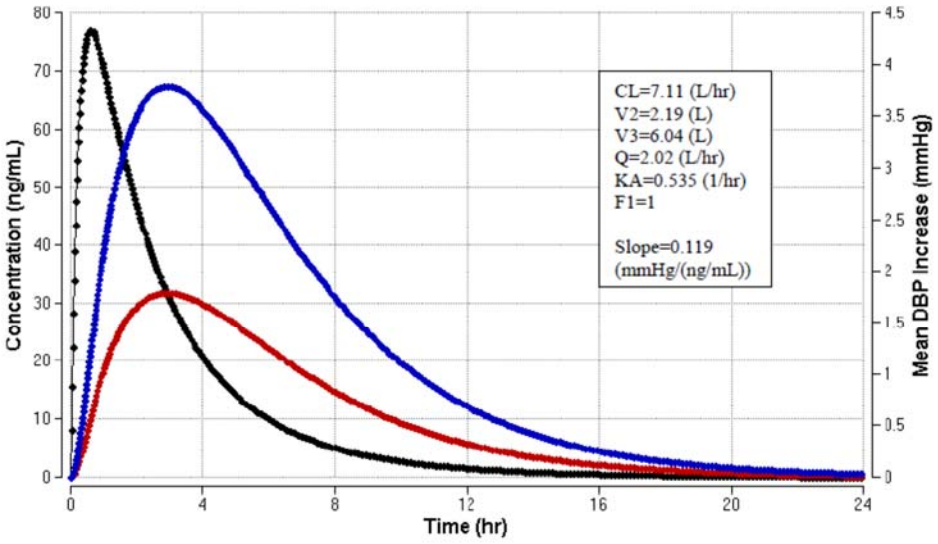
Simulations: A simulation was conducted with the software Berkeley Madonna to demonstrate the typical concentrations in the plasma and peripheral compartment after a single SC dose of 1.75 mg of BMT and the associated DBP increase (**Figure 13**).

The simulation showed that after a SC dose of 1.75 mg BMT, the typical Cmax in the plasma and in the peripheral compartment was 77.1 and 31.9 ng/mL, respectively, and the Tmax in the peripheral compartment was about 2 hrs after the Tmax in the plasma. The mean and upper bound of the 95% one-sided CI of the largest DBP increase were calculated as follows:

- Mean of the largest DBP increase = 31.9 (ng/mL) x 0.119 mmHg/(ng/mL) = 3.80 mmHg
- Upper bound of the 95% one-sided CI of the largest DBP increase = 31.9 (ng/mL) x 0.149 mmHg/(ng/mL) = 4.75 mmHg

where 0.119 and 0.149 mmHg/(ng/mL) were the median and the upper bound of the 90% two-sided CI from the bootstrap results for the typical slope . The upper bound of the 95% one-sided CI = The upper bound of the 90% two-sided CI.

Figure 13: Simulated Typical Concentrations in the Plasma and Peripheral Compartment and Mean DBP Increase after a Single SC Dose of 1.75 mg BMT



Black line: concentrations in the plasma; red line: concentrations in the peripheral compartment; blue line: mean DBP increase.

Source: Figure 27 on page 84 of Applicant's population PKPD report PPK1819

Parameter	Plasma	Peripheral
Typical T_{max} (hr)	0.6	2.9
Typical C_{max} (ng/mL)	77.1	31.9

Simulations of Mean BP Increase after SC Dose of 1.75 mg BMT: A overlay plot of typical concentration in the plasma and peripheral compartment and mean BP increase after a single SC dose of 1.75 mg BMT is shown in **Figure 14.**

Figure 14: Simulated Typical Concentrations in the Plasma and Peripheral Compartment and Mean BP Increase after a Single SC Dose of 1.75 mg BMT

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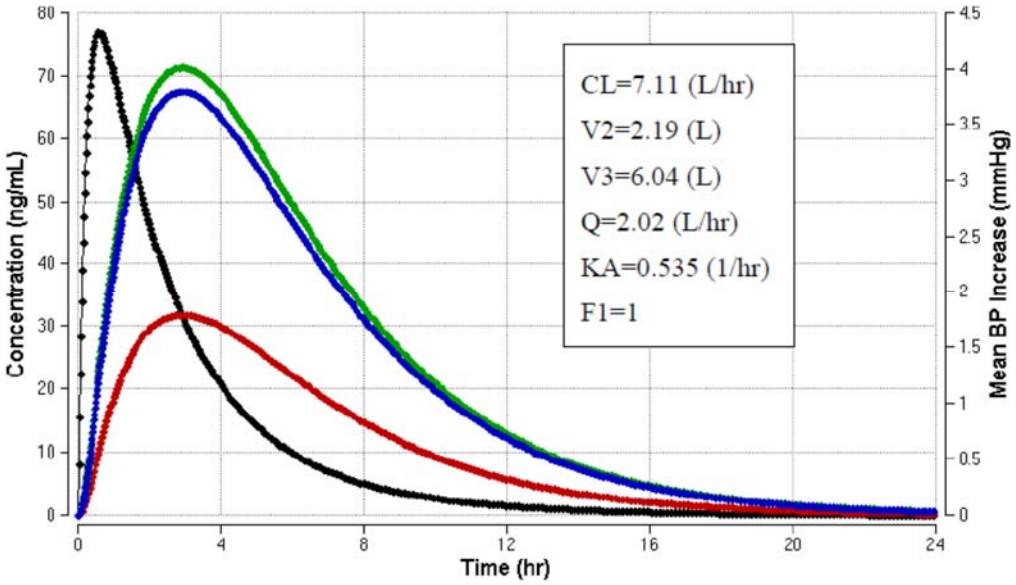

Black line: concentrations in the plasma; red line: concentrations in the peripheral compartment; green line:
mean SBP increase; blue line: mean DBP increase

Source: Figure 41 on page 106 of Applicant's population PKPD report PPK1819

Additional analyses were conducted by the Applicant to simulate the time course of mean change of SBP and DBP at 0.75 mg, 1.25 mg, 1.75 mg, 5 mg dose using the final ddSBP and ddDBP model,in response to FDA information request of Aug 18, 2018. The simulated mean SBP and DBP increases vs time after a single SC dose of 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT are shown in **Figure 15**. The largest mean SBP increase was predicted to be 1.72, 2.87, 4.02 and 11.5 mmHg after a single SC dose of 0.75 mg, 1.25 mg, 1.75 mg and 5 mg BMT, respectively (Figure 15; **Table 9**). The predicted mean increase for DBP was slightly lower than that for SBP, for a given dose (**Figure 15**; **Table 9**).

Figure 15: Simulated Mean SBP and DBP Increases after a Single SC Dose of 0.75 mg,1.25 mg, 1.75 mg, and 5 mg BMT

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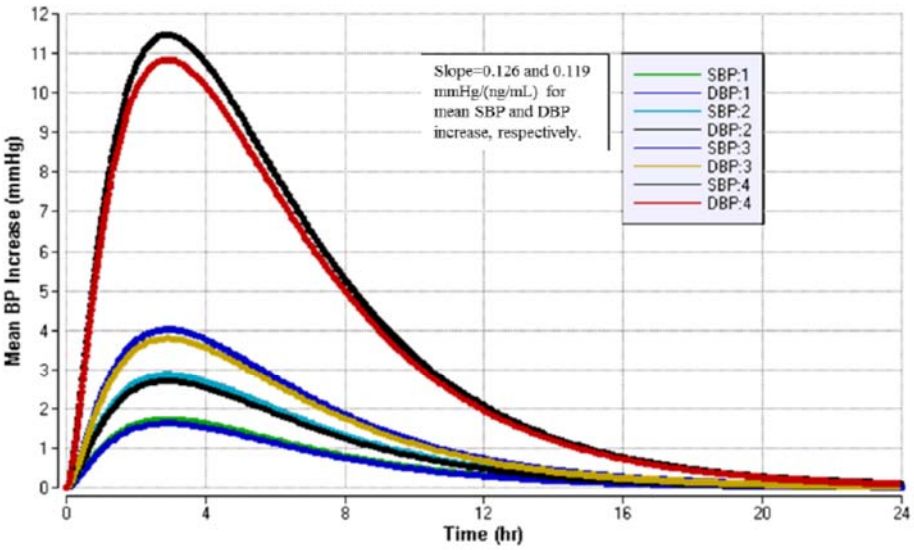


Runs 1, 2, 3 and 4 were for 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT, respectively.
The underlying PK model contained the following parameters: CL=7.11 L/hr, V2=2.19 L, V3=6.04 L, Q=2.02 L/hr, KA=0.535 /hr, and F1=1.
The mean SBP and DBP increases were calculated as the product of slope × concentration in the peripheral compartment.
The slope values of 0.126 and 0.119 mmHg/(ng/mL) were the median from the bootstrap results for the typical slope for SBP and DBP, respectively (PPK1819, Table 9 and Table 10).
The simulations were conducted using the software Berkeley Madonna Version 8.3.18.

Source: Figure 1 on page 4 of Applicant's response to Information Request of Aug 15, 2018

Table 9: Simulated Largest Mean SBP and DBP Increases after a Single SC Dose of 0.75 mg, 1.25 mg, 1.75 mg, and 5 mg BMT

Dose (mg)	Largest Mean SBP Increase (mmHg) with Slope=0.126 mmHg/(ng/mL)	Largest Mean DBP Increase (mmHg) with Slope=0.119 mmHg/(ng/mL)
0.75	1.72	1.63
1.25	2.87	2.71
1.75	4.02	3.80
5	11.5	10.8

The Cmax in the peripheral compartment was 31.9 ng/mL for the 1.75 mg dose. The Cmax in the peripheral compartment for other doses was calculated assuming dose proportionality.
The largest mean SBP and DBP increases were calculated as the product of slope × the Cmax in the peripheral compartment, with slope=0.126 and 0.119 mmHg/(ng/mL), respectively, for SBP and DBP.

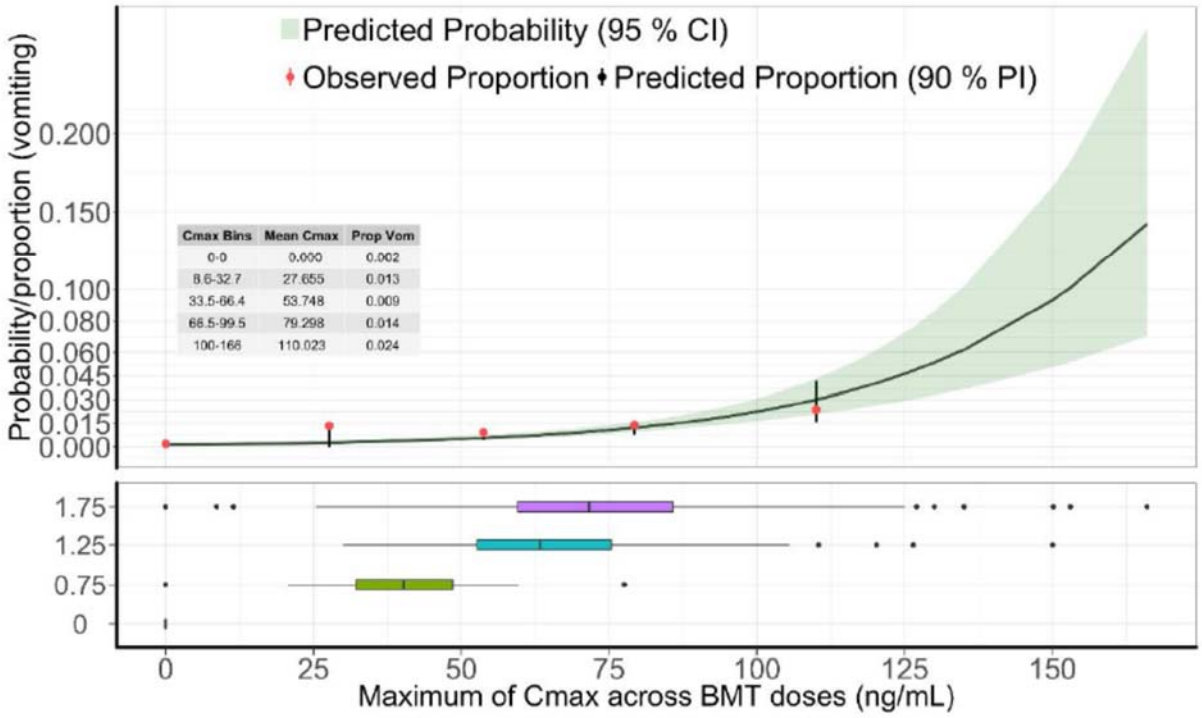
Source: Table 1 on page 4 of Applicant's response to Information Request of Aug 15, 2018

Reviewer's Comments: The final model for ddSBP and ddDBP were similar. The increase in blood pressure can be characterized with a Base model and a linear drug effect term. There was a clear association between the drug effect and the concentrations in the peripheral compartment. However, while the models were able to describe the over association between blood pressure and drug concentrations, due to large inter-subject variabilities, the predicted mean change of blood pressure should be interpreted with caution and cannot be considered as representative for certain individuals or subgroups of patients.

6.2 Exposure/Dose Response Relationship for Safety

Vomiting: The exposure-response relationship for safety were conducted using data from 1621 subjects enrolled studies 54, 301, and 302. The effect of bremelanotide on nausea and vomiting were characterized, including body weight as a covariate. A logistic regression analysis was used. The maximum of the actual C_{max} values across intervals for each subjects from the three studies were used as the exposure metric. The maximum observed BMT Cmax was a good predictor of the probability of having a vomiting event. There was a clear relationship between vomiting and Cmax (**Figure 16**).

Figure 16: Relationship between Probability of Vomiting per Dose using Cmax as a Predictor at an Adjusted Body Weight of 74.2 kg



The inset table shows the mean cmax of each bin and the corresponding proportion of vomiting events. The bottom panel provides the distribution of Cmax in each dose group corresponding the x-axis on the top plot.

Source: Figure 36 on page 97 of Applicant's population PKPD report PPK1819

The plasma exposures after a BMT dose were body weight dependent with higher body weight showing lower exposures than lower body weight for the same fixed dose. After adjusting for body weight, a 10-ng/mL and a 50-ng/mL increase in Cmax increased the odds of experiencing a vomiting event by 1.35 times (35%) and 4.5 times, respectively. These results indicated that the general incidence of experiencing a vomiting event was low, but amongst those patients experiencing an event, the probability of vomiting was dependent on maximum plasma exposures, which in turn was a function of the body weight.

Nausea and Nausea Severity Over Time: The longitudinal binary outcome of nausea occurrence was modeled using the generalized linear mixed effects modeling (GLMM) method.

The logit of the probability of nausea occurrence was found to be related to C_{max}, with a random effect (η1) for between subject variability included on the intercept. Weight and injection site were tested for inclusion in this model in addition to Cmax, but were found to be not statistically significant. Therefore, the final model only contained C_{max} as the predictor. The final model parameter estimates are given in **Table 10**. In this final model, the odds of a person experiencing nausea was 2 times the odds in the same person per 10 ng/mL increase in Cmax (i.e., odds ratio=exp(0.0698×10)=2). The variance (ω2) for between subject variability was estimated to be 27.5.

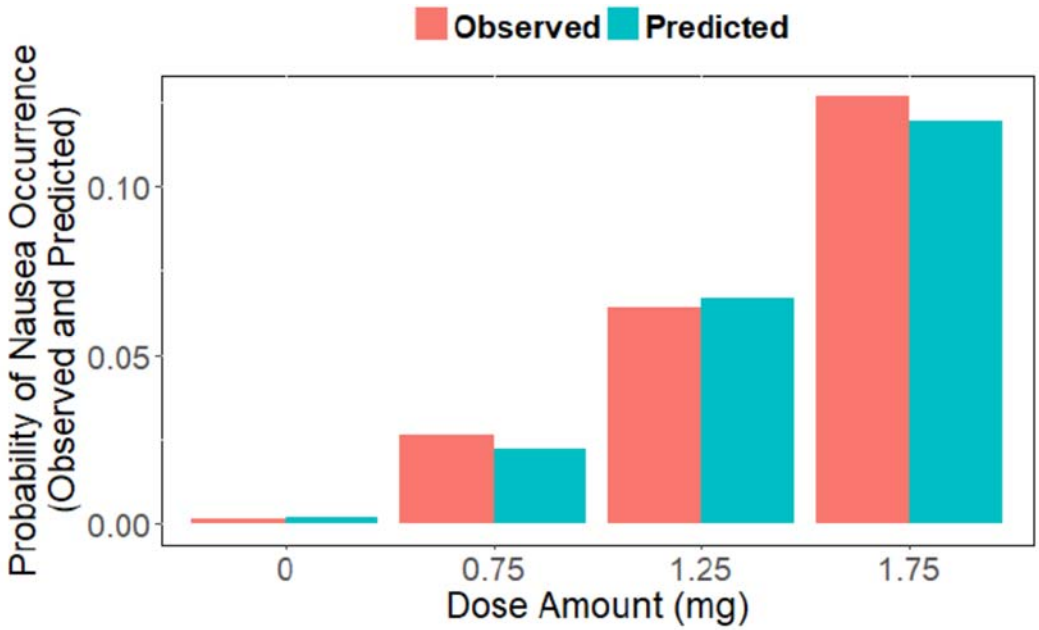
Table 10: Final Parameter Estimates and Odds Ratios for Nausea Occurrence Related to Cmax

Parameter	Estimate	Standard Error	Relative SE (%)	P-value	Odds Ratio
Intercept	-11.1	0.448	4.04	<2E-16	1.54E-5
Slope on Cmax	0.0698	0.00354	5.07	<2E-16	1.07

RSE = Relative standard error, calculated as Standard error/parameter estimate*100

The predicted and observed probabilities of nausea by dose group is shown in **Figure 17**.

Figure 17: Bar Chart of Predicted and Observed Probability of Nausea per Dose by Dose Group



Source: Figure 38 on page 100 of Applicant's population PKPD report PPK1819

Reviewer's Commments: The incidence rate shown in **Figure 16** *and* **Figure 17** *were based on per dose data from 1822 subjects receiving placebo or 0.75, 1.25, or 1.75 mg BMT from Studies 54, 301, and 302. Each subject had multiple rows of longitudinal data with each row describing each dosing event. For each dosing event, nausea occurrence (0 = no, 1 = yes) and nausea severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) were included in the dataset. Only nausea events occurring within four hours after*

a dosing event were included in the analysis because nausea was deemed to be an acute response after BMT dosing. Independent analysis was conducted by the reviewer using proportions of subjects experiencing at least one nausea is shown in Figure 19. Same conclusions were reached with the Applicants regarding the effect of C_{max} and body weight on nausea.

Relationship between body weight and nausea occurrence was also explored using the Generalized Estimating Equation (GEE) METHOD. Weight was found to be a statistically significant covariate (p-value=0.0034). The final linear model is shown as follows:

$$Logit\ (p(Nausea=1)) = \beta 0 + \beta 1 * Weight$$

The final model parameter estimates are given in **Table 11**. With every 10 kg decrease in weight, the odds of nausea increased by 16%. Additionally, a weight decrease from the 90th to 10th percentile (108.1 kg to 58 kg, respectively), resulted in a 109% increase in the odds of nausea occurrence. This was consistent with the finding that heavier subjects tended to have lower Cmax and lower probability of nausea compared to lighter subjects.

Table 11: Final Parameter Estimates and Odds Ratios for Nausea Occurrence Related to Weight

Parameter	Estimate	Standard Error	Relative SE (%)	P-value	Odds Ratio
Intercept	-0.519	0.384	74.1	0.177	0.595
Slope on Weight	-0.0147	0.005	34.0	0.0034	0.985

RSE = Relative standard error, calculated as Standard error/parameter estimate*100. Standard error

Nausea Severity: The relationship between weight and severe nausea (compared to none, mild, or moderate nausea) was also tested using logistic regression analysis. Cmax was also the only statistically significant predictor for severe nausea vs. none, mild, or moderate when Cmax, weight and injection site were all included in the model for evaluation.
The final model is shown as follows:
Logit (P(NauseaSev=Severe)) = $\beta 0 + \beta 1 * Cmax + \eta 1$

The final parameter estimates for this model is shown in **Table 12**. The odds of severe nausea were found to be 1.79 times the odds within the same individual per 10 ng/mL increase in C_{max} (i.e., odds ratio=exp(0.058×10)=1.79). The variance (ω2) for between subject variability was estimated to be 110.

Table 12: Final Estimates and Odds Ratios for Nausea Severity (Non, Mild, or Moderate vs. Severe) Related to Cmax

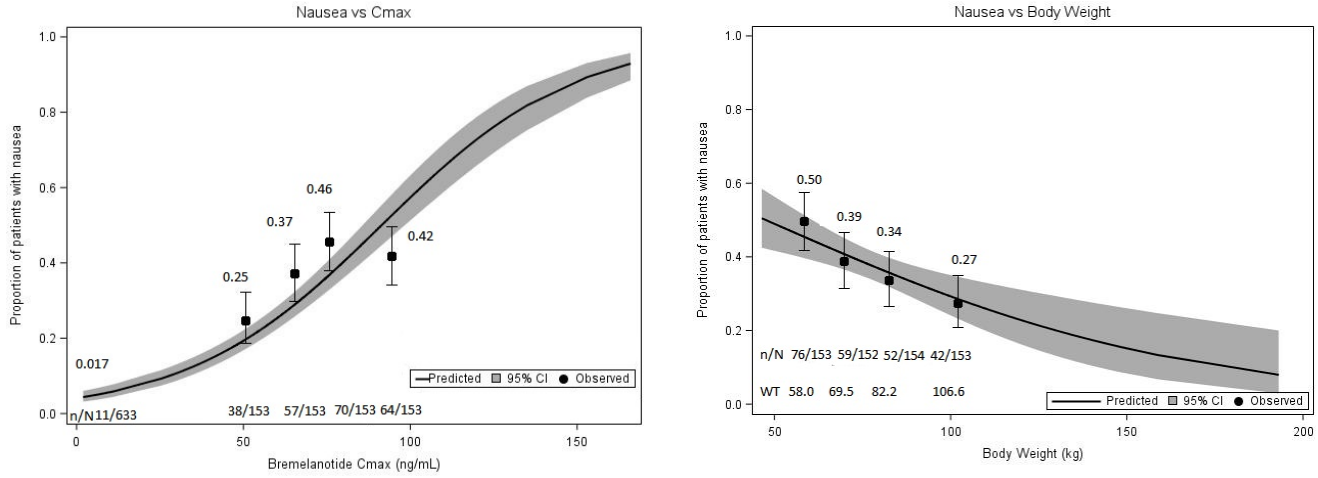
Parameter	Estimate	Standard Error	Relative SE (%)	P-value	Odds Ratio
Intercept	-17.6	2.44	13.9	5.61E-13	2.34E-8
Slope on Cmax	0.058	0.0199	34.3	0.0035	1.06

RSE = Relative standard error, calculated as Standard error/parameter estimate*100

Source: Table 20 on page 103 of Applicant's population PKPD report PPK1819

*Reviewer's Comments: Independent analysis by the reviewer reached the same conclusion as the Applicant's analysis regarding the relationship between vomiting/Nausea and bremelanotide C_{max} and body weight. The reviewer used a logistic regression model to describe nausea data from Phase 3 studies 301 and 302 in subjects receiving placebo or BMT 1.75 mg SC (***Figure 18***). The proportions of subjects who ever experienced at least one nausea event was plotted with values of Cmax or body weight. As shown in the figure, lower body weight subjects have higher drug exposure and were observed and predicted to have higher risks of nausea. The lowerest body weight quartile had about 50% of nausea rate compared to about 40% of overall rate in subjects administered BMT 1.75 mg SC. While dose adjustment is not necessary, subjects with lower body weight might use the drug with caution.*

Figure 18. Predicted and Observed Probability of Nausea by Cmax and Body Weight



Source: created by FDA reviewer using data file "nausea.xpt." Data were from 1245 subjects from study 301 and 302 receiving BMT 0 mg and 1.75 mg SC in the plot for Cmax (left) and were from 612 subjects receiving BMT 1.75 mg SC for body weight (right). Observed (dots) and model predicted probabilities (line) with 95% CI is (shaded area) based on a logistic model plotted at the median of individual C_{max} or body weight values.

7. Mechanistic Safety Assessment

7.1 Study PT-141-2005-28

Title: A Double-Blind, Randomized, Parallel Trial to Assess the Electrocardiographic Effects of BMT Using a Single Clinical and a Single Supratherapeutic Dose Compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women

Objectives:

- To assess the electrocardiographic effects of a single 5-mg dose and a single 20-mg dose of BMT compared to both placebo and moxifloxacin in healthy male and female subjects
- To assess the single-dose PK of BMT, and to evaluate potential electrocardiographic PK-PD interactions of BMT in healthy male and female subjects

Reviewer's Comments and Notes:

- *The study design and study results can be found in Dr. Moh Jee NG's review documented in DARRTS on April 30th 2013.*
- *Per Review by Dr. Moh Jee NG, no significant QTc prolongation effects of BMT (doses of 5 mg and 20 mg) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between BMT and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.*
- *The mean PK parameters indicated that there was a disproportionate increase in BMT exposure as the dose increases following IN administration. Particularly, the 4-fold increase in dose from 5 mg to 20 mg IN resulted in an approximately 8-fold increase in C_{max} and an approximately 7-fold increase $AUC_{0\text{-}inf}$. As the decline in BMT concentrations following the 20-mg IN dose paralleled that following the 5-mg IN dose, any difference in BMT exposure was expected to be related more to IN absorption than to systemic elimination.*
- *IN administration was associated with a moderate-to-high degrees of PK variability, as evidence by the mean CV values ranging between 56% and 89% for 5 and 20 mg BMT doses.*
- *Although the selected supratherapeutic dose (20 mg IN) produced only about 2.5-fold higher exposures (C_{max} and AUC) than the therapeutic dose (1.75 mg SC), the level of BMT exposure is higher than those observed in patients with renal and hepatic impairment. Therefore, it is considered that the selected supratherapeutic dose covered the worst-case scenario of BMT exposure and is acceptable for the QTc study.*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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06/18/2019 10:40:53 AM

Interdisciplinary Review Team for Ambulatory Blood Pressure Monitoring Study Consultation Review

Submission	NDA 210557
Submission Number	048 / 049
Submission Date	3/29/2019
Date Consult Received	4/1/2019
Clinical Division	DBRUP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's ABPM evaluation. The IRT reviewed the following materials:

- AMAG-BMT-HSDD-101 study report (NDA 210557 / SDN 053; link);
- PT-141-54 study report (NDA 210557 / SDN 002; link);
- Sponsor's response to justification for population definition for AMAG-BMT-HSDD-101 (NDA 210557 / SDN 041; link);
- BMT-101 study report (NDA 210557 / SDN 002; link);
- "*Cardiovascular Assessment of the Effects of Bremelanotide for Premenopausal Women with Hypoactive Sexual Desire Disorder*" (NDA 210557 / SDN 053; link);
- Response to IR dated 03/05/2019 (NDA 210557 / SDN 048; link).
- DCRP review for IND 64199 by Dr. Hicks dated 12/30/2016 in DARRTS;
- DBRUP protocol review for NDA 210557 by Dr. Whitaker dated (12/21/2018); and
- DCRP review for IND 64199 by Dr. Dunnmon dated 09/08/2017 in DARRTS.

1 SUMMARY OF FINDINGS

A dedicated ABPM study was conducted for bremelanotide to characterize the effects of bremelanotide on BP with chronic dosing and to assess whether the effect on BP persisted after stopping treatment.

The study consisted of two parts: open-label dosing for 8 days followed by a randomized withdrawal (Figure 1). The overall findings of the study show an increase in daytime systolic and diastolic BP (primary endpoint; Table 1; Figure 3) at the end of the open-label period. The changes in BP and HR were transient and peaked between 0 and 8 h post-dose (Table 2; Figure 4). In the randomized withdrawal, BP returned to baseline in subjects randomized to placebo, and, for subjects randomized to bremelanotide, the increase over baseline was similar to the systolic and diastolic pressure elevations that were present at the end of the open-label period (Table 3; Figure 5).

In brief, the results of the study suggest that the effects of bremelanotide are transient, do not continue to increase between days 8 and 16 of dosing, and resolve to baseline by the next day following drug discontinuation.

During the conduct of the dedicated ABPM study, the review division raised concerns about the increase in BP by bremelanotide in patients receiving concomitant anti-hypertensives. To evaluate this the sponsor conducted a DDI PK/PD study with five anti-hypertensives. The results of this study are not conclusive but suggest that bremelanotide increases blood pressure in patients receiving anti-hypertensives and these increases are of a similar magnitude to those observed in patients who are not on antihypertensives. The study also suggests that the effect of bremelanotide on BP might be reduced, but the study was not adequately designed to quantify this.

Table 1: Mean and 95% CI for change from baseline for SBP, DBP and HR on Day 8 (FDA Analysis)

ABPM parameter	Time	Δ (mmHg/BPM)	95% CI (mmHg/BPM)
Systolic BP	Daytime* average	1.9	(1.0, 2.7)
Diastolic BP	Daytime average	1.7	(0.9, 2.4)
HR	Daytime average	-0.5	(-1.6, 0.7)

* Daytime is defined as 6 am to 10 pm.

Table 2: Mean and 95% CI for change from baseline for SBP, DBP and HR on Day 8 by time (FDA Analysis)

ABPM parameter	Time	Δ (mmHg/BPM)	95% CI (mmHg/BPM)
Systolic BP	0 to 4 h	2.5	(1.2, 3.8)
	>4 to 8 h	2.8	(1.5, 4.1)
	>8 to 12 h	1.9	(0.7, 3.2)
	>12 to 24 h	-0.1	(-1.4, 1.2)
Diastolic BP	0 to 4 h	2.7	(1.6, 3.9)
	>4 to 8 h	2.3	(1.2, 3.5)
	>8 to 12 h	1.5	(0.4, 2.7)
	>12 to 24 h	0.1	(-1, 1.2)
HR	0 to 4 h	-1.7	(-3.3, -0.1)
	>4 to 8 h	-2.2	(-3.8, -0.5)
	>8 to 12 h	0.0	(-1.6, 1.6)
	>12 to 24 h	0.9	(-0.7, 2.5)

Table 3: Mean and 95% CI for change from baseline for SBP, DBP and HR on Day 16 compared to Day 8 (FDA Analysis)

ABPM parameter	Time	ΔBMT→BMT (mmHg/BPM)	ΔBMT→Placebo (mmHg/BPM)
Systolic BP	0 to 4 h	-0.5 (-2.8, 1.7)	-4 (-6.2, -1.7)
	>4 to 8 h	-0.8 (-3, 1.4)	-3.9 (-6.1, -1.6)
	>8 to 12 h	-2.3 (-4.6, -0.1)	-1.6 (-3.8, 0.7)
	>12 to 24 h	-2.8 (-5.1, -0.6)	-2.7 (-5, -0.5)
Diastolic BP	0 to 4 h	0.3 (-1.8, 2.4)	-3.4 (-5.5, -1.3)
	>4 to 8 h	0.6 (-1.4, 2.7)	-2.8 (-4.9, -0.7)
	>8 to 12 h	-2.4 (-4.5, -0.3)	0.6 (-1.5, 2.7)
	>12 to 24 h	-1.6 (-3.7, 0.5)	-1.7 (-3.8, 0.4)
HR	0 to 4 h	0.4 (-2.2, 3)	3.1 (0.5, 5.7)
	>4 to 8 h	0.5 (-2.1, 3.1)	5.6 (3, 8.2)
	>8 to 12 h	-2.2 (-4.8, 0.3)	4.8 (2.1, 7.4)
	>12 to 24 h	0 (-2.6, 2.6)	-0.8 (-3.4, 1.8)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

None.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

None.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0040 (link) from the IRT.
Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Transient Increases in Blood Pressure

In a dedicated open-label ambulatory blood pressure monitoring study of 127 subjects receiving 1.75 mg bremelanotide once-daily, an increase in daytime SBP and DBP of 1.9 mmHg (95% CI: 1.0 to 2.7) and 1.7 mmHg (0.9 to 2.4), respectively, was observed after 8 days of dosing. The increase in SBP and DBP was transient with a peak effect

in SBP of 2.8 mmHg between 4 to 8 h post-dose and 2.7 mmHg for DBP at 0 to 4 h post-dose. The increase in BP was accompanied by a simultaneous and transient decrease in HR of -2.2 bpm (95% CI: -3.8 to -0.5). The SBP and DBP values for the 12 to 24 h window were similar to baseline.

(b) (4)

We recommend describing the findings of the dedicated ABPM study.

3 BACKGROUND

3.1 REGULATORY HISTORY

The sponsor is developing bremelanotide (BMT), a synthetic analog of alpha melanocyte-stimulating hormone, for as-needed treatment of female sexual dysfunction in premenopausal women with hypoactive sexual desire dysfunction. Bremelanotide is administered as a 1.75 mg subcutaneous injection no more than once a day.

In 2016, DCRP was asked to provide comments whether other studies, which collected BP measurements (PT-141-2006-32, PT-141-2005-23, PT-141-54, and BMT-301 and 302), were adequate to characterize the effects of bremelanotide on BP and HR. A DCRP review dated 12/30/2016 concluded that these studies were not adequate to characterize the effects of bremelanotide on BP and HR. The main limitation with the previous studies was the lack of information about effects of chronic dosing of bremelanotide on BP and how long the effects on BP and HR persist. An ABPM study was recommended that should evaluate the impact of repeat dosing of bremelanotide on BP.

Based on the recommendations in the DCRP review, DBRUP issued an advice letter to the sponsor recommending that they conduct a placebo-controlled, double-blind, ABPM study with at least 14 days of dosing followed by a 7-day randomized withdrawal in a study population that is representative of the patients likely to receive bremelanotide (DARRTS 03/03/2017). The sponsor was also advised that this dedicated ABPM study should enroll subjects whose overall cardiovascular risk profile would approximate that of the to-be-marketed-to population. Specifically, a follow-up advice letter to the sponsor stated that, "*Although the protocol indicates that subjects with controlled diabetes (HbA1c ≤ 8.0%) will be enrolled and at least 20% of enrolled subjects will have controlled hypertension (defined as receiving treatment with ≤ 2 anti-hypertensive medications), the overall study population remains a relatively low-risk population. We recommend enrolling a population that reflects the overall cardiovascular (CV) risk of the to-be-marketed-to population.*" (DARRTS 12/31/2018). The same advice letter recommended that the study should be powered to exclude a 4 mmHg increase in daytime SBP or a 3 mmHg in MAP. The sponsor responded to this advice letter on 01/14/2019 noting that the sample size had been increased to 140 subjects and that the 20% target for enrolling subjects with controlled hypertension was based on the prevalence of hypertension in 20 to 55 year old women using the NHANES database (SDN 41).

On 01/14/2019 and 01/17/2019, two additional information requests (IRs) were issued recommending that the sponsor prohibit the use of NSAIDs and power the study to exclude a 4 mmHg increase in daytime systolic with a two-sided 95% CI, respectively. These changes were incorporated by the sponsor (DARRTS 01/28/2019).

In the final version of the protocol, the sponsor increased the sample size from 140 to 150, changed the definition of hypertensive status based on the 8th Joint National Committee treatment guidelines and made other minor edits (DARRTS 02/04/2018).

While the dedicated ABPM study was ongoing, DBRUP raised concerns that subjects with controlled hypertension on medication might experience sustained blood pressure elevations following single and multiple doses of bremelanotide based on the results of a PK/PD DDI study with bremelanotide and five anti-hypertensives (BMT-101). Therefore, in addition to reviewing the dedicated ABPM study (AMAG-BMT-HSDD-101), the ABPM data from study BMT-101 was also analyzed for this review.

3.2 KEY REVIEW QUESTIONS

1. Does the increase in BP due to bremelanotide increase with chronic dosing?

2. How long does the increase in BP due to bremelanotide persist?

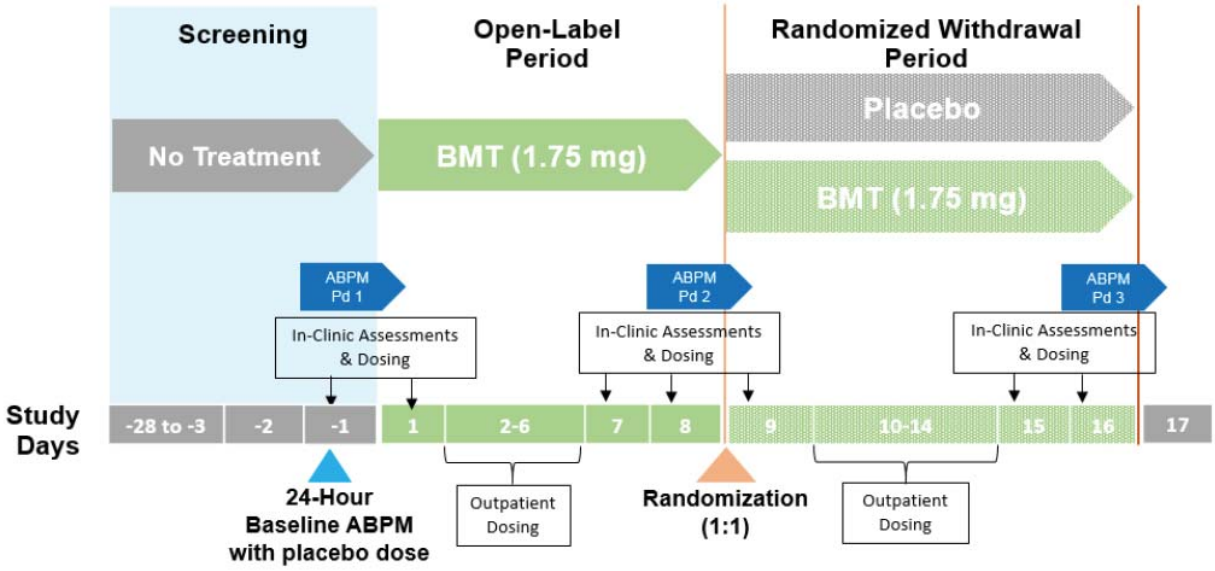
3. How is the increase in BP due to bremelanotide impacted by concomitant administration of anti-hypertensives?

4 STUDY 1: AMAG-BMT-HSDD-101

4.1 DESIGN

This was a two-period study: open-label treatment period with daily dosing of bremelanotide followed by a randomized withdrawal period (Figure 1) in healthy premenopausal females. The study included collection of 24-h ABPM recordings at baseline and at the end of the open-label and randomized withdrawal periods.

Figure 1: Study design for AMAG-BMT-HSDD-101



Source: AMAG-BMT-HSDD-101 Report, Figure 1

The primary endpoint of the study was change from baseline in daytime systolic BP (6 am to 10 pm) on day 8 (end of open-label treatment). The study was designed to exclude a 4 mmHg increase assuming an increase of 2 mmHg and standard deviation of 9 mmHg. Based on these assumptions and an estimated 15% dropout, the sponsor enrolled 150 subjects to ensure 127 completers.

A key secondary endpoint was the evaluation of the changes in BP at the end of the randomized withdrawal period. Additional secondary endpoints included assessment of diastolic BP, MAP, and heart rate during the daytime as well as during the nighttime and 24 h at both the end of the open label and randomized withdrawal periods.

The ABPM recordings were initiated while the subjects were in the clinical unit before the daily morning dose of BMT or placebo. The study also included collection of PK as well as office BP, which overlapped with the 24 h ABPM recording. Of note, PK samples were collected on post-dose ABPM visits, but not during the baseline ABPM visit. The ABPM recordings included collection of measurements every 30 min throughout the recording period and repeat ABPM sessions were only permitted for the baseline recording. Furthermore, the protocol did not specify criteria for determining if an ABPM recording was valid based on quality control metrics.

4.2 REVIEWER'S ASSESSMENT

4.2.1 Demographics

The study enrolled 146 premenopausal women with 127 completing the open-label period. The demographics of the study population are shown in Table 4. As discussed in section 3.1, the sponsor planned to enroll up to 20% patients with controlled hypertension, which was initially defined as having ≤ 2 anti-hypertensive medications and later revised to be 3 anti-hypertensive

medications (SDN 44). However, the sponsor was able to enroll only 2 patients with controlled hypertension (~1.6%).

Table 4: Study demographics

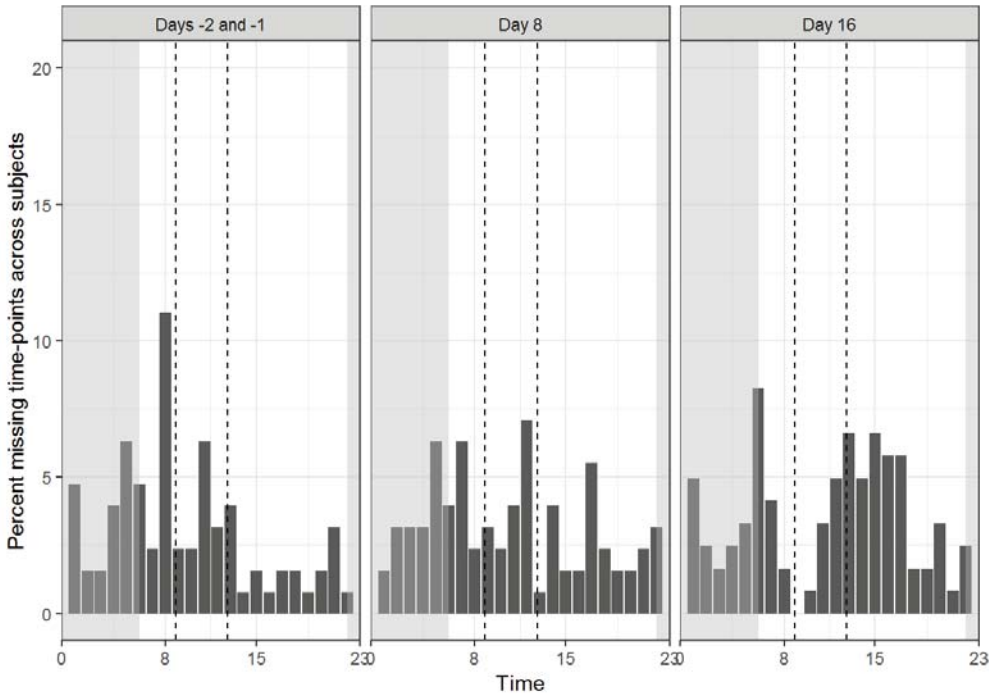
Characteristics		Open-Label Period	Randomized Withdrawal Period		
		BMT (N=136)	BMT (N=64)	PBO (N=63)	Overall (N=146)
Age (years)	Mean (SD)	36.2 (9.17)	35.8 (8.63)	37.2 (9.53)	36.5 (9.26)
	Min, max	18, 54	20,51	18, 54	18, 55
Race, n (%)	White	83 (61.0%)	40 (62.5%)	38 (60.3%)	92 (63.0%)
	Black or African American	46 (33.8%)	21 (32.8%)	22 (34.9%)	47 (32.2%)
	Asian	3 (2.2%)	0 (0.0%)	3 (4.8%)	3 (2.1%)
	American Indian or Alaska native	2 (1.5%)	1 (1.6%)	0 (0.0%)	2 (1.4%)
	Multiple	2 (1.5%)	2 (3.1%)	0 (0.0%)	2 (1.4%)
Ethnicity, n (%)	Hispanic or Latino	51 (37.5%)	25 (39.1%)	24 (38.1%)	57 (39.0%)
	Not Hispanic or Latino	85 (62.5%)	39 (60.9%)	39 (61.9%)	89 (61.0%)
Fertility Status n (%)	Childbearing potential	96 (70.6%)	47 (73.4%)	44 (69.8%)	100 (68.5%)
	Surgically sterile	40 (29.4%)	17 (26.6%)	19 (30.2%)	46 (31.5%)
Weight at Screening (kg)	Mean (SD)	72.63 (11.445)	72.09 (11.170)	73.07 (11.662)	72.29 (11.389)
	Min, max	50.6, 97.3	50.6, 97.2	51.3, 97.3	50.6, 97.3
BMI at Screening (kg/m^2)	Mean (SD)	26.81 (3.854)	26.68 (3.931)	26.94 (3.809)	26.77 (3.851)
	Min, max	18.7, 34.7	18.7, 34.7	18.8, 33.9	18.7, 34.7

Source: AMAG-BMT-HSDD-101 study report, Table 7

4.2.2 Data quality

The percent of missing data was generally less than 10% during the 24 hours on the baseline and post-dose visits (Figure 2), demonstrating good overall data quality.

Figure 2: Percent missing data by time for each cohort. Gray shaded areas represents night and vertical dashed lines represent median dosing time and median dosing time plus 4 h.



Source: Reviewer's analysis

4.2.3 Blood pressure assessment

The reviewer analyzed the changes in systolic and diastolic BP and HR using a paired t-test in R.

Changes from baseline in the mean SBP, DBP, and HR on day 8 were calculated and evaluated for the day time (6 am to 10 pm) and night time (10:01 pm to 5:59 am) for the ABPM population. The results are shown in Figure 3 and are similar to the results of the sponsor's primary analysis (AMAG-BMT-HSDD-101 CSR, Page 76).

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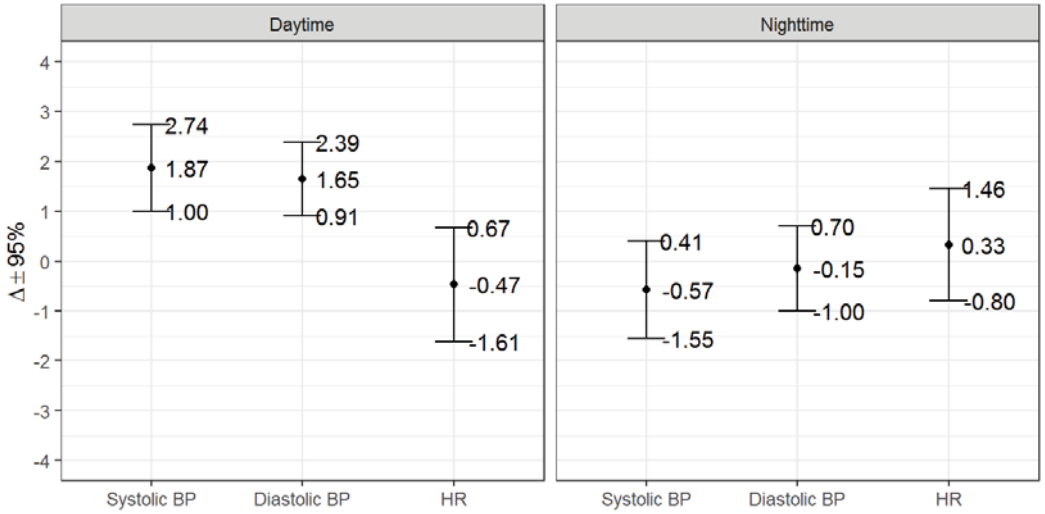
Figure 3: Change from baseline (day -1) to end of open-label treatment (day 8) for systolic BP, diastolic BP and HR for day time (left) and night time (right).



Source: Reviewer's analysis

As noted previously, the increase in bremelanotide has been observed to be time-dependent with a peak in the first 4 hours and return to baseline after 8 h (e.g., see Table 12-12 in PT-141-54 CSR). The results of this study were therefore regrouped into four post-dose time intervals: 0 to 4 h, >4 to 8 h, >8 to 12 h and >12 to 24 h and analyzed using a MMRM model with change from baseline as the dependent variable and visit, time window, and an interaction between visit and time window as fixed effects and a random intercept. Degrees of freedom were estimated using the Kenward-Roger method and the model was fitted using the lme4 package in R.

The results of this analysis are shown in Figure 4 and demonstrate that the increase in BP is largest in the first 4 to 8 h post dose and for HR the largest decrease is in the first 8 h. These results are consistent with the results of PT-141-54 and suggest that the peak increase in systolic and diastolic BP is 2 to 3 mmHg.

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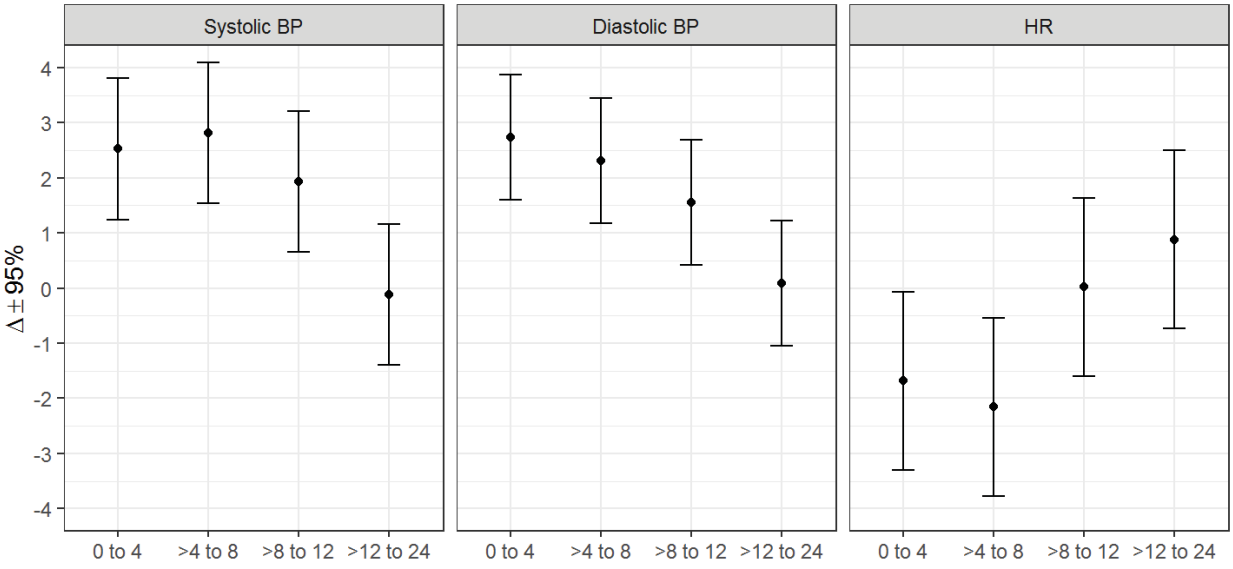
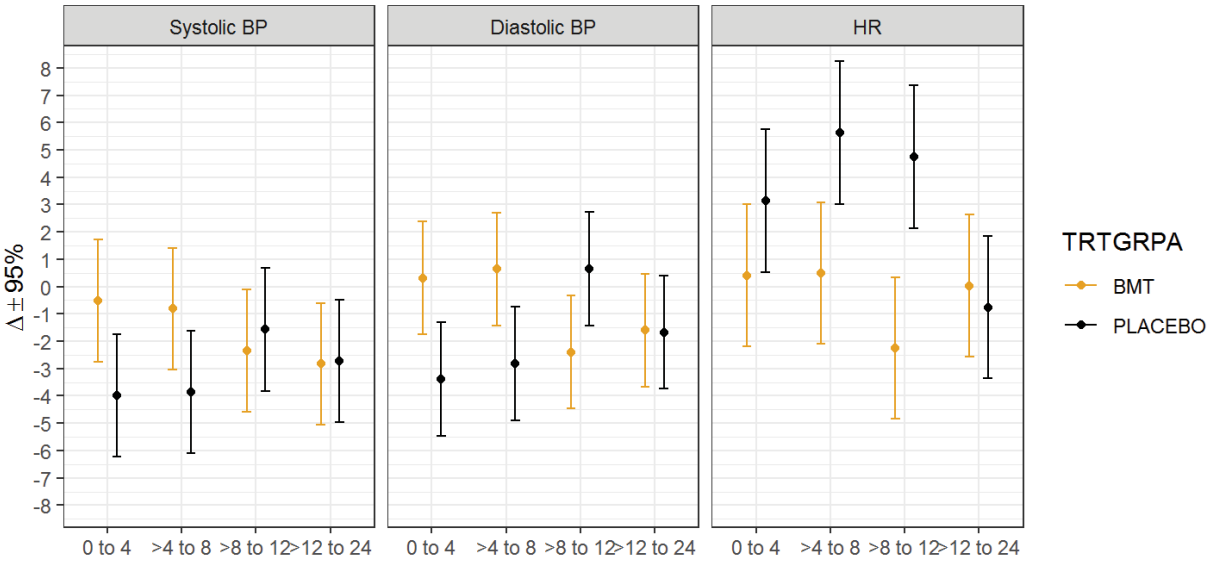
Figure 4: Change from baseline (day -1) to end of open-label treatment (day 8)



Source: Reviewer's analysis

A comparison of the changes in BP using the same time windows as described above showed that the increase in BP observed after 8 days of dosing did not increase further with 8 additional days of dosing and that increase in BP was reduced after 8 days of placebo dosing (Figure 5).

Figure 5: Change from day 8 (end of open-label treatment) to day 16 (end of randomized withdrawal) for patients receiving bremelanotide/placebo (black: Placebo) and bremelanotide/ bremelanotide (orange: bremelanotide)



Source: Reviewer's analysis

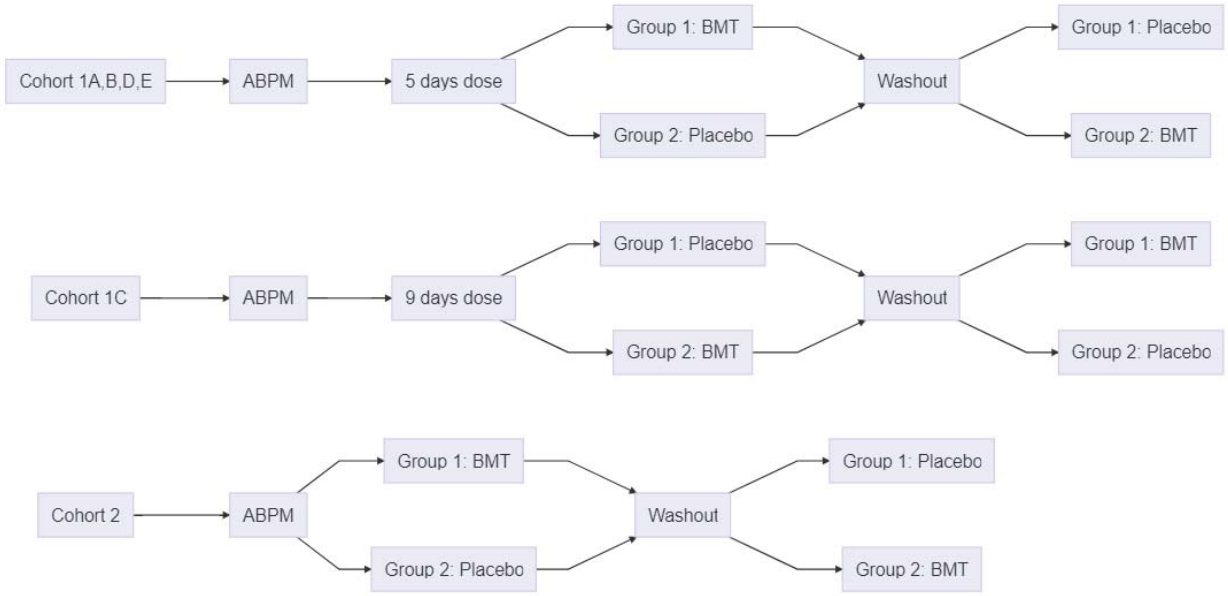
This study demonstrates that the increase in BP with bremelanotide after 16 days of dosing is similar to 8 days of dosing, and that increase in BP is transient during the day and returns to baseline by 12 to 24 h after dosing.

5 STUDY 2: BMT-101

5.1 DESIGN

BMT-101 was a double-blind, randomized and placebo-controlled study. The objective of this study was to evaluate the potential for PK and PD mediated drug-drug interactions (DDIs) between bremelanotide and six antihypertensives (HCTZ, metoprolol, amlodipine, lisinopril, losartan and furosemide) in pre- and postmenopausal women. The study included three cohorts; however, no ABPM data was collected in the third cohort. The study design of the first two cohorts is shown in Figure 6.

Figure 6: Study design of Cohorts 1 (A: HCTZ; B: metoprolol; C: amlodipine; D: lisinopril; E: losartan) and 2 (BMT alone) in BMT-101.



Source: Reviewer's schematic based on BMT-101 study report

The doses of antihypertensives used in Cohort 1 correspond to the recommended initial dose per label (HCTZ [microzide] 12.5 mg qd; metoprolol [lopressor] 100 mg qd; amlodipine (norvasc) 5 mg qd; lisinopril (prinivil) 10 mg qd; losartan (cozaar) 50 mg qd).

Each of the panels in cohort 1 included ~22 normotensive pre and postmenopausal women (~15 premenopausal / ~6 postmenopausal per panel). Cohort 2 included ~27 postmenopausal women. No formal justification for the sample size was provided.

The study included collection of 24-h ABPMs at baseline and during the bremelanotide and bremelanotide-placebo treatment days. The ABPM recordings were initiated while the subjects were in the clinical unit before the daily morning dose of BMT or placebo. Of note, the study also included collection of PK as well as office BP, which overlapped with the 24 h ABPM recording. BP measurements were collected using ABPM every 15 min from 07:00 to 14:59; every 30 min from 15:00 to 21:59 and every 60 min from 22:00 to 06:59. In addition, BP measurements was obtained manually at the same time-points as PK collection. The protocol did not specify criteria triggering a repeat ABPM session or criteria to determine whether an ABPM record was not valid based on quality control metrics.

5.2 REVIEWER'S ASSESSMENT

5.2.1 Demographics

The demographics of the study population for BMT-101 are shown in Table 5. Unlike the dedicated ABPM study, this study excluded patients with concomitant use of any anti-hypertensive drugs at baseline, and cohort 2 included only post-menopausal women whereas cohort 1 included pre and postmenopausal women.

Table 5: Study demographics

	Cohort 1					Cohort 2 (n=27)
	HCTZ (n=22)	Metoprolol (n=22)	Amlodipine (n=20)	Lisinopril (n=21)	Losartan (n=27)	
Age* (years)	42.1 (14.03)	46 (11.58)	38.9 (14.35)	42.4 (12.47)	38.6 (14.15)	60.5 (2.58)
Race, n (%)						
White	14 (63.6)	8 (36.4)	7 (35)	8 (38.1)	11 (40.7)	22 (81.5)
Black or African American	7 (31.8)	12 (54.5)	12 (60)	9 (42.9)	15 (55.6)	5 (18.5)
American Indian or Alaska Native	0 (0)	1 (10)	1 (5)	2 (9.5)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)	1 (9.1)	0 (0)	0 (0)
Other	1 (4.5)	1 (10)	0 (0)	1 (4.8)	1 (3.7)	0 (0)
Ethnicity, n (%)						
Hispanic or Latino	2 (9.1)	2 (9.1)	1 (5)	3 (14.3)	3 (11.1)	5 (18.5)
Not Hispanic or Latino	20 (90.9)	20 (90.9)	19 (95.5)	18 (85.7)	24 (88.9)	22 (81.5)
Fertility Status, n (%)						
Post-menopausal	6 (27.3)	6 (27.3)	3 (15)	6 (28.6)	8 (29.6)	27 (100)
Surgically stable	4 (18.2)	5 (22.7)	6 (30)	5 (23.8)	2 (7.4)	0 (0)
Child-bearing potential	12 (54.5)	11 (50)	11 (55.5)	10 (47.6)	17 (63)	0 (0)
Baseline weight* (kg)	66.23 (7.611)	70.81 (7.958)	73.32 (8.379)	71.60 (8.892)	77.52 (8.947)	70.79 (8.135)
Baseline BMI* (kg/m^2)	24.55 (2.782)	26.48 (2.656)	26.69 (2.720)	26.61 (2.626)	27.15 (2.172)	26.89 (3.050)

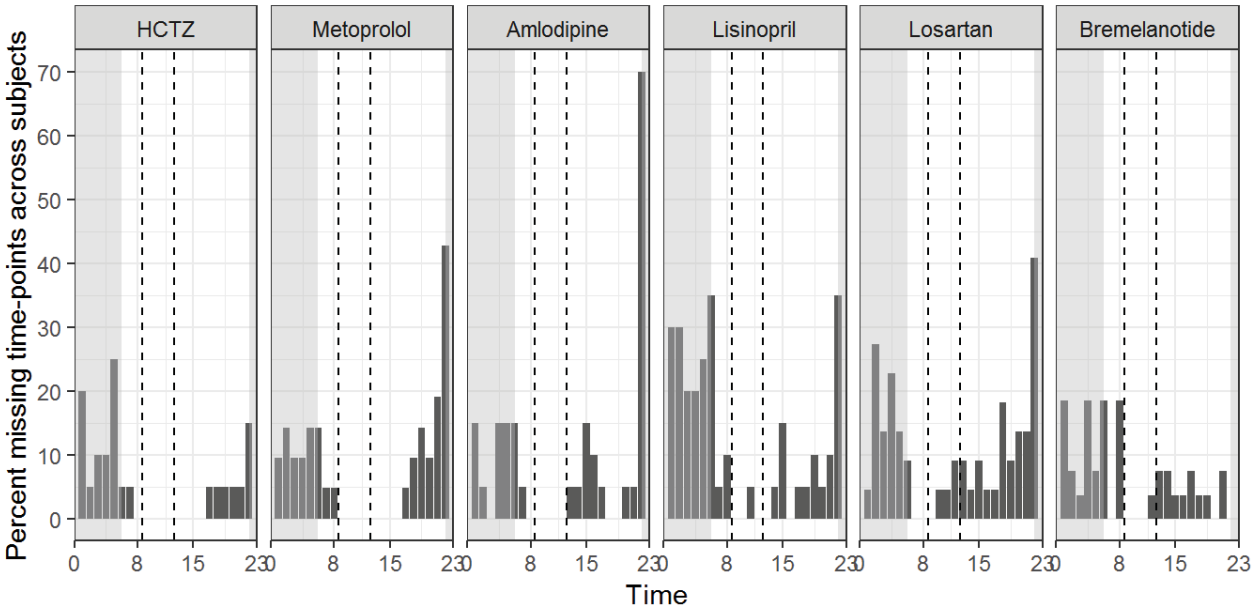
** Mean (SD)*

Source: Reproduced by reviewer based on Table 14 and 15 in BMT-101 study report. Please note that the Anti-hypertensive group is reported for all panels in cohort 1.

5.2.2 Data quality

During the daytime the percent missing data (across baseline and post-dose visits) was generally < 20%. In contrast, during the night time the percent missing data was higher than the daytime (20% to 70%) (Figure 7). Overall, the data quality during the day appears reasonable, but nighttime results, particularly for amlodipine, should be interpreted with caution.

Figure 7: Percent missing data by time for each cohort. Gray shaded areas represents night and vertical dashed lines represent median dosing time and median dosing time plus 4 h.



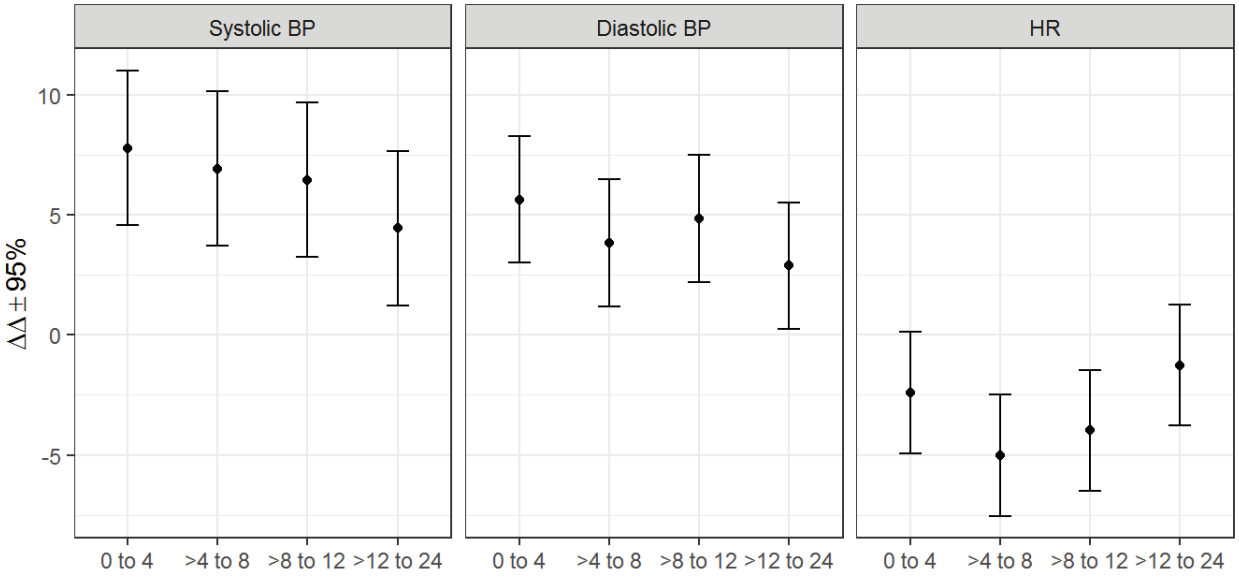
Source: Reviewer's analysis

5.2.3 Blood pressure assessment

The reviewer analyzed the changes in systolic and diastolic BP and HR using a MMRM model with change from baseline within different time-windows as the dependent variable and sequence, treatment, cohort, time window and interactions between treatment, time window and cohort. Additionally, a random effect was included on the intercept, which was nested within cohort. Degrees of freedom were estimated using the Kenward-Roger method and the model was fitted using lme4 package in R. Because of the ABPM sessions were performed during study visits, all the results are placebo-adjusted. Of note, the baseline used for both visits was the same baseline.

Increases in systolic and diastolic BP and decrease in HR was observed following a single dose of bremelanotide (Figure 8). The increases in BP observed in this study were higher than that of the dedicated ABPM study (AMAG-BMT-HSDD-101). The reason for the higher increase in BP observed in this study is unclear; however, it is possible that it could be partially explained by differences in patient demographics as the bremelanotide-alone cohort in BMT-101 only included post-menopausal women whereas the dedicated ABPM study included only premenopausal women.

Figure 8: Change from baseline and placebo for systolic BP (left), diastolic BP (middle) and HR (right) for a single dose of bremelanotide



Source: Reviewer's analysis

While, the study was not designed to evaluate the effects of antihypertensives in normotensive patients due to differences in study procedures (i.e., blood draws were performed only post-baseline; hence, there was a difference in the procedures conducted at post-baseline and baseline), a decrease in BP was observed for 3 out of 5 of the antihypertensives (Figure 9). The product inserts for the two antihypertensives that did not decrease BP (HCTZ and amlodipine) also notes that decreases in BP are expected to be minimal in normotensive subjects, which could explain the absence of a decrease for these two drugs at the time of the second ABPM for subjects in cohort 1 of this study. As expected, a decrease in HR was observed for metoprolol.

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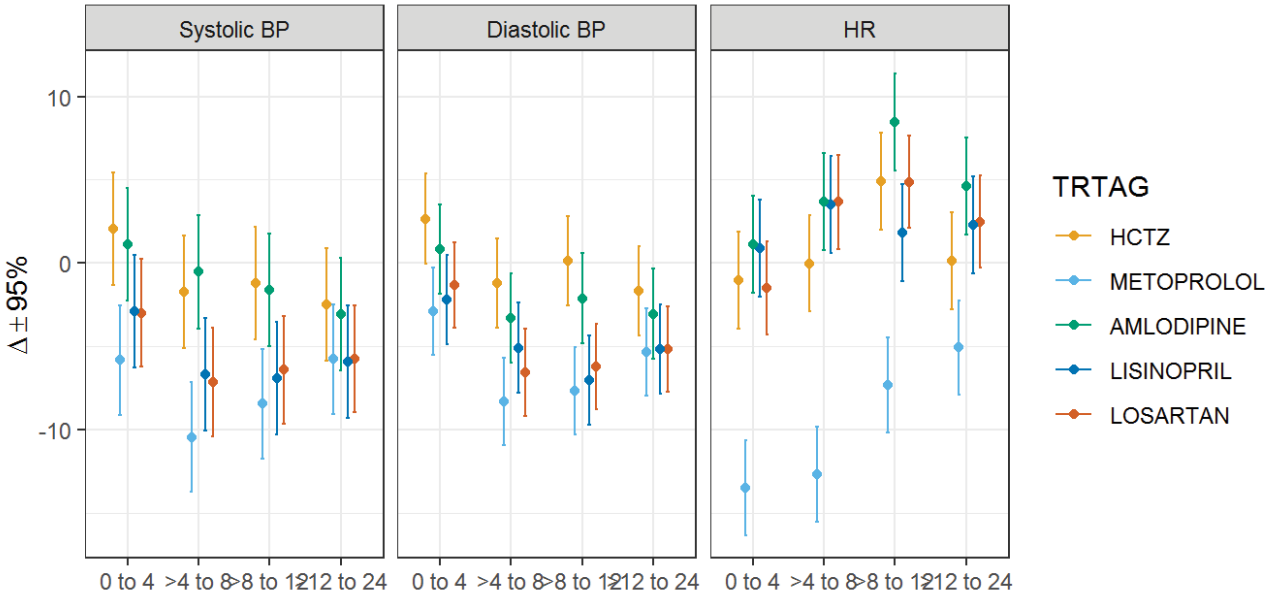
Figure 9: Change from baseline for systolic BP (left), diastolic BP (middle) and HR (right) for HCTZ; metoprolol; amlodipine; lisinopril and losartan.



Source: Reviewer's analysis

Comparison of the change from baseline between the bremelanotide + antihypertensive vs. bremelanotide-placebo + antihypertensive is shown in Figure 10. The results of this analysis show a numerically lower increase in systolic and diastolic BP for bremelanotide + antihypertensive compared to bremelanotide alone, which was statistically significant only for bremelanotide + HCTZ vs. bremelanotide-placebo + HCTZ. The significance of this observation is unclear as no decrease was observed for HCTZ by itself (Figure 9) and this was a post-hoc comparison in a small study. While, the numerically lower systolic and diastolic BP for the bremelanotide + antihypertensives compared to bremelanotide alone for all antihypertensives suggest that antihypertensives could lower the bremelanotide induced increases in BP, the study was not powered to quantify the magnitude and the increase with bremelanotide alone in this study was higher than previously conducted studies (dedicated ABPM: ~3 mmHg; DDI study: ~7 mmHg).

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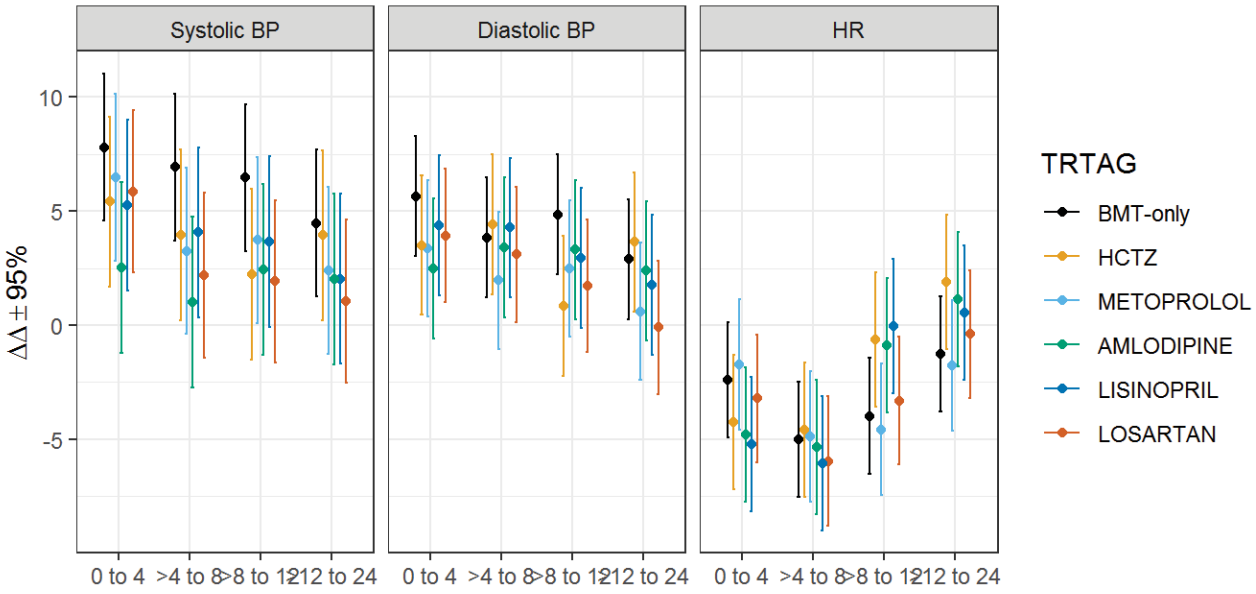
Figure 10: Change from baseline and bremelanotide-placebo



Source: Reviewer's analysis

In summary, the results of this study show that the bremelanotide-induced increase in BP is still observed in the presence of low-dose anti-hypertensives, although there is, as expected, a trend toward consistent blunting of the BMT-induced pressor effect on SBP during the 24-hour period, and a similar overall trend toward the blunting of BMT's diastolic pressor effects, especially in the first four hours after dosing. The results of the study suggest that there might be a decrease in BP when comparing bremelanotide alone (cohort 2) to bremelanotide + anti-hypertensive (cohort 1); however, the study was not designed to compare across cohorts.

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KAREN A HICKS
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NORMAN L STOCKBRIDGE
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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2018101
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 210557/IND 064119
Sponsor/Applicant:	AMAG Pharmaceuticals, Inc.
Established Name/Trade Name:	Bremelanotide/VYLEESI™
Indication:	Treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women
Meeting Type/Deliverable:	N/A
Review Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Clinical Reviewer	Marcea Whitaker
Clinical Team Leader (TL)	Christine Chang
Review Division Project Manager:	Jeannie Roule
COA Reviewer:	Wen-Hung Chen
COA TL:	Selena Daniels
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	April 3, 2018
Date COA Review Completed:	April 6, 2019

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

This Clinical Outcome Assessment (COA) consult review is related to NDA 210557 (referenced IND 064119) for bremelanotide. The applicant is in phase 3 of their drug development program, with two completed phase 3 clinical trials. The proposed indication is for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women.

The applicant included the following patient-reported outcome (PRO) measures in their two identical phase 3 randomized, double-blind, placebo-controlled trials (Studies NCT02333071 and NCT0233896) in adult premenopausal women (≥18 years) with acquired, generalized HSDD of at least 6 months' duration:

Table 1. COAs Included in Studies NCT02333071 and NCT0233896

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
Female Sexual Function Index (FSFI) Desire Domain (PRO)	Sexual desire	Co-primary	Appendix A
Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Question 13, "bothered by low desire" (PRO)	Distress with low sexual desire	Co-primary	Appendix B
Female Sexual Encounter Profile-Revised (FSEP-R) Question 10 Satisfying Sexual Event (SSE) (PRO)	Satisfaction with sexual event	Secondary	Appendix C

ClinRO= Clinician-reported outcome; **ObsRO**= Observer-reported outcome; **PerfO**= Performance outcome; **PRO=** Patient-reported outcome

This submission included a clinical overview, summary of clinical findings, study reports, and applicant responses to information requests.

The Division requested COA Staff input on the adequacy of submitted PRO data. The applicant did not provide a PRO evidence dossier for review. However, the Division had previously agreed on the acceptability of the FSFI Desire Domain and FSDS-DAO Question 13 as co-primary endpoints during the IND phase (IND 064119). (Note: both COAs were used to support labeling claims in another HSDD application [flibanserin; NDA 022526]).

The review concludes the following:

- The FSFI Desire Domain and FSDS-DAO Question 13 includes concepts that are content relevant to HSDD patients based on discussion with Clinical and previous application that labeled data from this instrument (NDA 022526). This review concludes that the FSFI Desire Domain and FSDS-DAO Question 13 assesses desire and bother associated with low desire in the target patient population and is appropriate for labeling.
- The applicant defined a clinically meaningful score change in the FSFI Desire Domain and FSDS-DAO Question 13 scores as 0.6-points and 1-points, respectively, based on anchor-based methods using phase 3 clinical trial data. While we agree with the applicant's proposed threshold for the within-patient meaningful score change in the FSDS-DAO Question 13 (i.e., one-point change), we disagree with the proposed threshold for the FSFI Desire Domain as the data from the anchor-based methods and combined with patient input from exit surveys and interviews indicated that ≥1.2 score points change is a more appropriate threshold in FSFI Desire Domain.

For future medical product development, sponsors should use multiple anchor scales to provide an accumulation of evidence to help interpret a within-patient meaningful score change in the

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

proposed COAs. Anchor scales should be carefully selected to derive the threshold for within-patient meaningful change (improvement or deterioration). At the minimum, a static current state global impression of severity scale (e.g., patient global impression of severity scale) and a global impression of change scale (e.g., patient global impression of change scale) should be used to generate a threshold for improvement that represents a meaningful amount of change in the target population. Integrating patient input from an exit survey as an anchor may also be helpful to supplement patient-reported global anchors scales to inform the threshold of improvement. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments and associated anchors are fit-for-purpose and the studies are designed appropriately for the context of use prior to initiation of pivotal studies.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Disease Background:

Abnormalities of female sexual desire or arousal, occurring as an acquired condition reflecting loss of prior function, not associated with depression, relationship dysfunction, or other identifiable causes and accompanied by distress, have been characterized as HSDD and female sexual arousal disorder (FSAD), respectively.

Investigational Product:

BMT (or PT-141), a cyclic heptapeptide, is a melanocortin (b) (4) receptor agonist that is currently being developed for the treatment of premenopausal women with acquired, generalized HSDD (with or without arousal difficulties). Efficacy analyses in this NDA focus on the results from NCT02333071 (Core Study and OLE) and NCT0233896 (Core Study and OLE). These studies used BMT 1.75 mg administered subcutaneous on an as-needed basis (PRN).

Regulatory Background:

At the end of phase 2 meeting held with the Agency and the applicant on 09 April2013, there was detailed discussion regarding the 2 pivotal studies for this NDA. Agreement was reached regarding the use of premenopausal women in the Phase 3 studies,

In the October 2015 FDA Workshop on female sexual dysfunction (FSD), the workshop panel recommended that the optimal clinical efficacy endpoints for HSDD studies are the FSFI-desire domain and the Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO) Item 13, which correlate with the 2 key aspects of the diagnosis of HSDD. Based on this recommendation, the applicant requested that the co-primary endpoints for their Phase 3 studies be revised to the FSFI-desire domain and FSDS distress/desire item 13, with the number of SSEs as a key secondary endpoint of which the Agency agreed in September 2016, and the protocols and statistical analysis plan were revised accordingly prior to locking the database.

A Pre-NDA Meeting was held on 18 September 2017 to discuss results from the pivotal Phase 3 clinical studies of BMT in support of an indication of HSDD in premenopausal women, and the submission strategy. The FDA deemed the existing studies (NCT02333071 and NCT0233896) were acceptable to support filing the NDA.

The COA Staff has been consulted for the IND regarding the adequacy of the PRO measures, the study protocols, the psychometric analysis, and the derivation of the within-patient meaningful change scores. The general conclusion from the previous reviews for INDs and NDA was that while the FSFI desire domain (and with a 28-day recall) was not an optimal measure of desire, however, any beneficial effect on the FSFI desire domain could be better interpreted and supported by the FSDS-DAO Question 13 that would allow us to see that the level of distress changed together with the change of the desire domain.

Previous COA Reviews:

- AT 2014-037_IND 64119_Slagle, dated April 24, 2014 (Reference ID: 3495586) which provided comments on the proposal for the use of FSFI desire domain as a co-primary endpoint
- AT 2014-161_IND 064119_Slagle, dated December 05, 2015 (Reference ID: 3849212) which provides comments on the BMT 301 protocol dated Oct 9, 2014
- AT 2015-036_NDA 22526_Slagle, dated April 20, 2015 (Reference ID: 3735668) which provided review on Flibanserin
- AT 2015-174_IND 064119_Slagle dated December 05, 2015 (Reference ID: 3849230) which provides comments on the second Protocol Amendment 2, dated August 13, 2015
- AT 2016-149_IND 064119_Chen, dated September 20, 2016 (Reference ID: 3984640) which provides comments on the Sponsor's proposed minimal clinically important difference (MCID) estimates derived based on Study 54 data.
- AT 2016-243_IND 064119_Chen, dated November 4 (Reference ID: 4017642) which provided comments on psychometric analysis plan including a proposal of an Independent Anchor Assessment Committee to inform the sponsor's selection of responder definitions
- C2017181_IND 064119_Chen, dated September 7, 2017 (Reference ID: 4154420) which provide comments on the meaningful within-patient change established by the Independent Anchor Assessment Committee
- C2018045_IND 064119_Chen, dated March 16, 2018 (Reference ID: 4235425) which provided comments on additional information needed to enhance the understanding of the meaningful change from the patients' perspectives and to facilitate the interpretation of the study results

Other materials reviewed:

- 20170817-preNDA Meeting Briefing Package, Palatin Technologies, July 2017
- 20170918-preNDA Meeting Minutes, October 17, 2017 (Reference ID: 4168612)
- Complete clinical study report Exit Trial, Evidera for Palatin Technologies, June 18, 2017

- BMT-301 Report Body, AMAG, January 15, 2018
- BMT-302 Report Body, AMAG, January 22, 2018
- Clinical Information Amendment - Response to Filing Review Issue, AMAG, June 1, 2018
- Response to Information Request - 20 Jun 2018, AMAG, June 20, 2018
- BMT-301 - Response to Information Request - Appendix A & B eCDF Curves, AMAG, June 20, 2018
- BMT-302 - Response to Information Request - Appendix A & B eCDF Curves, AMAG, June 20, 2018

2 FIT-FOR-PURPOSE SUMMARY

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Names	Attribute sufficiently established[2]	Supported by:	Location of Supporting Materials
Female Sexual Function Index (FSFI) Desire Domain (PRO)	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☒ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☒ COA well-defined and concept is able to be accurately communicated ☒ COA is sensitive to detect change ☒ COA is culturally adapted and adequately translated, if appropriate	See previous COA Reviews
Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Question 13, "bothered by low desire" (PRO)	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☒ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☒ COA well-defined and concept is able to be accurately communicated	See previous COA Reviews

[2] See Sections 5 and 6 of this COA review for more detailed information.

COA Names	Attribute sufficiently established[2]	Supported by:	Location of Supporting Materials
		☒ COA is sensitive to detect change ☒ COA is culturally adapted and adequately translated, if appropriate	

3 CONTEXT OF USE

3.1 Clinical Trial Population

The target population for Studies NCT02333071 and NCT0233896 were women, ≥18 years of age, who were premenopausal and experiencing acquired HSDD (with or without decreased arousal), in the absence of a concomitant relationship dysfunction, depression, or substance abuse that might negatively impact sexual function.

A complete list of the inclusion and exclusion criteria is summarized in BMT-301 Report Body (AMAG, January 15, 2018) and BMT-302 Report Body (AMAG, January 22, 2018).

3.2 Clinical Trial Design

Table 3 describes the clinical trial design of Studies NCT02333071 and NCT0233896.

Table 3. Clinical Trial Design for Studies NCT02333071 and NCT0233896

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority	24 Weeks double-blinded, placebo controlled followed by 52 weeks open label safety extension.	Yes

Refer to the BMT-301 Report Body (AMAG, January 15, 2018) and BMT-302 Report Body (AMAG, January 22, 2018) for more details on the clinical trial design.

Reviewer's comment(s):

Studies NCT02333071 and NCT0233896 were identical. Both studies consisted of 2 parts: A Core Study and an Open-Label Extension (OLE) Study. The Core Study consisted of a 4-week no drug Screening period, followed by a 4-week single blind placebo period, with the first dose

administered in-clinic. Following the end of the single-blind period, which served as Baseline, eligible subjects were then randomized to a 24-week double-blind outpatient treatment period, with the first dose administered in-clinic. The OLE Study consisted of approximately 52-week open-label treatment phase during which all subjects received BMT 1.75 mg SC.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Studies NCT02333071 and NCT0233896.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Studies NCT02333071 and NCT0233896

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Co-Primary (COA and/or biomarker)	Female Sexual Function Index (FSFI) Desire Domain	Sexual desire	The change from Baseline to EOS in the desire domain from the FSFI Q1 and Q2	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Every 4 weeks** ☐ Assessment at cross-over or early discontinuation
Co-Primary	Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Question 13, "bothered by low desire"	Distress by low sexual desire	The change from Baseline to EOS in the score for feeling bothered by low sexual desire as measured by the FSDS-DAO Q13	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Every 4 weeks** ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Female Sexual Encounter Profile-Revised (FSEP-R) Question 10 Satisfying Sexual Event (SSE)	Satisfaction with sexual event	Change from Baseline to EOS in the number of SSEs that occurred within 16 hours of study drug dosing and reported within 72 hours	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Within 24 hours of each sexual encounter** ☐ Assessment at cross-over or early discontinuation

ClinRO= Clinician-reported outcome; **ObsRO**= Observer-reported outcome; **PerfO**= Performance outcome; **PRO=** Patient-reported outcome

Reviewer's comment(s):

FSFI and FSDS-DAO were assessed at Study visits 1 to 9 that occur every 4 weeks. FSEP-R is a diary where subjects completed within 24 hours of each sexual encounter, whether or not study drug was used before that encounter.

3.4 Labeling or promotional claim(s) based on the COA

The sponsor proposed specific targeted COA-related labeling claims.

- *Change from baseline to end of study* (b) (4) *in the desire domain from the Female Sexual Function Index (FSFI) (Questions 1 and 2). Question 1 asks patients "Over the past 4 weeks, how often did you feel sexual desire or interest?", with responses ranging from 1 (almost never or never) to 5 (almost always or always). Question 2 asks patients "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?", with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI desire domain* (b) (4) *score was calculated by adding the patient's responses to these two questions then multiplying that sum by 0.6. The FSFI desire domain score ranged from 1.2 to 6. An increase in the FSFI desire domain score over* (b) (4) *denotes improvement in sexual desire.*
- *Change from baseline to end of study* (b) (4) *in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13). This question asks patients, "How often did you feel: Bothered by low sexual desire?" Patients assessed their sexual distress over a 30-day recall period and responded on a scale of 0 (never) to 4 (always). A decrease in the FSDS-DAO Q13 score over time denotes improvement in the level of distress associated with low sexual desire.*

Reviewer's comment(s):

Per Division's request that the labeling for bremelanotide (VYLEESI) be consistent with that for flibanserin regarding the percentages of responders that met the within-patient meaningful changes on the co-primary endpoints, the COA Staff drafted the following labeling text for the Division's consideration:

> ***"Supportive analyses were conducted to help interpret the clinical meaningfulness of the observed treatment effects. These analyses defined responders for each efficacy endpoint by anchoring change from baseline to end of treatment with multiple anchor measures. Each anchor analysis considered responders to be those who reported that they experienced meaningful change according to the respective anchor measure. In this analysis, the absolute difference in the percentage of responders with VYLEESI and the percentage of responders with placebo across the two trials was 12-14% for FSFI Desire domain (34-36% for VYLEESI; 22% for placebo), and 9-20% for FSDS-DAO Question 13 (51-56% for VYLEESI; 36-42% for placebo)."***

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

Table 5. Concepts of Interest for COAs Included in Studies NCT02333071 and NCT0233896

COA name	Concept(s)
FSFI Desire Domain	Sexual desire
FSDS-DAO Question 13 ("bothered by low desire")	Distress with low sexual desire
FSEP-R Question 10 (SSE)	Satisfaction with sexual event

5 CLINICAL OUTCOME ASSESSMENT(S)

Female Sexual Function Index (FSFI) Desire Domain:
The FSFI is a multidimensional 19 item self-report questionnaire developed to assess female sexual function in women with HSDD. The instrument consists of 6 domains: sexual desire, arousal, lubrication, orgasm, satisfaction, pain. The version employed in Studies NCT02333071 and NCT0233896 uses a 4 week recall period.

The assessment of desire in the FSFI includes introductory instructions that define desire as being "a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex." Item 1 asks "How often did you feel sexual desire or interest?" with response options ranging from 5 (Almost always or always) to 1 (Almost never or never). Item 2 asks "How would you rate your level (degree) of sexual desire or interest?" with response options ranging from 5 (Very high) to 1 (Very low or none at all).

Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Question 13:
The FSDS-DAO is a 13-item questionnaire that asks women to evaluate how often a given problem has "bothered you or caused you distress" over the past 30 days. Specifically, item 13 asks, "How often did you feel bothered by low sexual desire?", with response options (0-4) that range from "never," "rarely," "occasionally," "frequently," to "always."

Female Sexual Encounter Profile-Revised (FSEP-R) Question 10 Satisfying Sexual Event (SSE):
FSEP-R Question 10 is a single item from a 10-item questionnaire designed to identify a satisfactory sexual event. FSEP-R Question 10 is rated on a yes/no response scale.

6 SCORING ALGORITHM

FSFI Desire Domain:
The FSFI produces a total score, however, only the Desire Domain score was used as a co-primary endpoint. The FSFI Desire Domain consists of Questions 1 and 2. The Desire Domain score is calculated as the sum of the 2 items multiple by a factor of 0.6. The score range is 1.2 – 6.0, with lower scores indicating greater impairment in desire.

FSDS-DAO Question 13
Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO) Question 13 is a single item scored from 0 (never) to 4 (always), with higher score indicating greater sexual distress.

FSEP-R Question 10
The number of satisfying sexual events (SSEs) will be counted based on 'Yes' responses to FSEP-R Question 10.

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Copy of instrument☒ Literature review and/or publications
- ☒ Documentation of expert input
- ☒ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☒ Synopsis of qualitative findings
- ☒ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Table 6 documents the adequacy of the content of the COAs.

Table 6. Review of Content Validity for FSFI Desire Domain

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☒ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	AT 2015-036_NDA 22526_Slagle, dated April 20, 2015 (Reference ID: 3735668) which provided review on flibanserin

Reviewer's comment(s):

The content validity of FSFI Desire Domain was reviewed and documented in previous COA review for the approval of flibanserin (AT 2015-036_NDA 22526_Slagle, dated April 20, 2015 (Reference ID: 3735668) which provided review on flibanserin). The relevance and importance of concept assessed was further confirmed in the PFDD meeting on female sexual dysfunction.

The content validity of FSDS-DAO, item 13 was not reviewed for NDA 22526 or for this submission as a measure of distress related to desire, this item has been consistently agreed upon by the Agency across multiple programs for HSDD. Additional details of this instrument

were provided and discussed during the DRUP AC meeting in 2010, and are not reconsidered here.

8 OTHER MEASUREMENT PROPERTIES

This submission did not include evidence of other measurement properties for review.

Reviewer's comment(s):

A brief review of the measurement properties of FSFI Desire Domain was provided in previous COA review for the approval of flibanserin (AT 2015-036_NDA 22526_Slagle, dated April 20, 2015 (Reference ID: 3735668). Its test-retest reliability was adequate.

9 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- ☒ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☒ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Anchor-based probability density function (PDF) curves
- ☒ PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Qualitative support for meaningful change (e.g., patient input)

Table 7 documents the adequacy of the score interpretability of the COAs.

Table 7. Review of Score Interpretability for FSFI Desire Domain and FSDS-DAO Question 13

COA Name	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Female Sexual Function Index (FSFI) Desire Domain	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Appropriate global anchor scales were included for anchor-based analyses ☒ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☒ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☒ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☐ Other (see Reviewer's comments)	Appendix D of the pre-NDA briefing package: 20170817-preNDA Meeting Briefing Package, Palatin Technologies, July 2017); Complete clinical study report Exit Trial, Evidera for Palatin Technologies, June 18, 2017

COA Name	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) Question 13, "bothered by low desire"	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Appropriate global anchor scales were included for anchor-based analyses ☒ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☒ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☒ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☐ Other (see Reviewer's comments)	Appendix D of the pre-NDA briefing package: 20170817-preNDA Meeting Briefing Package, Palatin Technologies, July 2017); Complete clinical study report Exit Trial, Evidera for Palatin Technologies, June 18, 2017

Reviewer's comment(s):

Results of anchor-based methods using data from phase 3 clinical trials combined with patient input from exit interviews were reviewed. In Appendix D of the pre-NDA meeting package, the Independent Anchor Assessment Committee described its rationales and decision-making process on determining the within-patient meaningful change for FSFI Desire Domain and FSDS-DAO Question 13. The Committee recommended FSFI Desire Domain score change >= 0.6 and FSDS-DAO Q13 score change >= 1.0 as meaningful change scores.
Based on our review of the results, we agree with the within-patient meaningful change score that the applicant proposed for FSDS-DAO Question 13. However, we conclude that a higher within-patient meaningful change score, 1.2 points, is more appropriate that the 0.6 point that the applicant proposed. The anchor-based methods suggested a cut-points of 0.6 or 1.2. However, the results from patients who reported having experienced meaningful changes identified in exit survey and exit interview shown an average change score of 1.2.
Triangulating the results of the anchor-based methods and patient exit survey and exit interview, a change score of 1.2 is more appropriate for use as the meaningful within-patient change score.

D. APPENDICES

Appendix A. Female Sexual Function Index (FSFI)

INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse.

Sexual intercourse is defined as penile penetration (entry) of the vagina.

Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

CHECK ONLY ONE BOX PER QUESTION

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

☐ Very high
☐ High
☐ Moderate
☐ Low
☐ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turned on") during sexual activity or intercourse?

☐ No sexual activity
☐ Very high
☐ High
☐ Moderate
☐ Low
☐ Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

☐ No sexual activity
☐ Very high confidence
☐ High confidence
☐ Moderate confidence
☐ Low confidence
☐ Very low or no confidence

6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult

9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

☐ No sexual activity
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

☐ No sexual activity
☐ Extremely difficult or impossible
☐ Very difficult
☐ Difficult
☐ Slightly difficult
☐ Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

☐ No sexual activity
☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

☐ No sexual activity
☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied

15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied

16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?

☐ Very satisfied
☐ Moderately satisfied
☐ About equally satisfied and dissatisfied
☐ Moderately dissatisfied
☐ Very dissatisfied

17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?

☐ Did not attempt intercourse
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?

☐ Did not attempt intercourse
☐ Almost always or always
☐ Most times (more than half the time)
☐ Sometimes (about half the time)
☐ A few times (less than half the time)
☐ Almost never or never

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?

☐ Did not attempt intercourse
☐ Very high
☐ High
☐ Moderate
☐ Low
☐ Very low or none at all

Thank you for completing this questionnaire.

Appendix B. Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO)

INSTRUCTIONS

Below is a list of feelings and problems that women sometimes have concerning their sexuality. Please read each item carefully, and circle the number that best describes HOW OFTEN THAT PROBLEM HAS BOTHERED YOU OR CAUSED YOU DISTRESS DURING THE PAST 30 DAYS INCLUDING TODAY. Circle only one number for each item, and take care not to skip any items. If you change your mind, erase your first circle carefully. Read the example before beginning, and if you have any questions please ask about them.

Example: How often did you feel: **Personal responsibility for your sexual problems?**

NEVER	RARELY	OCCASIONALLY	FREQUENTLY	ALWAYS
0	1	2	3	4

HOW OFTEN DID YOU FEEL:

1.	Distressed about your sex life	0	1	2	3	4
2.	Unhappy about your sexual relationship	0	1	2	3	4
3.	Guilty about sexual difficulties	0	1	2	3	4
4.	Frustrated by your sexual problems	0	1	2	3	4
5.	Stressed about sex	0	1	2	3	4
6.	Inferior because of sexual problems	0	1	2	3	4
7.	Worried about sex	0	1	2	3	4
8.	Sexually inadequate	0	1	2	3	4
9.	Regrets about your sexual functioning	0	1	2	3	4
10.	Embarrassed about sexual problems	0	1	2	3	4
11.	Dissatisfied with your sex life	0	1	2	3	4
12.	Angry about your sex life	0	1	2	3	4
13.	Bothered by low sexual desire	0	1	2	3	4
14.	Concerned by difficulties with sexual arousal	0	1	2	3	4
15.	Frustrated by problems with orgasm	0	1	2	3	4

Appendix C. Female Sexual Encounter Profile -Revised (FSEP-R)

FSEP-R

2. Do you have a sexual encounter to record (circle one)? Yes No *(if no, no further questions need to be answered; if yes, questions 2a and 2b and the FSEP-R must be answered)*

2a. If yes, please enter the Date of Sexual Encounter: _____/_____/_____
Month Day Year

2b. Time beginning sexual activity: _____ AM / PM (fill in time)

Please circle your answers to ALL questions.

1. Please circle all activities that apply for this sexual encounter:
   A. Genital stimulation by partner (manual)
   B. Genital stimulation by partner (oral)
   C. Masturbation (genital stimulation by self)
   D. Intercourse

2. Did you initiate this sexual encounter?
   A. Yes
   B. No

3. How would you rate your level of sexual desire associated with and during this sexual encounter?
   A. No desire
   B. Slight desire
   C. Moderate desire
   D. High desire

4. Are you satisfied with your level of desire (interest/motivation/drive) associated with and during this sexual encounter?
   A. Not at all satisfied
   B. Slightly satisfied
   C. Moderately satisfied
   D. Completely satisfied

5. Did you achieve enough lubrication (wetness) to allow comfortable intercourse (even if you did not actually have intercourse)?
   A. Yes
   B. No

6. How would you rate your level of sexual arousal (excitement) during this sexual encounter? (circle one answer only)
   A. Not at all aroused
   B. Slightly aroused
   C. Moderately aroused
   D. Highly aroused

7. Were you satisfied with your sexual arousal (excitement) during this sexual encounter?
   A. Not at all satisfied
   B. Slightly satisfied
   C. Moderately satisfied
   D. Completely satisfied

8. Did you achieve orgasm?
   A. Yes
   B. No

9. Were conditions appropriate for a satisfactory sexual encounter (enough time, no distractions, etc.)?
   A. Yes
   B. No

10. Did you consider this sexual encounter satisfactory for you?
    A. Yes
    B. No

Thank you for completing this diary

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WEN-HUNG CHEN
05/16/2019 01:48:35 PM
Two errors were found in the previous communication: direction of score for FSFI and recall period for FSDS-DAO. Errors are corrected in the revised communication

Memorandum

PHARMACOLOGY/TOXICOLOGY SUPERVISOR MEMO

Date:	April 8, 2019
NDA #	210557
Sponsor:	AMAG Pharmaceuticals, Inc
Drug/Indication:	Bremelanotide/Female hypoactive sexual desire disorder
Reviewer:	Mukesh Summan, PhD, DABT

Background: The sponsor AMAG Pharmaceuticals Inc., is seeking marketing approval for the use of Bremelanotide for hypoactive sexual desire disorder (HSDD) in premenopausal women. Bremelanotide (BMT) is a synthetic cyclic heptapeptide analog of α-melanocyte-stimulating hormone (α-MSH); but a nonselective high-affinity ligand and agonist at multiple melanocortin receptors (MCRs), specifically MCR1, MCR3 and MCR4. The sponsor proposes therapeutic efficacy (b) (4) The melanocortin system plays a role in sexual function, the regulation of feeding and obesity and immune modulating function.

NDA 210557 was submitted to the Agency as a 505(b)1 NDA on March 23, 2018. The initial clinical studies in women were conducted via the intranasal route with safety determination based on intranasal formulation use in males. However, due to variable systemic exposure via the intranasal route, the applicants' current treatment paradigm in women with HSDD, is as needed bremelanotide at 1.75 mg via subcutaneous injection, once per 24 hours with no more than eight treatments per month.

The clinical team and Division of Cardiovascular and Renal Products (DCRP) identified increases in systolic and diastolic blood pressure (BP) with clinical BMT use (approx. 4 mmHg) raising a concern for cardiovascular adverse events. Consequently, the Division recommended the applicant complete an ambulatory blood pressure monitoring (ABPM) study to characterize the BP elevations.

Summary of nonclinical data:
The absorption, distribution, metabolism and excretion of bremelanotide was characterized in single- and multiple-dose studies in both genders of mouse, rat, rabbit, ferret, dog, and monkey by the subcutaneous (sc), intravenous (iv), and intranasal routes, respectively.

The subcutaneous route of administration resulted in rapid (≤ 1 hr) absorption across species and exposure was proportional to dose. Bioavailability was 100%, with low volume of distribution, rapid elimination, and no gender differences.

BMT protein binding was 32%, 6%, 13% and 13% for mouse, rat, dog and humans, respectively. In a mouse radiolabel distribution study, subcutaneous BMT distributed quickly and widely to tissues and organs, with peak radioactivity (0.5 hrs) in the excretory tissues (liver, kidney, small intestine and pancreas). Males additionally showed high concentrations in the bulbo-urethral gland.

Bremelanotide was shown to cross the blood brain barrier at 10% of the plasma concentration, but with a significant delay. Radioactivity concentrations in the cerebellum, cerebrum, medulla, and spinal cord peaked at a low level 24 hrs after sc injection in males, and 4 hrs after injection in females. The reason for this sex difference is unknown. Clearance from the CNS was slow relative to systemic clearance, and measurable concentrations that were 3-6X the (low) plasma concentration, remained at 28 days post-dose in both male and female mice.

In female mice, low levels of radioactivity were measured for up to 28 days post-dose in uterus and ovary. In males, radioactivity slowly crossed the blood:testis barrier, peaking at low levels at 24 hrs post-dose, and then was slowly cleared. BMT was not found to be associated with melanin-containing tissues.

Distribution in pregnant animals was not assessed and it is not known whether BMT crosses the placenta. As expected, in vitro metabolism of BMT was accomplished by hydrolysis of peptide bonds.

In vivo metabolism was characterized only in the mouse. The synthetic amino acid D-phenylalanine was one major metabolite (M3), that accounted for 11.3% and 8.3% of the dose in males and females, respectively, and is not known to have melanocortin receptor activity. Human metabolism in vivo was similar. Conversion of BMT to the M3 metabolite occurs between 4 and 8 hrs post-dose and is complete by 24 hrs. Consequently, the time that BMT circulates in its pharmacologically active form appears limited.

Bremelanotide safety pharmacology studies were negative for CNS and respiratory studies. Emetic (gastrointestinal) effects were seen in studies in the ferret with some incidental emesis in dog studies. Standard in vitro cardiovascular (CV) studies showed no proarrhythmic risk. No single in vivo study adequately evaluated cardiovascular safety; but a series of studies in the rat, dog and non-human primate (NHP) were conducted by the applicant to support CV safety via the intravenous (iv), subcutaneous (sc) and intranasal routes. Intranasal BMT did not show ECG abnormalities in the dog and NHP. Dose and time-dependent increases in blood pressure (BP) and heart rate (HR) were observed in single ascending dose (SAD) studies in both the rat and dog following either sc and iv BMT treatment. The no effect level (NOEL) for both BP and HR in the dog was 0.5X the human therapeutic exposure (based on AUC). No cardiovascular or ECG abnormalities were observed in the SAD male-only NHP study with intranasal BMT administration. A NOAEL was not determined. In the rat SAD study, iv administration of BMT dose-dependently increased BP and HR. The BP was significantly elevated at a dose approaching toxic levels (1 mg/kg), where the rat LD_{50} is 2 mg/kg. 1 mg/kg is approximately 1X the human dose based on AUC.

BMT was well tolerated in single dose studies in the mouse and dog via the sc route. Rats were intolerant of the sc route; but tolerated lower doses via the intravenous route. Acute dose toxicity was not achieved via the intranasal route in the rat, dog or non-human primate, likely due to the highly variable systemic exposures. Pivotal sc repeat dose toxicity studies to evaluate the toxicity of BMT were conducted in mice and dogs for up to 26- and 32-weeks, respectively. BMT was well tolerated in the 26-week mouse study, except for skin reactions at the injection site of high dose animals (alopecia/hypotrichosis, epidermal hyperplasia, fibrosis, chronic inflammation, and erosion/ulcer), particularly in males. The NOEL was the mid dose and corresponds to 56X the proposed human dose based on AUC. In the 32-week dog study treatment-related findings included stereotypic behavior (treatment week 1 only), hair discoloration, injection site skin thickening and reduced body weight (approx. 10%) throughout the study, with a dose-dependent reduced body weight in females. The reduced body weight is likely due to action of the drug. A NOEL was not set for male dogs and was the low dose in female dogs, corresponding to 10X the proposed human dose based on AUC.

In the rat lower dose repeat dose toxicity studies were conducted via the intranasal route. Dose-dependent weight loss was observed. In the 28- and 90-day repeat dose studies vacuolization of the adrenal cortex was observed in males. In the 2-year rat carcinogenicity study, intranasal administration of BMT over the same range, resulted in benign cortical adenomas. The effect of BMT on the adrenal gland is likely indirect. MCR2 is the only melanocortin receptor found in the adrenal glands and is known to bind to adrenocorticotropic hormone (ACTH). BMT may act in the brain to produce corticotropin releasing hormone (CRH), which in turn causes ACTH production in the pituitary, and consequently acts at the adrenals. No single nonclinical study evaluated the morphological changes in the adrenal gland and also measured ACTH, cortisol or corticosterone.

BMT was negative in a standard battery of genotoxicity assays. The carcinogenic potential of BMT was assessed in 2-year studies conducted in the mouse (sc route) and the rat (intranasal route) and was found negative for tumorigenicity.

Fertility studies were conducted in male and female mice by the sc route and in male rats by the intranasal route. High doses of BMT showed no effects on female fertility in mice by the sc route. Fertility indices and sperm parameters were unaffected in male sc-treated mice and intranasally-treated male rats; the latter at much lower exposures. The epididymides, seminal vesicles, and testes organ to body weight ratios were statistically decreased approx. 7-12%, respectively, at the high dose; despite increased terminal body weight. The decrease in relative weights of testes and seminal vesicles may suggest an effect on pituitary-gonadal axis or a direct effect on gonadal tissues, which are known to express melanocortin receptors.

Embryofetal toxicity studies were conducted in multiple species (mouse, rat, rabbit, and dog). However, due to excessive maternal toxicity in the rabbit, and low margins of exposure in the rat with iv treatment (1X the human therapeutic exposure); the definitive embryofetal and pre- and postnatal toxicology studies was conducted in the mouse and the dog.

In a combined embryofetal and pre- and postnatal development study in mice, there was no evidence of teratogenicity in pregnant mice. However, high doses resulted in reduced maternal body weight and body weight gain. Development delays were observed in all treatment groups, and pup viability at the high dose was reduced during parturition and weaning; likely due to maternal body weight effects. Behavior and reproductive performance were unaffected in F1 mice. Lower pup body weight was propagated in the F2 generation at the high dose. Consequently, a developmental NOEL could not be set in the F1 generation mice. The NOEL for maternal toxicity and reproductive performance was 327X and 702X (averaged gestation day (GD)6 and GD15 exposure), respectively, the human dose based on AUC. The NOEL for F1 behavior and reproductive performance 702X (averaged GD6 and GD15 exposure), respectively, the human dose based on AUC. The NOEL for F2 growth and development 327X (averaged GD6 and GD15 exposure), respectively, the human dose based on AUC. A developmental NOEL for the F1 generation was not set.

The dog is a non-standard species for reproductive development. The applicant evaluated embryo-fetal development in the dog in both a pilot and definitive studies. The definitive study evaluated BMT treatment during gestation day (GD) 18-35. Stereotypic behavior (stretching, yawning), inappetence and lower gestational body weight gain with correlative reduced food consumption, were observed at all doses predominantly in the treatment period. Body weight gain was similar in all groups at study termination. Excessive shedding and black discolored hair was observed in all treatment groups predominantly in the post-dose observation period, until termination. Pre- and post-implantation loss over and above control animals was observed in all treatment groups. Due to the low number of pregnant animals in each group (n= 5-7), statistic could not be applied. However, due to the non-dose-dependent apparently treatment-related pre- and post-implantation loss, a developmental NOEL was not set. The maternal lowest observed effect (LOEL) was the low dose or 17X (average of GD 18 and GD 35 exposures) the human dose, based on AUC.

Label: No significant nonclinical labeling issues were identified.

Outstanding Nonclinical Issue: None.

Conclusion(s): Dr. Leslie McKinney, the primary nonclinical reviewer, concludes that the pharmacology and toxicology data support approval of bremelanotide for treatment of premenopausal women with HSDD. I concur with Dr. McKinney's assessment.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUKESH SUMMAN
04/12/2019 08:59:53 AM
Supervisor memo

My review of NDA 210557 is complete. This review has been condensed and incorporated into the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210557
Supporting document/s:	2
Applicant's letter date:	03-28-2018
CDER stamp date:	03-28-2018
Product:	Bremelanotide
Indication:	(b) (4)
Applicant:	Amag Pharmaceuticals, Inc
Review Division:	Division of Bone, Reproductive, and Urologic Products
Reviewer:	Leslie McKinney, PhD
Supervisor/Team Leader:	Mukesh Summan, PhD, DABT
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 210557 are owned by Amag Pharmaceuticals, Inc. or are data for which Amag Pharmaceuticals, Inc. has obtained a written right of reference.

Any information or data necessary for approval of 210557 that Amag Pharmaceuticals, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 210557.

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1 Executive Summary

1.1 Introduction

Bremelanotide (BMT) is a synthetic cyclic heptapeptide analog of α-melanocyte-stimulating hormone (α-MSH) being developed for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal females. It is a nonselective, high-affinity ligand and agonist for melanocortin receptors (MCRs), specifically MC1R, MC3R, and MC4R. Bremelanotide is the first compound to be designated a melanocortin receptor agonist for purposes of NDA approval. The sponsor proposes that the (b) (4) However, the actual mechanism of action in humans is speculative.

BMT drug product is formulated in a liquid solution for subcutaneous (sc) injection. The recommended frequency of use will be not more than once daily, with a likely limitation of use of not more than eight times per month

Bremelanotide has had a long development period (~20 years). Earlier development programs for BMT included the treatment of erectile dysfunction in males (b) (4) which did not lead to approved products. Nonclinical studies to support these earlier indications, as well as HSDD, were conducted in mouse, rat, rabbit, ferret, dog, and monkey, by the intravenous, subcutaneous, and intranasal routes.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology

Binding:

Bremelanotide (BMT) is a synthetic cyclic heptapeptide analog of α-melanocyte-stimulating hormone (α-MSH). It is a high-affinity ligand and agonist for melanocortin receptors (MCRs), of which there are 5 subtypes. BMT is selective for MC1R and MC4R, but also binds MC3R. The relative binding affinity of BMT is: MC1R > MC4R > MC3R > MC5R. BMT does not appreciably bind to MC2R (the ACTH receptor expressed on the adrenal gland; Kd > 1000 nM). For the purposes of this application, the pharmacologically relevant receptors are MC4R (b) (4) MC3R, and MC1R.

There were no data presented for binding of BMT to the MCRs of nonclinical species (other than MC1R in the mouse). For that reason, pharmacodynamic effects are the most reliable indicators of activity in nonclinical species. However, literature states that MC4Rs are highly conserved across many species, with, for example, 93% identity between rat and human.

There was no off-target activity of BMT against a panel of receptors at therapeutically relevant concentrations.

Distribution and function of MCRs:

MC1R is expressed on melanocytes; its activation leads to production of melanin. Expected pharmacology for BMT binding to MCR1 is enhanced pigmentation, which was observed in dogs and in humans. It is also expressed on cells of the immune system and may play a role in regulating the inflammatory response.

MC4R is expressed on neurons of the central nervous system (CNS). It is expressed at high density in the paraventricular region of the hypothalamus and in the dorsal motor

nucleus of the vagus in the hindbrain. Peripheral expression is less well characterized, but it is expressed on nerve endings of the penis. Melanocortin induction of penile erection has been shown to be modulated by MC4R and penile erection is an expected pharmacodynamic effect in males.

MC3R is expressed in the CNS and GI tract. It may have overlapping functions with MC4R. BMT can induce emesis, which may be related to MC3R expression.

It is expected that a therapeutic dose of BMT will yield tissue concentrations that are sufficient to produce pharmacological activity at the MC1R, MC4R and possibly MC3R.

The sponsor proposes that the therapeutic effect for HSDD occurs (b) (4)

(b) (4)

Safety pharmacology

Bremelanotide was negative for CNS and respiratory safety. Gastrointestinal (emetic) effects were demonstrated in the ferret at doses estimated to be near the therapeutic dose range. Emesis was also incidentally observed in several studies in the dog. It is not known whether the emetic effect is due to a direct effect on the stomach or is a centrally mediated effect.

To evaluate cardiovascular (CV) safety, standard in vitro studies were conducted and BMT was found negative for proarrhythmia risk. However, there was no single adequate in vivo study that evaluated cardiovascular parameters. Rather, the sponsor relied on weight of evidence from a series of studies conducted in the rat, dog and monkey to support CV safety. In vivo studies were conducted by the iv, sc, and intranasal routes. ECG studies were conducted in the dog and monkey, by the intranasal route, and were negative. The effect of bremelanotide on blood pressure (BP) was examined in rat, dog, and monkey and yielded positive findings in the rat and dog. Both heart rate (HR) and BP were elevated by BMT. No observed effect levels (NOELs) were obtained in the dog that were approximately half the human therapeutic dose based on AUC. Weight of evidence therefore indicates that elevated BP and HR are possible following BMT exposure, and that the threshold for CV changes to appear in the rat and the dog are near the human therapeutic range based on AUC. The likely mechanism of action, based on literature, is activation of central MC4 and/or MC3 receptors. Elevated BP has been observed in humans following therapeutic doses of BMT.

ADME:

The absorption, distribution, metabolism and excretion of bremelanotide was characterized in single- and multiple-dose studies in both genders of mouse, rat, rabbit, ferret, dog, and monkey by the sc, iv, and intranasal routes.

Absorption:

Focusing on the therapeutically relevant sc route of administration, absorption across species was rapid (≤ 1 hr), and exposure was proportional to dose. Bioavailablity was 100%. There were no significant differences between genders. Volume of distribution was low, and the time course of elimination was rapid ($T_{1/2}$ = 1-2 hrs).

Distribution:

BMT binding to protein for nonclinical species was 32%, 6%, and 13% for mouse, rat, and dog, respectively. Mean values for BMT protein binding in human serum was 13% and closely resembles protein binding in the dog. There was no evidence for distribution to blood cells.

In a mouse radiolabel distribution study, subcutaneous BMT was found to distribute quickly and widely to tissues and organs. Most tissues had peak radioactivity concentrations at 0.5 hours postdose (the first evaluation time point). In males and females, the tissues showing the highest peak concentrations of radioactivity (after the dose site) reflected the routes of excretion: kidney, liver, small intestine, and pancreas. Males additionally showed high concentrations in the bulbo-urethral gland.

(b) (4) bremelanotide was shown to cross the blood brain barrier, but with a significant delay. Radioactivity concentrations in the cerebellum, cerebrum, medulla, and spinal cord peaked at a low level 24 hrs after injection in males, and 4 hrs after injection in females. The reason for this sex difference is unknown. The average peak radiolabel concentration (ng.equivalents ^{14}C-BMT/g tissue) in the CNS was ~1000 in both males and females (~10% of plasma concentration), which, if assumed to be all parent compound, is equal to a tissue concentration of 1000 nM, well above the Ki for the MC4 receptor of 14 nM. Clearance from the CNS was slow relative to systemic clearance, and measurable concentrations that were 3-6X the plasma concentration remained at 28 days postdose in both male and female mice.

In female mice, low levels of radioactivity were measured for up to 28 days postdose in uterus and ovary. In males, radioactivity slowly crossed the blood:testis barrier, peaking at low levels at 24 hrs post dose, and then was slowly cleared.

BMT was not found to be associated with melanin-containing tissues.

Distribution in pregnant animals was not assessed. It is not known if BMT crosses the placenta.

Metabolism:

In vitro metabolism was characterized in mouse, rat, dog, and human hepatocytes. In vitro, no unique human metabolites were found. As expected, in vitro metabolism of BMT was accomplished by hydrolysis of peptide bonds.

In vivo metabolism was characterized only in the mouse. There was one major metabolite (M3), the synthetic amino acid D-phenylalanine, that accounted for 11.3% and 8.3% of the dose in males and females, respectively and is not known to have melanocortin receptor activity.

Human metabolism in vivo was similar. Conversion of BMT to M3 occurs between 4 and 8 hours and is complete by 24 hrs. Thus, the time that BMT circulates in its pharmacologically active form is limited.

Excretion:

BMT was rapidly excreted in urine and feces after sc dosing in the mouse. Hepato-biliary and renal excretion were the major routes of elimination. Excretion profiles were similar across sex with renal and fecal excretion being nearly equal. The excretion profile in the human was similar.

Comparative TK

The sponsor did not provide an analysis of dose equivalency across species but did provide a table with all the TK data collated (see Table 2.6.4-9 Summary of exposure – Comparison across species, p71 of the PK written summary in section 2.6.4 of the submission). Inspection of this data showed that exposure in nonclinical species was comparable to human for the mouse and pregnant rabbit, and lower in the dog and rat based on human equivalent dose (HED) in mg/kg.

General toxicology:

Single dose toxicity

Single dose toxicity studies by the sc route showed that BMT was well tolerated by mouse and dog. In the mouse, there were significant clinical signs at the maximum tolerated dose (MTD) of 150 mg/kg. In the dog, single dose studies were conducted up to 15 mg/kg and were well tolerated other than for injection site reactions. Rats were intolerant of sc dosing; by the iv route, an MTD of 1.5 mg/kg was set; however, mortality above that dose, starting at 2 mg/kg, was not well explained. Acute dose toxicity by the intranasal route was not achieved in rat, dog, or monkey. Overall, species sensitivity by the sc route was rat > dog > mouse. Studies in the rabbit were conducted for reproductive toxicity and the rabbit, like the rat, was found to be extremely sensitive and intolerant to treatment with BMT, although no single-dose MTD was defined.

Repeat dose toxicity:

Pivotal repeat-dose studies to assess the nonclinical toxicity of BMT were conducted in mice, and dogs following once a day sc administration for up to 26 and 32 weeks, respectively. A 4-week nonpivotal study in the rat was also conducted by the sc route.

Mouse: BMT administered at 15, 30, or 75 mg/kg/d sc for 26 weeks was well-tolerated by the mouse. The primary toxicity was skin reactions at the high dose. There were mild reactive changes in liver and kidney that were not considered adverse. A trend for increased body weight and food consumption was observed at the high dose during the treatment period. However, by the end of the recovery period, food consumption and group mean body weights in the 75 mg/kg/day group were lower than controls. TK: Exposures were stable or slightly increased over the duration of the study. There were no gender differences. Based on these findings, NOEL = 30 mg/kg/day. At that dose, MOE compared to the proposed human dose based on AUC on d180 was 56.

Dog: BMT administered at 2, 8, or 20 mg/kg/d for 32 weeks was tolerated overall, but there were treatment related findings that included stereotypic behavior, black discoloration of the hair, injection site reactions, decreased body weight gain, mild liver enzyme elevation, and increased adrenal weight (without corresponding histology) in females only. These findings were likely due to exaggerated pharmacology of BMT. The sponsor did not consider any of these findings adverse and set the NOAEL at the high dose. Reviewer preferred a more conservative NOAEL of 2 mg/kg, which still produced exposures that were ~10-fold greater than the proposed therapeutic dose.

Rat: Most of the repeat-dose studies carried out in the rat were conducted by the intranasal route, which allowed for longer duration dosing. We briefly mention rat studies in this summary in order to highlight the fact that in a more sensitive species such as the rat, dose-dependent weight loss is one of the signs of BMT activity. We also note that in two of the

repeat-dose intranasal studies in the rat (28 and 90-day), vacuolization of the adrenal cortex was observed in males. Interestingly, in the two-year carcinogenicity studies, males that were intranasally dosed over the same range as in the repeat-dose tox studies were found to have benign cortical adenomas, which did not rise to the level of significance as a tumor finding.

A further comment on adrenal findings:
There were findings in the adrenal in three species: rat, rabbit, and dog. In the rat, vacuolation in the adrenal cortex was found (without a corresponding increase in weight), and the sponsor conducted a dedicated study to characterize the finding, ultimately concluding that it was not treatment related. In the pregnant rat, ACTH and corticosterone were found to be significantly elevated. Unfortunately, adrenal weight and histopathology was not assessed in that study. In the pregnant rabbit, adrenal weights were elevated but no histopathology was done. In the dog, adrenal weights were elevated, but there was no corresponding histopathology. Unfortunately, ACTH and cortisol or corticosterone measurements were not conducted as part of these last two studies. Thus, there was no single nonclinical study that looked for an association between morphological changes in the adrenal glands and that also measured ACTH and cortisol or corticosterone.

We speculate that if there is an effect of BMT on the adrenal gland, it is not direct. BMT does not bind to MCR2, which is the only melanocortin receptor that is expressed on the adrenal gland and binds ACTH. Rather, if BMT affects the adrenals, it is likely via an indirect mechanism, by simulating production of corticotropin releasing hormone (CRH) in the brain, which would subsequently cause ACTH production to increase in the pituitary and then subsequently act on the adrenals.

Summary:
Little frank toxicity of BMT was observed in repeat-dose toxicity studies in mouse, rat, and dog. Findings could largely be characterized as exaggerated pharmacology, with the primary pharmacodynamic effect being reduced body weight gain and in males, penile erection. Overall, reviewer concludes that, at low dose ranges, or in less sensitive species such as the mouse, peripheral effect of BMT will dominate (nausea, vomiting, skin darkening). Very high exposures that can elevate tissue concentrations in the brain can begin to influence the HPA axis and autonomic systems. An unanswered question about the therapeutic use of BMT for HSDD is how it can exert its putative effect on brain circuitry to transiently elevate sexual response without also affecting other physiological functions.

Genetic toxicity:
Genetic toxicity was assessed in a standard panel of in vitro and in vivo studies and was found to be negative.

Carcinogenicity:
The carcinogenic potential was assessed in 2-year studies conducted in the mouse and the rat and were found negative for tumorigenicity.

Mouse: The mouse study was conducted by the sc route at doses of 3, 9, and 15 mg/kg/d. There were no treatment related tumor findings and the NOAEL was set at the high dose. By body surface area, the MOE at the NOAEL compared to the human therapeutic dose is 41X. The MOE based on exposure can be estimated from TK values. Exposures were stable over the course of the study up to 1 year and were consistent with other

measurements obtained in the mouse by the sc route. Based on Cmax values obtained at 1 year, the MOE is 141X for males and 183X for females.

Rat: The rat study was conducted by the intranasal route at comparatively low doses: 0.5, 2.5, and 5 mg/kg/d. There were no treatment-related tumor findings and the NOAEL was set at 5 mg/kg/d. By body surface area, the MOE at the NOAEL is 27X compared to the human therapeutic dose. By exposure, the MOE changes dramatically depending on whether it is calculated from plasma values taken at 3 months vs 19 months. As was observed in other, shorter duration repeat-dose tox studies by either the sc or intranasal routes, exposures in the rat decline over time with repeat dosing. Thus, based on Cmax, the MOE determined from initial exposure values is 2-3X, but declines to less than half the human exposure at the end of the study.

Reproductive toxicity:

Fertility:
Fertility studies were conducted in male and female mice by the subcutaneous route and in male rats by the intranasal route.

Females: In a study conducted in mice by the sc route, there was no effect of BMT on female fertility indices when mice were dosed 14 days prior to mating through GD15 at doses up to 150 mg/kg/d, which is 639X the human therapeutic dose based on AUC. There were also no findings for embryotoxicity.

Males: There no effects of BMT on male fertility indices, as tested in mice by the sc route up to 75 mg/kg/d. There were also no findings in the rat, but that study was conducted by the intranasal route at much lower exposures.

Embryofetal toxicity and pre and postnatal development:
Embryofetal toxicity studies were conducted in multiple species (mouse, rat, rabbit, and dog). Due to excessive maternal toxicity in the rabbit, and limitations of dosing in the rat, the definitive Segment 2 and Segment 3 studies were conducted in the mouse and the dog.

Mouse: In the mouse, a combined Segment 2/3 study was conducted by the subcutaneous route. Pregnant mice were dosed at 30, 75, and 150 mg/kg/d from GD6 through LD28. Conclusions from the study were:

- There was no evidence for teratogenicity.
- There was maternal toxicity (reduced body weight and body weight gain) at the high dose.
- There was no evidence of embryofetal toxicity through organogenesis (GD15). There was, however, evidence of reduced pup viability and developmental delays if dosing continued through parturition and weaning. This was probably due to reduced food consumption and weight gain in the dams. In the high dose group, lower pup body weight was propagated into the F2 generation. Consequently, a developmental NOEL could not be set.

Dog: In the Beagle dog, which is a nonstandard species for reproductive toxicity, 8 pregnant animals/dose were dosed at 2, 8, or 20 mg/kg/d from gestation day GD18-35. The study was ended near the end of gestation, on GD57. The number of litters evaluated was 5-7 per dose. There was maternal toxicity at the mid and high dose, in the form of inappetance and lower body weight gain. Discoloration (blackening) of the coat was also noted. Regarding embryotoxicity, there was no evidence for teratogenicity, but there was some

evidence for embryofetal toxicity (postimplantation loss) at all doses. For that reason, a developmental NOEL was not set.

Given the findings in the mouse and the dog, we conclude that BMT is unlikely to affect fertility in humans but has the potential to cause fetal harm if dosing occurs during pregnancy.

Abuse potential:
Abuse potential was assessed in a standard series of behavioral studies in the rat. These were reviewed by Dr. Kit Bonson of the Controlled Substances staff. It was concluded that BMT has negligible abuse potential.

Immunotoxicity:
Immunotoxicity was based on a risk assessment evaluation. No in vivo nonclinical studies were done to address immunogenicity. The following conclusion was made by the OPQ reviewers (Davinna Ligons and Susan Kirshner) who evaluated in vitro data submitted by the sponsor (review completed on May 10, 2018).

"A competitive binding assay demonstrates that bremalanotide most likely does not bind HLA class II alleles, which is required to drive an anti-drug antibody response. Consistent with these findings, pharmacokinetic and clinical efficacy responses do not appear to be impacted by anti-drug antibody responses."

1.3 Recommendations

1.3.1 Approvability

From a PharmTox perspective, we recommend approval of the application.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Labeling will be addressed in a separate review.

2 Drug Information

2.1 Drug

CAS Registry Number : 189691-06-3

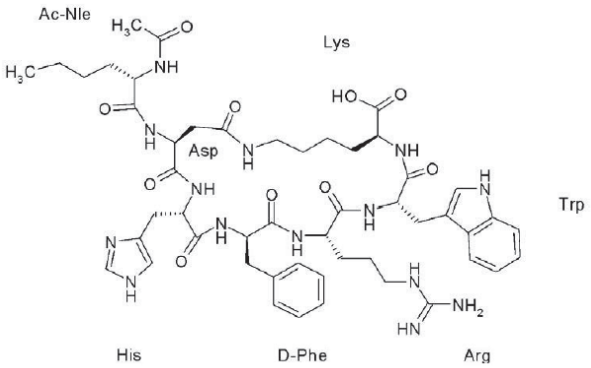
Generic Name: Bremelanotide (BMT)

Code Name: PT-141 (Palatin)
PI-001 or PI-001 acetate (b) (4)

Chemical Name: 2,7-anhydro(N-acetyl-L-2-aminohexanoyl-L-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine)

Molecular Formula/Molecular Weight: $C_{50}H_{68}N_{14}O_{10}$ / 1025.16 Note: 1 ng/mL ~ 1 nM

Structure or Biochemical Description:
Amino acid sequence: Ac – Nle – cyclo (Asp – His – D-Phe – Arg – Trp – Lys – OH
Norleucine (Nle) and D-phenylalanine (D-Phe) are isomers of leucine and phenylalanine respectively and are metabolized similarly to the standard amino acids.



Bremelanotide (BMT) is freely soluble in water, methanol, and DMSO, and is soluble in ethanol. The freely soluble concentration range for BMT is ~0.1 – 1 M. In response to a request for information on solubility in solvents other than saline, the sponsor faxed the following solubility information on 11-5-02:

- 20 mg/ml (20 mM) in normal saline at room temperature (RT)
- 200 mg/ml (200 mM) in water @RT
- 400 mg/ml (400 mM) in DMSO @RT

pH: The intrinsic pH of an aqueous solution of bremelanotide at ~6 mg/mL at RT is between pH 4 and pH 6.

pKa: There are three ionizable groups in bremelanotide: the C-terminal carboxylate (pKa 3.4), the imidazole of the side chain histidine (pKa 6.6) and the guanidium side chain of arginine (pKa 12.7).

Pharmacologic Class: melanocortin receptor agonist

Bremelanotide is the first compound to be designated a melanocortin receptor agonist for purposes of NDA approval. This designation is acceptable based on mechanism of action.

2.2 Relevant INDs, NDAs, BLAs and DMFs

[redacted]					
IND-061706	PALATIN TECHNOLOGIES	NASAL SPRAY	DBRUP	Withdrawn	ERECTILE DYSFUNCTION
IND-064119	AMAG PHARMACEUTICALS	INJECTION	DBRUP	Active	FEMALE SEXUAL DYSFUNCTION
[redacted]					

2.3 Drug Formulation

Parenteral BMT drug product for subcutaneous (SC) injection is formulated at 5.83 mg/mL in an aqueous system containing 2.5% [redacted] glycerin at pH [redacted] It is packaged in single-use prefilled disposable syringes designed to deliver a volume of 0.3 mL.

Sponsor's Table 3.2.P.1-1.

Component	Composition[a]	Quality or Standard[b]	Function
BMT drug substance[c]	1.75 mg	[redacted]	Active pharmaceutical ingredient
Glycerin, [redacted]	[redacted]	USP/NF	[redacted]
Hydrochloric acid		USP/NF	To adjust pH
Sodium hydroxide		USP/NF	To adjust pH
Water for injection		USP/NF	[redacted]

a Component quantities are for a single pre-filled syringe which delivers 0.3 mL injection
b Abbreviations: NF = National Formulary; QS = quantity sufficient; USP = United States Pharmacopeia
c Anhydrous, free base equivalent

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

A total of 6 studies were conducted to address qualification of impurities and to assess toxicity of degradants: 2 in vitro genetox studies, and 4 repeat-dose general tox studies in the mouse. All the studies met GLP and QA standards and none revealed any new toxicities. These studies are discussed below, and comparisons to human exposure are presented for specified impurities.

There were no structural alerts for impurities in the drug substance.

Specified Impurities

There are 4 specified drug substance impurities, designated A, B, C, and D, which were characterized as [redacted]. Structures, and relative retention time (RRT) values for 2 different HPLC methods are given in Table 3.2.S.3.2-1. Proposed specifications [redacted] The sponsor has proposed specification limits of [redacted]% for Impurities A, C, and D, and [redacted]% for Impurity B.

The pharmacological activity of the impurities has not been tested. The impurities were qualified per ICH Q3A requirements for impurities present in drug substances at [redacted]% by testing two lots of drug substance containing elevated levels of the specified impurities. Lot 16 contained elevated levels of impurities A and B. Lot 2 contained elevated levels of impurities C and D. *Confusingly, the COAs for these two lots submitted to the study reports do not list the amounts of the specified impurities*. The sponsor's data on the actual levels of impurities in Lot 16 and Lot 2 are in Table 3.2.S.4.5-17 under Control of Drug Substance p 26 (shown below). The manufacturer for Lots 16 and 2 was [redacted] We also note that the COAs for Lots 16 and 2 submitted to the study reports list slightly different values for purity by the [redacted] method. Our review will list the purity as given on the COA.

Sponsor's Table 3.2.S.4.5-17: Summary of Related Impurities in Preclinical Bremelanotide Samples Used Safety Studies (Lot 2 and Lot 16, [redacted] Method)

Lot 2											
Purity	Total Impurities	Total Unspecified	Imp A	ImpB	Imp C	Imp D	RRT [redacted]	RRT	RRT	RRT	RRT
[redacted]											

Lot 16											
Purity, Area%	Total Impurities	Total Unspecified	Imp A	ImpB	Imp C	Imp D	RRT [redacted]	RRT	RRT	RRT	RRT
[redacted]											

Two genetox (Ames and chromosomal aberration) and two repeat-dose (28-day and 26-week mouse) studies were conducted to qualify the impurities. The genetox studies were combined studies for impurities and degradants and are reviewed under degradants. The 28-day study is summarized below. Because the 26-week study (996-028) is one of the long-duration pivotal studies supporting approval, it is reviewed later under Section 6.2 General Toxicity.

Study title: A 28-day subcutaneous dose impurity qualification study of PT-141 in B6C3F1 mice.	
Study no.:	996-035 4.2.3.7.6.
Study report location:	Applica56tion 210557 - Sequence 0002 - Study 996-035
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 29, 2006
GLP compliance and QA:	Yes and Yes
Drug, lot #, and % purity:	PT-141, Lot 16, 97.6%, (b) (4)% peptide content. Contains elevated levels of impurities A and B

Methods	
Doses:	0, 15, 30, 75 mg/kg
Route of administration / Formulation:	Daily SC injection 4 mL/kg in 2.5% glycerin/sterile water
Number/Sex/Group:	10/sex/dose
Satellite groups for TK:	5/sex/dose control; 25 sex/dose high dose Samples taken on day 1
Deviations from study protocol:	None significant

Results:

There were no treatment-related effects on survival, clinical observations, ophthalmology, or food consumption. Body weights in treated animals trended slightly higher by the end of the study. There were elevated clinical chemistry values for AST and ALT in males at all doses, but these were significant only at the low dose. Males at 75 mg/kg/day showed a statistically significant increase in both relative (to BW) kidney and liver weights; ~ 9% for both. However, other than injection site reactions, there were no histopathology findings.

TK: PT- 141 was absorbed rapidly following SC dosing, with Tmax occurring 1.0 hr post-dose. TK was similar for males and females. Mean plasma Cmax and $AUC_{0-\infty}$ on Day 1 at the high dose were 27.1 ug/mL and 52.7 ug.hr/mL, respectively (M/F combined). TK agreed with a previously completed SC dose 4-week mouse study (#996-009). However, data from 996-009 showed higher exposure (about 50% higher) on day 28, so it is possible that exposure increased over the duration of this study.

Sponsor's NOEL = 75 mg/kg/d. Reviewer's NOEL = 30 mg/kg/d

NOTE: A NOEL of 75 mg/kg/d is higher than the NOELs for the other mouse studies by the SC route of similar or longer duration. Based on changes in liver and kidney weights, the reviewer feels that a *more conservative NOEL of 30 mg/kg is more appropriate* to use for calculating the MOE for impurities A and B. Using that value, MOEs based on dose/unit weight can be calculated for each impurity that range from (b) (4) and are considered adequate.

Reviewer's table

Impurity	Specification limit	Amount present in a 1.75 mg human dose	Mouse study used for qualification and NOEL	Lot # and % impurity	Animal dose of impurity at the NOEL (ug/kg)	HED (ug/kg)	MOE Based on HED
A		(b) (4)	996-035 28 day SC study NOEL = 30 mg/kg/d	Lot 16 Elevated A and B (b) (4)			(b) (4)
B							
C			996-028 26 wk SC study NOEL = 30 mg/kg/d	Lot 2 Elevated C and D (b) (4)			
D							

For purposes of comparison, the sponsor's calculation of the MOEs for impurities is shown below. The sponsor calculates larger MOEs based on the use of a higher NOEL for the 28-day study, and because the sponsor used the actual and not the maximum allowed human exposure to the impurity based on specification limit.

Sponsor's Table 3.2.S.4.5-10: Calculation of Human Safety Margins for Each Specified Impurity

Impurity	Imp A	Imp B	Imp C	Imp D
impurity peak area% (lot 2/16)[b]	(b) (4)			
Impurity NOEL in Mouse				
Mouse Dose of Impurity, µg/kg/day				
Impurity HED_{NOEL}, µg/kg/day				
Human Safety Margin				
Impurity HED_{HSM}, µg/kg/day				
$Area\%_{HSM}$				
Proposed Specification				

Unspecified impurities

Unspecified impurities in the drug substance were considered qualified according to ICH Q3A according to the same criteria as the specified impurities. Lot 2 had 13 unspecified impurities ranging from (b) (4)% for a total of (b) (4)%. Lot 16 had 11 unspecified impurities ranging from (b) (4)% for a total of (b) (4)%. (Table 3.2.S.4.5-8).

Measurements of unspecified impurities in BMT drug substance for the batches used in clinical testing (see 3.2.S.4. Batch Analyses) are shown below. At the proposed unspecified impurity limit of NMT (b) (4)%, a single injection of drug product (1.75 mg) would deliver a (b) (4)µg dose of each unspecified impurity (b) (4)

Sponsor's Table 3.2.S.4.5-11: Unspecified Impurities in GMP Clinical Batches

Batch	30	31	32	101
Largest Unspecified Impurity	(b) (4)			
Each Unspecified Proposed Specification				

The CMC reviewer reports that the maximum total unspecified impurities observed in registration / clinical batches (6 batches) of the drug product at all storage conditions (accelerated storage through 6 months and long-term through 36 months) was (b) (4)% and the average of the 6 batches was (b) (4)%. This is comparable to the percentage of unspecified impurities in Lot 2 and Lot 16, which were tested for toxicity at higher doses in animals.

Lastly, we note that the *total* impurities limit (specified and unspecified) for clinical batches is set at (b) (4)%, or (b) (4)ug per 1.75 mg dose.

Degradants

The sponsor has stated that both the drug *substance* and the specified impurities of the drug *substance* are stable and do not degrade at the long term [redacted] (See data from lots 30, 31, and 32, in Sections 3.2.S.7.3 and 3.2.S.4.5.6.1).

The sponsor investigated the potential toxicity of degradants that might arise in the BMT drug *product,* that is, BMT in solution, by subjecting aqueous solutions of BMT to thermal stress, then assessing the toxicity of these thermally degraded solutions of BMT in vitro and in vivo.

Toxicity of putative degradants was assessed in the studies shown in the table below. The test lot for degradants was either Lot 1, thermally stressed at 50 °C for 30 days, or Lot 701504, thermally degraded at 70 °C for 100 hours (note that there is an error in the sponsor's Table 3.2.P.5.5-8, which states that this lot was thermally degraded for 100 days). Lot 16 was used as the 'non-degraded' control in these studies (except for 996-020) and is the same lot that was used for the impurity testing. Degraded drug product lot 1 has the designation NB0170-1. Thermally treated drug product lot 16 has the designation NB0170-16.

Reviewer's table

Study # Year	Type	Dose	Lot	Comments
961039 2006	Ames	Up to 5000 ug/plate	Lot 16 and Lot 1 thermally degraded	Negative findings for both control and degraded BMT
961040 2007	Chrom ab using human lymphocytes	Up to 5000 ug/mL	Lot 16 and Lot 1 thermally degraded	Negative findings for both control and degraded BMT
996-020 2006	Mouse 28-day tox	0, 30, 75 mg/kg/d 0, 15, 30, 75 mg/kg/d	Lot 16 thermally treated Lot 1 thermally degraded	No new toxicity for degraded BMT compared to other BMT studies
996-041 2007	Mouse 3-month with 1-month recovery	0, 15, 30, 75 mg/kg/d	Lot 701504 thermally degraded	No new toxicity for degraded BMT compared to other BMT studies

The manufacturer for Lots 1 and 16 was [redacted] and the manufacturer for Lot 701504 was [redacted].

Thresholds for qualification of degradants are given in ICH Q3B. For a maximum daily dose of <10 mg, the qualification threshold is [redacted]% or [redacted]ug total daily intake, whichever is lower.

Because the sponsor did not identify any specific degradants of concern, they did not carry out a calculation of what the possible human exposure to these putative degradants might be. They stated only that "At the levels of each bremelanotide degradant in the degraded bremelanotide administered sc in the 28 and 91-day repeat dose tox studies in male and female mice, these bremelanotide degradants would have been qualified for safety".

At the highest sc dose of 75 mg/kg/d, the MOE based on body surface area compared to the human dose is [redacted]

Tox study reports used for qualifying impurities and degradants are reviewed below.

The sponsor notes that the genetox studies (Ames and chromosome aberration) were designed to meet the requirements of ICH S2B (1997). Since their studies were submitted, this guidance has been updated to: Guidance for Industry S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use. June 2012.

Study title: Bremelanotide and Degraded Bremelanotide Drug Product Bacterial Mutation Test (Ames)	
Study no.:	961039 4.2.3.3.1.
Study report location:	Application 210557 - Sequence 0002 - Study 961039
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 29, 2006
GLP compliance and QA:	Yes and Yes
Drug, lot #, and % purity:	PT-141, Drug substance lot 16, 97.6%, peptide content (b) (4) %. This lot contains elevated levels of Impurities A and B.
Drug, lot #, and % purity:	PT-141, Drug product Lot NB0170-1, 93.5%. The 150 mg/mL solution (b) (4) mg/mL by HPLC) underwent forced degradation (stressed at 50 °C for 30 days), resulting in a final concentration of (b) (4) mg/mL in terms of API. The purity of the drug product was 93.5% with (b) (4) % degradation products by HPLC. All concentrations in this report are expressed in terms of API.

Methods	
Strains:	*Salmonella typhimurium, TA98,* TA100, TA1535, TA1537 *Escherichia coli* WP2
Concentrations in definitive study:	0, 15.8, 50, 158, 500, 1581, or 5000 ug/plate Same concentrations used for both lots
Basis of concentration selection:	Not stated
Vehicle and Negative control:	2.5% glycerol
Positive control:	Without S9: Na azide, 9AC, 2NF, NQO With S9: 2AA, benzopyrene
Incubation & sampling time:	The initial test used the standard plate incorporation method (48-72 hr incubation after plating) which was negative. A confirmatory test was then conducted that utilized preincubation of the test article for 30 minutes with the bacterial mixture prior to plating.

Study Validity

Study was deemed valid.

Results

Invalid results (unusually low counts) were obtained at the 158, 500 and 1581 µg/plate dose in the confirmatory test. Therefore, this section of the confirmatory test was repeated.

Positive and negative controls were appropriate. Bremelanotide and degraded bremelanotide drug product did not show any evidence of genotoxic activity.

Study title: Bremelanotide and Degraded Bremelanotide Drug Product Chromosome Aberration Test	
Study no.:	961040 4.2.3.3.1.
Study report location:	Application 210557 - Sequence 0002 - Study 961040
Conducting laboratory and location:	(b) (4)
Date of study initiation:	29 May 2006
GLP compliance and QA:	Yes and Yes
Drug, lot #, and % purity:	PT-141: Drug substance lot 16, purity 97.6%, peptide content (b) (4)%. This lot contains elevated levels of impurities A and B.
Drug, lot #, and % purity:	PT-141: Drug product lot NB0170-1, purity 93.5% with (b) (4)% degradation products. Lot 1 was stressed at 50 °C for 30 days (Appendix 2)

Methods	
Cell line:	Human lymphocytes (male donors)
Concentrations in definitive study:	Bremelanotide and degraded bremelanotide: 10, 20, 40,80, 160, 320, 640, **1280, 2560, 5001 ug/mL** Concentrations in bold were analyzed for metaphase aberrations. Formulation analysis showed acceptable concentration except for the bremelanotide (b) (4) mg/mL. All concentrations are expressed in terms of API.
Basis of concentration selection:	MFD based on solubility
Formulation / vehicle and Negative control:	2.5% glycerol in water
Positive controls:	Mitomycin C (50, 100 and 200 ng/mL) in cultures without S9 and cyclophosphamide (8, 12, and 16 ug/mL) in cultures with S9
Incubation & sampling time:	Duplicate cultures were exposed to the test article with and without metabolic activation for 4 hours. An additional set of duplicate cultures was exposed to the test article without metabolic activation continuously for 19 hours. Colcemid (final concentration of 0.1 ug/mL) was present for the final two hours of incubation.
Cell harvest:	Cells were harvested at the end of the culture period and assessed for viability. Microscope slides were prepared from the fixed samples and scored for the percentage of metaphase cells (mitotic index), the percentage of polyploid metaphase cells (polyploidy index), and structural chromosomal damage. 200 metaphases per treatment group were examined.

Study Validity

Study was deemed valid.

Results

Positive and negative controls were appropriate. Relative mitotic index was reduced at the high dose for BMT and degraded BMT. Bremelanotide and degraded bremelanotide drug product did not show any evidence of genotoxicity in the chromosomal aberration assay.

General tox:
Study 996-020 (similar in design to impurity study 995-035), specifically looks at degraded (Lot 1) or thermally treated (Lot 16) drug substance. The sponsor described how Lot 1 was thermally degraded but did not provide details regarding how Lot 16 was 'thermally treated'.

Study title: A 28-day subcutaneous dose toxicity study of thermally-treated PT-141 drug product and degraded PT-141 drug product in B6C3F1 mice.	
Study no.:	996-020 4.2.3.7.6.
Study report location:	Application 210557 - Sequence 0002 - Study 996-020
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 11, 2006
GLP compliance and QA:	Yes and Yes
Drug, lot #, and % purity:	PT-141, drug product lot NB0170-1 stressed at 50 °C for 30 days, purity 93.5% PT-141, drug product lot NB0170-16, thermally treated, purity 97.6%

Methods	
Doses:	0, 15, 30, 75 mg/kg/d degraded Lot 1 0, 15, 75 mg/kg/d thermally-treated Lot 16
Route of administration:	SC injection 4 mL/kg in 2.5% glycerin/sterile water
Number/Sex/Group:	10/sex/dose No TK groups
Deviation from study protocol:	None significant

Results

There were no treatment-related effects on survival, clinical observations, or ophthalmology. Injection site reaction were noted. There were slightly increased body weights (~4%) in males at the end of 4 weeks but no effects in females. Both males and females in the high dose groups consumed 9 -17% more food between weeks 2 and 4.

Clinical chemistry: All treated males showed increased transaminases that did not show dose-dependence and did not achieve statistical significance to due high variability. Total protein and albumin were statistically increased relative to control in nearly all treated females (not dose-dependent). Calcium was statistically increased in both groups of females receiving thermally-treated PT- 141, but the values remained within expected ranges and were attributed to the higher albumin values.

Organ weights: Liver: A 14% increase in both absolute and relative liver weights were observed in the high dose females of the thermally-treated PT-141 group. Histologically, 2 of the 10 females in this group exhibited minimally increased hepatocellular glycogen.

Kidney: Minimally increased absolute or relative kidney weights were observed in all treated groups. A slightly increased incidence of chronic progressive nephropathy was observed in the high dose groups. Toxicological relevance is uncertain.

Formulation analysis: Lot 1 dosing solutions at the high dose were 16% above expected, and Lot 16 at the high dose were 19% above. These differences were not thought to affect the results of the study.

Conclusion: There was no new toxicity noted with degraded or thermally-treated test articles.

Study title: A 91-day subcutaneous toxicity study of degraded Bremelanotide (PT-141) in B6C3F1 mice with a 28-day recovery period.	
Study no.:	996-041
Study report location:	Application 210557 - Sequence 0002 - Study 996-041
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 27, 2007
GLP compliance and QA:	Yes and Yes
Drug, lot #, and % purity:	PT-141, Lot 701504 thermally degraded at 70°C for 100 hours, purity 95.6%, total degradants (b) (4)% (specified and unspecified) From the COA p 128: The 125 mg/mL solution underwent forced degradation resulting in a final concentration of (b) (4) mg/mL.

Methods	
Doses:	0, 15, 30, 75 mg/kg/d
Route of administration:	SC injection 4 ml/kg in 2.5% glycerin/sterile water
Number/Sex/Group:	20/sex/dose (control and high dose) 10/sex/dose (low and mid dose) 10/sex/dose in the low and high dose for recovery No TK groups
Deviation from study protocol:	None significant

Results

Mortality was observed but was not treatment-related. Injection site reactions were noted. Body weight and food consumption was stable in females and stable or slightly increased in males during the middle portion of the study.

Hematology: In male mice but not female mice, hematocrit, erythrocytes, and hemoglobin were mildly increased in all dose groups with a trend toward dose-dependence with most changes being statistically significant but not adverse.

Clinical chemistry: Chloride was decreased in males 8% and 5%, and in females 6% and 6% at the 30 and 75 mg/kg/day doses respectively. These changes resolved by recovery in males but remained decreased in the females at the 75 mg/kg/day dose group with limited data. These changes appeared to be test article-related and adverse, but no mechanism was proposed for why chloride levels were decreased.

There were sporadic individual animals in all groups, including controls that had increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and/or sorbitol dehydrogenase. All changes were reversed during the recovery period except that AST values were abnormally high in the control groups in both males and females.

Organ weights: The statistically significant mean liver, kidney, and lung weight changes were either inconsistent or lacked microscopic correlates. Mean absolute kidney weights were less than 10% greater than controls in all dose groups of both sexes. Mean absolute liver weight at 75 mg/kg/day in males was only 10% greater than controls and in females was only 16% greater than controls. Mean absolute lung weight in males at 30 mg/kg/day was only 12% less than controls while the lung weight at 75 mg/kg/day was essentially the same as the control weight (0.191 grams in controls and 0.196 grams at 75 mg/kg/day). These small weight differences, though statistically significant, were not considered toxicologically significant.

Formulation analysis: Acceptable.

Conclusion: Based on these results the NOAEL was 30 mg/kg/day degraded bremelanotide, which is the same as the NOAEL for 4-week and 26-week repeat dose studies with other bremelanotide lots (6AB2 and Lot 2, respectively). There were no new toxicities that arose from testing with thermally degraded BMT drug product.

The MOE at the NOAEL based on BSA was 82.

Additional comments:

For documentation purposes, we list a description about the lots that were used for qualifying impurities that were not specified by the sponsor:

- How the elevated impurities in Lots 2 and 16 were generated was not specified. Were the impurities spiked in the final drug product or did the impurities result from thermal stress applied to the drug substance or drug product?
- The specified impurities were not identified on the COAs for Lots 2 and 16 submitted to the study reports. At present, the only information that we can find on the levels of the specified impurities appears in Table 3.2.S.4.5-17.
- The purity levels of Lots 2 and 16 given in Table 3.2.S.4.5-17 do not exactly match the COAs.
- In study #996-020, (28-day mouse degradant study), how Lot 16 was thermally treated was not stated.
- The duration for thermal degradation for Lot 701504, used in study 996-041 (91-day mouse degradant study) was erroneously stated in Table 3.2.P.5.5-8 to be 100 days. The correct duration, 100 hours, is stated on the COA in the study report on p 128.

Leachables / extractables:

No concerns.

2.6 Proposed Clinical Population and Dosing Regimen

BMT is indicated for the treatment of premenopausal women with hypoactive sexual desire disorder (HSDD).

The recommended dosage is 1.75 mg in an 0.3 mL solution administered via an autoinjector pen into the abdomen or thigh, to be dosed 45 minutes before anticipated sexual activity. Tmax occurs ~60 min post-injection, and the half-file is ~2-3 hrs. **For a 1.75 mg dose, mean Cmax was 77.1 ng/mL and AUC_{0-4h} was 276 ng.hr/mL.**

The allowed frequency of use has not yet been determined by the clinical team but will not exceed once daily. There will likely be a limitation of use not-to exceed 8 times per month.

2.7 Regulatory Background

Earlier development programs for BMT included the treatment of erectile dysfunction in males (b) (4), 61706, and (b) (4) and (b) (4) Most of the nonclinical program for bremelanotide was conducted under IND 61706 for the male indication. (b) (4) IND 61706 was withdrawn in 2017. Study reports for the various indications were submitted in paper format until September 2016, when electronic submission began.

The IND supporting this NDA for hypoactive sexual desire disorder (HSDD) in females is 64119, which was opened in 2001. The initial clinical studies in females were conducted by the intranasal route, similarly to males. It is not clear whether IND 64119 (female indication) was cross-referenced to IND 61706 (male indication) at the time of initiating clinical trials in females; safety determinations were based on equivalence of the intranasal formulation that had been tested in males. Dr. Krishan Raheja was the primary nonclinical reviewer for IND 64119 until 2013, at which time the IND was transferred to this reviewer and an EOP2 meeting was held. At that time, the nonclinical program was deemed sufficient to progress to Phase 3 clinical testing. Phase 3 clinical testing was conducted by the subcutaneous route.

3 Studies Submitted

3.1 Studies Reviewed

All the studies submitted in paper format to IND 61706 have been submitted to this NDA in electronic format (b) (4) .

All the studies submitted to this NDA except the analytical methods and validation reports under section 4.2.2.1, and some pharmacology studies related to the male indication of erectile dysfunction, have been reviewed by this reviewer, including those originally reviewed by Dr. Raheja.

Studies on abuse potential are being reviewed by Dr. Katherine Bonson, of the controlled substances staff. Her review will be filed to DARRTS separately.

An assessment of immunogenicity was made by Dr. Susan Kirshner, CDER/OPQ.

3.2 Studies Not Reviewed

Analytical methods and validation reports under section 4.2.2.1 have not been reviewed. Pharmacology studies related to the male indication of erectile dysfunction have not been reviewed.

3.3 Previous Reviews Referenced

The nonclinical development program conducted under the various INDs submitted to DBRUP was reviewed by Dr. Krishan Raheja. His reviews, primarily of studies submitted to IND 61706, were written over a 12-year period have been collated, edited for clarity by this reviewer, and will be submitted to IND 64119 when this review is filed. Some of Dr. Raheja's comments have been incorporated into this NDA review. In addition, some of the nonclinical studies conducted by the sponsor have been published and are referenced when appropriate.

4 Pharmacology

4.1 Primary Pharmacology

Bremelanotide is a synthetic cyclic heptapeptide analog of α-melanocyte-stimulating hormone (α-MSH). It is a high-affinity ligand and agonist for melanocortin receptors (MCRs), specifically MC1R, MC3R, and MC4R. The sponsor proposes that the therapeutic effect for HSDD occurs [redacted] (b) (4) However, this mechanism of action in humans is speculative.

α-MSH is a cleavage product of proopiomelanocortin (POMC). Its primary function is to stimulate production of melanin by melanocytes. It also plays a role in feeding behavior, energy homeostasis, sexual activity, and protection against ischemia and reperfusion injury.

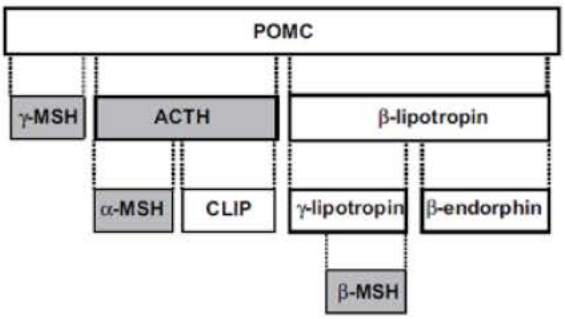


FIG. 1. Melanocortin peptides, ACTH and α-, β-, and γ-MSH, derive from post-translational processing of POMC, which is also the precursor for opioid peptides and CLIP (corticotropin-like intermediate lobe peptide). From Catania et al., 2004.

Distribution of receptors, and naturally occurring agonists and antagonists are listed in the table below. Ref: Catania et al., 2004 and RD Cone 2006; also Yang 2011.

Receptor	Sites of expression	Functions	Agonists	Antagonists
MC1R	Melanocytes; Immune / inflammatory cells, keratinocytes, endothelial cells, glial cells	Pigmentation Antipyretic / anti-inflammatory	αMSH = βMSH = ACTH > γMSH	Agouti
MC2R	Adrenal cortex	Steroidogenesis	ACTH	
MC3R	CNS, GI tract, kidney, macrophages	Autonomic functions, anti-inflammatory	γMSH = αMSH = ACTH > βMSH	Agouti related peptide (AgRP) (inverse agonists)
MC4R	CNS	Feeding and energy homeostasis, erectile activity	αMSH = βMSH = ACTH > γMSH	AgRP, Agouti
MC5R	Exocrine glands, lymphocytes	Regulation of exocrine secretion, immunoregulatory function	αMSH > βMSH = ACTH > γMSH	

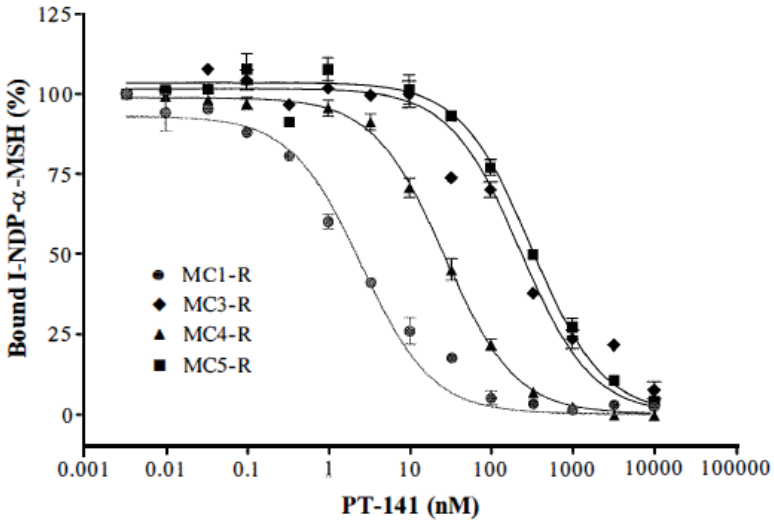
Binding assays:
Study # PL-27: PT-141 (BMT) binding to various melanocortin subtypes.
This non-GLP study measured the relative binding affinity of BMT to MC1R, MC3R, MC4R and MC5R melanocortin receptor subtypes in a competitive binding assay with [I^{125}]-NDP-α-MSH as the radioligand. Studies were carried out on membranes isolated from various cell lines expressing melanocortin receptors. MCR1 containing membranes were isolated from B16-F10 mouse melanoma cells. Other MCR subtypes were isolated from transfected HEK-293 cells overexpressing cloned human MCRs.

Bremelanotide is selective for MC1R and MC4R, with 98% inhibition of the reference compound, but also binds MC3R. The relative binding affinity of BMT was: MC1R > MC4R > MC3R > MC5R. The sponsor stated that bremelanotide does not bind to MC2R (the ACTH receptor expressed on the adrenal gland; Kd > 1000 nM), but no source data on MC2R was provided. The K_i of the receptor for PT-141 was calculated from the IC_{50} (shown in the sponsor's table below).

	K_I (nM)			
	MC1-R	MC3-R	MC4-R	MC5-R
Mean	0.7	98	14	225
Range*	0.4 – 0.9	77 - 137	7.3 – 19.4	220 – 248
n	3	3	7	3

*K_I range is from a number (n) of separate experiments performed over several months.

Sponsor's Figure: Binding Curves of Bremelanotide (PT-141) to Melanocortin Receptors



There were no data presented for binding of BMT to the MCRs of other nonclinical species, but literature states that MC4Rs are highly conserved across many species, with, for example, 93% identify between rat and human (Tao, 2010).

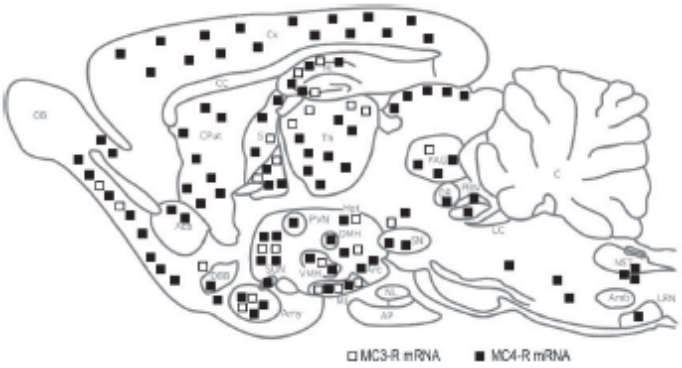
It is expected that a therapeutic dose of BMT will yield tissue concentrations that are sufficient to produce pharmacological activity at the MC4R. Human PK data show that the Cmax following a single 1.75 mg injection of bremelanotide is 72.8 ng/mL. Assuming 13% bound (see section 5.1 of this review for protein binding data), this yields a free concentration in plasma of 63 nM, well above the Ki for binding to MCR1 and MCR4. Also, MC3R might be partially bound.

It should be remembered that, while BMT concentration in peripheral tissues may be close to the levels in plasma, BMT access to the CNS, (b) (4) is limited. Distribution studies (discussed below) indicate that BMT concentration in the brain peaks several hours later than in plasma and reaches only ~10% of the maximal plasma free concentration. This implies that MC4Rs in the brain might be only partially activated.

Functional assays:
Bremelanotide was shown to be an agonist at MC4R in functional assays (Studies PL-03 and PL-35). BMT induced cAMP production in MC4R-transfected HEK-293 cells with a mean EC_{50} of 1.1 nM. Thus, the EC_{50} is about 10-fold lower than the Ki derived from binding experiments. The maximum cAMP level was 825 pmol/10^6 cells, which was 68% of the response produced by α-MSH. Additional detail regarding signalling pathways activated by MC4 agonists is available in Yang, 2011.

Distribution of MC4R receptors
Specificity of BMT action is determined by the distribution of melanocortin receptors to which it binds. MC4Rs are located primarily on neurons in the central nervous system but have also been identified on peripheral nerve endings in the penis (Van der Ploeg et al., 2002).

Distribution of MCRs in the brain has been extensively characterized in many nonclinical species. In the rat, MC4 receptors are present in virtually every region of the brain, and in some regions of the spinal cord (Nahon, 2006; Mountjoy et al., 1994). Areas of expression of MC4 and MC3 receptors often overlap.



Distribution of MC3R and MC4R mRNA expression in the rat brain.
Open and black squares correspond to MC3R and MC4R, respectively.
Fig. 1 from Nahon 2006.

The *highest density* of MC4 receptors are in the following regions of the rat brain:

Forebrain
- Hypothalamus
  - Periventricular zone
    - Anteroventral periventricular nucleus (APV)
    - Supraoptic nucleus (SO)
  - Medial zone
    - Medial preoptic nucleus
    - Anteroventral preoptic nucleus
- Septal region
  - Lateral septal nucleus
  - Medial septal nucleus

Midbrain and Brainstem
- Dorsal motor nucleus (DMN) of the vagus nerve
- Superior colliculus (SC)
- Pretectal region
  - Nucleus of the optic tract

Functions mediated by MC4 receptors:

As would be expected from their widespread distribution in the brain, MC4 receptors mediate a diverse array of physiological functions and behaviors (Adan and Gispen, 1997; Wikberg and Mutulis, 2008; Tao, 2010; and Mul et al., 2013). For the purposes of discussing the expected pharmacology of BMT administration, we will focus on four of these.

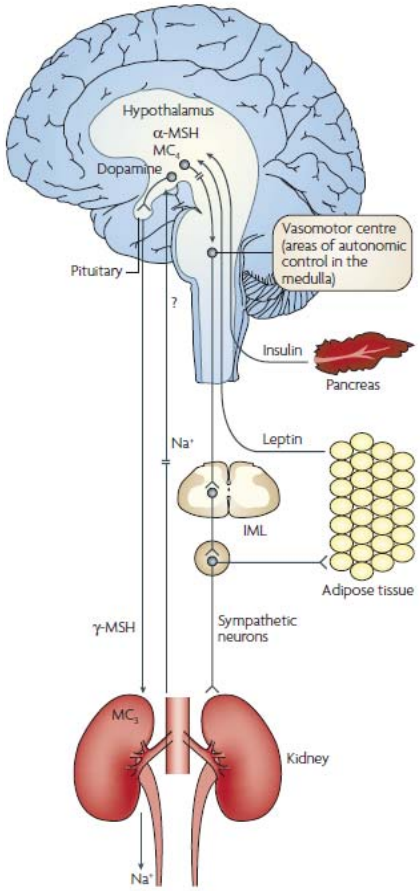
1. Energy homeostasis and feeding behavior
   MC4R has been primarily associated with energy homeostasis and has been extensively investigated in obesity research. Although the brain circuitry regulating feeding behavior and body weight is complex, it is clear from many studies that agonism at the MC4R reduces body weight, and that antagonism leads to obesity. Knock out of the MC4R in the mouse produces animals that are obese, hyperphagic, and hyperinsulinemic (Cone, 2006; Huszar et al., 1997). In mice, central administration of the MC4R agonist MT-II inhibits basal insulin release (Tao, 2010). Expected pharmacology following administration of an MC4 agonist would thus be expected to be reduced feeding and weight loss, reduced insulin production and possible glucose elevation.

2. Sexual function
   Induction of penile erection by melanocortin agonists in multiple species has long been noted (for review see King et al., 2007). (b) (4)

   (b) (4)

3. Autonomic functions
   The high density of MC4Rs in the hypothalamus and the DMN of the vagus suggests their involvement in the regulation of many types of autonomic output (for reviews see Tao, 2010, and Adan and Gispen, 1997). We focus here on the cardiovascular system and, briefly, the GI system, in order to explain findings that were observed in clinical alone and both clinical and nonclinical studies.

Cardiovascular function:
The role of the melanocortin system in the regulation of hemodynamics is very complex and not completely understood (do Carmo et al., 2017). The circuitry that has been described to date involves the hypothalamus, brain stem, and spinal cord, MC4 and MC3 receptors, α and γ MSH, and feedback from peripheral tissues, including the kidney (see diagram below for overview).



Melanocortin-mediated cardiovascular control. Peripheral signals transmitted by leptin and insulin reach the hypothalamus and stimulate proopiomelanocortin (POMC) neurons, which in turn activate melanocortin 4 (MC4) receptors. MC4 receptor activation then mediates peripheral sympathetic activation, presumably by both direct and indirect signalling processes, leading to increased peripheral vascular resistance and sodium reabsorption in the kidney. This cascade of events manifests as an increase in blood pressure. Conversely, sodium stimulates the production and release of γ-melanocyte-stimulating hormone (γ-MSH) from the pituitary into the peripheral circulation. This activates MC3 receptors in the kidney, which exerts a natriuretic effect that reduces the amount of extracellular body water and cardiac load, thus reducing blood pressure. There is evidence that the actions of dopamine in the CNS may have a role in connecting the peripheral signal of Na+ to γ-MSH in the pituitary. However, the exact pathway for the effect of Na+ on dopamine is not known as indicated by the question mark.
IML, intramediolateral column.
Figure 2 Wikberg and Mutulis, 2008.

It is beyond the scope of this review to fully describe this system. Rather, we will highlight what is known about MC4 receptors specifically, and later, under the Safety Pharmacology section, discuss the findings obtained by the sponsor using bremelanotide.

Literature studies describing the cardiovascular response to MC4R activation have shown that cardiovascular effects vary depending on the species, the type of MC4R agonist used, the route of administration, the site of administration, that is, which region of the brain or brainstem is stimulated, and whether administration is acute or chronic (Rinne et al, 2012). In rodents, direct activation of MC4 receptors in the DMN of the vagus by injection of α-MSH into the brainstem produces bradycardia and hypotension (Li et al., 1996). In contrast, injection of α-MSH intracerebroventricularly (ICV), targeting the MC4 receptors of the hypothalamus, produces the opposite effect: tachycardia and hypertension (Ni et al., 2006). Increased HR and BP have also been noted when the MC4R agonist MT-II is perfused ICV, and the effect is mediated by adrenergic activation (Kuo, et al., 2004). Mixed results have been obtained when comparing acute vs chronic administration. The acute hypertensive response of α-MSH abates with chronic administration via the ICV route (Hill and Dunbar, 2002), a result that was not duplicated with MT-II (Kuo et al., 2003). It has been suggested

that functional responses to melanocortins may depend on the balance between MC4 and MC3 receptors, and obesity may also play a role (Da Silva et al., 2006).

In humans, sc infusion of an MC4R agonist leads to elevated blood pressure, and subjects with loss of function mutations in MC4R have a reduced incidence of hypertension (Greenfield et al., 2009). Prior clinical experience in males with BMT also indicates that a hypertensive response to MC4R activation is the more likely response (Rosen et al., 2004).

GI function:
MC4 receptors are expressed on vagal afferents, and the stomach and duodenum are innervated by MC4R vagal afferents and efferents. Injection of melanocortin agonists into either the DMV or NTS decreases phasic gastric contractions. There is also evidence the MC4 receptors are expressed on enteroendocrine L cells in the GI tract (Panaro et al., 2014). Thus, MC4R agonists can play a role in slowing gastric emptying, which could affect drug absorption. The effect of BMT on the kinetics of drug absorption and drug-drug interaction was investigated in a nonclinical study in the mouse but no effect was found. BMT was found to have emetic activity in the ferret.

4. HPA axis

The presence of MC4 receptors at high density in the periventricular region of the hypothalamus indicates that the melanocortin system influences the HPA axis, however, there is not a large literature defining what these effects might be. MC4Rs are expressed on both magnocellular and parvocellular neurons in the PVN. Magnocellular neurons project to the posterior pituitary (neurohypophysis) and secrete vasopressin and oxytocin; parvocellular neurons project to the median eminence and secrete releasing factors (CRH, TRH, etc.) that stimulate release of hormones from the anterior pituitary (adenohypophysis). In the rat, ICV injection of MT-II has been shown to induce synthesis of CRH (and presumably ACTH), followed by a rise in plasma corticosterone (Lu et al., 2003). MC4 receptors also play a role in grooming behavior in rodents, which may be tied to a stress response (Mul et al., 2013). In the description of the MC4R knockout mouse – no particular emphasis was placed on distruption of the HPA axis, which indicates that melanocortins may play a more limited, modulatory role. Effects on the HPA axis were infrequently monitored in nonclinical studies for this application. Elevated ACTH and cortisol was noted in only one study in the pregnant rat (996-029) that used intravenous dosing at maternally toxic levels.

4.1.2 Drug mechanism related to indication

A mechanism of action for the treatment of HSDD in females has not been established. There were no studies submitted by the sponsor investigating the effect of BMT on sexual behavior in female animals. There are a few published studies that indicate that melanocortins in general, and bremelanotide in particular, can induce sexual receptivity in the female rat (Nocetto et al., 2004; Pfaus et al., 2004). Bremelanotide is effective in female rats for solicitation behaviors following either subcutaneous administration or following infusion into the lateral ventricles or medial preoptic area (mPOA) (Pfaus et al., 2004 and 2007).

(b) (4)

(b) (4)

4.2 Secondary Pharmacology

MC1 receptor

Because BMT binds with higher affinity to MC1 receptors than to MC4Rs, secondary pharmacology mediated by the MC1 receptor is expected. MC1 receptors are expressed on melanocytes and have also been reported on cells of the immune system. Activation of the MC1 receptor leads to melanin production by melanocytes, producing hyperpigmentation. Treatment with bremelanotide produced blackening of the coat in the dog (Study #996-003) and hyperpigmentation was noted in clinical studies as well.

Melanocortins also act as anti-inflammatory and anti-pyretics via MC1 but this effect was not assessed in nonclinical studies (Catania et al., 2004).

Other receptors

Off target binding was assessed in (b) (4) study #5040a: "Study of PT-141 in a pharmacological profile". Bremelanotide (1 uM) showed weak activity at the muscarinic acetylcholine (M) and the alpha-2 adrenergic (α2) receptor and there was some evidence of binding to vasoactive intestinal peptide 1 and neuropeptide Y receptors.

Bremelanotide was *not* reported to bind to serotonin receptors – but no subtypes were specified. Regarding the assay used to assess binding, the sponsor referenced a publication by Peroutka and Snyder from 1979, which describes a method for distinguishing between 5-HT1 and 5-HT2 receptors. However, the reference compound used in the screening assay was serotonin, which would not have distinguished between receptor subtypes.

Weak activity at serotonin transporters was reported, equal in magnitude to activity at dopamine transporters. Thus, if bremelanotide acted as a weak SSRI, some indirect activation of 5-HT receptors might occur.

Binding at these off-target receptors occurred at concentrations that are not therapeutically relevant.

4.3 Safety Pharmacology

Twenty studies were conducted to assess safety pharmacology – broken down as follows:

- o Central nervous system (CNS) – 1 in vivo study in the male rat
- o Cardiovascular – 2 in vitro and 12 in vivo studies in dog, rat, and monkey.
- o Respiratory – 1 in vivo study in the male rat
- o Gastrointestinal – 4 in vivo studies in the male ferret

There were no findings in the CNS study, but dosing (by the iv route) did not reach therapeutically relevant concentrations.

Cardiac safety studies were negative for cardiac arrhythmia, but positive for elevated heart rate (HR) and blood pressure (BP) at high multiples of human exposure.

BMT produced an emetic response in ferrets at doses that were comparable to human therapeutic exposures.

BMT was negative for effects on the respiratory system at doses comparable to human therapeutic exposure.

4.3.1 CNS

Study #1468-PAL-01. Effects of PT-141 on behavior and physiological state as assessed by the Irwin test and on body temperature in rats. Conducted by (b) (4) , in 2001. GLP + QA. PT-141 lot 0539373. Purity 94%.

Methods:

Dose and Route: 10, 75, 300 ug/kg iv	Injection volume 2 mL/kg
N = 5 male SD rats/dose	No TK
Vehicle: 0.9% saline	Positive control: Apomorphine 0.3 mg/kg iv

Results:
There was no mortality. There was no effect on body temperature. The results of the Irwin test were reported in tabular fashion with no narrative. Animals were scored on 27 behaviors. Twenty-six of these were specific – tremor, convulsion, piloerection, etc. One of these was nonspecific – "typical" or "global behavior'. The animals showed a dose- and time-dependent statistically significant change in 'typical' behavior, with scores trending downward toward the apomorphine score and becoming maximal at the 60-minute time point, which was the last time point reported. However, while there were occasional trends toward increased frequency in some of the other 25 specific behaviors, none reached dose or time-dependent significance. It is thus somewhat unclear as to whether the observed changes were adverse. The sponsor did not set a NOAEL.

Results of the dosing solution analysis were not included in the study report. From TK measurements obtained in study #91-0501 (4.2.2.2.) an intravenous dose of 250 ug/kg produced an AUC = 69 ng.hr/mL which is ~25% of the therapeutic AUC.

4.3.2 Cardiac

The sponsor's tabulated summary (2.6.3) of cardiovascular safety pharmacology studies lists 2 in vitro studies and 11 in vivo studies in dog and monkey. In addition, one drug-drug interaction study was conducted in the rat to determine whether co-administration of bremelanotide and sildenafil would affect CV parameters. These studies, plus several others conducted to evaluate CV safety, are listed either under the safety pharmacology section (4.2.1.3) or the general toxicology section (4.2.3.2.) of the submission.

The two in vitro studies, a hERG channel assay and a cardiac action potential assay, followed standard study designs and were negative.

In vivo studies were conducted by the iv, sc, and intranasal routes. ECG studies were conducted in the dog and monkey, by the intranasal route, and were negative. The effect of BMT on blood pressure was examined in rat, dog, and monkey and yielded positive findings in the rat and dog. However, no one study met all the criteria necessary to be considered a valid GLP study for assessing CV safety. For that reason, conclusions regarding CV safety are based on weight of evidence from the in vivo studies listed in the table below. Detailed reviews of selected studies follow.

Study number /Section	Conducting Lab / Year	Test system / Species	Doses (mg/kg) / Route	Results	MOE	Comments
In vitro						
hERG assay 010911.QBM 4.2.1.3	(b) (4)	HEK-293 cells	0.25, 2.5, 10, 100, 1000 uM	No effect at ≤ 10 uM IC_{50} 4610 uM	--	
Action potential assay 20020616 PECM 4.2.1.3		Cardiac Purkinje fibers (dog)	0.15, 1.5, 15 uM	No effect	--	
		In vivo single dose				
12513 02 01B* 4.2.1.3		Dog (M) N=3	0.1, 1.0 IV 0.01, 0.1, 1, 3, 10 SC	↑ BP @ >0.1 sc ↑ HR @ >0.01 sc	BP: >0.5X HR: <0.5X	Continuous monitoring 4 hrs post dose then hourly to 24 hrs
SP-SPG-2299* 4.2.1.3		Dog (M) N=2	0.05, 0.205 IV two-step infusion	↑ HR (slight)	6.5X	Continuous recording for 5 hrs post-dose and for 1.5 hrs @ 24 hrs
SP-SPG-2403* 4.2.1.3		Dog (M) N=4	0.05, 0.205 IV	↑ HR @ high dose; trend toward ↑ BP	2-8X	Continuous recording for 24 hrs post-dose
131-007* 4.2.3.1		Dog N=2M/2F	3, 6, 9, 12 SC	no effect on BP		BP/HR @ 15-90 min
131-008 4.2.3.1		Dog N=4M/4F	9, 12, 15 SC	No effect on BP; ↑ HR @ all doses 1-3 hrs	56.6X at the low dose	BP/HR 0.25, 0.5, 1, 3, 6, 24 hrs sparse
WTAW-103 4.2.1.3		Monkey N=4M	0.2, 0.6, 1, 2 IN	No effects on ECG, HR, BP		10 and 40 min only
3133 4.2.1.3		Monkey N=4M	0.05, 0.2, 1 IN	No effects on ECG, cardiac function, CV parameters	3.6X at the low dose by AUC; no TK data at the high dose	Every 5 min for 2 hrs
Single dose Drug interaction PL-40* 4.2.1.3	Palatin Technologies 2003	SD rat	0.003, 0.1, 1, IV w/ or w/out 5 mg/kg sildenafil or 50 mg/kg ISDN	↑BP and HR	1X at the high dose	Continuous monitoring
		In vivo repeat dose				
28-day 131-011 4.2.3.2	(b) (4)	Dog N=4M/4M	2, 4, 8 SC	No effects on BP, HR		BP measured at 30, 60 min post dose only
32-week 996-003 4.2.3.2		Dog N=4M/4F	2, 8, 20 SC	No effects on ECGs, BP, HR	198X at the high dose	ECG and BP measured at 1 hr post dose only
28-day WTAW-107 4.2.1.3		Dog N=3M	0.65 IN	No effects on ECGs, BP, HR	0.5X	Continuous monitoring

28-day 131-001 4.2.3.2	(b) (4)	Dog N=4M/4F	0.03, 0.15, 0.65 IN	No effects on BP, HR	0.5X at the high dose	Tmax @5 min
90-day 131-002 4.2.3.2		Dog N=4M/4F	0.03, 0.15, 0.65 IN	No effects on ECG or BP	0.5X at the high dose	Times not given

* Non-GLP

In vitro studies

Standard in vitro studies demonstrated no block of the hERG channel by BMT, and no effect on action potential duration in cardiac Purkinje fibers, at doses that exceeded the therapeutic range.

In vivo studies

Single dose studies in the dog by the iv and sc routes

Three studies were conducted by the iv route in the dog, one of which included dosing by the sc route for comparison. These studies were conducted in 2008 and 2009, after the other safety pharmacology studies had been completed and after the single-dose general tox studies in the dog had been conducted. Even though these studies did not meet GLP criteria, the continuous monitoring for BP and HR changes, acquired by telemetry, was far superior to the limited BP and HR measurements made in the single dose general tox studies that the sponsor has cited to support cardiovascular safety. For that reason, results of these studies are presented in detail below, and are used in the overall assessment of cardiovascular response to BMT.

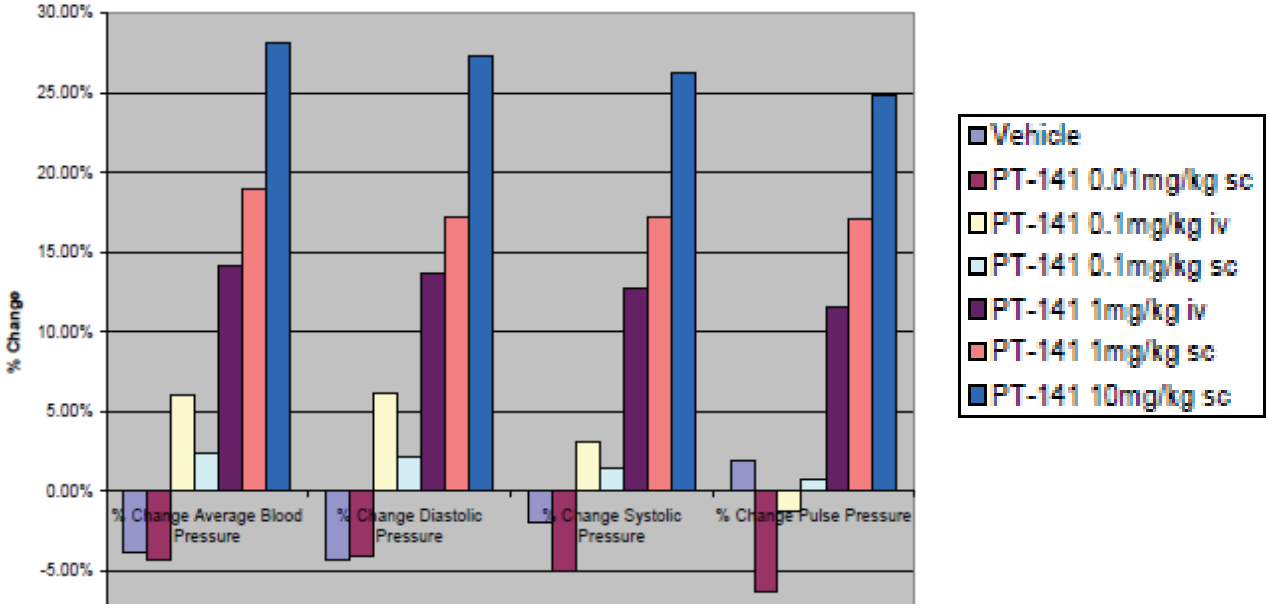
12513 02 01B: Exploratory Pharmacokinetic Study and Cardiovascular Evaluation of PT-141 in Beagle Dogs. Non-GLP. PT-141 Lot 32. This study compared administration of bremelanotide via the iv versus the sc route and had both PK and CV endpoints. The sc doses (0.01, 0.1, 1, 3, and 10 mg/kg) ranged 10-fold higher than the iv doses in order to produce adequate exposure. The iv doses used (0.1 and 1 mg/kg) were higher than the doses used in the two other preliminary studies (SP-SPG-2299 and SP-SPG-2403) that were similarly conducted. Dosing formulations were not verified.

Methods:
Blood pressures and heart rates were monitored continuously using telemetry for 4 hrs before dosing, 4 hrs after dosing, and then every 60 minutes thereafter through 24 hrs after dosing. Systolic and diastolic blood pressures and heart rates were recorded. ECGs were not recorded. Blood samples for plasma drug level analysis were collected prior to dosing and at 15 and 30 minutes and at 1, 2, 4, and 8 hours after dosing. The results are reported in Palatin Study Report #PL-76 (Section 4.2.2.2)

Results:

- Clinical signs: There was excessive stretching and/or panting at all dose levels.
- CV parameters. There was dose- and time-dependent increased mean BP and HR for either the iv or sc route. The greatest increase was observed for 10 mg/kg sc, which produced a mean 28% increase in BP over the 4-hour continuous monitoring period. Blood pressure values were consistently elevated over the highest predose values for an average 25 minutes following dosing and remained elevated up to 19 hours after dosing. BMT administered at 1 mg/kg iv and sc produced average increases of 14.2% and 19% in blood pressure, respectively, over the same period. Heart rate also increased in a dose- and time-dependent manner. Data from the sponsor's study report are shown below.

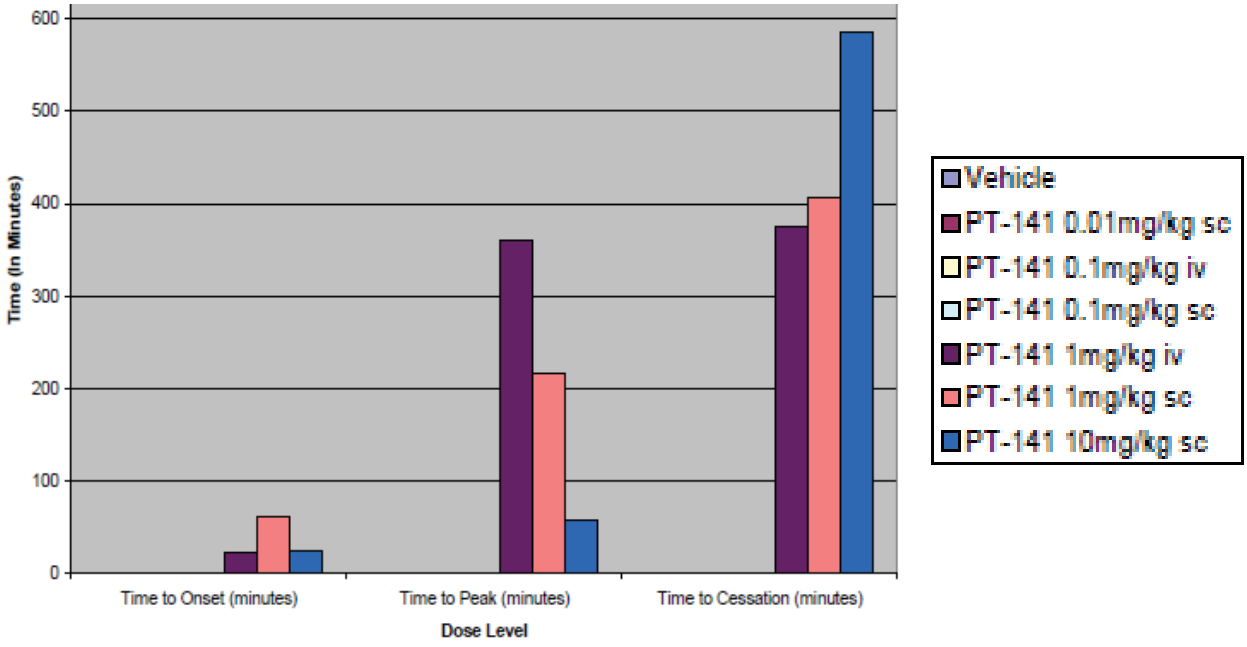
Percent Changes by Dose Group in Blood Pressure 4 Hours After Dosing
Figure B4 Appendix B p 65



The 4 groupings show the dose-dependent change in average blood pressure, diastolic pressure, systolic pressure, and pulse pressure (systolic – diastolic).

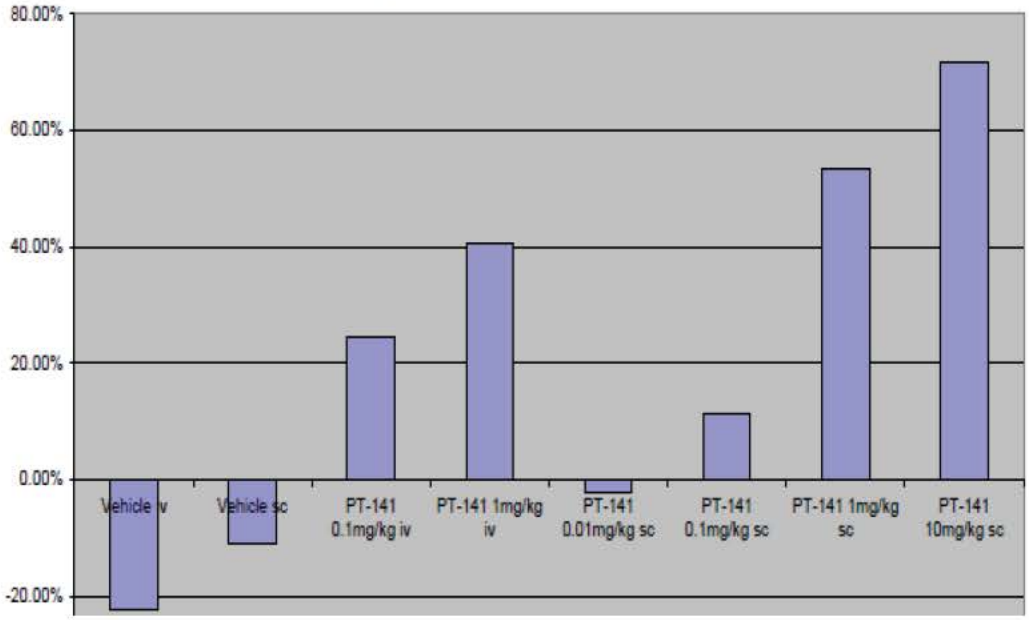
The onset and duration of the BP effect was dose-dependent, and the peak effect at the lower doses lagged behind the Tmax, which was 0.5-0.7 hrs. The peak effect on BP at 1 mg/kg iv or sc was ~4-6 hrs post dose. The peak effect on BP for a 10 mg/kg SC dose was ~ 1 hr.

Average Time after Dosing to Onset of Key Blood Pressure Points by Dose Group
Figure B5 Appendix B p 66

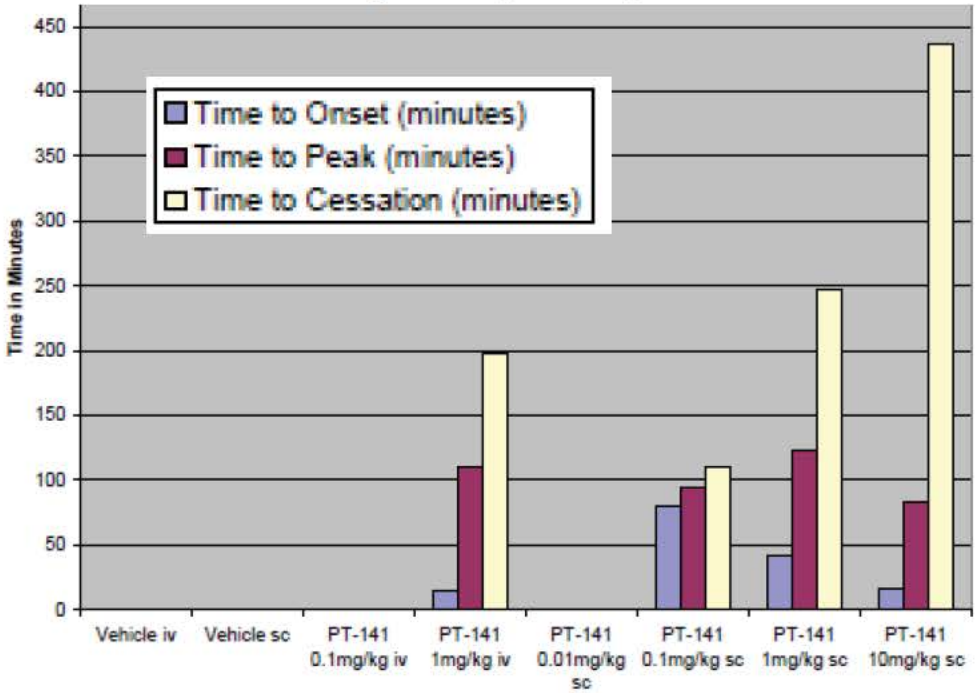


Heart rate was also increased in a dose-dependent way by bremelanotide, and the dynamics of the response were also dose-dependent. In contrast to BP, HR tracked closely with Tmax at all doses, and effects occurred at lower doses than for BP.

Per Cent Change Average Heart Rate After Administration of PT-141
Figure C4 Appendix C p 106

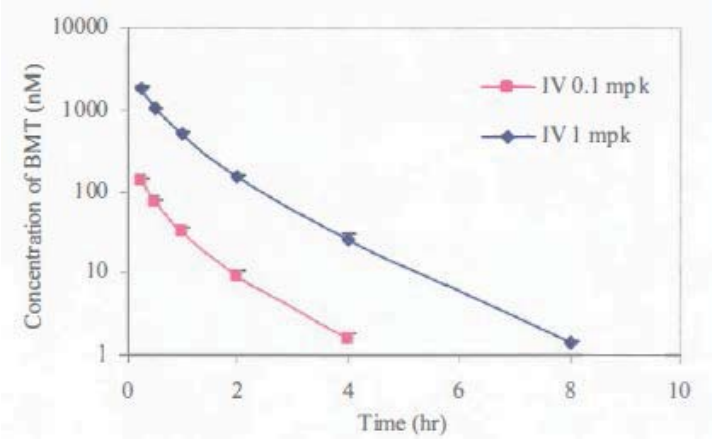


Effect on HR: Important Timepoints After Administration of PT-141
Figure C5 Appendix C p 107



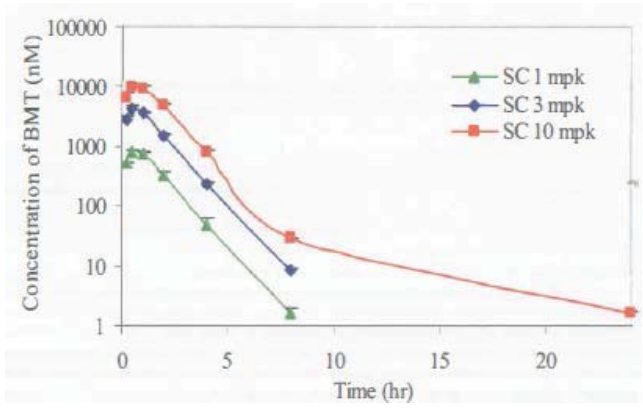
PK data from non-GLP study # PL-76 (4.2.2.2). PT-141 lot 31.

Mean concentration vs time in male Beagle dogs. N=3.
Fig 2A and 2B p. 7



Dosing Route	IV					
Dose (mg/kg)	0.1			1		
$AUC_{0-\infty}$ (nM.hr)	133	±	8	1951	±	80
CL (mL/min/kg)	12	±	1	8.4	±	0.36
V (L/kg)	0.5	±	0.03	0.4	±	0.03
$T_{1/2}$ (hr)	0.5	±	0.05	0.7	±	0.03

Bioavailability (%F) was calculated based on the AUC obtained from each dog dosed IV at 1 mg/kg.



Dosing Route	SC								
Dose (mg/kg)	1			3			10		
$AUC_{0-\infty}$ (nM.hr)	1467	±	150	7282	±	97	19856	±	1558
Cmax (nM)	808	±	57	4484	±	383	10249	±	1090
Tmax (hr)	0.5	±	0.5	0.7	±	0.2	0.7	±	0.2
$T_{1/2}$ (hr)	0.8	±	0.01	0.8	±	0.00	0.8	±	0.01
%F	75			124			102		

Human therapeutic AUC = 276 ng.hr/mL or 276 nM.hr. Cmax = 73 ng/mL = 73 nM

NOEL for increased BP:

< 0.1 mg/kg iv	MOE = 0.5X the human therapeutic AUC
0.1 mg/kg sc	No TK data was available at this dose. A 10-fold higher dose of 1 mg/kg sc, which produced large effects on HR and BP, had an MOE of 5.3X the human therapeutic AUC. The high dose of 10 mg/kg sc, AUC = 19856 nM.hr, is 72X the observed human AUC at the therapeutic dose.

The NOEL for increased HR was *lower* than the NOEL for increased BP.

NOEL for increased HR:

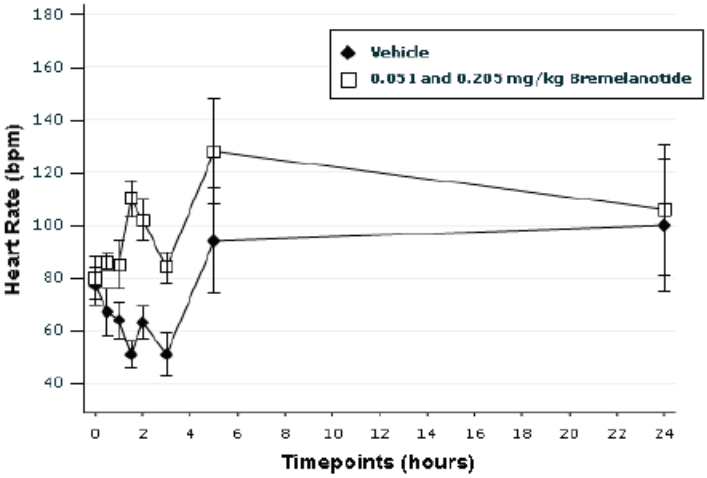
< 0.1 mg/kg iv	MOE = 0.5X the human therapeutic AUC
0.01 mg/kg sc	No TK data available at this therapeutic dose

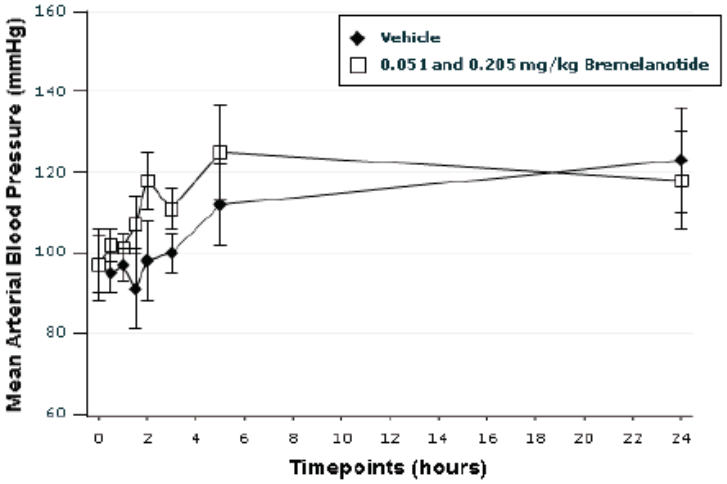
Data from the other two preliminary studies conducted by the iv route in the Beagle dog were consistent with the previously described study. The two studies had identical study design, but the first study used only two animals and yielded only qualitative results. The first study (SP-SPG-2299) is not reviewed here and the second is summarized below.

SP-SPG-2403: Bremelanotide: Cardiovascular effects in conscious, telemetered Beagle dogs following intravenous infusions. This non-GLP study was conducted by [redacted] (b) (4) in 2009.

Study design: Beagle dogs were infused stepwise for 30 min with buffered saline vehicle, followed by 0.051 and 0.205 mg/kg bremelanotide. N=4 males. TK samples were collected pre-dose, 15, 29, 59, 65 and 90 minutes, 2, 5, and 24 hours after start of infusion.

Results: Bremelanotide induced a significant increase in HR at the high dose that resolved at the 24 hr time point. Bremelanotide did not significantly affect mean arterial blood pressure, systolic or diastolic, but there were trends toward increased values for all three parameters, and a trend toward decreased body temperature. *Data from the two doses were averaged.* Bremelanotide also evoked clinical signs of stretching, yawning, licking, vomiting, and panting.





Total plasma concentrations (mean+/-SD) following iv infusions are given in table below:

Dose	0 mg/kg	0.05 mg/kg	0.205 mg/kg
Cmax (nM)	<5	142 +/- 16	639 +/- 56
Tmax (min)	N/A	29	59

Compared to the human therapeutic Cmax, the lower dose is 2X and the higher dose is 8.8X the human plasma level.

Two single-dose general tox studies (131-007 and 131-008) conducted by the sc route in the dog were cited by the sponsor in support of cardiovascular safety. The sponsor reported both as being negative for cardiovascular effects. This reviewer disagreed, based on sparse sampling in 131-007, and on positive findings for increased heart rate in 131-008. Neither study had ECG measurements. Brief summaries of these studies are given below.

131-007: Range-finding toxicity study of PT-141 administered subcutaneously to Beagle dogs. Doses: 3, 6, 9, 12 mg/kg. N=2M/2F. Non-GLP. No TK.

Blood pressure (systolic, diastolic), was measured prior to dosing and at 15, 30, 45, 60, 75, and 90 minutes postdose. Two measurements were made at each time point and an average value was recorded. Pulse rates were also reported. Sponsor reports no effect but there were not enough measurements taken to create accurate BP averages.

131-008: Single-dose toxicity study of PT-141 administered subcutaneously to Beagle dogs. Doses: 9, 12, 15 mg/kg. N=4M/4F. GLP. Blood samples were taken but no TK was reported.

Blood pressure and pulse rate were measured following each bioanalytical collection (predose and at approximately 15 and 30 minutes, and 1, 3, 6, and 24 hours postdose). Three measurements were recorded, and the calculated average was reported.

In males, pulse rates were significantly elevated in the 12 and 15 mg/kg dose groups at 3 hrs post dose (p 120 of the study report), which is well past the Tmax. In females, there were significantly elevated pulse rates in all treated groups at 1 and 3 hrs post dose and in the highest dose group also at 30 min post dose, indicating slightly greater sensitivity of the females. The largest increase (37%) was observed at the 1 hr time point at the high dose. There were no significant trends for altered BP, only sporadic differences.

The sponsor set the NOEL = 15 mg/kg, but the reviewer disagrees based on elevated HR that was dose and time-dependent in males and females, so no NOEL was set. From other TK studies, 9 mg/kg has an AUC of 15625 ng.hr/mL by the sc route in the dog which is 56.6X the human therapeutic exposure.

This study is consistent with the range-finding studies in demonstrating that BMT can produce elevated HR. The lack of a finding for increased BP in this study may have been due to the comparatively sparse sampling, which also had a lot variability.

Summary statement for single dose CV studies in the dog:

Of the five in vivo CV studies in the dog that were conducted, the three that utilized continuous recording detected elevated HR and BP. The two that did not use continuous recording did not measure changes in BP, even when doses where higher. One picked up increased heart rate. Although the dose-dependence of the cardiovascular effects was not well-defined in the dog, it seems that the effect on heart rate appeared at lower doses than the effect on blood pressure. A firm NOEL for CV effects was not established, but no effect levels were in the range of 0.5X the human therapeutic dose, based on AUC.

Single dose studies in the monkey by the intranasal route:

Two single dose studies (WTAW-103 and 3133) conducted in the monkey by the intranasal route were also cited by the sponsor in support of cardiovascular safety. Each was conducted in males only (N=4). Both were GLP and both have ECG measurements. WTAW-103 covers a higher dose range than 3133 but is less useful for evaluating BP because BP measurements were indirect and therefore less accurate. Brief summaries are given below.

3133: PT-141: A hemodynamic and cardiac function study in conscious cynomolgus monkeys following intranasal administration.

Doses: 0.05, 0.2, 1 mg/kg. Lot #522871.

Methods:
Arterial and femoral catheters were implanted one day prior to the start of treatment. Animals were not fitted with telemetry transmitters. Hemodynamic and cardiovascular assessment: Baseline measurements were taken over 30 minutes and hemodynamic and CV parameters were monitored for 2 hrs post-dose (every 5 minutes). ECGs: once during the pretreatment period and once at –15 min prior to each dosing (baseline period), and at 15, 30, 45, 60, 75, 90,

105 and 120 minutes post-dose. Other parameters were recorded 30 minutes prior to and every 15 minutes post dosing: cardiac output (CO)*, pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR)**, respiration rate ((RR; visual), right and left cardiac work (RCW, LCW)**, right and left ventricular stroke work (RVSW, LVSW)**, stroke volume (SV)**, systemic vascular resistance (SVR)**

*CO was recorded at least 3 times over a period of 3 minutes.

** Calculated values

Results:
There was no mortality. One animal in the mid dose group had an erection that lasted for one hour. Males in the mid and high dose groups did not show the clinical signs (shivering/tremors) that had been previously reported in female monkeys in a dose finding study under (b) (4)

There were no cardiovascular or ECG findings. No NOAEL was determined.

Because exposure was not measured in this study, an MOE could not be determined. It is known from PK studies (see WTAD-100) that bioavailability via intranasal administration is highly variable.

Sponsor's table Study #PL-10 p 212

Route	Dose (ug/kg)	AUC (ng min/ml)	Tmax (min)	Cmax (ng/ml)	% bioavailability	Comments
IV	50	5261 ± 775	0	1136		
IN						
# 1	50	482	5	34	9.1	Bloody nose
#2	50	667	45	31	12.7	Incomplete
#3	50	1825	30	37	34.7	delivery

N=3 / group.

The mean of the 3 AUC values by the intranasal route was 991 ng.hr/mL, which is 3.6X the human therapeutic dose by AUC. The AUC by the iv route is 19X the human therapeutic dose.

WTAW-103: Dose range finding study of PT-141 administered intranasally to cynomolgus monkeys.
Doses: 0.2, 1, 2 mg/kg
ECGs were conducted using standard methodology. BP and HR measurements were stated to be indirect, with limited accuracy. There were no treatment-related findings.
The sponsor set the NOEL at 2 mg/kg. No TK measurements were made.

Summary statement for the monkey: Of the two studies conducted to evaluate CV effects in the monkey, Study #3133 above is deemed reliable to use for weight of evidence. Dosing and monitoring were both adequate, and there were no CV findings.

Single dose pharmacodynamic study in the rat

Bremelanotide was initially developed for the treatment of erectile dysfunction in males. A drug-drug interaction study was conducted in the rat to determine whether there was any adverse effect of co-administering bremelanotide with sildenafil or a nitrate (isosorbide dinitrate, or ISDN). This study was cited by the sponsor to support cardiovascular safety because one arm of the experiment used bremelanotide alone and yielded useful data.

PL-40: Cardiac safety pharmacology of PT-141 in the rat alone and in combination with a nitrate or sildenafil.
Doses: PT-141 0.003, 0.1, 1 mg/kg administered intravenously
Sildenafil: 5 mg/kg administered orally
ISDN 50 mg/kg administered orally
N = 6M / dose

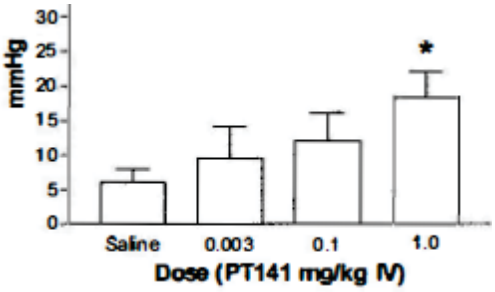
The sponsor presented a control experiment showing that BP, PP, and HR changed similarly for a vehicle control by the iv or oral routes. A positive control experiment using phentermine (10 mg/kg) was also included.

Baseline telemetry recordings were taken for 30 min prior to and 60 min post-dosing. The first 15 min following dosing were eliminated from data analysis due to handling artifact. The effects of treatment on CV parameters were determined by comparing each rat's post-treatment recordings to its baseline readings on that day. Data are represented as the group mean ± SE (n=6) of the change in each parameter.

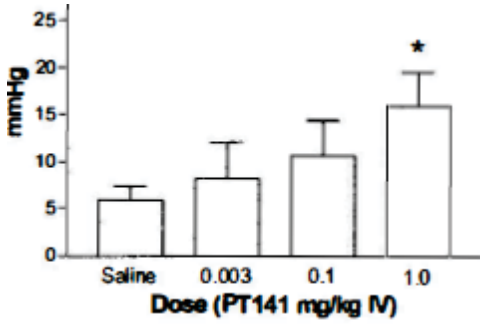
Results:

PT-141 increased BP and HR in a dose-dependent manner. The sponsor stated that peak efficacy (PD effect?) in the rat is 0.003 mg/kg and the LD_{50} is 2 mg/kg. Thus, changes in BP became significant only at a dose approaching toxic levels (1 mg/kg). The increase in HR did not reach significance. These findings are consistent with those obtained in the dog. TK data from female rats is: 276 ng.hr/mL at 1 mg/kg iv, which is approximately equal to human AUC.

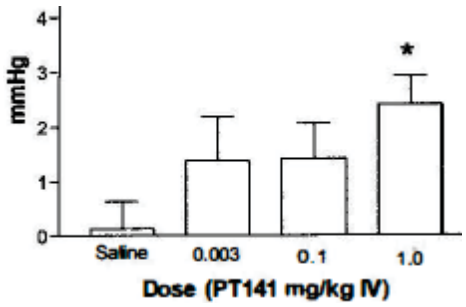
Change in systolic from baseline



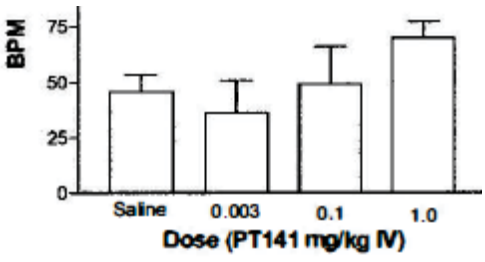
Change in diastolic from baseline



Change in pulse pressure from baseline



Change in heart rate from baseline



Interestingly, co-administration of ISDN or sildenafil counteracted the increase in systolic, diastolic, and pulse pressures induced by PT-141, but synergistically increased HR.

Repeat dose studies in the dog

Several repeat dose studies conducted in the dog by the intranasal and subcutaneous routes were cited by the sponsor in support of cardiovascular safety. Of these, the study that had the highest quality data was a 28-day repeat dose study, using the intranasal route. This study is reviewed below. Other repeat dose studies are reviewed under Section 6 of this review, General Toxicology.

WTAW-107: A cardiovascular telemetry study in dogs to evaluate the effects of 28-day intranasal dosing with PT-141. GLP / QA.
Dose: 0.65 mg/kg (0.325 mg/kg/nostril) PT-141 Lot #0535068 N=3/dose
Exposure: From study PL-18 the AUC for a dose of 0.65 mg/kg administered intranasally is 126.2 ng.hr/mL (see p3). This is approximately half the human therapeutic dose.

Methods: ECG evaluations were performed in all animals at baseline. Parameters and waveforms were collected as 10-second waveform scans and saved approximately every 15 minutes, 24 hours/day throughout the study.

Results:
Clinical observations: All group 2 animals exhibited soft feces during Days 12-19 and this adverse effect decreased by Day 22. One animal (2002) was lethargic from Day 14 to 19 and had a markedly swollen penis on Day 2, 3 and 4. There were no treatment-related effects on body weight or body temperature.

Telemetry data: ECGs were normal. Because the animals were manually restrained during intra-nasal dosing and then placed in their cages to capture telemetry data, large variations were noted in HR and BP. Average baseline BP for 2 dogs in control group 1 was 116/80 and 124/76 mmHg and mean arterial pressure was 94 mmHg for both prior to dosing. BP values fluctuated with time of the day as much as 50% up or down.

BP at baseline for treated animals was higher than controls, i.e. 142/87, 140/89 and 131/68 mmHg. MAP was 109, 110 and 92 mmHg, respectively. Wide fluctuations in BP as seen in control group was reported but treatment did not cause any consistent or significant change except in one treated dog (#2002). In dog # 2002, decreased MAP was observed towards the latter half of the study and was attributed to decreased SAP rather than DAP. The sponsor discounted the finding, stating that it was not significantly different from controls.

However, review of the (MAP) values showed that at least 11 times (out of total of 2688 observations) during the course of the study, MAP decreased to values below 50 mm Hg and some values were as low as 8 mm Hg, i.e., a change of –93% compared to baseline value. These were associated with a significant decrease in systolic and diastolic blood pressures. However, the decrease in MAP was seen sporadically and was not continuous. Also, in spite of the dramatic drop in MAP, the dog survived and no clinical adverse findings were reported. No such severe hypotension was observed in any other dog although one control dog had one decreased MAP (51 mmHg) value during the course of the study.

Heart rate fluctuated but there did not seem to be any obvious difference between controls and PT-141 treated dogs. Also, no dramatic change in heart rate was associated with decreased MAP in dog # 2002.

Conclusion: Although there was a great variability due to handling and dosing procedures in all parameters evaluated, episodes of hypotension in one dog seemed to be drug-related based on additional clinical observations. Clinical relevance is not known.

Summary and conclusions for CV safety studies:

Briefly, bremelanotide can produce elevated BP and HR when administered iv or sc in the dog and the rat. Although TK data were not available for all doses tested, it can be estimated that the threshold for CV changes to begin to appear in the rat and the dog are near the human therapeutic range based on AUC. BP ranged as much as 25% higher in the dog at 72X the human therapeutic dose. Negative findings in some single-dose and repeat-dose studies were likely due to inadequate exposure or monitoring.

In the monkey, there were no findings for effects on ECG or CV parameters following intranasal dosing. The NOEL was 3.6X the human therapeutic dose based on AUC and monitoring was adequate. The highest dose tested was 20X higher.

4.3.3 Renal

Not done

4.3.4 GI

Ferret studies: emesis and TK (iv, in, and sc administration):

The emetic effect of bremelanotide was assessed in 4 different studies in male ferrets. The ferret is a standard animal model for testing emesis / anti-emetics. (The rat does not have an emetic response.) Emesis occurred following bremelanotide doses of 9 mg/kg SC (Study 04-037), 30 and 75 µg/kg iv (Study 20010474PGF), and 300 and 500 µg/kg intranasal (Studies 03-112 and 20010666PGF). The sponsor states that no true dose-dependence was established in any of these studies. However, the reviewer notes that there was a clear threshold for the emetic response, which occurred at doses that were estimated to be comparable to the human therapeutic dose.

Studies 20010474PGF and 20010666PGF were GLP-compliant studies conducted in 2001 at the (b) (4) to determine the possible emetic effect of BMT in ferrets following single iv or intranasal administration, respectively. N=6 male animals/dose. For both studies, the positive control, (cisplatin, 115 mg/m^2, iv) induced, as expected, an emetic effect in all 6 ferrets, demonstrating the validity of the method used.

Study No. 20010474PGF. PT-141 and MT II evaluation of emetic effect in the ferret following a single intravenous administration. Located in Section 4.2.1.3 under Safety Pharmacology.

> Vehicle (saline), bremelanotide 10, 75, and 30 µg/kg iv that order with ≥ 48-hour interval between doses. Animals were observed for 5 hours post-dosing. In a separate experiment, animals were dosed at 30 µg/kg, and blood sampling was performed 45 minutes postdose to enable assay of plasma concentrations of bremelanotide. Results of the plasma analysis are presented in Study 03-112 (see Section 2.6.4.3).
>
> Results of emesis assessments are summarized in Table 2.6.2-20. At 30 µg/kg iv, vomiting was seen in 6/6 animals. At the highest dose, the times to onset of emesis were more variable and slightly shorter and the duration of the emetic phase was more long lasting as compared to 30 µg/kg. No true dose-dependence was characterized, and the no effect dose level for bremelanotide was **10 µg/kg iv.**

Study No. 20010666PGF. PT-141 and MT II evaluation of emetic effect in the ferret following single intranasal administration. Located in Section 4.2.1.3 under Safety Pharmacology.

Study 20010666PGF was conducted in a similar fashion as 20010474PGF except that bremelanotide was administered intranasally, and dose levels tested in order (at 48-hour minimum intervals) were 100, 500, and 300 µg/kg intranasally (with each dose divided equally between 2 nostrils). Plasma concentrations were determined following a 300 µg/kg (150 µg/kg in each nostril) dose. Results of the plasma analysis are presented in Study 03-112 (see Section 2.6.4.3)

Results of emesis assessments are summarized in Table 2.6.2-21. Emesis occurred at doses ≥ 300 µg/kg; 1 of 6 ferrets had an emetic episode at the 300 and 500 µg/kg doses and no ferrets had emesis at 100 µg/kg. The no-effect dose level was **100 µg/kg in.**

Study #03-112. Systemic Exposure of PT-141 and MT-11 following intranasal and intravenous administration to ferrets. Non-GLP. (b) (4). Located in section 4.2.2.2 and summarized in section 3.1.6.1 of the Pharmacokinetics Written Summary.

Six male ferrets were dosed with **300 µg/kg** bremelanotide intranasally and blood samples were obtained 45 minutes later. On Study Day 6, the same 6 ferrets were dosed with **30 µg/kg iv,** and blood samples were obtained 5 minutes later. The mean ± sem plasma concentrations of bremelanotide were **12.5 ± 2.5 and 111.7 ± 30.8 ng/mL** following intranasal and iv administration, respectively. (Note that the Pharmacokinetic Written Summary erroneously lists the units as µg/kg not ng/mL). Original data for plasma values are in Appendix 1 of the study report.) Thus, a 10-fold higher dose administered intranasally yielded a roughly 10-fold lower plasma exposure than the iv administration. Human therapeutic Cmax is 77.1 ng/mL.

There was no emesis observed in any of the ferrets, with either route of administration. This study showed no-effect levels higher than the previous studies.

Study No. 04-037: Toxicokinetics of PT-141 following subcutaneous administration to ferrets. non-GLP. (b) (4). Located in section 4.2.2.2 and summarized in section 3.1.6.2 of the Pharmacokinetics Written Summary.

The toxicokinetics and emetic response to two separate lots of bremelanotide were compared following sc administration to ferrets.

Study design: Fourteen male ferrets were treated in 3 groups with 9 mg/kg sc bremelanotide in 3 different formulations. Group 1 was a single-dose preliminary assessment of the PK and tolerability in ferrets of bremelanotide manufactured by a new supplier (b) (4); Groups 2 and 3 evaluated lots from the 2 manufacturers in a side-by-side comparison of the single-dose PK of bremelanotide manufactured by (b) (4) batch #400609506 was used for groups 1 and 2. (b) (4) ot # 6AB2 was used for group 3.

Group No.	Number of ferrets	Test article	Dose (mg/kg)	Dosing frequency	Route of administration
1	6	Pt-141 (b) (4)	9	Once	Subcutaneous
2	4	PT-141 (b) (4)	9	Once	Subcutaneous
3	4	PT-141 (b) (4)	9	Once	Subcutaneous

For Group 1, blood samples were collected predose and at 0.5, 1, 2, 4, and 8 hours postdose. For Groups 2 and 3, blood samples were collected at 0.5 hours postdose (the time of peak plasma concentration of bremelanotide based on Group 1).

Toxicokinetics: Plasma PT-141 values in group 1 male ferrets expressed as mean+/-sem for a dose of 9 mg/kg sc. The MOE at this dose is 62X the human therapeutic AUC of 276 ng/hr/mL.

Cmax (ng/mL)	9,168 +/- 727
Tmax (hr)	0.8 +/- 0.1
$AUC_{0\text{-}8\ hr}$ (ng/mL*hr)	17,106 +/- 1,422
$AUC_{0\text{-}inf}$ (ng/mL.hr)	17,183 +/- 1,412

For the Group 2 and 3 comparisons by manufacturers, plasma concentrations at 30 minutes postdose were 12,109 ± 656 ng/mL and 6,618 ± 71 ng/mL.

Emetic activity was observed in 12 out of the 14 ferrets, indicating that this dose is well above the no-effect level, and occurred ~20-80 minutes postdose. The results demonstrated that there were no differences in the emetic response between two lots of PT-141. However, plasma drug concentrations were very variable between groups.

4.3.5 Respiratory

Study 20010473: Evaluation of effect on respiration in the unrestrained conscious rat following single intravenous administration. Conducted by (b) (4) in 2001. GLP and QA. PT-141 Batch 0539373, purity 99.5%, peptide content (b) (4)%.

Methods:
Male Wistar rats, N=8/group; whole body plethysmography prior to and after iv dosing
Doses: 10, 75, 300 ug/kg, saline negative control, carbamylcholine positive control
No TK groups. No significant deviations.

Results:
There were no treatment-related effects on respiratory function up to 6 hrs post-dose.
Positive and negative controls gave appropriate results.
NOEL > 300 ug/kg iv. MOE based on BSA is >1.6X.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

ADME studies were carried out in mice, rats, rabbits, ferrets, dogs, and monkeys. Overall, the nonclinical PK profile for bremelanotide was consistent across species and genders. The most robust PK data was collected in mice and dogs. Bremelanotide was poorly tolerated in rats (LD_{50} = 2 mg/kg iv) and rabbits, and PK profiles were not as well-developed in these species. Ferrets were utilized only as a model for emesis, so only a limited amount of PK data was collected in that species. PK of bremelanotide was evaluated in monkeys following iv and intranasal administration, but sc dosing was not undertaken, so a PK profile was not developed. Distribution studies with radiolabeled bremelanotide were conducted in the rat and mouse, but, due to problems with stability of the labeled compound, only the mouse study was considered to be definitive.

Analytical methods:
Sixteen study reports were submitted related to analytical methods and validation of bremelanotide measurement in dosing solutions and/or plasma from mouse, rat, rabbit, dog, and human, a few of which were reviewed by the previous reviewer.

The sponsor explored several methods for the quantification of bremelanotide: HPLC-MS/MS, radioimmunoassay (RIA) and scintillation proximity assay (SPA). HPLC-MS/MS measures bremelanotide concentration directly while both RIA and SPA measure bremelanotide-like immunoreactivity and rely on the specificity of the antibody used for accuracy. Using the same antibody, RIA and SPA differ mainly in their method of signal detection and assay parameters, which in turn shifts their linear range of detection.

In Study #PL-15, the three methods were compared for analysis of bremelanotide in rat plasma. The linear range and sensitivity varied between methods. Linear ranges were as follows: RIA, 0.05 - 2 ng/ml, SPA, 0.5 – 16 ng/ml, HPLC-MS/MS, 5 – 2500 ng/ml. RIA and SPA were more sensitive than HPLC-MS/MS but had a much more limited range.

The sponsor therefore validated HPLC-MS/MS methods for measuring bremelanotide concentrations in and dosing solutions and in plasma samples collected from mice, rats, rabbits, dogs, and humans. Linear ranges were similar across nonclinical species, but lower in humans.

Study (b) (4) 16183	Mouse	5-2500 ng/mL	
Study 16190	Rat	5-2500 ng/mL	
Study # 48734	NZW Rabbit	5-2500 ng/mL	Partial validation
Study #49108	DB Rabbit	5-1000 ng/mL	Partial validation
Study # 47133	Beagle dog	5-1000 ng/mL	
Study # 46581	Human	0.5-100 ng/mL	

Stability was assessed in plasma and in various dosing formulations. Briefly, bremelanotide was stable in dosing solution or plasma at ambient temperature for a duration of hours-days, when stored refrigerated for a duration of days-weeks, and when stored at -70 °C was stable for up to a few months and able to withstand several freeze-thaw cycles.

Absorption:

Single dose
Single dose TK was obtained in mouse, rat, ferret and dog, and monkey by the iv, sc, and/or intranasal (in) route. Because administration by the intranasal route yielded low and highly

variable exposure, the sponsor did not pursue clinical development by that route. The table below shows available PK data primarily from the sc route, with selected studies using the intranasal route also included for comparison of bioavailability.

Reviewer's table. Values taken from the Pharmacokinetics Tabulated Summary and selected study reports. See also Sponsor's Table 2.6.4-9.

Species	Route	TK Study # Main study #	Dose mg/kg	Cmax ng/mL	$AUC_{0-\infty}$ ng.hr/mL	Tmax hr	T ½ hr	%F
Mouse (M/F)	SC	PL-34 996-002 4.2.3.2	1 3 9	533 1830 4180	427 1483 5056	0.3 0.3 0.3	0.4 0.45 0.6	
Mouse (M/F)	SC	PL-41 996-009 4.2.3.2	15 30 75	9272 10609 26341	16117 18335 56880	1.0 0.5 1.0		
Mouse (M/F)	SC	PL-54 996-029 4.2.3.2	15 30 75	9806 12685 25614	15093 22227 46532	0.5 0.4 1.0		
Mouse (F)	SC	PL-53 996-032 4.2.3.5.3 Reprotox PPD	30 75 150	17575 31132 56540	31194 76990 176379	1.0 1.0 1.0		
Mouse (M/F)	SC	PL-49 996-035 4.2.3.7.2 Impurity study	75	27121	52683	1.0		
Mouse (M/F)	SC	PL-45 996-018 4.2.3.7.7 Formulation study	75 75 (b) (4)	52390 53464	58665 53414	0.5 0.5		

Species	Route	TK Study # Main study #	Dose mg/kg	Cmax ng/mL	$AUC_{0-\infty}$ ng.hr/mL	Tmax hr	T ½ hr	%F
Rat (M)	IV	PL-09	0.1	--	--			
Rat (F)	IV	91-0501 4.2.2.2.	0.25 1.0 2.0 (LD_{50})		69 275 --		0.1 0.2 --	
Rat (M/F)	SC	PL-16 131-013 4.2.2.2	0.5 2.0 3.5	96.3 243 353	371 690 1312	0.3 1.0 0.5	2.6 1.3 1.1	
Rat (M/F)	SC	8360928 4.2.3.7.4. ~25 min post-dose	0.5 2.0 3.5	180 786 1024				
Rabbit NZW (F)	SC	04-014 4.2.2.2.	9	5439	14988			
Rabbit NZW (F)	SC	PL-44 996-014 4.2.3.5.2. Reprotox	15 30 75 150	11288 28533 71249 108728	26030 74948 214030 475631	0.9 0.8 1.0 2.4		
Ferret (M)	SC	04-037 4.2.2.2	9	9168	17183	0.8		

Species	Route	TK Study # Main study #	Dose mg/kg	Cmax ng/mL	$AUC_{0-\infty}$ ng.hr/mL	Tmax hr	T ½ hr	%F
Dog (M)	IV	PL-76 12513 02 01B 4.2.1.3	0.1		133		0.5	
			1.0		1951		0.7	
	SC		1	808	1467	0.5	0.8	72
			3	4484	7782	0.7	0.8	119
			10	10249	19856	0.7	0.8	97
Dog (F)	SC	996-034 4.2.2.2	2	2010	4140	1.0		
Dog (M/F)	SC	PL-17 131-011 4.2.2.2	2	1352	3598	0.9	1.1	
			4	2667	7348	0.9	1.2	
			8	6311	16589	0.6	1.25	
Dog (M/F)	SC	PL-26 4.2.2.2	9	5235	15625	0.8	1.3	
			12	8800	25572	1.0	1.5	
			15	10694	31316	1.0	1.3	
Dog (M/F)	SC	PL-42 996-006 4.2.3.2	8	9032	20241	1.25		
			15	14554	38438	1.0		
			40	49268	140652	1.5		
Dog (M/F)	SC	PL-43 996-003 4.2.3.2	2	1946	3855	0.8		
			8	9635	18346	0.8		
			20	24886	54610	0.9		
Dog (F)	SC	PL-50 996-031 4.2.3.5.2 (Reprotox)	2	3213	7556	1.0		
			20	40783	87082	1.0		
Dog (F)	SC	PL-51 996-033 4.2.3.5.2 (Reprotox)	2	1988	4650	1.0		
			8	9923	23330	0.9		
			20	32275	75706	0.9		
Dog (M/F)	SC	PL-46 996-019 4.2.3.7.7 Formulation study d7	20 (b) (4)	32197	61759	0.6		
			20	32380	67888	0.6		
Dog (M/F)	IV	PL-18 (131-012) 4.2.2.2.	0.2	4600	500			
	IN		0.65	51	126	38		7.8
			0.65	35	60	20		3.7
			1.5	218	199	18		5.3
			3.0	794	815	18		10.9
Monkey (M)	IV	PL-10	0.05	1136	5261			
	IN			37	1473	30		32

Bioavailability for the sc route was assessed for only one species, the dog, and was found to be essentially 100%. Bioavailability for the intranasal route was assessed in dog and monkey and was predictably much less: 32% in the monkey and ~7% in the dog.

In general, bremelanotide administered by the sc route was rapidly absorbed (Tmax < 1 hr) and rapidly cleared ($T_{1/2}$ < 2 hrs in mice and dogs, ≤ 3 hrs in rat). Clearance was roughly biphasic, and was seen in rat iv, rabbit sc, dog sc, and monkey iv.

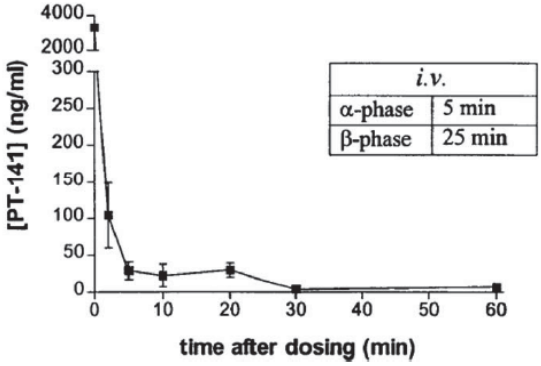


Figure 2.6.4-2 PK profile in rats dosed with 100 ug/kg IV Bremelanotide. Study #PL-09. Mean of 3 per time point.

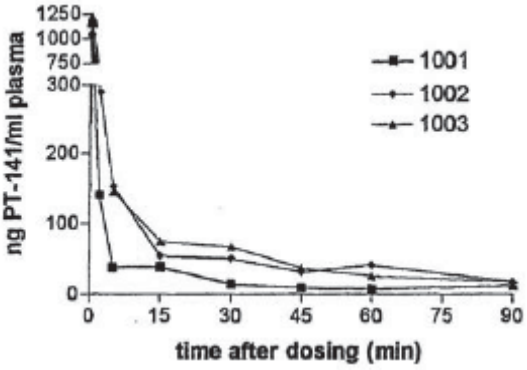


Figure 2.6.4-6 Individual Bremelanotide Concentration Time Curves for Monkeys Following 50 µg/kg IV Bremelanotide (PL-10)

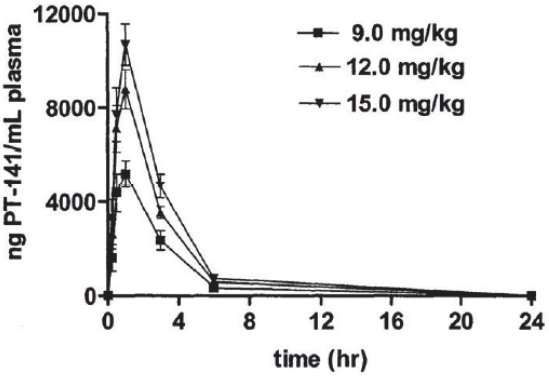


Figure 2.6.4-5 Plasma Concentration in Beagle Dogs After Single SC Doses. Study # PL-26.

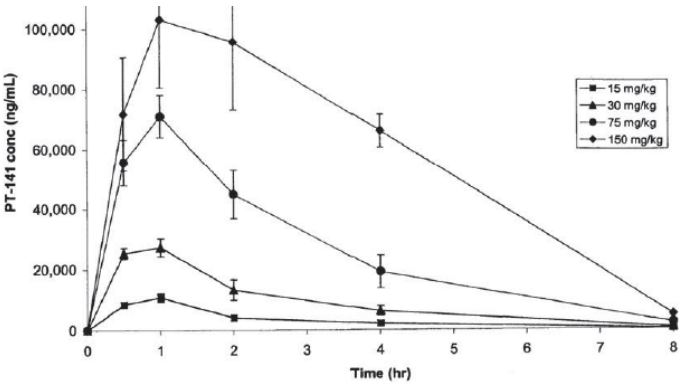


Figure 2.6.4-4 Plasma Concentration after 15, 30, 75, or 150 mg/kg SC Dosing to Female Rabbits on GD6

In the female rat, following iv administration, the volume of distribution (Vd) was 0.34 and 0.38 L/kg for doses of 0.25 or 1 mg/kg, respectively, and clearance was 63 and 61 mL/min/kg (Study 91-0501).

In the male dog, following iv administration, Vd was small, 0.5 and 0.4 L/kg for an 0.1 or 1.0 mg/kg iv dose, and clearance was low: 12 and 8.4 mL/min/kg respectively. Table 2.6.4-1.

Comparing AUC values from the table above, it appears that exposure was roughly proportional to dose, but the sponsor did not provide graphical analysis of dose proportionality, or of dose equivalence across species. The reviewer notes that the numbers of samples taken for the calculation of AUC values was variable between studies and may have produced some of the variability in AUC values seen across studies for a given dose of bremelanotide.

Repeat dose:
Repeat dose TK will be presented with respective tox studies. Briefly, there was no consistent evidence of accumulation with repeat dosing, nor of dramatic declines in exposure over time, at least for the mouse and dog.

Distribution and Excretion:

Protein binding:

Values for plasma protein binding were reported in 3 different studies: 5151 (b) (4), 2001), 7545 (b) (4), 2003) and 100040177 (b) (4) 2017). The first two studies used ultrafiltration to test binding of a 10 uM sample, and the last used equilibrium binding of 1 uM bremelanotide and also assessed partitioning to blood cells.

Binding to human serum protein varied from a low of 3% (study 7545, test concentration 10 uM) to a high of 21% (study 5151, test concentration 10 uM). Study 100040177 was intermediate at 16% (test concentration 1 uM). Mean of these three values is 13%. We note that the Clinical Pharmacology reviewer has allowed the value of 21% to be used in the label.

Protein binding to nonclinical species was 32%, 6%, and 13% for mouse, rat, and dog, respectively.

Tissue distribution and routes of excretion in the rodent:

Over the course of development, three distribution / excretion studies were conducted with radiolabeled bremelanotide. The first used tritiated and the second used ^{14}C-labled bremelanotide, and each was conducted by the iv and intranasal routes in the rat (46438 Parts A and B, and 7514-122). Conclusions from these studies were called into question when it was determined that the radiolabel on each of the compounds was quickly cleaved, rendering conclusions about the fate of the parent compound uncertain.

For that reason, a third study was conducted (8349336), this time with a compound stably labeled on the phenylalanine ring, using the clinically relevant sc route in the mouse. The results of this study are described below. For completeness, supportive data from the other two studies conducted in the rat are briefly described following the definitive study.

Mouse Study #8349336: Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-Bremelanotide Following Subcutaneous Administration to Mice. (b) (4) 2017. Non-GLP. Lot 30. Radiolabeled lot PT03-017-0551-A-20160926-DJI.

Study design:

Male and female B6C3F1/Crl mice were dosed with 30 mg/kg bremelanotide in 2.975% glycerin by the subcutaneous route. A 30 mg/kg dose corresponds to a HED of 2.44 mg/kg. The proposed human therapeutic dose is 1.75 mg (b) (4) Thus, the dose administered in this distribution study was 81X the proposed human dose.

	Number of Animals		Dose	Target Dose Level	Target Dose Volume	
Group	Male	Female	Route	(mg/kg)	(mL/kg)	Sample Collections
1	40	40	SC	30	4	Blood
2	9	9	SC	30	4	Urine, Feces, Carcass
3	18	18	SC	30	4	Blood and Carcasses for QWBA

cture) at

Urine was collected at 0-8 and 8-24 hours postdose, and at 24-hour intervals through 168 hours postdose. Feces were collected at 24-hour intervals through 168 hours postdose.

After each 24-hour excreta collection through 144 hours postdose, cage rinse samples were collected.

Two animals/sex/time point were prepared for quantitative whole-body autoradiography (QWBA) at 0.5, 4, 8, 24, 48, 72, 168, 336, and 672 hours postdose. The last three time points correspond to 7, 14, and 28 days respectively.

Results:

Exposure:

AUC_{0-t} for bremelanotide in plasma in male and female mice represented 13.8% and 16.6%, respectively, of the total radioactivity in plasma, indicating the presence of circulating metabolite(s).

The mean blood to plasma concentration ratios were < 1 through 24 hours postdose, indicating that there was no distribution to the cellular component of blood.

Table 2.6.4-6 Pharmacokinetic Parameters for Total Radioactivity and Parent Bremelanotide in Blood and Plasma Following SC [^{14}C]-Bremelanotide in Mice

	Male			Female		
Parameter	Radio-equivalents in Blood	Radio-equivalents in Plasma	Bremel-anotide in Plasma	Radio-equivalents in Blood	Radio-equivalents in Plasma	Bremel-anotide in Plasma
C_{max} (ng-eq/g or ng/mL)	9,890	21,600	12,700	8,890	18,300	10,600
t_{max} (hr)	1.00	1.00	1.00	1.00	1.00	1.00
$t_{1/2}$ (hr)	NC	29.6	NC	NC	NC	NC
AUC_{0-t} (ng-eq·hr/g or ng·hr/mL)	115,000	153,000	21,200	79,100	104,000	17,300
$AUC_{0-\infty}$ (ng-eq·hr/g or ng·hr/mL)	NC	188,000	NC	NC	NC	NC

Tissue distribution:

[^{14}C]-bremelanotide-related radioactivity was quickly and widely distributed in tissues and organs and there were no notable gender differences.

Most tissues had peak radioactivity concentrations at 0.5 hours postdose (the first evaluation time point). In males and females, the tissues showing the highest peak concentrations of radioactivity (after the dose site) reflected the routes of excretion: kidney, liver, small intestine, and pancreas. Males additionally showed high concentrations in the bulbo-urethral gland.

[redacted] (b) (4), bremelanotide was shown to cross the blood brain barrier, but with a significant delay. Radioactivity concentrations in the cerebellum, cerebrum, medulla, and spinal cord peaked at a low level 24 hrs after injection in males, and 4 hrs after injection in females. The reason for the sex difference for this distribution is unknown. The average peak radiolabel concentration (ng.equivalents ^{14}C-BMT/g tissue) in the CNS was ~1000 in both males and females (~10% of plasma concentration), which, if assumed to be all parent compound, is equal to a tissue concentration of 1000 nM, well above the Ki for the MC4 receptor of 14 nM. Clearance from the CNS was slow, and measurable concentrations that were 3-6X the plasma concentration remained at 28 days postdose in both male and female mice.

In female mice, low levels of radioactivity were measured for up to 28 days postdose in uterus and ovary. In males, radioactivity slowly crossed the blood:testis barrier, peaking at low levels at 24 hrs post dose, and then was slowly cleared.

[^{14}C]-bremelanotide-related radioactivity was not found to be selectively associated with melanin-containing tissues.

The elimination of drug-derived systemic radioactivity was essentially complete by 28-days postdose.

Tissue distribution by QWBA is tabulated in Section 2.6.5.5.2 and Section 2.6.5.5.3 for male and female mice, respectively, and tissue/plasma ratios are tabulated in Section 2.6.5.5.4 and Section 2.6.5.5.5 for male and female mice, respectively.

Excretion:
^{14}C-BMT-derived radioactivity was rapidly excreted in urine and feces after sc dosing. Approximately 86.4% and 82.2% of the dose was excreted in the first 48 hours in male and female mice, respectively. Excretion profiles were similar across sex with renal and fecal excretion being nearly equal in abundance. Hepato-biliary and renal excretion were the major routes of elimination.

Mean cumulative percent of radioactive dose in pooled urine and feces at specified intervals after a single subcutaneous administration of ^{14}C-BMT female mice (Group 2, 30 mg/kg). Study report 8349336 Figure 2 p 59.

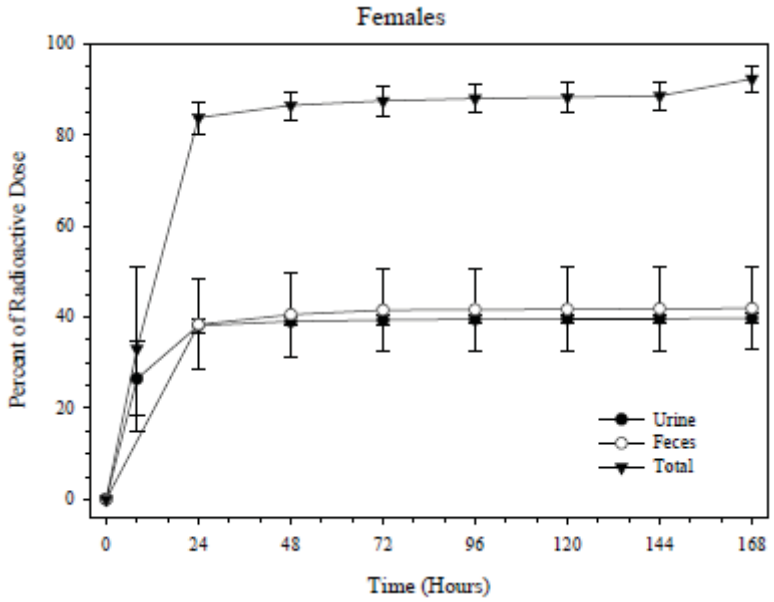


Table 2.6.4-8 Mean % (± SD) Recovery of Administered Dose after a Single SC Dose of [14C]-Bremelanotide in B6C3F1 Mice. 168 hours (7 days) post-dose

	% Total Recovery	% Dose in Urine	% Dose in Feces	% Dose in Carcass	% Dose in Cage Rinse
Male	92.2 ± 2.96	42.0 ± 11.9	43.3 ± 9.78	2.78 ± 0.508	3.42 ± 1.76
Female	88.5 ± 7.33	39.7 ± 0.971	41.9 ± 9.11	2.03 ± 0.111	3.16 ± 0.266

We briefly summarize the major findings from the radiolabeled distribution / mass balance studies conducted in the rat that were previously reviewed by Krishan Raheja. The doses administered, by iv and intranasal routes, were much lower than the doses administered in the mouse study. One study also included data from bile-duct cannulated animals.

Results were reasonably consistent with those obtained in the mouse. However, data obtained using the particular forms of radiolabeled bremelanotide given below *must be interpreted with caution,* since the sponsor determined that these compounds were rapidly metabolized. Thus, presence of radiolabel does not necessarily correspond to the parent compound.

Rat Study #46438 Part A: Absorption, excretion, distribution and metabolism in male and female SD rats after intranasal or intravenous administration of [^{3}H]PT-141 (bremelanotide). GLP. Conducted in 2003.

For both intranasal and iv mass balance studies a single dose of [^{3}H]PT-141 was administered at 0.004 mg/kg body weight (about 100 uCi/kg BW). The dose level for the intranasal tissue distribution study was increased to about 0.05 mg/kg to enable detection of PT-141 equivalents in tissues. Dose volume for both routes was 100 ul/kg BW.

Distribution: Radiolabel slowly crossed the blood brain barrier: the brain/plasma concentration ratio at 20 minutes was higher after intranasal (0.18-0.38) than iv (<0.1) administration but steadily approached 1 by 24 hours via both routes.

Excretion:
A majority of the radioactivity was recovered in 8-24 hr feces and 0-8 hr urine for all rats.

Matrix type	Males % dose	Females % dose
Urine	21.21	17.70
Feces	56.27	68.69
Cage wash	2.77	2.38
Carcass	13.37	6.75
Total %	93.62	95.52

The iv dose was excreted into the small intestine by 3 hours, probably by biliary excretion. Significant excretion also occurred via the kidney. When administered by the intranasal route, much of the dose was swallowed and eliminated via the digestive system.

Rat Study #7514-122: Absorption, distribution, metabolism, and excretion of radioactivity following a single intravenous administration of ^{14}C-PT-141 (PT-141[Acetyl-1-^{14}C]) and quantitative whole-body autoradiography after intranasal administration to rats. (b) (4) Non-GLP. Conducted in 2006. Radiolabeled lot 3526186. Labeled on the acetyl group.

Sponsor's Comment: In this study, loss of the ^{14}C-label from the molecule appeared to occur readily via deacylation, leaving the resulting ^{14}Cacyl group available to undergo normal metabolism to ^{14}CO2 and subsequent incorporation of the ^{14}C into endogenous metabolic products such as amino acids, fats, and proteins. Thus, elimination of [^{14}C]-bremelanotide-derived radioactivity was rapid, and occurred primarily via the expired air as ^{14}CO2, with over 83% of the radioactivity captured as expired ^{14}CO2 in the first 8 hours following iv

administration. Due to the apparent premature cleavage and loss of the radiolabel from the bremelanotide molecule, results from this study should be interpreted with caution.

Intranasal dosing was 3 mg/kg (N=5). Intravenous dosing was 1.25 mg/kg (n=3-10). Two strains of male rats were used: albino SD and pigmented LE. Three SD animals that were dosed iv were bile-duct cannulated.

Distribution:
Following iv administration the plasma Cmax values were 1370 and 1330 ng equivalents at 0.167 hours post-dose in both LE and SD rats. The highest concentrations of radioactivity in SD rats were reported in bile, small intestinal contents, urine, renal medulla, cecum contents, liver, kidney, small intestine, renal cortex and aorta. In LE rats, highest concentrations were observed in bile, small intestinal contents, urine, cecum contents, small intestine, liver, large intestinal contents, Harderian gland, renal cortex and kidney.

Following intranasal administration, the Cmax in plasma was 221 ng equivalents ^{14}C-PT-141/g at 6 hours post-dose and the highest concentrations of radioactivity were observed in stomach contents, esophageal contents, small intestine contents, nasal turbinates, esophagus, large intestine contents, Harderian gland, small intestine, cecum contents, bile, salivary gland and intra-orbital lacrimal gland.

Low levels of radioactivity crossed the blood/brain and blood/testis barriers.

[^{14}C]-Bremelanotide-derived radioactivity did not accumulate in the eyes, uveal tract, or skin of pigmented LE rats, suggesting that bremelanotide does not bind to melanin.

Excretion:
Following iv administration in bile duct intact rats, expired air was the major route of elimination of PT-141 derived radioactivity. Urine, feces and residual carcass accounted for 17.2, 2.82 and 3.94%, respectively. As stated above, this is an anomalous finding due to breakdown of the parent compound. It was stated that overall mean recovery of iv administered radioactivity in all matrices was 99.1%.

In bile duct cannulated rats at 96 hours post-dose, bile, urine, and feces accounted for mean values of 77.6, 16.0 and 0.11% of the radioactive dose, respectively. 76% of radioactivity was excreted in the first 2 hours post-dose and overall recovery in all matrices was 94.2%.

Metabolism:
Parent drug and eleven metabolites were observed in urine, bile, and liver and brain samples. Seven metabolites were identified i.e., linear form of ^{14}C-PT-141, three dioxy-^{14}C-PT-141 and 3 oxy-^{14}C-PT-141 metabolites.

It was reported that on HPLC profiling, parent compound represented the largest single peak in urine and bile. In plasma, liver, and brain, parent compound represented the largest single radioactive peak at 0.167 hours and then rapidly disappeared over time.

Metabolism:

<u>In vitro metabolism:</u>

In vitro metabolites were characterized in the following non-GLP studies using radiolabeled bremelanotide:

Study # Location	Year	Study description	Compound used	Comments
5151 4.2.2.3	2001	Stability study in rat, dog, monkey, and human liver S9 fraction	BMT	Stable; no metabolism
7545 4.2.2.3	2003	Stability study in CD1 mouse S9 fraction	BMT	Stable; no metabolism
7514-124 4.2.2.4	2006	Metabolism study in mouse, rat, rabbit, dog, and human hepatocytes	^{14}C-BMT Labeled on the acetyl group	Limited analysis due to cleavage of acetyl group
8349337 4.2.2.4	2017	Metabolism study in mouse, rat, dog, and human hepatocytes	^{14}C-BMT Labeled on the phenylalanine ring	No unique human metabolites found
8349338 4.2.2.4	2017	Stability study in human feces		Extrahepatic metabolites characterized

Study 7514-124 was conducted in mouse, rat, rabbit, dog, and human hepatocytes. As described above, the sponsor's initial distribution and metabolism studies that utilized BMT labeled on the acetyl carbon were limited in their usefulness because of rapid cleavage of the label. Briefly, the sponsor established the overall stability of BMT in the hepatocyte preparation and made an initial description of the metabolite profile. What was described as a major metabolite that eluted in the void volume was thought to be the deacylated product. Mention was made of a unique metabolite in the dog, but this was not characterized. The definitive characterization of metabolites was carried out in study 8349337.

Study 8349337 characterized the in vitro metabolic profile of BMT in mouse, rat, dog, and human hepatocytes. Unfortunately, this later study did not include rabbit hepatocytes. In agreement with study 7514-124, BMT was found to be relatively stable in human and dog hepatocyte incubations, and moderately metabolized in rat and mouse hepatocytes.

The hydrolysis metabolite (M5) was the only major metabolite found in human and dog hepatocytes. In mouse hepatocytes, M5 and M4 (a secondary metabolite formed via the amide hydrolysis of M5 between the aspartic acid and histidine residues) predominated, and in rat hepatocytes, M33 (formed via the hydrolysis between the tryptophan and lysine residues of M4), along with M3, M4, and M5 were found. All other metabolites were relatively minor across species, and **no human unique metabolite** nor any disproportionately expressed metabolite was detected in hepatocyte incubations.

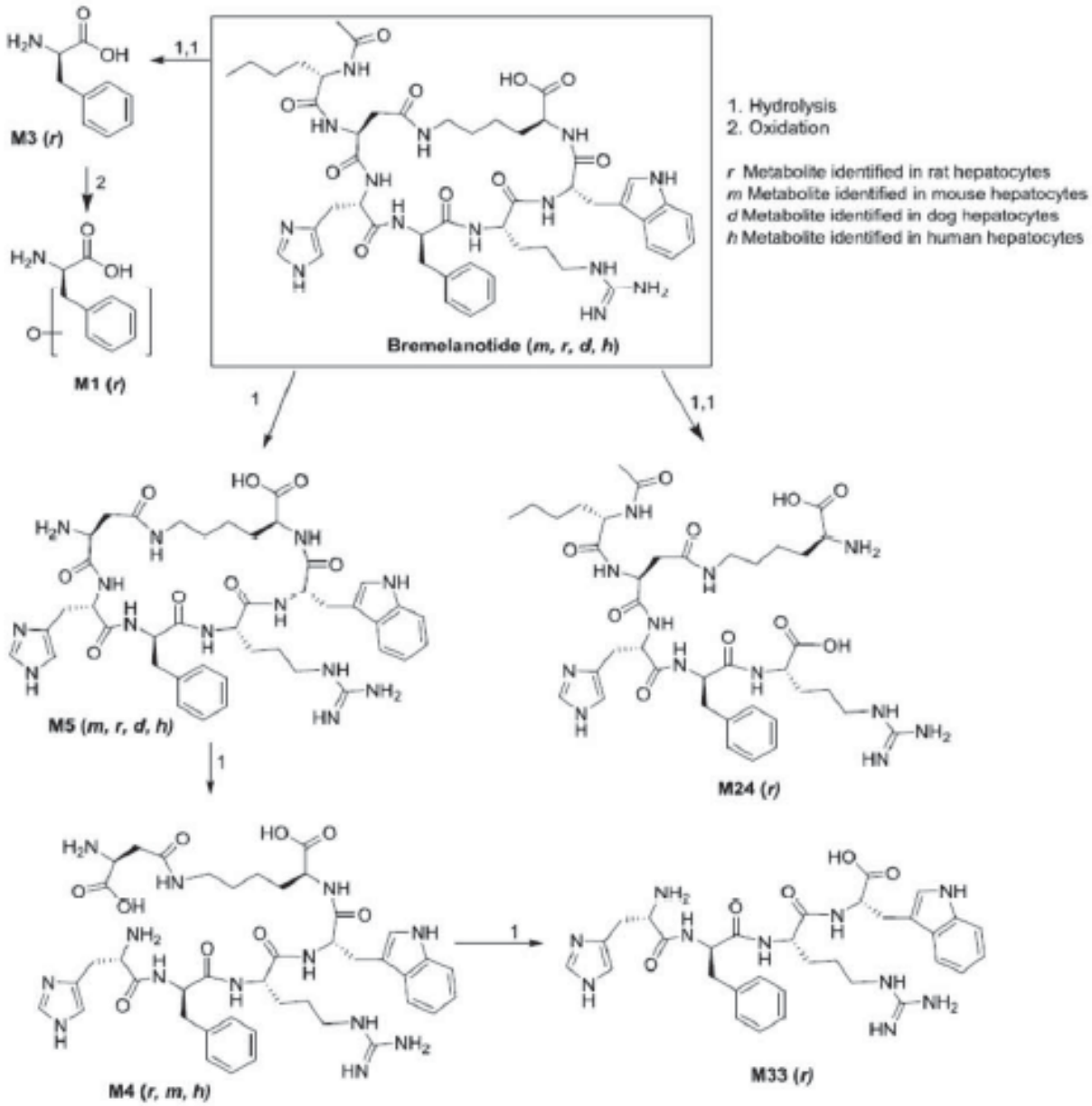
M35 through M38 appeared to be present in culture media controls, suggesting that they might not be true metabolites of bremelanotide, but bremelanotide degradants.

Sponsor's table 2.6.5.10.2.55

Retention time (minutes):	Metabolite designation	Percent of Radioactivity							
		Mouse/CD-1		Rat/Sprague-Dawley		Dog/Beagle		Human	
Incubation time (minutes):		0	240	0	240	0	240	0	240
2.00	M1	--	--	--	1.42	--	--	--	--
3.00	M32	--	--	--	2.06	--	--	--	--
5.50	M3	--	--	--	5.41	--	--	--	--
14.00-14.33	M4	--	17.43	--	4.82	--	--	--	1.49
14.83	M33	--	--	--	7.98	--	--	--	--
16.83-17.00	M5	--	10.47	--	3.81	--	4.23	--	8.27
17.33	M34	--	--	--	2.25	--	--	--	--
20.00	M24	--	--	--	1.56	--	--	--	--
24.83	M35	--	--	1.12	0.64	--	--	--	--
30.17-30.33	M36	1.57	1.61	1.80	1.88	1.72	1.63	1.32	1.32
32.00-32.17	M37	--	--	1.05	0.69	--	--	--	--
32.33-32.50	M38	--	--	0.79	1.24	1.18	1.05	--	--
36.50-36.83	bremelanotide	94.49	66.41	93.41	63.85	94.05	89.48	94.75	85.20

The primary metabolic pathway involved the hydrolysis of the amide bond between the N-acetyl-norleucine moiety and aspartic acid to form M5. A second-step amide hydrolysis of M5 between the aspartic acid and histidine residues produced M4, which further underwent hydrolysis between the tryptophan and lysine residues to form M33. A double amide hydrolysis of bremelanotide (between arginine and tryptophan; and between tryptophan and lysine) by loss of tryptophan residue yielded M24. In addition, M3 was identified as a D-phenylalanine, which further formed M1 via aromatic hydroxylation.

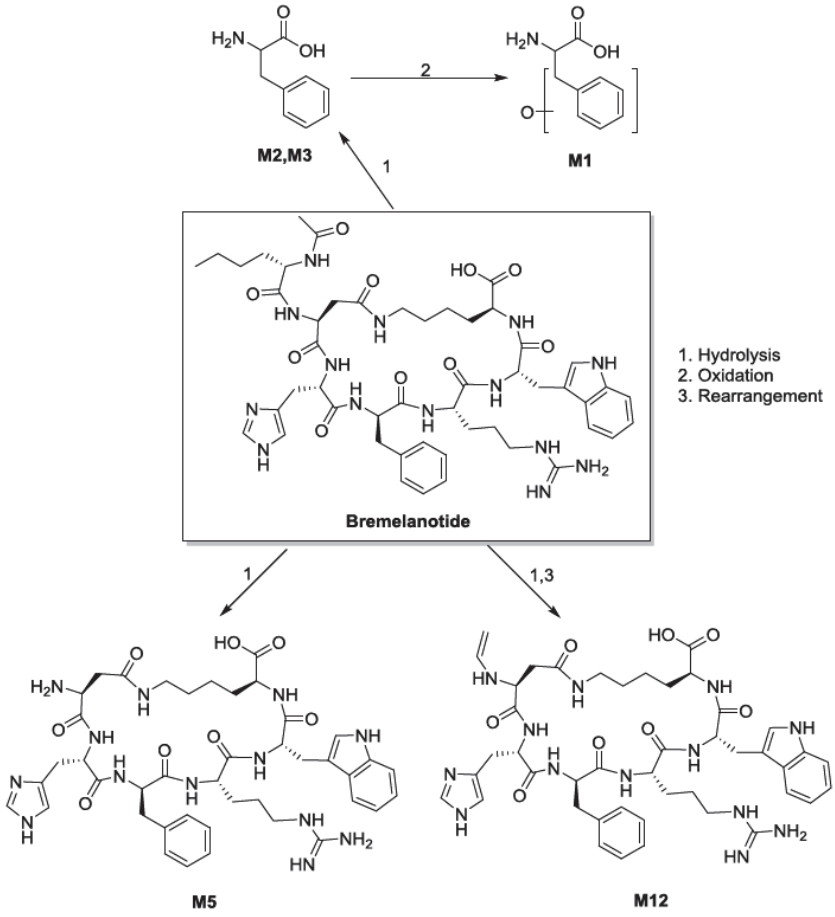
Sponsor's figure 2.6.5.11.2. 2.6.5.11.2 Proposed Biotransformation Pathways of Bremelanotide in Mouse, Rat, Dog, and Human Hepatocytes (Study 8349337)



Study 8349338 was conducted to characterize the extrahepatic metabolism / degradation pathways of bremelanotide in human feces. 10 uM bremelanotide was added directly to female human fecal samples. The predominant metabolite M5 was accompanied by a few minor metabolites that were not observed in the human hepatocyte incubations, including M2 and M3 (a pair of phenylalanine isomers), M12 (α,β-unsaturated M5), and M1 (a hydroxylated phenylalanine). Sponsor's Table 2.6.5.10.3 shown below.

		Average[a] Percent of Radioactivity Injected (% of Run)			
		Incubation time (hours):			
Retention time (minutes):	Metabolite designation	0	1	6	24
2.00	M1	NA	0.105	1.24	2.52
4.83-5.00	M2	NA	NA	1.29	5.90
5.50-5.67	M3	NA	NA	0.780	5.73
14.83-14.67	M4	NA	0.300	0.840	2.27
17.00-17.17	M5	0.120	18.3	51.5	41.3
18.00-1867	M6	NA	NA	1.40	0.955
21.33	M7	NA	NA	NA	0.980
22.83-23.00	M8	NA	0.0900	0.640	0.870
24.67-25.00	M9	0.245	0.480	0.425	1.48
25.67-26.00	M10	NA	0.415	1.15	1.70
27.33-27.50	M11	0.0500	0.215	0.645	3.43
29.67-30.33	M12	0.325	0.560	0.525	4.99
32.00-32.50	M13	1.10	1.13	0.555	1.01
36.17-36.67	Bremelanotide	92.9	72.6	29.4	10.2
46.83-47.33	M14	0.635	0.630	0.930	0.87
	Total:	**95.4**	**94.8**	**91.3**	**84.2**

Sponsor's Figure 2.6.5.11.3.



In vivo metabolism: see PK Tabulated summary for lists of metabolites

Study # Location	Year	Study description	Compound used / Dose	Comments
46438 Part B 4.2.2.4	2001	Absorption, Excretion, Distribution and Metabolism in male and female rats after intranasal or iv administration of [^{3}H]PT-141	[^{3}H]PT-141 0.004 mg/kg iv 0.05 mg/kg in	Limited analysis due to unstable labeling; male and female rats, iv and intranasal routes
7514-122 4.2.2.4	2006	Absorption, Distribution, Metabolism, and Excretion of Radioactivity Following a Single IV Administration of ^{14}C-PT-141 and QWBA After Intranasal Administration to Male Rats	^{14}C-BMT Labeled on the acetyl group 1.25 mg/kg iv 3 mg/kg in	Limited analysis due to cleavage of acetyl group; Male rats only; iv route tissue analysis of metabolites
8349336 4.2.2.3	2017	Pharmacokinetics, Distribution, Metabolism, and Excretion of [^{14}C]-Bremelanotide Following SC Administration to Male and Female Mice	^{14}C-BMT Labeled on the phenylalanine ring 30 mg/kg sc	Definitive study. Stable label. Male and female mice. SC route.

Rat Study #46438 Part B (Metabolism): Absorption, excretion, distribution and metabolism in male and female SD rats after intranasal or intravenous administration of [^{3}H]PT-141 (bremelanotide). GLP. Conducted in 2003.

For both intranasal and iv mass balance studies a single dose of [^{3}H]PT-141 was administered at 0.004 mg/kg body weight (about 100 uCi/kg BW). The dose level for the intranasal tissue distribution study was increased to about 0.05 mg/kg to enable detection of PT-141 equivalents in tissues. Dose volume for both routes was 100 uL/kg BW.

Plasma samples collected at 0.33, 3, and 24 hours after intranasal and iv dosing, fecal samples collected at 8 to 24 hours and 24 to 48 hours after iv dosing, and urine samples collected at 0 to 8 hours and 8 to 24 hours after iv dosing were used for metabolic profiling.

The results of the metabolic radioprofile of components in plasma are tabulated in Section 2.6.5.9.2 and Section 2.6.5.9.3 for iv and intranasal administration of [^{3}H]-bremelanotide, respectively. Metabolite profiles in feces and urine are tabulated in Section 2.6.5.9.4 and Section 2.6.5.9.5, respectively.

Parent [^{3}H]-bremelanotide accounted for 26-37% and 66-68% of the radioactivity in plasma samples collected at 20 minutes after intranasal and iv dosing, respectively. Parent compound declined to <10% at 3 and 24 hours after intranasal and iv dosing.

Linear bremelanotide, formed by hydrolysis of the strained lactam ring, was the only metabolite identified in plasma, and was found at low levels (≤ 12%) only in the 20-minute plasma samples from intranasal or iv dosed rats. Unidentified polar components (U1; including U1a and U1b) predominated in plasma at 3 and 24 hours after intranasal (54% to 80% of chromatographed radioactivity) or iv (38% to 73% of chromatographed radioactivity) administration. Lyophilization of the plasma samples suggested that tritiated water accounted for most of the polar radioactivity in the 3- and 24-hour plasma samples.

Following iv administration of [^{3}H]-bremelanotide, 10% to 11% of the dose was excreted as parent, with 7% to 9% in urine and 3% to 4% in feces. Linear bremelanotide accounted for 19% to 26% of the dose and was primarily eliminated in the feces. Unidentified polar components were present in the urine (about 3% of the dose) and feces (20% to 21% of the dose), and probably represented radiolabeled, water-soluble small molecules not likely to be tritiated water. At least 2 (feces) or 3 (urine) other minor metabolites were detected in the excreta but were not identified.

Study 7514-122 was a non-GLP study to assess the ADME profile [^{14}C]-bremelanotide (formulated with the ^{14}C radiolabel located on the terminal acetyl group) following administration of a single 1.25 mg/kg iv or 3.0 mg/kg intranasal dose to male SD rats, and a single 1.25 mg/kg iv dose to male LE rats. The absorption and distribution results from this study are discussed in Section 4.1.3, and excretion and mass balance results are summarized in Section 6.3.

Metabolic profiling was conducted on pooled samples of urine (0 to 8-hour collection, 3 rats), bile (0 to 2-hour collection, 3 rats), plasma (pooled by time point, 9 rats), liver (pooled by time point, 9 rats), and brain (pooled by time point, 9 rats) following administration of 1.25 mg/kg iv [^{14}C]-bremelanotide to male SD rats. The time points for the plasma, liver and brain samples were 10 minutes, 2, and 6 hours postdose. All samples were analyzed by LSC and HPLC. Results of the metabolic profile are tabulated in Section 2.6.5.9.6.

The parent drug and 11 metabolites (designated M1 through M11) were observed in urine, bile, plasma, liver, and brain samples. Seven of the metabolites (M3 through M9) were tentatively Identified. The identities of M1, M2, M10, and M11 were not determined. Parent [^{14}C]-bremelanotide represented the largest single radioactive peak in urine and bile. In plasma, liver, and brain, parent [^{14}C]-bremelanotide represented the largest single radioactive peak at 10 min, then rapidly disappeared over time.

Study 8349336 was a non-GLP study to determine ADME profile of [^{14}C]-bremelanotide after administration of a single (30 mg/kg nominal) sc dose to male and female B6C3F1/Crl mice. [^{14}C]-bremelanotide (formulated with the ^{14}C radiolabel located in the aromatic ring of the D-phenylalanine moiety) was administered at a target radioactive dose of 300 µCi/kg animal weight.

Absorption and distribution results from this study are discussed in Section 4.1.1, and excretion and mass balance is summarized in Section 6.1. For evaluation of metabolism, selected samples of plasma (40 mice/sex), urine (9 mice/sex), and feces (9 mice/sex) were pooled by matrix to ensure sufficient radioactivity for any necessary extraction and reconstitution procedures and analyzed by LC-MS for bremelanotide metabolite profiling and identification. This study was conducted in conjunction with Study 8349338 (see Section 5.2.4) in which metabolites were assigned, and the numbering scheme was continued in this study. The metabolite profile is tabulated in Section 2.6.5.9.1.

Bremelanotide underwent moderate metabolism in male and female mice to produce 21 radioactive components, of which 8 were identified/characterized by LC-MS. Amide hydrolysis was the predominant biotransformation pathway.

2.6.5.9.1. Metabolite Profiling and Identification after a Single SC Dose of [14C]-BMT in the Mouse (Study 8349336)

Summary of Metabolites Detected in Plasma, Urine and Feces

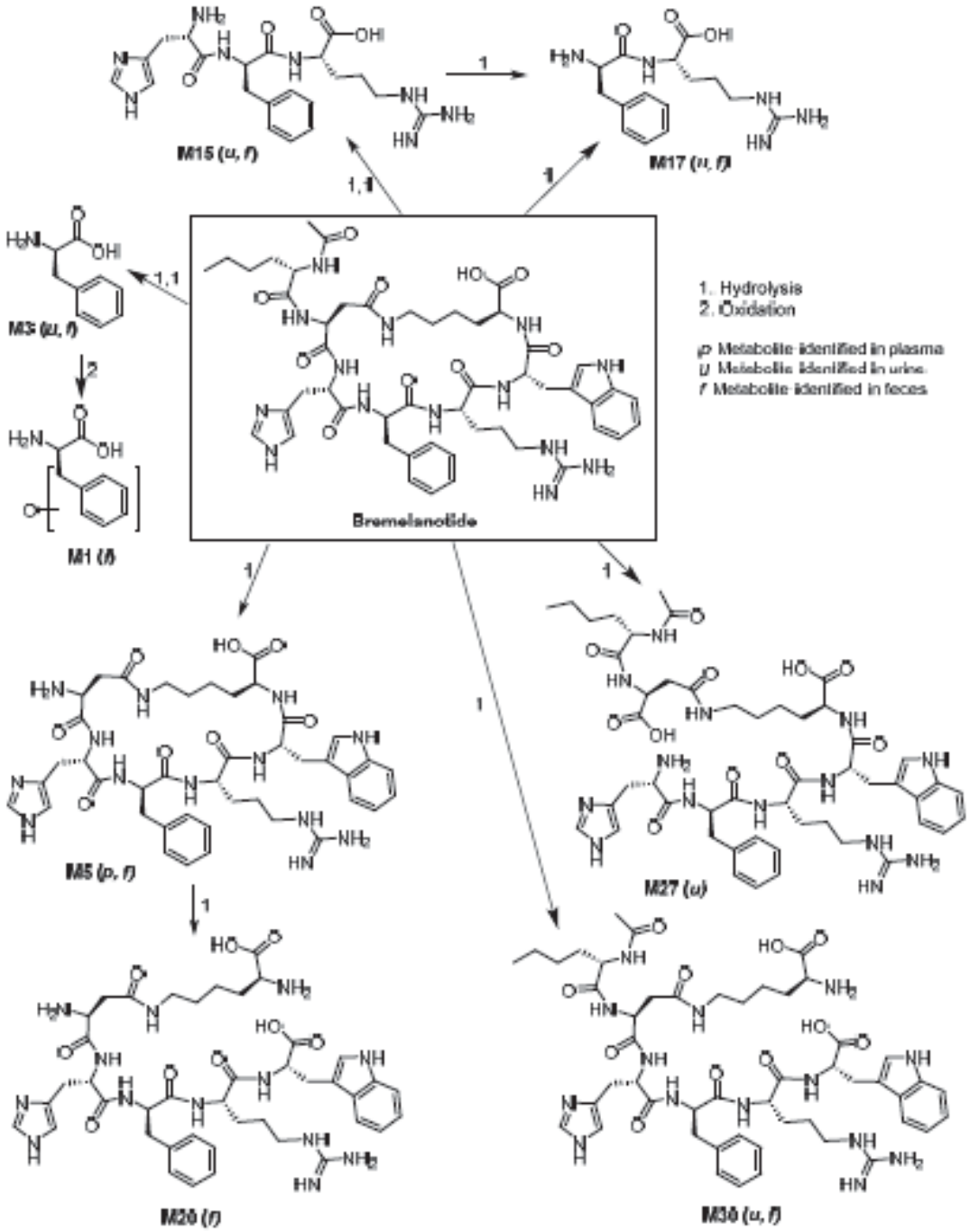
Metabolite Designation	Retention Time (minutes)	Proposed Identification	Matrix		
			Plasma	Urine	Feces
M1	1.67	hydroxy-Phen			X
M15	2.67-4.17	His-D-Phen-Arg		X	X
M16	3.17	below identification limit			X
M17	4.00-5.00	D-Phen-Arg		X	X
M3	5.33-6.00	D-Phen		X	X
M18	10.50-10.67	unknown			X
M19	12.17-12.33	below identification limit			X
M4	14.17	below identification limit			X
M20	15.50	Lys-Asp-His-D-Phen-Arg-Trp			X
M5	17.00-16.83	des-Ac-Nle-BMT	X		X
M21	19.17	unknown	X		
M22	19.33	unknown		X	
M23	19.00-19.17	unknown			X
M24	20.00	below identification limit			X
M25	21.83	below identification limit			X
M26	25.67-25.83	below identification limit			X
M27	26.67	His-D-Phen-Arg-Trp-Lys-(Ac-Nle)-Asp		X	
M28	27.33	unknown			X
M29	29.50	below identification limit		X	
M30	30.33-30.50	Lys-(Ac-Nle)-Asp-His-D-Phen-Arg-Trp		X	X
BMT	36.33-36.67	bremelanotide	X	X	X
M31	47.17	unknown	X		

- M3 (D-phenylalanine), the sole major metabolite, cumulatively accounted for 11.3% and 8.3% of dose in male and female mice, respectively. Observed primarily in feces and to a lesser extent in urine, resulted from double amide hydrolysis of bremelanotide at the histidinyl-D-phenylalanine and D-phenylalanyl-arginine bonds.
- M5 (des-Ac-Nle-bremelanotide), a minor circulating metabolite resulting from amide hydrolysis of bremelanotide at the N-acetyl-norleucinyl-aspartic acid bond. Accounted for 0.69% total AUC for radioactivity from plasma in male mice and 1.85% total AUC for radioactivity from plasma in female mice.
- M27 (His-D-Phen-Arg-Trp-Lys-[Ac-Nle]-Asp) - trace to minor urinary metabolite resulting from amide hydrolysis of bremelanotide at the aspartyl-histidine bond.
- M30 (Lys-[Ac-Nle]-Asp-His-D-Phen-Arg-Trp) - trace to minor urinary and fecal metabolite resulting from amide hydrolysis of bremelanotide at the lysinyl-tryptophan linkage.
- M20 (Lys-Asp-His-D-Phen-Arg-Trp) - comparatively abundant, albeit minor, fecal metabolite resulting from secondary amide hydrolysis of M5 at the lysinyl-tryptophan bond.
- M1 (hydroxyphenylalanine) - minor fecal metabolite resulting from oxidation of phenylalanine. M15 (His-D-Phen-Arg) and M17 (D-Phen-Arg) - minor urinary and fecal metabolites resulting from double amide hydrolysis of bremelanotide.

The low percentages of profiled plasma metabolites represent the low extraction recovery of radioactivity from plasma (~ 24% to 36%) as well as the likely presence of numerous low-level (BLQ; <1% of sample radioactivity and 10 cpm peak height) metabolites.

The proposed biotransformation pathway for bremelanotide in vivo in mice is presented in Section 2.6.5.11.1.

2.6.5.11.1 Proposed Biotransformation Pathways of Bremelanotide in Mice in vivo. (Study 8349336)



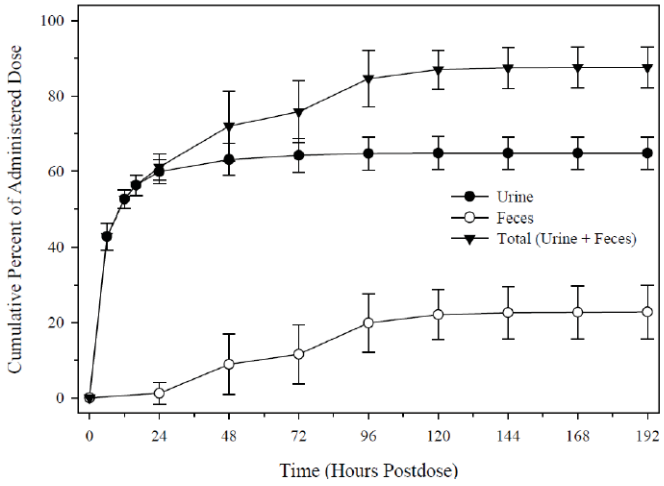
Human ADME

BMT-107 (5.3.3.1): An Open-label, Single Center, Single Subcutaneous Dose Study to Investigate the Pharmacokinetics, Absorption, Metabolism, and Excretion of [^{14}C]-Labeled Bremelanotide in Healthy Females and Males. 2017.

Synopsis: Human PK study 1.75 mg sc injection ^{14}C labeled BMT

- Following sc administration, BMT was rapidly absorbed (Tmax ~0.5 hrs). Plasma BMT concentrations declined in a generally biphasic manner, with a mean $T_{1/2}$ of ~ 2.7 hours.
- The primary route of elimination was in the urine (64.8% of the radiolabeled dose, 36.5% as unchanged BMT), with most excreted within 6 hrs post-dose. 22.8% was recovered in feces. Total recovery of radioactivity in all excreta (urine and feces) was 87.6% of the administered dose.
- The AUC ratio of plasma BMT to plasma total radioactivity was 0.150, indicating that unchanged BMT was a minor component of plasma total radioactivity. Radioactivity was quantifiable in plasma through the last sampling timepoint (8 days post-dose).
- The AUC_{0-192} blood/plasma ratio was 0.733, indicating minimal partitioning of total radioactivity into red blood cells.
- The overall distribution and excretion profiles were similar between males and females.

Figure 11-2: Mean (±SD) Cumulative Percent Recovery of Total Radioactivity in Urine and Feces. Study report BMT-107 p 33



Human metabolism

In humans bremelanotide was metabolized primarily via amide hydrolysis of the cyclic peptide ring, considering both circulating and urinary metabolites (for discussion see p 67-68 of the Pharmacokinetic Written Summary).

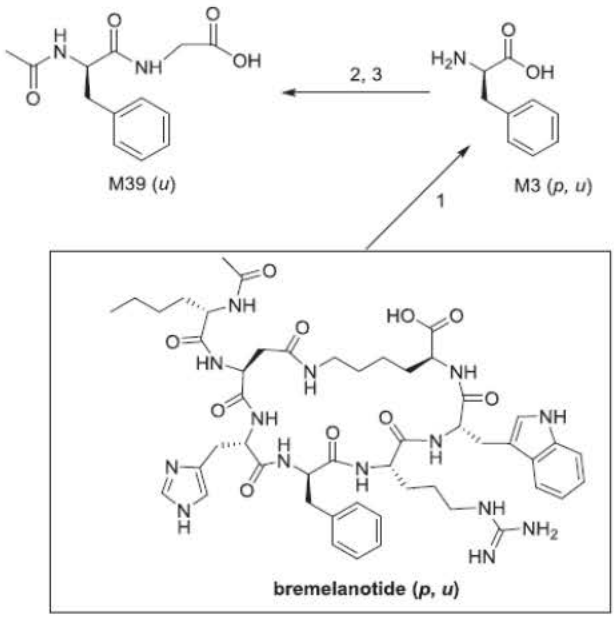
In plasma, the calculated AUC_{0-96h} suggested bremelanotide and D-phenylalanine (M3) accounted for approximately 74% and 24% of the radioactivity, respectively (98% of total radioactivity). Three impurities were present in the 0.5 and 1 hr post-dose samples and accounted for less than 1% of the radioactivity each. **Conversion of bremelanotide to M3 occurs between 4 and 8 hours and is complete by 24 hrs (see Table 2 p 361 of Study BMT-107).**

In urine, bremelanotide, M3 and M39 accounted for approximately 42%, 10%, and 6% of the radioactive dose, respectively (58% total radioactivity). Other metabolites, degradants, and impurities accounted for less than (b) (4)% of the radioactive dose each.

In feces, no parent bremelanotide was detected and M51 accounted for approximately 8% of the radioactive dose. Other metabolites accounted for less than 2% of the radioactive dose each.

Proposed biotransformation pathways of bremelanotide in humans

Study # BMT-107 (5.3.3.1) Appendix 16.2.5.4. accessed from p 35 of the study report
Figure 12 p 382 of the Appendix showing metabolites in urine



p Identified in plasma
u Identified in urine
f Identified in feces

1. Hydrolysis
2. AA conjugation
3. Acetylation

Summary of Metabolites / Impurities in Humans

Metabolite Designation	Retention Time (minutes)	Matrix: Plasma	Urine	Feces	Dose Formulation
(b) (4)					

Comparison of mouse and human metabolites from the Nonclinical Overview

In humans, 6 metabolites were characterized/identified, 13 metabolites were characterized, but structures could not be proposed, and 9 impurities were identified (Study BMT-107, Metabolite Profile Report 8350446).

The major metabolite in mice and humans, M3, was identified as [^{14}C] D-phenylalanine. indicating that the predominant biotransformation pathway is the hydrolysis of the amide bonds of the cyclic peptide forming its constitutive amino acids. These amino acids are assumed to be recycled through normal pathways.

Plasma:
Unchanged bremelanotide was the most abundant component in mouse plasma and was the only non-impurity circulating component detected in human plasma samples up to 4 hours postdose. Minor hydrolyzed metabolite M5 was the only identified bremelanotide metabolite in mouse plasma whereas M3 was detected up to 24-hrs postdose in human plasma, with bremelanotide and M3 accounting for ~ 52% and ~ 47% of the radioactivity, respectively.

Urine:
Mouse: Bremelanotide was also the most abundant component in mouse urine (0 to 24 hours), with minor metabolites M3, M15, M17, M27, and M30 accounting for <2% individually and ~ 6% cumulatively of dose, and 2 unidentified/uncharacterized metabolites (M22 and M29) detected at <5% of dose, each. In total, unidentified urinary metabolites accounted for ~ 4% to 6% of dose in mouse urine.

Human: In human urine (0 to 72 hours), bremelanotide and 10 metabolites, degradants and/or impurities were detected. Bremelanotide and M3 accounted for ~ 42% and ~ 10% of the dose, respectively. In addition, M39, a metabolite formed via acetylation and glycine conjugation of M3, accounted for ~ 6% of the dose, and other metabolites, degradants, and impurities accounted for (b) (4)% each.

Feces:
Mouse: In mouse feces (0 to 48 hours), M3 was the most abundant component, and bremelanotide was a minor component accounting for ~ 2% to 3% of dose. Amide hydrolyzed metabolite M5 and its secondary hydrolyzed metabolite M20 were minor fecal components each accounting for ≤ 5% of dose; hydrolyzed metabolites M15, M17, and M30 and hydroxyphenylalanine (M1) individually accounted for ≤ 2% of dose. In addition, 9 uncharacterized or unidentified components (M16, M18, M19, M4, M23, M24, M25, M26, and M28) were trace (<1% dose) to minor metabolites accounting for <2% individually and <8% cumulatively, of dose.

Human: In human feces (0 to144 hours), no bremelanotide was detected, and a total of 12 unidentified metabolites (M42, M43, M44, M45, M46, M48, M49, M50, M51, M52, M53, M54) were present, with M51 accounting for ~ 8% and the other 11 metabolites accounting for <2% each, of the dose.

In vivo metabolism was not characterized for the other nonclinical species.

Enzyme induction / Inhibition / Drug-Drug Interaction:

P450 inhibition: In human liver microsomes, bremelanotide did not demonstrate any clinically meaningful inhibition of CYP enzymes.

Study 46818: Human liver microsomes pooled from 20 subjects were used to investigate the potential of PT-141 to inhibit human liver microsomal CYP 450 isozymes (CYP 1A2, CYP 2A6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4). The incubations were performed in the absence or presence of 5 concentrations of PT-141 i.e., 10, 25, 50, 100 and 200 uM.

At concentrations of 10 to 200 µM, BMT did not inhibit the activity of CYP isozymes 1A2, 2C9, 2D6, or 2E1.

At 200 µM, bremelanotide caused inhibition of CYP2C19 (~85%) and CYP3A4 (~60%), and marginal inhibition of CYP2A6 (~40%). There was no inhibition of these 3 CYP isozymes at 20 µM (Study 46818). Results are tabulated in Section 2.6.5.12.1.

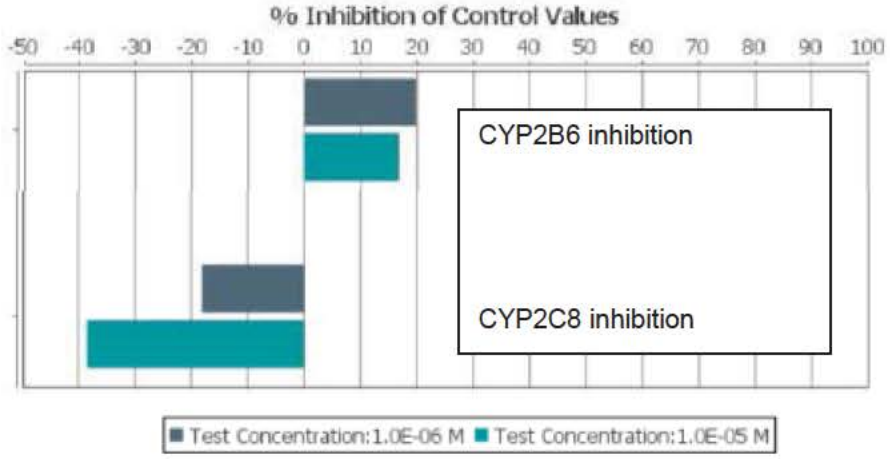
To determine the Ki of bremelanotide for CYP2C19 and 3A4, human liver microsomes (pooled from 20 subjects) at a concentration of ~ 0.2 mg protein/mL were incubated at 37 °C for 10 minutes. At least 3 concentrations of each probe substrate (~ 0.5, 1, 5, or 10 times Km) were used, along with 5 concentrations of bremelanotide (~ 25, 50, 75, 150 and 300 µM).

For CYP2C19, bremelanotide decreased Vmax, while the Km remained unchanged, suggesting a noncompetitive mechanism of inhibition. The Ki was determined graphically to be ~ 35 µM.

For CYP3A4, each substrate exhibited a pattern consistent with competitive inhibition by bremelanotide. The Vmax remained unchanged while Km was increased for each substrate. The Ki of bremelanotide using substrates testosterone and midazolam were graphically determined to be ~ 60 and ~ 16 µM, respectively, which was in agreement with the calculated Ki values. However, in the case of nifedipine, the calculated value was ~ 15 µM, whereas, graphically, the Ki was determined to be ~ 35 µM.

Two other enzymes assayed: (Study 100026669).
At concentrations up to 10 µM, bremelanotide showed minimal inhibition of the CYP isozymes 2B6 and 2C8.

Figure 2.6.4-14 Peak Inhibition of CYP2B6 and CYP2C8 Caused by Bremelanotide at 1 and 10 µM



P450 induction

Study MD-3-3-474-1827 was a non-GLP study to determine if treatment with bremelanotide induced the expression of CYP450 enzyme genes in human primary hepatocytes in vitro. Cryopreserved human hepatocytes from 3 donors were used to assess CYP induction.

The panel of P450s selected for this study included CYP1A2, CYP2B6, CYP3A4, CYP2C19, and CYP2A6. The activity of these enzymes was assessed by measuring mRNA expression using quantitative PCR following drug stimulation. Positive controls, were known inducers of CYP genes and included omeprazole, phenobarbital, rifampicin, and metaxalone. The vehicle control was dimethyl sulfoxide (DMSO).

Bremelanotide demonstrated little to no potential to induce gene expression for CYP enzymes.

DDI

One in vitro and one in vivo study was conducted to assess inhibition of drug transporters by BMT.

Study 100026666 was a non-GLP study to test the in vitro inhibition of drug transporters by BMT in absorption assays using fluorimetry as the detection method. BMT at a concentration of 1 mM was incubated for 20 minutes at 37ºC with OCT2, BCRP, OAT1, OAT3, OATP1B1, and OATP1B3 in human recombinant CHO-K1 cells, and with P-gp in MDR1-MDCKII cells. Results are tabulated in Section 2.6.5.12.4. Mean absorption (%inhibition of control, mean of 2 tests) for 1 µM bremelanotide is summarized in Table 2.6.4-7.

Bremelanotide caused low inhibitory activity against all 7 transporters. Inhibition (as a percent of control) was 20.9% for OATP1B3, 12.0% for P-gp, and 5.0% for OAT3. This level of inhibition is not clinically relevant.

Table 2.6.4-7 Drug Transporter Inhibition by Bremelanotide

Isoenzyme	Percent Inhibition of Control Values
OATP1B3	20.9
P-gp	12.0
OAT3	5.0
BCRP	1.6
OAT1	-5.4
OATP1B1	-15.9
OCT2	-27.0

An in vivo study to test the effect of BMT on the kinetics of absorption of orally administered drugs was submitted in response to an RFI by the NDA review team (SDN 39, 12-14-2018, Appendix 1). BMT is known to reduce gastric contractility and to therefore slow gastric emptying, which could alter the kinetics of drug absorption. This study has been fully discussed by Clinical Pharmacology in their review. Briefly, BMT was administered sc to mice plus or minus orally administered furosemide, naltrexone, or naltrexone. None of the drugs affected BMT pharmacokinetics, nor did BMT affect kinetics of the drugs tested.

5.2 Toxicokinetics

Comparison of TK across species

TK by the subcutaneous route was obtained in mouse, rat, rabbit, and dog. There was also limited TK information from intranasal dosing in the monkey. In general, absorption by the sc route was complete, and exposure was proportional to dose. Absorption was rapid and elimination occurred over a time frame of several hours. There were no striking gender differences, and no evidence for accumulation. There was no evidence of saturation of exposure with dose. In a few studies, there was evidence of declining exposure with repeat-dosing.

The sponsor did not provide an analysis of dose equivalency across species but did provide a table with all of the TK data collated (see Table 2.6.4-9 Summary of exposure – Comparison across species, p71 of the PK written summary in section 2.6.4 of the submission).

	Mouse	**Rat**	**Pregnant Rabbit**	**Dog**
Range of sc administered doses (mg/kg)	1-150	0.5-3.5	0.03-150	1-40
Range of sc administered doses (mg/m2)	3-450	3-21	0.36-1800	20-800

To get a sense of comparative exposure for the species used in the pivotal repeat-dose tox studies, here are the values for Cmax and AUC for equivalent doses (based on mg/m^2) in the mouse and dog (average of M/F on d1 of dosing):

	Mouse 15 mg/kg = 45 mg/m^2 Study #996-028	**Dog 2 mg/kg = 40 mg/m^2 Study # 996-003**
Cmax (d1) ng/mL	**9806**	**1946**
AUC (d1) ng.hr/mL	**15093**	**3855**

This comparison shows that equivalent doses in the mouse produced higher exposures than in the dog, based on body surface area.

Highest doses delivered to nonclinical species produced the following exposures:

Rat: 3.5 mg/kg (0.56 mg/kg HED) *C_{max} 353 ng/mL, AUC 1306 ng·hr/mL*
Mouse: 75 mg/kg (6.1 mg/kg HED) *C_{max} 32,150 ng/mL, AUC 56,700 ng·hr/mL*
Pregnant Rabbit: 150 mg/kg (48 mg/kg HED) *C_{max} 108,728 ng/mL; AUC 475,631 ng.hr/mL*
Dog: 40 mg/kg (22 mg/kg HED) *C_{max} 49,300 ng/mL, AUC 140,700 ng·hr/mL*

Comparison to human: (Study PT-141-56) BMT administered sc at a dose of 1.75 mg (0.03 mg/kg or 1.1 mg/m2) resulted in a mean C_{max} of 72.8 ng/mL (~73 nM), and a mean $AUC_{0=inf}$ value of 276 ng·hr/mL (276 nM.hr). Assuming proportionality of dose, exposure in nonclinical species was comparable to human for the mouse and pregnant rabbit, and lower in the rat and dog based on HED.

6 General Toxicology

Bridging studies were conducted in mouse and dog (996-018, 996-019, section 4.2.3.7.7), respectively to evaluate toxicity and TK with BMT from different manufacturers (b) (4). Carcinogenicity studies, 39-week chronic tox in dogs, and most of the reproductive tox studies were conducted using BMT from (b) (4). The 26-week chronic tox study in the mouse and genetox studies (Ames and chromab) were conducted using BMT from (b) (4). Dr. Raheja noted in one of his reviews that some of the early acute tox studies were done with BMT from (b) (4), but this reviewer did not identify exactly which ones. It does not appear that a bridging study was done to the (b) (4) drug substance.

996-018: A 7-day repeated-dose toxicokinetic study of PT-141 in B6C3F1 mice: Comparison of (b) (4) API.

Two treatment groups of 30/sex were dosed sc for 7 days with 75 mg/kg/day of PT-141 using dosing solutions formulated with (b) (4) API. Clinical observations, body weight, and food consumption were recorded. At necropsy, organ weights were recorded, and selected tissues were microscopically examined. Blood samples TK were taken on d7. There was no necropsy. There were no treatment related findings and TK between the two groups were similar. Mean plasma AUC as well as Cmax values for the two formulations were within 11 % of each other, establishing bioequivalence of (b) (4) API in dogs.

MOUSE

	Cmax (ng/mL)	AUC0-inf (ng.hr/mL)	Tmax (hr)
(b) (4)	M 53622 F 51158	M 64755 F 50247	0.5
	M 56682 F 52575	M 59741 M 47088	0.5

996-019: A 7-day repeated-dose toxicokinetic study of PT-141 in Beagle dogs: Comparison of (b) (4) API.

Two treatment groups of 4/sex were dosed sc for 7 days with 20 mg/kg/day of PT-141 using dosing solutions formulated with (b) (4) API. Clinical observations, body weight, and food consumption were recorded. At necropsy, organ weights were recorded, and selected tissues were microscopically examined. Blood samples TK were taken on d1 and d7. There was no necropsy. There were no treatment related findings and TK between the two groups were similar. Mean plasma AUC as well as Cmax values for the two formulations were within 11 % of each other, establishing bioequivalence of (b) (4) API in dogs.

DOG

	Cmax (ng/mL)	AUC0-inf (ng.hr/mL)	Tmax (hr)
(b) (4)	M 35592 F 31801	M 61144 F 62374	0.6
	M 31105 F 33656	M 66287 F 69490	0.6

Dr. Raheja also noted that a 14-day formulation study was conducted in the rat (996-021) to establish equivalence between BMT in a formulation of (b) (4). This formulation was tested for use in intranasal administration (but was not the formulation used in the 2-year rat carci study). Briefly, after intranasal dosing with 5 mg BMT (b) (4) formulations, clinical observations, body weight, and food consumption were recorded. At necropsy, organ weights were recorded, and selected tissues

were microscopically examined. There were no findings other than mild microscopic changes in the noses of the dosed animals. These findings were similar to those from other studies, specifically 996-010, a 14-day study that used 2.5% glycerin as the vehicle.

6.1 Single-Dose Toxicity

There were 5 single-dose tox studies conducted in the mouse, rat, and dog between 1999 and 2004 that have been submitted to the NDA. The results of the acute toxicity studies are shown in table form below. In the rat by the iv route, an MTD of 1.5 mg/kg was identified that was also the NOEL. By the subcutaneous route, mice were able to tolerate up to 150 mg/kg without mortality but with significant clinical signs. The NOEL set in that study did not include an evaluation of injection site reactions, which were a significant factor in the rat and the dog. Acute toxicity was not achieved by the intranasal route.

Study #	Species	Route	Doses (mg/kg)	MTD	NOEL	Comments
996-005*	Mouse	SC	15, 30, 75, 150	150	15	Clinical signs included tremors, impaired limb function; injection site reactions not described
103-003*	Rat	IV IN	3, 3.5, 4 3, 3.5, 4	<3 >4	-- >4	IV: Some mortality at all doses. Dose finding study showed complete mortality at 4.2 and 5 mg/kg IV; all rats treated IV had clinical signs. There were no clinical signs by the IN route
103-006*	Rat	IV SC	0.75, 1.5, 3 2.5, 5, 7.5	1.5 >7.5	1.5 --	IV: Mortality and ↓ activity at the high dose SC: Injection site reactions at all doses
131-007	Dog	SC	3, 6, 9, 12	>12	>12	No clinical signs; no injection site reactions
131-008*	Dog	SC	9, 12, 15	>15	--	Injection site reactions in some animals at all doses not dose-dependent

*GLP compliant

The sponsor sets the NOEL for SC administration in the dog at 15 mg/kg but reviewer disagrees and sets no NOEL due to injection site reactions.

6.2 Repeat-Dose Toxicity

A total of 13 repeat dose toxicity studies were conducted in the mouse, rat, and dog over the time frame of 1999-2006. Six of these were conducted by the intranasal route: 2 week, 1 month, and 3 month studies in the rat (with an additional study on adrenal tissue sections), and a 1 month and 3 month study in the dog. The other 7 were conducted by the subcutaneous route: 1, 3 and 6 month studies in the mouse, a 1 month study in the rat, and 1 and 9 month studies in the dog plus a range-finding study.

6.2.1. Mouse

Study #	Route	Duration	Doses (mg/kg)	NOAEL or NOEL	Comments
996-009	SC	4 week	15, 30, 75	NOEL = 30	At the high dose, mildly increased Hb, HCT and erythrocytes; Trend toward elevated ALT/AST
996-002	SC	3 month	1, 3, 9	NOEL = 9	Unexplained mortality in a few animals at the high dose; no other findings
996-028	SC	26 week w/ 4 week recovery	15, 30, 75	NOEL = 30	Injection site reactions and mild reactive liver and kidney changes

Because studies conducted by the intranasal route did not achieve the systemic exposures the sc studies achieved, they will not be reviewed here, but will be referred to only for comparative purposes. Of the studies conducted by the SC route, only the longest duration study will be reviewed in full for each species; shorter duration studies will be summarized.

Study title: A 26-week subcutaneous dose toxicity study of PT-141 in B6C3F1 mice with a 4-week recovery group.	
Study no.:	996-028
Study report location:	Application 210557 - Sequence 0002 - Study 996-028
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8-25-05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, Lot 2, purity 98.6%, peptide content (b) (4) % This batch contains elevated levels of impurity C and D

Key Study Findings

There were no new toxicities that had not been previously observed in the mouse for shorter duration studies.

- At 75 mg/kg/day (the high dose), there was an increased incidence of scabbed areas, sparse hair and white hair in males and females.
- A trend for increased body weight and food consumption was observed at the high dose during the treatment period. However, by the end of the recovery period, food consumption and group mean body weights in the 75 mg/kg/day group were lower than controls.
- There were signs of mild reactive changes in the liver and kidney. There was a dose-dependent mild increase in serum transaminases (AST and ALT) particularly in females at termination. There were small (~10-12%) but statistically significant increases in relative liver and kidney weights in males and females, primarily at the mid and high doses, that did not have corresponding histopathology, and were considered reactive.
- TK: Exposures were stable or slightly increased over the duration of the study. There were no gender differences.
- Based on these findings, NOEL = 30 mg/kg/day. At that dose, MOE compared to the proposed human dose based on AUC on d180 was 56.

Methods	
Doses:	0, 15, 30, 75 mg/kg/d
Frequency of dosing:	Daily
Route of administration:	Subcutaneous
Dose volume:	4 mL/kg
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Mouse / $B6C3F_1$
Number/Sex/Group:	30 sex/group plus 10 animals in the low and high dose groups for recovery
Age:	5 weeks old
Weight:	M: 20.8-25.2 g; F: 17.0-20.1 g
Satellite groups:	90/sex/group for TK
Unique study design:	None
Deviation from study protocol:	None that affected outcome

Observations and Results

Mortality

Two control females, 1 male and 1 female at 15 mg/kg/day, and 1 male and 1 female at 30 mg/kg/day were found dead during the course of the study. None were considered treatment-related.

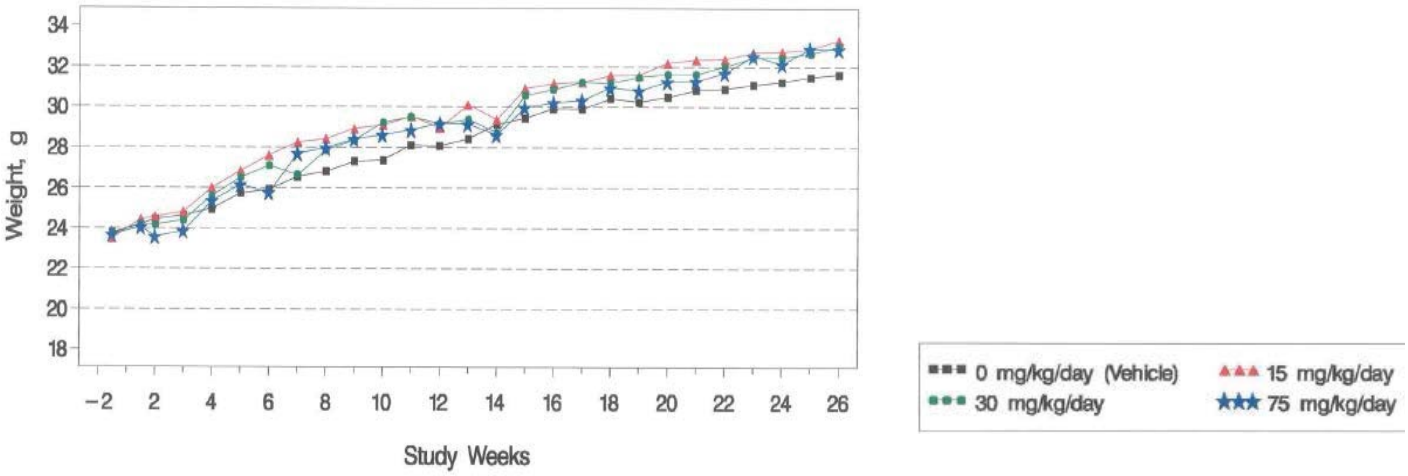
Clinical Signs

Cage side observations twice daily. Detailed clinical observations weekly.
Clinical signs consisted of alopecia observed in greater frequency in the high dose group (90% of males and 65% of females) than in controls (33% in males and 35% in females) during the treatment period. Scabbed areas were observed only in the high dose group (40% of males and 35% of females). Only one animal had a scabbed area during the recovery period. White colored hair was observed only at the high dose (23% of males and 10% of females). Alopecia and white coloration of hair were observed throughout the recovery period.

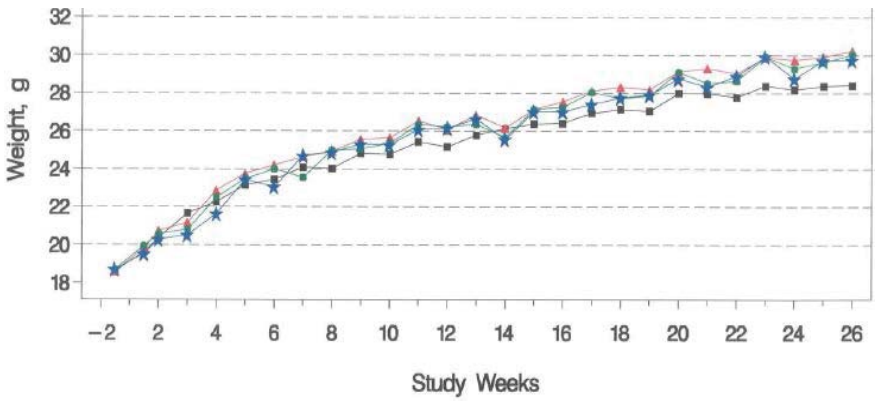
Body Weights

Prior to randomization and then weekly. At the high dose, body weights were significantly decreased in males during weeks 2 and 3 and in females during weeks 3 and 4. However, for the remainder of the 26-week dosing period, treated animals generally had higher body weights than control animals. No significant differences were observed during the 4-week recovery period.

Males



Females



Feed Consumption

Weekly. Generally, food consumption was higher in the treated groups which correlated with increased body weight. There was no dose-response relationship.

Ophthalmoscopy

Prior to necropsy. No treatment related findings.

ECG Not done

Hematology

Hemoglobin and MCH were slightly higher in both male and female treated groups with no dose-response relationship.

Clinical Chemistry

As shown in table 2 below there was a dose-dependent mild increase in serum transaminases (AST and ALT) particularly in females at termination. There were no test article related effects on clinical chemistry analytes at recovery.

Endpoint	Interval of study	0 mg/kg/day	15 mg/kg/day	30 mg/kg/day	75 mg/kg/day
Males					
AST (U/L)	week 13 terminal	123 174.6	77.1 147.9	91.2 122.4	168.2 117.2
ALT (U/L)	week 13 terminal	32.4 39.8	23.7 37.7	32.7 31.7	58.4 43.8
Females					
AST (U/L)	week 13 terminal	137.0 108.4	126.4 156.7	125.0 220.6	118.4 231.8
ALT (U/L)	week 13	38.0	27.0	46.3	38.9
	terminal	28.9	40.9	44.9	64.3[a]

[a] significantly different from control p<0.05 Values are mean of 10 observations

Urinalysis Not done

Gross Pathology

There was an increased incidence (~25% M and F) of alopecia in the high dose group at terminal necropsy. Mild alopecia was also observed at the injection site in males (2/20 left flank and 3/20 right flank).

Organ Weights

There were small (~10-12%) but statistically significant increases in liver and kidney weight in males and females, primarily at the mid and high doses.

Male- Mean organ weight values				
Endpoint	0 mg/kg/day	15 mg/kg/day	30 mg/kg/day	75 mg/kg/day
Kidney/body weight %	2.080	2.146	2.277[b]	2.237[a]
Liver/body weight %	4.431	4.891[a]	4.912[a]	4.699
Female- Mean organ weight values				
Kidney/body weight %	1.708	1.703	1.817[a]	1.923[b]
Liver/body weight %	4.781	5.081	5.261[b]	5.437[b]

[a] Significantly different from control)p<0.05) [b] Significantly different than control (p<0.01)

Other significant changes consisted of decreased weights of mandibular salivary gland and seminal vesicles in high dose males. Relative spleen weight in high dose females at the end of the recovery period was significantly higher than the controls (0.419% vs 0.290%), which was unexplained. Microscopic examination identified no test article-related abnormalities in the spleen of these animals, and spleen weights in the 75 mg/kg/day terminal necropsy females were normal. Therefore, the increased spleen weight in the recovery females was considered spurious and of no toxicological significance.

Histopathology

Adequate Battery: Yes Peer Review: Yes

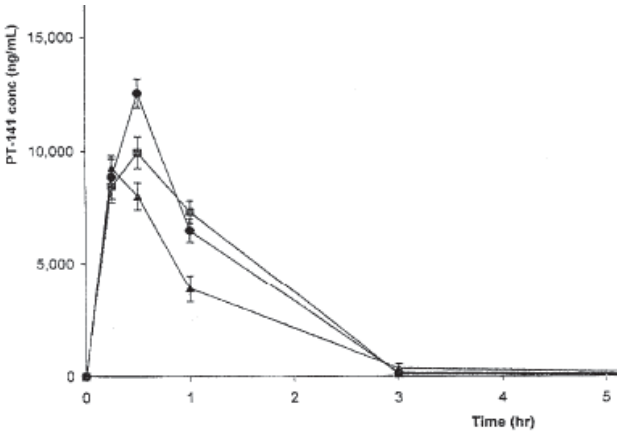
Test article related microscopic changes occurred in the skin and at the injection site, primarily at the high dose. In males these findings included alopecia/hypotrichosis, epidermal hyperplasia, fibrosis, chronic inflammation, and erosion/ulcer. In females, fibrosis, epidermal hyperplasia, and acute inflammation were observed. The incidence of skin alopecia in males was 0, 1, 1 and 6 out of 20 for control, 15, 30 and 75 mg/kg/day groups, respectively. In females the incidence of skin alopecia was 1, 2, 2 and 5 in control and dosed groups, respectively. Severity was minimal to mild. The incidence of alopecia at the high dose did not decrease during the recovery period.

Toxicokinetics

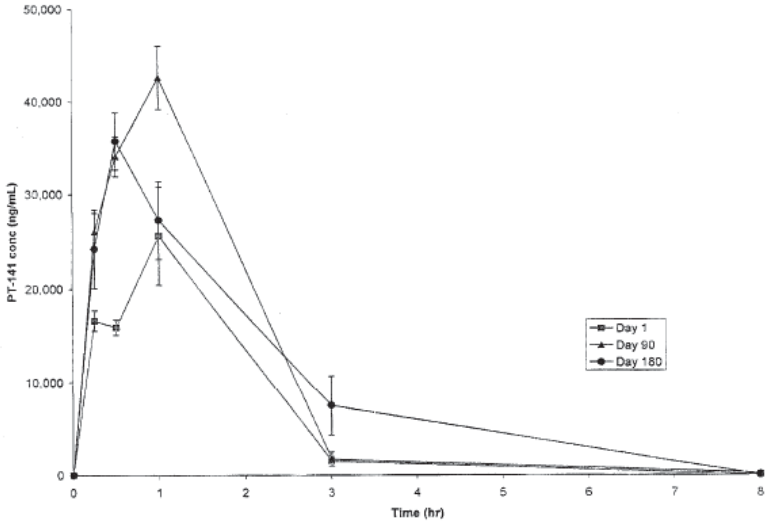
Bremelanotide was rapidly absorbed following SC dosing at all 3 dose levels, with Tmax occurring 20 to 60 minutes postdose. Mean Tmax occurred slightly later at the highest dose but did not change following multiple SC doses. A dose-related increase in average Cmax and $AUC_{0-\infty}$ was observed in male and female mice at all 3 study intervals (Days 1, 90, and 180). The data were highly variable; however, there did not appear to be a difference in exposure between male and female mice, and exposure was comparable to previously conducted mouse studies at these doses.

Day 1	15 mg/kg/day		30 mg/kg/day		75 mg/kg/day	
	Male	female	Male	female	male	female
Tmax (hr)	0.5	0.5	0.5	0.3	1.0	1.0
Cmax (ng/ml)	11,034	8,577	14,234	11,135	19,082	32,146
AUC_{0-8} (ng.hr/ml)	16,490	13,585	25,171	18,732	35,269	56,778
AUC_{0-inf} (ng.hr/ml)	16,557	13,630	25,599	18,855	36,273	56,792
Day 90						
Tmax (hr)	0.3	0.3	0.5	0.5	1.0	1.0
Cmax (ng/ml)	9,889	8,625	17,692	18,210	42,240	43,100
AUC_{0-8} (ng.hr/ml)	11,039	9,954	22,187	25,247	82,558	75,942
AUC_{0-inf} (ng.hr/ml)	11,392	10,177	22,350	25,522	83.275	75,954
Day 180						
Tmax (hr)	0.5	0.5	0.3	1.0	0.5	0.5
Cmax (ng/ml)	13188	12,043	20,526	19,156	35,235	36,241
AUC_{0-8} (ng.hr/ml)	17,067	13,707	30,665	33,331	101,925	50,574
AUC_{0-inf} (ng.hr/ml)	17,097	13,806	31,019	33,440	101,934	59,883

Concentration vs time female mice 30 mg/kg/d



Concentration vs time female mice 75 mg/kg/d



Dosing Solution Analysis

Stability and homogeneity were adequate. Analysis results during the first 13 weeks of the study periodically fell outside± 10% of the targeted concentrations. These results are believed to be due to sampling and dilution errors surrounding the collection of an exact 0.250 mL volume. After implementing changes in sampling and analysis procedures, subsequent analytical results were within 10% of the targeted concentration.

6.2.2. Rat

Most of the repeat-dose toxicity studies that were carried out in the rat were conducted by the intranasal route; only one study was conducted by the subcutaneous route. The sc study is reviewed here. The intranasal studies are briefly summarized at the end of this section only for purposes of comparison.

Study title: 28-Day Repeated Dose Toxicity Study of PT-141 Administration Via Subcutaneous injection to SD Rats	
Study no.:	131-013
Study report location:	Application 210557 - Sequence 0002 - Study 131-013
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 1, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141; Lot J2#614, purity 99.1%, peptide content (b) (4) %

Key Study Findings

- Injection site reactions occurred that were dose and duration dependent.
- Body weight changes in males exhibited a dose-responsive decrease in the rate of weight gain over the duration of the study. This effect resulted in incrementally lower mean body weights as the test article concentration increased. Mean body weights in the

two highest dose groups were significantly lower than controls at the end of the study. Effects on body weight were not considered by the sponsor to be adverse, but reviewer considers the significantly lower body weight at the two highest doses to be adverse.

NOAEL = 0.5 mg/kg based on injection site reactions at the two higher dose levels and reduced body weight gain. MOE ~ 1 based on AUC.

Cmax averaged 96.3, 243, and 353 ng/mL after a dose of 0.5, 2.0, and 3.5 mg/kg, respectively. AUC averaged 371, 690, and 1312 ng*hr/mL after a dose of 0.5, 2.0, and 3.5 mg/kg, respectively.

Methods	
Doses:	0, 0.5, 2.0, 3.5 mg/kg/d
Frequency of dosing:	Daily
Route of administration:	Subcutaneous
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.9% sterile NaCl
Species/Strain:	Rat / Cr;"CD(SD) IGSBR
Number/Sex/Group:	10/sex/dose main study
Age:	6 wks
Weight:	M: 142-191 G M: 123-152 g
Satellite groups:	20/sex/dose. 9 were used for blood collection on d1 and d29, with 2 held as extra
Unique study design:	None
Deviation from study protocol:	None that affected conclusions

Observations and Results

Mortality

Mortality (unscheduled death) was observed in 1 male and 1 female from the control and the mid-dose groups respectively. The deaths were attributed to a urinary tract disease and were not considered test article-related.

Clinical Signs

Daily. Daily. Scab formations at the injection sites were the only adverse clinical observation considered test article-related. This finding was observed in the two highest dose groups, and the onset and severity of the finding correlated with the increasing dose level. Scab formation was initially observed on Study Day 16 in Group 3 and on Study Day 4 in Group 4.

Body Weights

Weekly. There was a dose-dependent decrease in body weight gain in males that resulted in incrementally lower mean body weights as the test article concentration increased: 5, 8 and 15% lower for the three dose groups respectively. Mean values in the two highest dose groups were statistically different from control values.

Feed Consumption

Not recorded

Ophthalmoscopy / EEG

Not done

Hematology

Prior to necropsy. Sponsor noted a trend toward reduced MCV and MCH and a trend toward increased platelet counts and PT time in males. These were not considered toxicologically significant.

Clinical Chemistry

Prior to necropsy. Slight elevation in ALT / AST at the two highest doses that the sponsor considered to be artifacts of tissue injury at the injection site and hemolysis in some of the female samples.

Urinalysis

Not done

Gross Pathology

Injection site discoloration.

Organ Weights

No treatment-related changes in relative organ weights.

Histopathology

Adequate Battery Yes Peer Review No

Injection site reactions. Microscopic evaluation identified the nature of the injection site lesions as inflammatory responses to mild irritation. This inflammatory response was observed in a few control animals, but the findings in Groups 3 and 4 extended into hyperkeratosis, epidermitis, acanthosis, dermatitis, and underlying muscle degeneration. The incidence and severity of these findings were highest in Group 4 and were considered test article related and adverse.

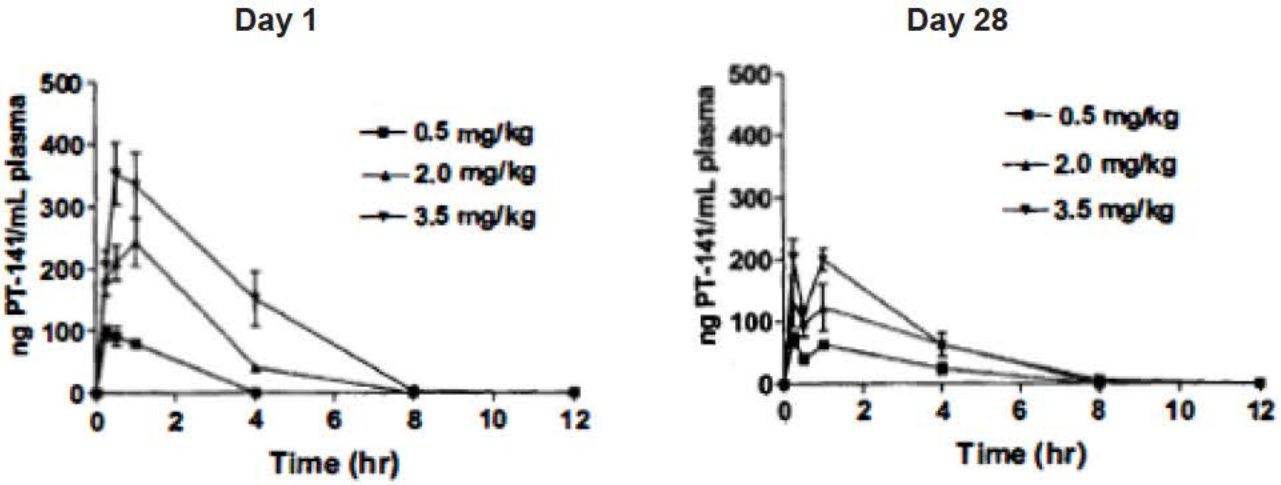
Dosing Solution Analysis

The formulation analysis from Weeks 1 and 4 indicated PT-141 concentration was within acceptable limits (±10%) with the following exception: the Group 3 (mid-dose) formulation used for the first week of dosing was 88.6% of theoretical. The formulation analysis also confirmed 19-Day refrigeration stability at a test article concentration of 0.1 mg/mL.

Toxicokinetics

Absorption was rapid, and exposure was less than dose-proportional. Exposure *decreased* with repeat-dosing. Data from Table 2.6.5.4.7. Values are from 6 animals (3M/3F) per time point.

Dose (mg/kg/day):		0.5	2.0	3.5
PK parameters[a]:				
C_{max} (ng/mL)	Day 1	96.3	243	353
	Day 28	70.6	129	204
t_{max} (hours)	Day 1	0.3	1.0	0.5
	Day 28	0.3	0.3	0.3
AUC_{0-4} (ng·hr/mL)	Day 1	77.8	611	1,306
	Day 28	178	378	674
AUC (ng·hr/mL)	Day 1	371	690	1,312
	Day 28	275	738	688
$t_{1/2}$ (hours)	Day 1	2.6	1.3	1.1
	Day 28	2.8	4.0	1.4



Figures are from the study report p 319.

Intranasal repeat-dose studies in the rat

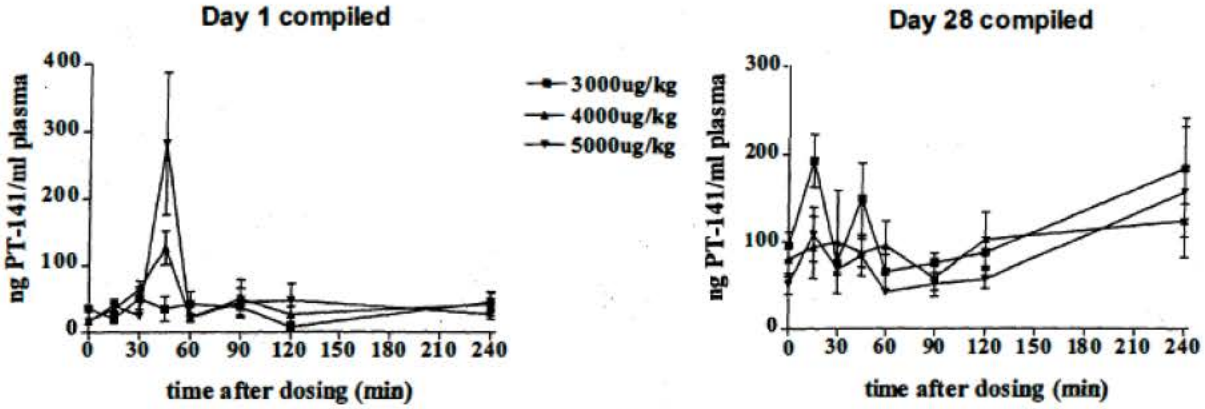
Three repeat-dose toxicity studies were conducted by the intranasal route and are briefly discussed below. Of note was a special evaluation of adrenal tissue sections from the 28 and 90-day studies to evaluate a finding of vacuolization in the adrenal cortex that occurred in both studies. The sponsor deemed the finding non-adverse but did not provide an explanation for what might have caused it. Limited TK was available from the 14 and 28-day studies; plasma was collected for TK but not analyzed for the 90-day study. The 90-day study was reviewed by Dr. Raheja and is briefly excerpted below.

Study # Year	Route	Duration	Doses	NOAEL or NOEL	Comments
996-010 2004	IN	14 day	0.5, 2.5, 5 mg/animal		Transient mild decrease in body weight gain at the 2 highest doses; decreased food consumption at the high dose on d1 only; mild microscopic changes in the nose of the high dose animals
103-004 2000	IN	28 day w 14 d recovery	3, 4, 5 mg/kg	No NOEL NOAEL >5	Adrenal cortex vacuolization in males at all doses that did not completely reverse but was not dose-dependent
131-003 2000	IN	90 day w 28 d recovery	0.2, 1, 3 mg/kg	NOAEL >3	Adrenal cortex vacuolization in a few male rats at the 2 highest doses – deemed not adverse; congestion of mandibular lymph node in some rats from all treated groups that was correlated with gross lesions

TK in the 14-day study: Samples taken on d14 at 15 and 30 minutes. N=5/dose

Dose mg/animal	Plasma concentration (ng/mL)	
	M	F
0.5	14.3	3.2
2.5	104.1	379.0
5	782.8	957.8

TK in the 28-day study:
exposure was variable, not necessarily dose-related,
and on average was higher at the end of the study.



Day 1

Time (min)	3000µg/kg	4000µg/kg	5000µg/kg
0	36.1 ± 3.9	17.6 ± 4.9	15.8 ± 4.5
15	20.4 ± 7.3	35.6 ± 6.4	41.1 ± 8.7
30	51.5 ± 16.7	65.2 ± 12.6	24.8 ± 5.8
45	35.5 ± 18.6	126.9 ± 24.9	282.2 ± 105.6
60	42.5 ± 18.7	22.2 ± 4.4	21.9 ± 6.5
90	38.0 ± 16.5	50.7 ± 28.4	45.9 ± 20.5
120	7.5 ± 3.5	26.6 ± 11.8	47.7 ± 25.4
240	45.7 ± 15.4	42.2 ± 17.3	27.2 ± 7.4

Day 28

Time (min)	3000µg/kg	4000µg/kg	5000µg/kg
0	95.7 ± 16.0	80.1 ± 19.7	52.0 ± 12.0
15	192.6 ± 30.3	93.9 ± 35.5	108.6 ± 31.0
30	75.6 ± 10.8	99.7 ± 58.7	68.9 ± 6.9
45	149.2 ± 41.0	87.3 ± 16.2	83.7 ± 22.9
60	65.9 ± 19.2	95.3 ± 18.9	42.9 ± 2.8
90	75.6 ± 11.1	58.9 ± 21.1	51.8 ± 7.0
120	87.4 ± 17.8	102.7 ± 31.0	56.9 ± 10.5
240	183.8 ± 57.6	124.2 ± 18.4	156.5 ± 75.0

Study 131-003: 90-day repeated dose toxicity of PT-141 administered intranasal to SD rats (with 28-day recovery period)

Key study findings: Significant treatment-related adverse effects consisted of the adrenal gland vacuolation and lymph node congestion. The vacuolation of the adrenal cortex was considered treatment related because there was a dose relationship. Similar vacuolation of the

adrenal cortex was observed in a previous 28-day study with PT-141. Considering adrenal gland vacuolation as treatment-related adverse effect since observed both in the present study as well as in the previous 28-day study, the NOAEL should be 200 ug/kg. Sponsor considered NOAEL of greater than 3000 ug/kg PT-141.

Results:
Mortality: one group 4 male died without any adverse clinical observations.

Gross pathology: mandibular lymph node was discolored in some animals from all drug treated groups (3 M / 2 F from the low dose group; 2 M /1 F from the mid dose group; and 3 M / 3 F from the high dose group; also 1 F from the control group).

Histopath: At the end of dosing period treatment-related findings were: 1) occurrence of adrenal gland microvacuolation in one mid dose and two high dose males, 2) congestion of the mandibular lymph node in 3 M / 2 F in low dose, 2 M / 1 F in mid dose and 4 M / 2 F in high dose groups. Also, Harderian gland congestion was reported in 3 M / 3 F in the high dose group. The vacuolation of the adrenal cortex was considered treatment related because there was a dose relationship. Similar vacuolation of the adrenal cortex was observed in a previous 28-day study with PT-141. The lymph node changes were correlated with gross lesions, but the cause was considered inconclusive because there was no dose-response.

Finalized independent pathology report based on slides from studies 103-004 and 131-003

Study #490-001: PT-141: review of adrenal tissue sections from rats in 28-day and 90-day studies. Conducted by (b) (4) on 8-9-02.

Sections evaluated:

- 28-day study (131-004): all rats in the high dose and control groups and the males in the low dose and mid dose groups. Doses were 3, 4, and 5 mg/kg. N=15/sex control and high dose. N=10/sex low and mid dose.
- 90-day study (131-003): all rats in all groups. Doses were 0.2, 1, and 3 mg/kg. N=15/sex control dose. N=21/sex dosed groups.
- Adrenal sections were also evaluated for rats from those studies after a recovery phase: (5/sex from low and high dose groups in the 28-day study and 5/sex from all groups in the 90-day study).
- Microscopic findings were graded for relative severity on a scale of 1 to 5.

Results: The incidence of cytoplasmic vacuolation in the adrenal cortex

Study 103-004	**Control**	**3 mg/kg**	**4 mg/kg**	**5 mg/kg**
After 28-day dosing	4/10	5/10	6/10	6/10
After 14-day recovery period	3/5			2/5
Total incidence of vacuolation	**7/15 (47%)**	**5/10 (50%)**	**6/10 (60%)**	**8/15 (53%)**
Study 131-003	**Control**	**0.2 mg/kg**	**1 mg/kg**	**3 mg/kg**
After 90-day dosing	3/10	4/16	5/16	7/16
After 28-day recovery period	1/5	2/5	2/5	1/5
Total incidence of vacuolation	**4/15 (27%)**	**6/21 (29%)**	**7/21 (33%)**	**8/21 (38%)**

Females were not affected in either study. Vacuoles were discrete round clear vacuoles distributed among few to several mid-zonal cells in the zona fasciculata. Those discernible at low magnification were recorded as grade 2. Grade 1 was used for similar vacuoles, although smaller or fewer, found at high magnification. All vacuolations were mostly grade 1 except one or two male rats with grade 2 in each study group. From these findings it was concluded that the cytoplasmic vacuolations were gender-related and had no relationship to PT-141 dose levels or duration of treatment.

These studies did not include measurements of corticosterone or ACTH so it is not known whether there was any physiological change associated with the histopath findings.

6.2.3. Dog

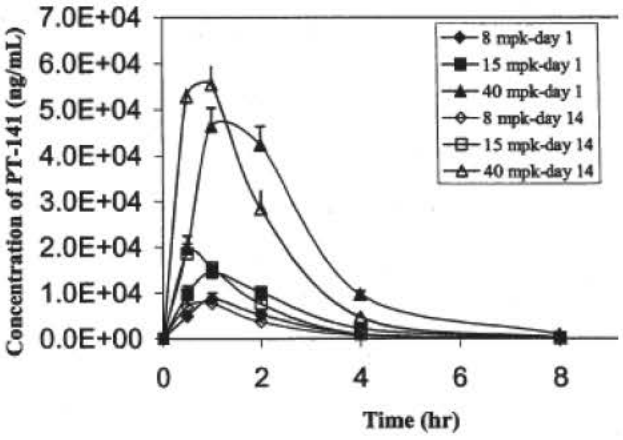
There were 3 repeat-dose studies conducted in the dog by the subcutaneous route. An MTD of 75 mg/kg was determined in study 996-006 based on generalized swelling of the face and snout. There were behavioral signs of limited duration in all treated groups. Weight loss was the primary adverse finding and is an expected pharmacological effect of BMT.

Study #	Route	Duration	Doses (mg/kg)	NOAEL or NOEL	Comments
996-006	SC	2 wk	8, 15, 40 N=2/sex/dose	Sponsor's NOAEL = 40; reviewer NOAEL < 8	Behavioral signs – aggression, stereotypy, panting, swelling, skin reddening in all treated groups. Body weight loss of 1-7%; very little food consumption on d1 that recovered; no other findings, including testes
131-011	SC	4 wk	2, 4, 8 N=4/sex/dose	--	Post-dose stretching, decreased activity, salivation, soft stool; base coat darkening in all treated groups; no ΔBP or BW or food consumption
996-003	SC	32 wk*	2, 8, 20 N=4/sex/dose	Reviewer's NOAEL = 2	No new toxicity; mild weight loss, reactive changes in liver enzymes, and unexplained increased adrenal weight without corresponding histopathology.

*DBRUP approved early termination due to no significant findings – TK out to 24 wks

996-006 2 week tolerability study: N=2/sex/group
Dosing based on range finding that established an MTD of 75 mg/kg based on generalized swelling of the face and snout.

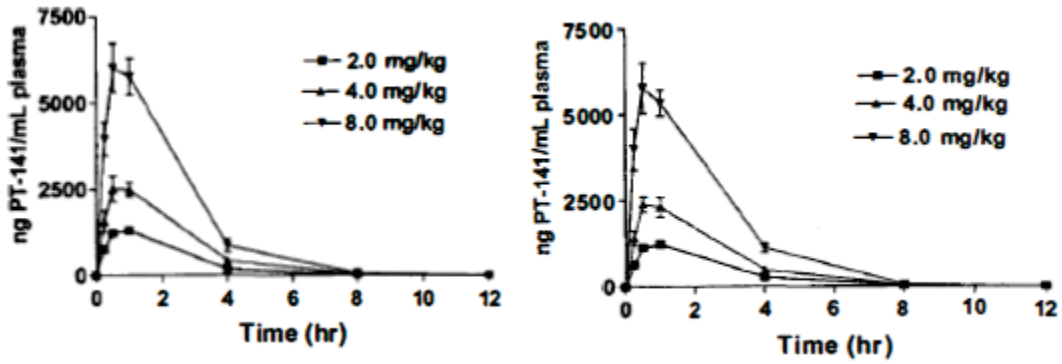
TK : Exposure was proportional to dose at the two lower doses and greater than proportional to dose at the highest dose; No significant gender differences; no significant accumulation or decline with duration of exposure. Tmax ~0.75 hr at all doses



Dose (mg/kg)	8	15	40
Cmax d1	9032	14554	49268
Cmax d14	8285	18852	56390
ng/mL			
$AUC_{0-\infty}$ d1	20241	38438	140652
$AUC_{0-\infty}$ d14	17148	35490	125207
ng.hr/mL			

131-011 4-week tolerability study
N=4/sex/dose. Data from Appendix 15 in the study report
TK : Exposure was proportional to dose; No significant gender differences; No significant accumulation or decline in exposure. Tmax ~0.75 hr at all doses

Day 1 **Day 28**



Day 1

Dose (mg/kg)	2.0	4.0	8.0
n	8	8	8
Cmax (ng/mL)	1353 ± 76.4	2668 ± 339	6311 ± 674
Tmax (hr)	0.88 ± 0.08	0.88 ± 0.08	0.63 ± 0.08
$AUC_{0\text{-}12\ hr}$ (ng/mL*hr)	3579 ± 143	7331 ± 503	16,575 ± 1031
AUC (ng/mL*hr)	3599 ± 142	7348 ± 503	16,589 ± 1031
Half-life (hr)	1.1 ± 0.06	1.2 ± 0.10	1.2 ± 0.15

Day 28

Dose (mg/kg)	2.0	4.0	8.0
n	8	8	8
Cmax (ng/mL)	1257 ± 56.6	2536 ± 269	6109 ± 554
Tmax (hr)	0.88 ± 0.08	0.63 ± 0.08	0.69 ± 0.09
$AUC_{0\text{-}12\ hr}$ (ng/mL*hr)	3761± 157	7099 ± 572	16,646 ± 537
AUC (ng/mL*hr)	3802 ± 160	7132 ± 578	16,678 ± 537
Half-life (hr)	1.2 ± 0.05	1.1 ± 0.06	1.0 ± 0.05

Study title: 39-week subcutaneous dose toxicity study of PT-141 in dogs.	
Study no.:	996-003
Study report location:	Application 210557 - Sequence 0002 - Study 996-003
Conducting laboratory and location:	(b) (4)
Date of study initiation:	2-26-04
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, 10AB1, purity >95%, peptide content (b) (4) %

Key Study Findings

- Treatment-related clinical findings included stereotypic behavior, black discoloration of the hair and thickening of the skin at injection sites. Stereotypic behavior was generally limited to the first week of dosing.

- Body weights were reduced by approximately the same amount (~10%) at all doses in males and in a dose-dependent manner in females (maximum ~10%).
- Liver enzyme elevation occurred in all drug-treated groups. Although treatment increased some hepatic enzymes primarily in females, no hepatic macroscopic or microscopic pathology was reported.
- There was treatment related increase in adrenal gland weight in females (significant at the high dose only) with no corresponding adrenal histopathological changes.
- There was no effect on sperm motility or morphology.
- TK: Systemic exposure *decreased* at all doses over the course of the study (~30%), which was unexplained.

The sponsor discounted changes in body weight, elevated liver enzymes, and increased adrenal weight and set the NOAEL at the high dose, 20 mg/kg/d. Reviewer disagrees. Body weight changes are likely due to action of the drug and are mildly adverse. Other changes are likely reactive. Based on changes in body weight, reviewer sets the NOAEL for females at 2 mg/kg and does not set a NOAEL for males. Compared to AUC at 2 mg/kg in week 24 of the study, MOE is 10.7.

Methods	
Doses:	0, 2, 8, 20 mg/kg/d
Frequency of dosing:	daily
Route of administration:	Subcutaneous
Dose volume:	1mL/kg
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Dog / Beagle
Number/Sex/Group:	4/sex/group
Age:	18 months
Weight:	M: 5.55-7.63 kg F: 5.13-6.66 kg
Satellite groups:	None; all animals used for TK at 4, 12, and 24 weeks
Unique study design:	Sperm analysis included
Deviation from study protocol:	None significant

Observations and Results

Mortality

There was no mortality.

Clinical Signs

Performed weekly. Drug-related clinical findings consisted of stereotypic behavior, black discoloration of the hair and thickening of the skin at injection sites.

Stereotypic behavior included forepaw padding, stretching, rolling, crouching, and yawning in a dose response-related pattern; increasing doses increased the number and types of behavior observed. These occurred in all treated animals but were generally limited to the first week of study.

A generalized darkening of the brown hair, noted as black discoloration was observed in all treated animals beginning in week 7. This change gradually resulted in a coat color that was black and white (instead of the normal distribution of brown, black, and white). There was no

apparent effect on the white or black hair, only the replacement of brown hair with black. There was no dose-response or sex relationship.

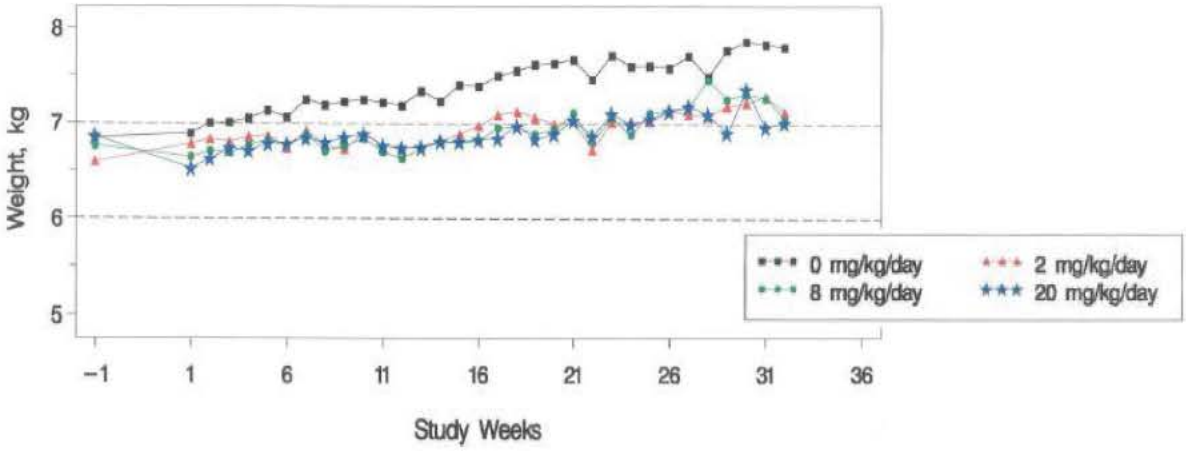
Thickening of the skin at the injection sites was observed in both sexes treated with 8 and 20 mg/kg/day as early as week 5 of the study. The skin thickening and leathery appearance continued to increase which necessitated the decision to move dosing to caudal region in week 19 of the study. By week 21, most observations for thickened and leathery skin at the original injection site were no longer present and none were present by week 23. For new injection sites thickening was noted in weeks 23 and 24 for 4 animals.

At study termination, physical examination revealed one female at 8 mg/kg/day dose had skin thickened and leathery for both left and right ears accompanied by erythema. Another finding was loss of elasticity on the dorsal surface in one female at 20 mg/kg/day dosage which corresponded with findings of clinical observations of skin thickened and leathery.

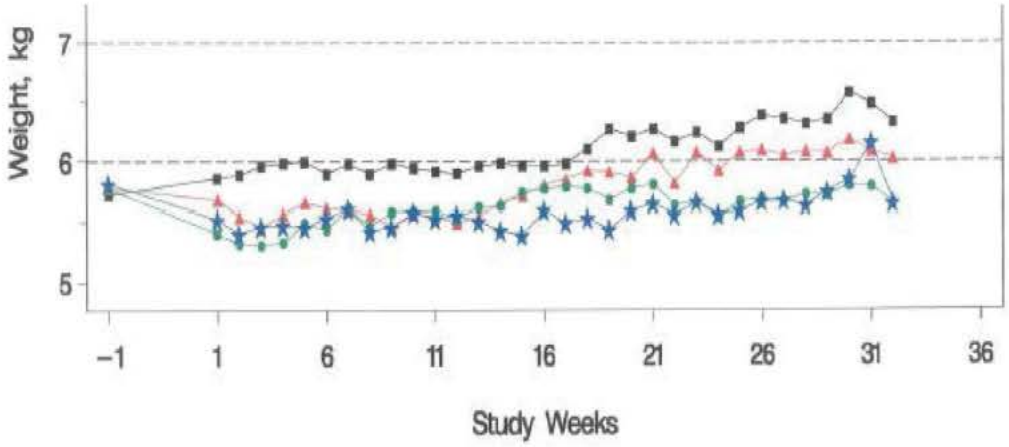
Body Weights

Weekly. Body weights were slightly reduced by approximately the same amount at all doses in males and in a dose-dependent manner in females.

Males



Females



Feed Consumption

Weekly. Decreased food consumption was observed in males in the mid and high dose groups and all treated females during the first week. Following week 1, food consumption increased and tended to higher than respective controls.

Ophthalmoscopy

Pre-test and prior to necropsy. No treatment-related effects.

ECG

ECG and indirect limb BP determined on all animals prior to dosing and one hour following dosing on weeks 4, 12, and 24.

No qualitative or quantitative ECG abnormalities were associated with treatment at week 24. There were no drug-related effects on the systolic, diastolic or mean arterial blood pressure measurements. There was however, a large variability in the data but were not considered treatment related due to the lack of dose-dependency or relative change from pretest values. No changes in heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc intervals were reported associated with treatment.

Indirect Blood Pressure

Blood pressure of each animal was measured and recorded pretest and in Weeks 4, 12, and 24, prior to dosing and one hour (±15 minutes) following dosing. Blood pressure measurements are reported using three consecutive readings that have the Mean Arterial Pressure (MAP) within 20 mmHg.

There were no test article-related effects noted on the systolic, diastolic or mean arterial blood pressure measurements. There was a large variability in the data, but they were not considered to be test article related due to the lack of dose-dependency or the relative change from pretest values.

Hematology

Pretest and at weeks 4, 12, and 24. There were statistically significant decreases in erythrocytes, hemoglobin and hematocrit in the low dose group females at weeks 8-24 and in the middose group at week 24. There was a decrease in platelet counts in the high dose group expressed as mean K/mm3 shown in the table below:

Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	452.5	369.0	359.5	291.8b
Wek 4	414.3	375.0	348.8	277.0b
Week 8	437.3	456.3	368.8	311.0
Week 12	405.8	409.8	320.3	283.8
Week 24	375.3	374.5	341.0	274.5a

a= significantly different from control ($p<0.05$)
b= significantly different from control ($p<0.01$)

Clinical chemistry

Pretest and at weeks 4, 12, and 24. There were no adverse, test article-related effects on clinical chemistry parameters. There were numerous statistical differences noted, predominantly in the females, but nearly all individual values remained within expected ranges. Total protein was below expected ranges in a few high dose females at weeks 4-12, but it was also lower relative to controls at pretest. Both albumin and globulins were slightly lower in the high dose females at week 4, but the albumin was increased relative to pretest.

Effect on potassium (mEq/L)				
Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	4.71	4.53	4.51	4.46
Week 4	4.68	4.50	4.38	4.30a
Week 8	4.47	4.26	4.49	4.40
Week 12	4.73	4.51	4.32a	4.21b
Week 24	4.45	4.58	4.23	4.43
Effect on GGT (U/L)				
Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	2.5	3.8	3.5	3.3
Week 4	2.8	4.8a	5.8b	4.8a
Week 8	3.0	5.3a	5.8b	5.0a
Week 12	3.3	5.8a	5.8b	4.3
Week 24	3.5	4.5	5.0a	4.5
Effect on ALT (U/L)				
Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	21.3	26.5	22.8	26.8
Week 4	20.5	31.3a	35.5b	33.5b
Week 8	23.8	28.8	34.5b	32.3a
Week 12	21.3	28.0a	30.8b	27.3a
Week 24	22.5	25.8	26.8	27.0
Effect on total protein (g/dl)				
Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	6.55	6.15	6.33	5.98b
Week 4	6.50	5.98a	6.03	5.48b
Week 8	6.63	6.18	6.33	5.83b
Week 12	6.23	5.90	5.95	5.58b
Week 24	6.23	5.98	5.93	5.88
Effect on cholesterol (mg/dl)				
Interval of study	0 mg/kg/day	2 mg/kg/day	8 mg/kg/day	20 mg/kg/day
Pretest	231.5	183.5	176.5	158.3a
Week 4	264.5	167.5	138.5a	119.3b
Week 8	212.3	162.3	125.5b	146.5a
Week 12	193.5	152.5	118.8b	144.3a
Week 24	189.3	150.8	157.3	128.3b

Urinalysis

Collected for at least 16 hrs. No treatment-related effects.

Gross Pathology

Not presented.

Organ Weight

Males: The absolute and relative right cauda epididymis were significantly increased at the mid and high doses, and both epididymides were elevated at the high dose. There was no dose response and there were no microscopic findings, so this was not considered toxicologically important.

Females
There was a trend toward decreased liver weight in females that was significant only when normalized to brain weight at the high dose.

There was a statistically significant increase in adrenal weight in a dose related manner. Although adrenal gland weight was significantly increased with treatment in females, no microscopic pathology was observed. *(Recall vacuolization in the adrenals in rats was in males only).*

	Dose (mg/kg/day)			
	0	2	8	20
Adrenal gland (g)	0.955	0.987	1.096	1.266[b]
Adrenal gland/Bwt %	0.0155	0.0172	0.0200	0.0231[b]
Adrenal gland/ Br Wt ratio	0.0149	0.0157	0.0172	0.0187[a]

a=p<0.05; b=p<0.01

Histopathology

Adequate Battery Yes Peer Review Yes – for adrenal glands only

Injection site reactions: Hemorrhage, pigment, inflammation, fibrosis and degeneration / regeneration of skeletal muscle fibers in the panniculus carnosus (subcutaneous layer of striated muscle). The sponsor noted that increased melanin in the medulla of hair shafts was difficult to discern due to skin sites having black hair.

Liver: No pathologic findings were reported for liver although liver enzymes were elevated with treatment.

Adrenals: No hypertrophy confirmed by peer review.

> Peer review was conducted on the control and high dose females to confirm that there was no hypertrophy of the adrenal cortex. The reviewing pathologist was in agreement with the study pathologist in concluding that no detectable hypertrophy was present.

Special Evaluation

Sperm analysis:
A section of the right vas deferens was utilized for videotaping a prepared sperm sample for automated evaluation of sperm motility (viability) utilizing the Hamilton-Thorne Computer Integrated Visual Optical System. The right cauda epididymis was separated, weighed, and used for manual (visual) assessment of sperm concentration. Slides were prepared for assessment of sperm morphology from the motility preparations. The right testis were frozen (approximately -20°C) and used to prepare samples for analysis of spermatid head count.

Treatment showed no effect on sperm motility, sperm concentration /gram cauda epididymis and total sperm concentration per cauda epididymis. Also, the number of homogenization resistant spermatids as well as percentage of abnormal sperm were similar among groups.

Dosing Solution Analysis

Average test article concentrations for the dosing formulations were determined for Weeks 1, 2, 3, 4, 8, 12, 16, 17, 20, 24, 28, and 32. The mean values of the test article concentrations were 87.5 to 109.2% of the nominal concentrations. Stability was verified.

Toxicokinetics

Blood samples (approximately 2 mL) were collected from four animals/sex/group via the jugular vein for determination of the plasma concentrations of the test article. Samples were collected predose and at 0.5, 1, 2, 4, and 8 hours postdose on Day 1, and Weeks 12 and 24. The animals were not fasted prior to blood collection.

Toxicokinetic data showed that Cmax and AUC decreased at week 24 compared to values reported for Day 90. Mean plasma AUC 0-inf values decreased by approximately 30% from Day 1 to Week 24 in both males and females at all three dose levels.

	Day 1 at 2 mg/kg/day		***Day 90 at 2 mg/kg/day***		***Week 24 at 2 mg/kg/day***	
	Male	female	male	Female	Male	Female
Tmax (hr)	0.88	0.75	0.63	0.75	0.63	1.00
Cmax (ng/ml)	1,986	1,906	2,129	1,624	1273	928
AUC 0-8 (ng.he/ml)	3,606	4,081	3,335	3,272	2428	2873
AUC0-inf (ng.hr/ml)	3,622	4,089	3,415	3,449	2494	2949
	Day 1 at 8 mg/kg/day		**Day 90 at 8 mg/kg/day**		**Week 24 at 8 mg/kg/day**	
	Male	Female	Male	Female	Male	Female
Tmax (hr)	0.88	0.75	0.75	0.75	0.63	0.63
Cmax (ng/ml)	9,206	10,065	7,397	7,721	6433	7534
AUC 0-8 (ng.he/ml)	16,680	19,980	14,843	15,006	11536	14461
AUC0-inf (ng.hr/ml)	16,709	20,048	14,864	15,025	11564	14483
	Day 1 at 20 mg/kg/day		**Day 90 at 20 mg/kg/day**		**Week 24 at 20 mg/kg/day**	
	Male	Female	Male	Female	Male	Female
Tmax (hr)	1.00	0.88	0.75	1.00	1.00	1.00
Cmax (ng/ml)	23,186	26,585	17,705	22,800	15411	16005
AUC 0-8 (ng.hr/ml)	49,917	58,869	41,239	52,759	37466	38881
AUC0-inf (ng.hr/ml)	50,076	59,143	41,384	53,027	37550	39198

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

For reasons that are unclear, the standard Ames test was conducted twice for bremelanotide, using identical methods. Two different lots were used.

Study title: Ames test results for sample: PT -141	
Study no.:	GLP-1999-0618
Study report location:	Application 210557 - Sequence 0002 - Study GLP-1999-0618
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 31, 1999
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Bremelanotide (PT-141), Lot 522871, purity not stated, no COA

Study title: Ames test results for sample: PT -141	
Study no.:	GLP-2000-PT-141A
Study report location:	Application 210557 - Sequence 0002 - Study GLP-2000-PT-141A
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 21, 2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Bremelanotide (PT-141), Lot 0539373, purity not stated in this study report. However, a COA was included for this same lot in Study C095-001 p 76 (see below). Purity was stated to be >94%. Peptide content (b) (4) %

Key Study Findings

Bremelanotide was found not mutagenic against any of the tester strains, either directly or with S9 metabolic activation in either test.

Methods	
Strains:	*Salmonella typhimurium, TA98,* TA100, TA1535, TA1537 *Escherichia coli* WP2
Concentrations in definitive study:	0, 50, 100, 500, 1000 or 5000 ug/plate.
Basis of concentration selection:	Not stated
Negative control:	0.9% saline
Positive control:	FNPA, 2-NF, 3-BPA. MMS w/out metabolic activation Benzopyrene, 2-AAN, proflavine with metabolic activation
Formulation/Vehicle:	0.9% saline
Incubation & sampling time:	72 hours

Study Validity

Study was deemed valid. Historical controls were not provided.

Criteria for scoring the samples:

1. For a negative Ames Test (not mutagenic), total revertants in any strain at any concentration should not be at or greater than three times background, with or without metabolic activation.
2. For a positive test (mutagenic) one of the following criteria must be met: a) a dose-related increase over the concentration range must be observed in the same strain either with or without metabolic activation, b) two or more consecutive average concentration points must be at or greater than two times background average in the same strain either with or without metabolic activation or c) a clear indication of mutagenicity is obtained when the sample average exceeds three times background average at any concentration in the same strain either with or without metabolic activation.
3. When the background is running low (e.g. 6 colonies or less) and a good response is obtained with the positive controls, then the number of revertants should exceed twenty colonies/plate for the sample to be scored as mutagenic.

Sponsor's comment about cytotoxicity testing:
"A separate toxicity evaluation was not run. Strain TA100 provides a concurrent reading on the sample's toxicity. The strain provides a large number of spontaneous revertant colonies which should decrease due to the presence of toxic agents. No toxicity was observed at any of the concentrations tested."

Results

Positive and negative controls were appropriate. There were no positive findings for mutagenicity in either study.

7.2 *In Vitro* Assays in Mammalian Cells

To assess in vitro clastogenicity in mammalian cells, two chromosomal aberration assays were conducted: one was carried out at the low micromolar range using saline as the vehicle, and the other at the high micromolar to millimolar range using water as the vehicle. The study carried out at low concentration was deemed by the reviewer not acceptable for use but is briefly summarized below for reference.

Study title: In vitro mammalian chromosomal aberration test in Chinese hamster ovary (CHO) cells with PT-141. Final report.	
Study no.:	C095-001
Study report location:	Application 210557 - Sequence 0002 - Study C095-001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12-20-2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Bremelanotide, Lot 0539373, purity >94%; peptide content (b) (4) %

Key Study Findings

There were no findings of chromosomal aberrations. However, the study was deemed not valid for regulatory purposes because the concentrations tested were too low. Cytotoxicity was not reached at any concentration, which is one of the criteria for valid study design*. In addition, a formulation analysis was not conducted, and concentrations could not be verified.

Methods	
Cell line:	Chinese hamster ovary cells
Concentrations in definitive study:	9.375, 18.75, 37.5, 75, 150, 200 and 230 ug/ml (~9-230 uM)
Basis of concentration selection*:	It is not clear what the basis for dose selection was. The top dose did not reach the limit of solubility of bremelanotide in saline of 20 mg/mL that was provided by the sponsor in response to an RFI. A dose range finding study was not conducted, and cytotoxicity was not observed.
Negative control:	0.9% saline
Positive control:	Mitomycin C and cyclophosphamide
Formulation/Vehicle:	0.9% saline Dosing solution analysis not accepted
Incubation & sampling time:	4 hours and 19 hours in the non-activation assay. Four hour incubation with S9 metabolic activation

*From the PharmTox GRP document:
Basis of concentration selection: Criteria for the selection of the highest concentration which would be used in the assay are cytotoxicity, solubility of the test material in the culture condition, pH, and the osmolality of the test system. Abnormal pH or high osmolality can cause DNA unwinding and subsequent damage due to non-physiological physico-chemical effects.

Cytotoxicity should be measured either by survival or by mitotic index. For non-cytotoxic freely soluble test material, the maximum concentration should be 5 mg/mL, 5 µL/mL or 0.01M. A preliminary dose range finding study is optional for the chromosomal aberration assay, however, analyzable cells must be obtained from three test concentrations, and these concentrations should range from the maximum to little or no cytotoxicity. At the time of harvesting, the highest concentration should show at least a 50% reduction in degree of confluency, cell count, or plating efficiency. For test material which is relatively insoluble, the recommended highest dose is a dose above the limit of solubility. The highest concentration may show visible precipitation; however, precipitation should not interfere with the scoring.

The definitive chromosomal aberration study is described below. The assay was run twice. The first attempt at scoring chromosomal aberrations failed. For the second run, the sponsor described different harvesting and fixation methods, and a sufficient number of cells were obtained for scoring. Results below are the from the second run.

Study title: In Vitro Chromosome Aberration Test in Chinese Hamster Ovary Cells with PT-141	
Study no.:	C122-002
Study report location:	Application 210557 - Sequence 0002 - Study C122-002
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 28, 2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, Batch# 0557647 for Expt #2, peptide purity (b) (4) %

Key study findings:

Bremelanotide was negative for the induction of structural or numerical chromosomal damage.

Methods	
Cell line:	Chinese hamster ovary cells
Concentrations in definitive study:	1009, 2017, 3026, 4035, or 5043 ug/mL (by weight) Actual doses adjusted for peptide purity: Expt #2: 802, 1604, 2406, 3208, 4009 ug/mL (~800 uM – 4 mM) Formulation analysis showed that concentrations were ~20% below the targeted concentration (Appendix II Dose Formulation Analysis Table 4 p A2-13).
Basis of concentration selection:	MFD based on solubility.
Negative control:	Water
Positive control:	Mitomycin C (75 and 150 ng/mL) in cultures without S9 and cyclophosphamide (5 and 10 ug/mL) in cultures with S9
Formulation/Vehicle:	Water*
Incubation & sampling time:	Duplicate cultures were exposed to the test article with and without metabolic activation for 4 hours. An additional set of duplicate cultures was exposed to the test article without metabolic activation continuously for 19 hours. Colcemid (final concentration of 0.1 ug/mL) was present for the final two hours of incubation.
Cell harvest:	Cells were harvested at the end of the culture period and assessed for viability. Microscope slides were prepared from the fixed samples and scored for the percentage of metaphase cells (mitotic index), the percentage of polyploid metaphase cells (polyploidy index), and structural chromosomal damage.

*The sponsor explored the use of DMSO as a vehicle for this assay in study C122-001 (Application 210557 - Sequence 0002 - Study C122-001). In that study, designed to measure cytotoxicity, dosing concentrations were apparently limited due to viscosity of the dosing solution. Data from the study were therefore not used for dose selection.

Study validity:

Criteria for a valid test: If the results are negative for chromosomal damage, the test article must induce at least a 50% decrease in viable cell number of MI or be tested up to the limit dose of 5000 ug/mL or be tested up to concentrations that result in precipitation but not at a level that adversely effects the integrity of the study.

Bremelanotide is free soluble in water, but in this study, a recommended top dose of 5000 ug/mL was not achieved, even though the sponsor stated that there was no precipitation and no change of pH in the cell cultures. Formulation analysis showed that actual concentrations were reduced by ~20%, so the top dose was ~3000 ug/mL or 3 mM. Also, cytotoxicity of 50% was not achieved.

The positive controls chosen were appropriate and overall, positive controls showed an appropriate response. However, there was variability in the measurements of cell viability and mitotic index (MI) that was unexplained by the sponsor.

Conclusion: The conduct of the study was acceptable, even though some aspects of design did not meet standard criteria. A high test concentration was achieved, and given that BMT is a peptide, it is likely that it is not permeable, and did not achieve access to the cell interior, which would account for the negative findings. Reviewer accepts the findings and will include them in weight of evidence for genotoxicity.

Results:

Cytotoxicity: Measurements of cytotoxicity and MI were highly variable and difficult to interpret for both bremelanotide and the positive controls.

For bremelanotide, viability showed non-dose dependent decreases up to 22% for the 4 hr exposure -S9, and little or no decrease under the other culture conditions. MI was sporadically decreased under the short but not the long-duration exposures.

The positive control mitomycin showed reductions in viability and MI that were not correlated with dose or duration of exposure. The sponsor presented mean reductions for the short duration exposure, but did not calculate mean values for the long duration exposure, stating only that *"The positive control, MMC, induced a significant decrease in the percentage of metaphase cells at 75 ng/mL but not at 150 ng/mL when compared to the concurrent solvent control. At 75 ng/mL, the mean total viable cell count was depressed by 36% and the mean MI was depressed by 77%. At 150 ng/ mL, the mean total viable cell count was not depressed, but the mean MI was depressed by 68%."*

Reviewer's table

Test condition	Bremelanotide		Mitomycin		Cyclophosphamide	
	Viability	Mitotic Index	Viability	Mitotic Index	Viability	Mitotic Index
4 hr exposure (-S9)	Max decrease 22%	Max decrease 19%	decreased 39%	decreased 49%		
4 hr exposure (+S9)	Max decrease 5%	Max decrease 47%			decreased by ~40% at both conc	decreased by >50% at 10 ug/mL
19 hr exposure (-S9)	None	None	decreased 36% max	decreased 68% max		

Structural Chromosomal Damage (percentage of metaphase cells with structural aberrations): Bremelanotide was found negative. Number of cells scored: 200/dose

Reviewer's table

Test condition	Bremelanotide	Mitomycin C	Cyclophosphamide
4 hr exposure (-S9)	negative	positive at 150 ng/mL	
4 hr exposure (+S9)	negative		positive
19 hr exposure (-S9)	negative	positive at 75 ng/mL	

Numerical Chromosomal Damage (polyploidy index): Bremelanotide was found negative. Number of cells scored: # cells scored: 400/dose.

Reviewer's table

Test condition	Bremelanotide	Mitomycin C	Cyclophosphamide
4 hr exposure (-S9)	negative	negative	
4 hr exposure (+S9)	negative		negative
19 hr exposure (-S9)	negative	negative	

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Mouse micronucleus test results for PT-141	
Study no:	GLP-2000-PT-141
Study report location:	Application 210557 - Sequence 0002 - Study GLP-2000-PT-141
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 10, 2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, lot # and purity not provided

Key Study Findings

PT- 141 was found to be not clastogenic in the mouse micronucleus assay. Although TK measurements were not done, using TK data from study 996-009 (PL-41) that the top dose in this study produced an exposure of ~17-18,000 ng.hr/mL, which is ~100X the human therapeutic AUC.

Methods	
Doses in definitive study:	6.25, 12.5 and 25.0 mg/kg
Frequency of dosing:	Daily at 0, 24 and 48 hrs. Blood samples were collected 24 hours after the final dose.
Route of administration:	Intraperitoneal
Dose volume:	Not stated
Formulation/Vehicle:	0.9% sodium chloride solution
Species/Strain:	BALB/c mice
Number/Sex/Group:	5/sex/group
Satellite groups:	None – no TK data was obtained
Basis of dose selection:	Solubility and dose range finding study. In this study dose levels were 0, 5, 10, 25, 100 and 250 mg/kg. The two highest doses exceeded the MTD.
Negative control:	0.9% sodium chloride solution
Positive control:	Methyl methanesulfonate 75 mg/kg body weight

Study Validity

Study was deemed valid. However, a number of experimental details were not provided.

Results

The frequency (%) of micronucleated reticulocytes (per 10,000 total reticulocytes/blood sample) and frequency of reticulocytes (% total erythrocytes) per approximately 1,000,000 erythrocytes/blood sample are shown in the sponsor's table below (from the Toxicology Tabulated Summary). Males and females are combined.

			Bremelanotide (mg/kg bw)			
Parameter	No. of Animals	Solvent Control	6.25	12.5	25.0	Positive Control
% Micronucleated retic.[a] ($\bar{x}$ ± SD)	5 male / 5 female	0.35 ± 0.04	0.36 ± 0.03	0.36 ± 0.04	0.35± 0.03	1.86 ± 0.31
% Retic.[b] ($\bar{x}$ ± SD)	5 male / 5 female	2.87 ± 0.80	4.09 ± 0.83	3.64 ± 0.80	3.81 ± 0.89	2.27 ± 0.64

7.4 Other Genetic Toxicity Studies

Genetox testing for impurities was conducted and is reviewed under section 2.5 of this review.

8 Carcinogenicity

Carcinogenicity studies for bremelanotide in the mouse and rat were conducted over a decade ago. The mouse study was conducted by the sc route, and the rat study was conducted by the intranasal route, which at that point in development was thought to be the clinically relevant route of administration.

For reasons that are unclear, when the carcinogenicity studies were reviewed by the previous CDER PharmTox reviewer, an independent statistical analysis of the data was not conducted. For the current NDA submission, the studies were formally reviewed by a CDER statistical reviewer. These conclusions are considered definitive, are included here, and may in some cases differ from comments made by the previous reviewer that are on file in DARRTS.

Study title: 104-week SC dose oncogenicity study of PT-141 in B6C3F1 mice	
Study no.:	996-007
Study report location:	Application 210557 - Sequence 0002 - Study 996-007
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/27/2004
GLP / QA compliance:	Yes / Yes
Drug, lot #, and % purity:	Bremelanotide (PT-141), Lot 10AB1, 95.5% purity, Lot 6AC1, 96.3% purity
CAC concurrence:	Yes

Key Study Findings:

There were no treatment related tumor findings. BMT was found not carcinogenic in the mouse. NOAEL = 15 mg/kg/d. By body surface area, the MOE compared to the human therapeutic dose is 41X. The MOE based on exposure can be estimated from TK values. Exposures were stable over the course of the study up to 1 year and were consistent with other measurements obtained in the mouse by the sc route. Based on Cmax values obtained at 1 year, the MOE is 141X for males and 183X for females.

Adequacy of Carcinogenicity Study:
Study protocols were approved by the CDER Executive CAC on 3/30/2004. The final study was reviewed and deemed adequate and negative for drug-related neoplasms by the CDER ECAC on 5-28-2013.

Appropriateness of Test Models: The mouse model was deemed appropriate.

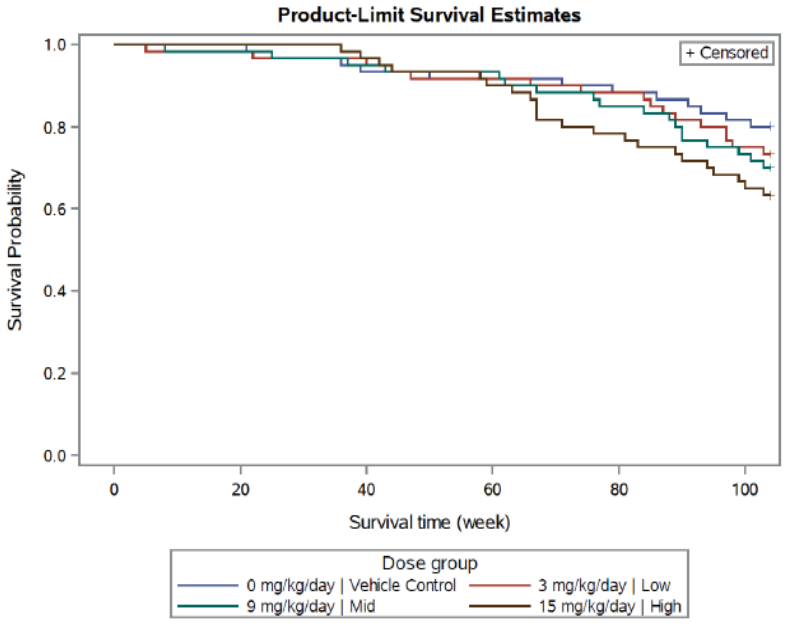
Methods	
Doses:	0, 3, 9, 15 mg/kg/d
Frequency of dosing:	daily
Dose volume:	4 mL/kg
Route of administration:	Subcutaneous
Formulation/Vehicle:	2.5% glycerin in sterile water for injection
Basis of dose selection:	As recommended by ECAC
Species/Strain:	mice/B6C3F1/Crl:BR
Number/Sex/Group:	60/sex/group, main study
Age:	7 weeks
Animal housing:	Individual housing
Paradigm for dietary restriction:	Available ad lib
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	18/sex/group for TK
Deviation from study protocol:	None

Observations and Results

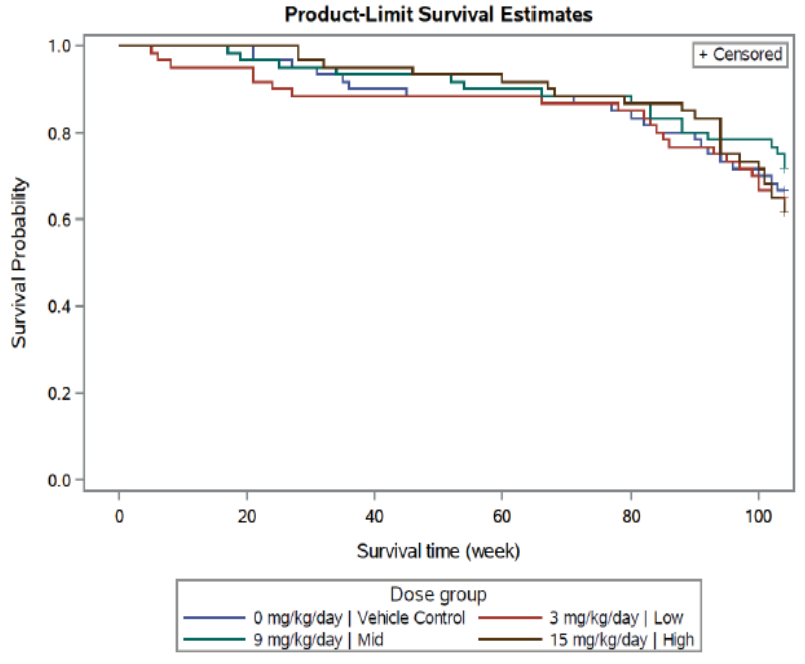
Mortality

Bremelanotide administered SC at 3 or 9 mg/kg/day did not affect survival. At 15 mg/kg/day, a possible test article-related trend for decreased survival was observed for male mice, 63% survival versus 80% survival for control male mice. At the high dose, there was an increased incidence of animals found dead; however, this finding was not associated with any particular assigned cause of death, and no increase in tumor incidence was noted. Kaplan-Meier survival curves generated by the FDA statistical reviewer are shown below.

Male mice



Female mice



Clinical observations:

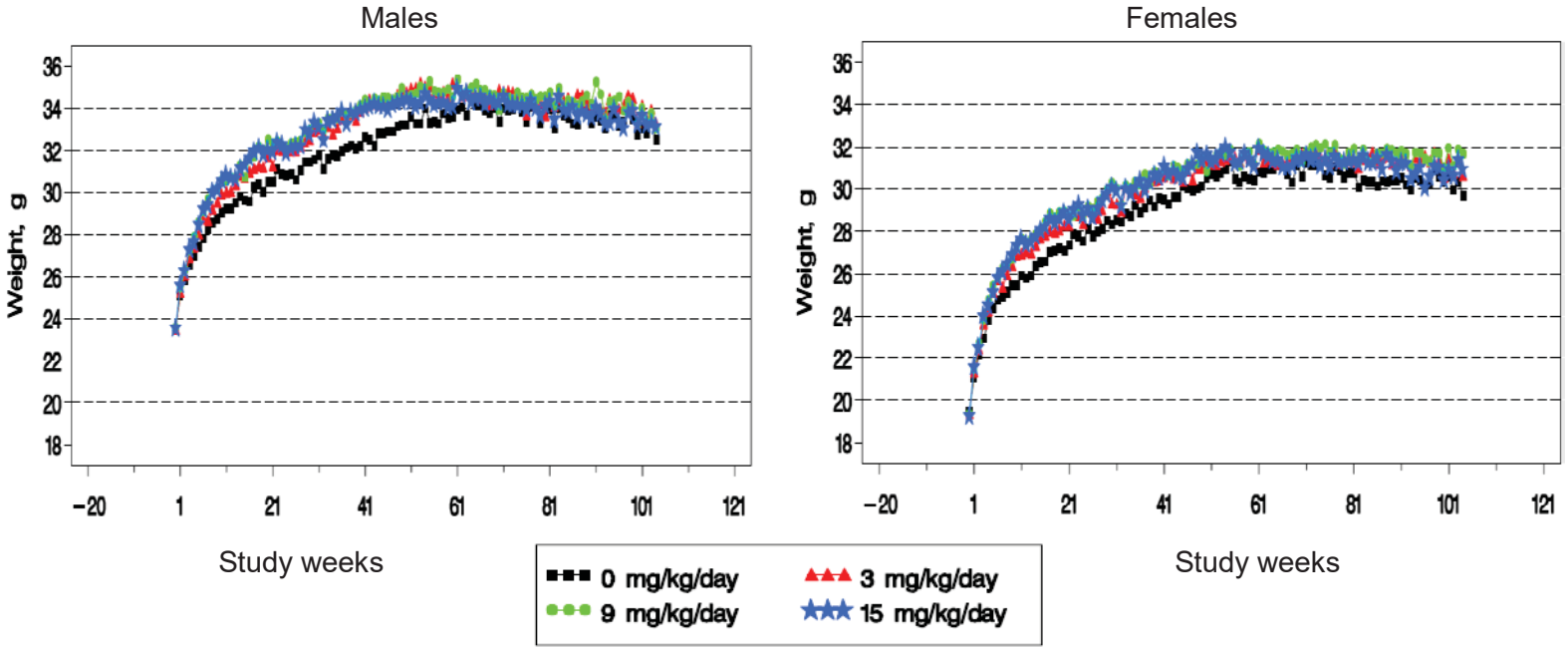
All mice were observed for morbidity and mortality twice daily throughout the duration of the study. A detailed clinical examination was performed prior to randomization and once weekly during the study.

There were no significant clinical observations other than a modest increase in the Incidence of sparse hair was increased in both male and female treated mice.

Body Weights

Body weights of all animals were measured 3 days after receipt, prior to randomization and weekly during the study. Body weights of TK animals were recorded for dosing purposes only.

A slight but treatment-related increase in body weight (g) was observed in both male and female mice especially during first half of the study period as shown in the sponsor's figures below:



Feed Consumption

Food consumption was measured weekly during the study for main study animals. The increase in treated animals was associated with increased food consumption.

Ophthalmoscopic examination

Ophthalmoscopic examination was performed pre-test and on all surviving animals prior to terminal necropsy. There were no treatment related findings.

Gross Pathology

Necropsy was performed on animals euthanized in extremis, animals found dead, animals dying prior to euthanasia, and all surviving animals at the scheduled necropsy.

There were no statistically significant treatment-related macroscopic changes. In male mice, there was an increased incidence of extended penis at the high dose. There was a small increase in skin alopecia (19 in control vs 28 in treated mice) and liver mass (4 in control vs 7 in treated). Incidence of skin alopecia was also higher in the female treated group.

Histopathology

Peer Review: Yes

A full complement of tissues and organs were collected from all animals. The review consisted of an examination of all tissues considered target organs, all neoplasms and all hyperplastic findings, and all tissues from 10% of the animals selected randomly from the 3 and 15 mg/kg/day dose groups.

Neoplastic:
Bremelanotide did not cause a statistically significant increase in the incidence of any neoplasm. The statistical reviewer noted a statistically significant trend in the incidence of hemangioma in male mice that was not significant by pairwise comparison, and therefore not significant overall. The previous reviewer of this study included a comment about increased incidence of hepatocellular carcinoma, but the statistical reviewer verified that there were no liver findings that were significant.

Non-Neoplastic:
Slight increases in the incidence of non-neoplastic lesions occurred in mice that received bremelanotide. These changes included lesions related to penis extension in males (penile congestion, erosion/ulceration, inflammation, necrosis), thymus gland lymphoid depletion in male mice, and skin/injection site lesions in both male and female mice (inflammation, epidermal hyperplasia, erosion/ulceration, and surface exudate). Lymphoid depletion was also observed in high-dose males, and the sponsor suggested that it was related to stress secondary to penile or skin lesions. None of the changes observed in male or female mice were considered statistically significant.

Toxicokinetics

Blood samples at each collection were collected from 5 TK animals/sex/group via cardiac puncture. Samples were collected 15 minutes post-dose after 3 months, 1 hour post-dose after 6 months, and 15 minutes post-dose after the number of surviving TK animals in any one group reached 5 animals (Day 368). The animals were not fasted prior to blood collection. Plasma drug concentration was analyzed by (b) (4)

	Bremelanotide Dose (mg/kg/day)							
	0 (Control)		3		9		15	
Gender	M	F	M	F	M	F	M	F
Toxicokinetics	18	18	18	18	18	18	18	18
Mean Plasma Concentrations (ng/mL) (time postdose)								
3 Months (15 min)	-	-	1,880	1,711	5,303	4,877	7,481	8,456
6 Months (1 hr)	-	-	402	303	1,797	1,798	3,451	4,258
1 Year (15 min)	-	-	2,728	3,249	6,879	6,494	10,907	14,102

Dosing Solution Analysis

Stock solution was analyzed monthly and dosing formulations were analyzed frequently throughout the course of the study. All dosing formulation results were within +/-10% of the nominal concentration.

Study title: A 104-week intranasal oncogenicity study of bremelanotide (PT-141) in Sprague-Dawley rats	
Study no.:	996-008
Study report location:	Application 210557 - Sequence 0002 - Study 996-008
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5/4/2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Bremelanotide (PT-141), 10AB1, 95.5%, 6AC1, 96.3%
CAC concurrence:	Yes

Key Study Findings

There were no treatment-related tumor findings. Bremelanotide was negative for oncogenic potential. NOAEL for carcinogenicity was 5 mg/kg/d by the intranasal route. By body surface area, the MOE is 27X compared to the human therapeutic dose. By exposure, the MOE changes dramatically depending on whether it is calculated from plasma values taken at 3 months vs 19 months. As was observed in other, shorter duration repeat-dose tox studies by either the sc or intranasal routes, exposures in the rat decline over time with repeat dosing. Thus, based on Cmax, the MOE determined from initial exposure values is 2-3X, but declines to less than half the human exposure at the end of the study.

Adequacy of Carcinogenicity Study

Study protocols were approved by the CDER Executive CAC on 3/30/2004. The final study was reviewed and deemed adequate and negative for drug-related neoplasms by the CDER ECAC on 5-28-2013.

Appropriateness of Test Models

The rat is an appropriate test model. The route of administration does not correspond to the proposed therapeutic route, but the study was conducted at a time when the intranasal route was being clinically tested.

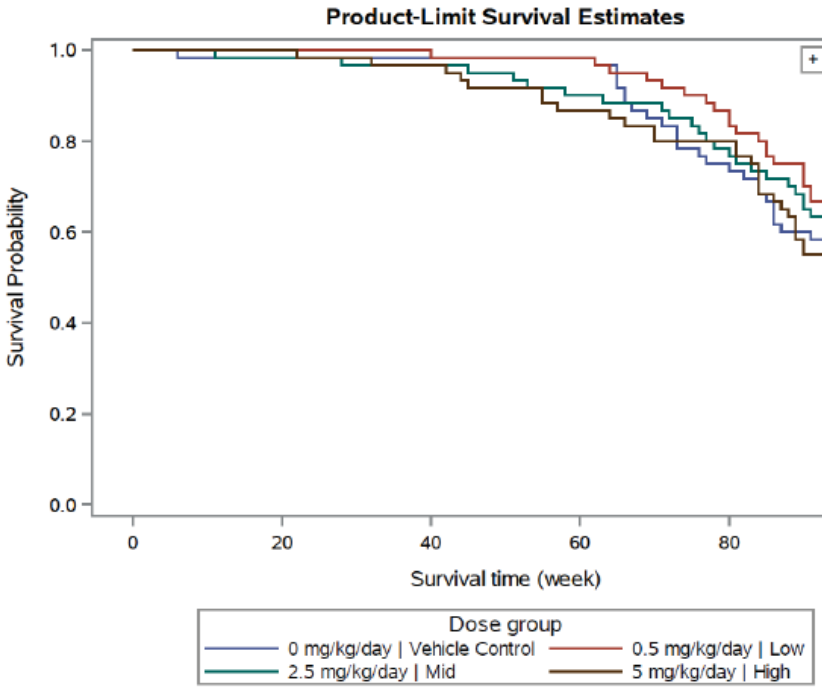
Methods	
Doses:	0, 0.5, 2.5, 5 mg/kg/d
Frequency of dosing:	daily
Dose volume:	25 uL
Route of administration:	Intranasal (right naris only)
Formulation/Vehicle:	2.5% glycerin in sterile water for injection
Basis of dose selection:	MFD by intranasal administration
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	60/sex/group, main study
Age:	6 weeks
Animal housing:	Individual housing
Paradigm for dietary restriction:	Available ad lib
Dual control employed:	No
Interim sacrifice:	No
Samples for TK:	5/sex/group from the main study groups
Deviation from study protocol:	None

Observations and Results

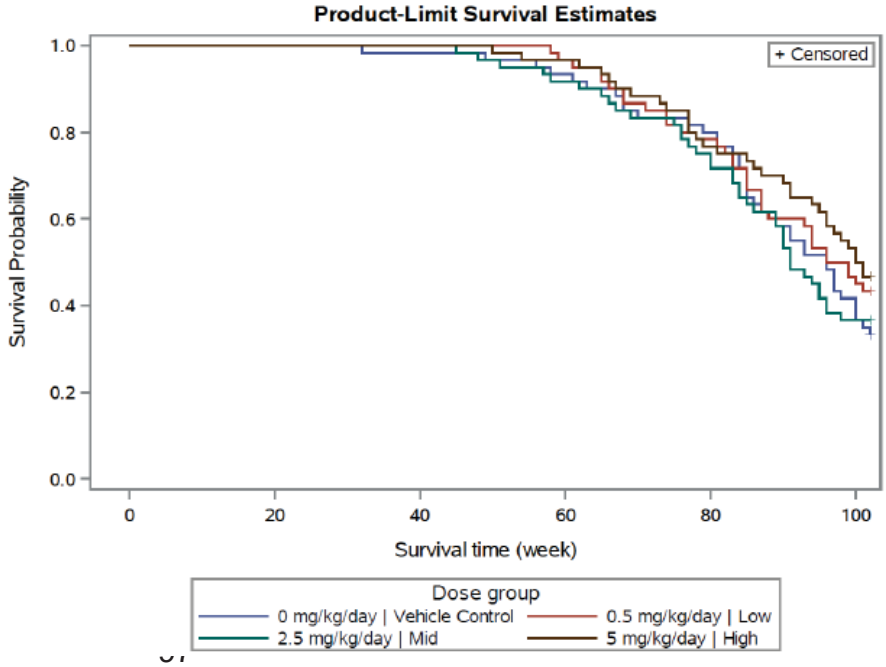
Mortality

All treated groups had increased survival compared to control groups. Thirty-five (35) to 47% of male rats survived to termination, Week 105. When the control group female rats reached 20 surviving animals, all remaining female rats, 33% to 47%, were terminated at Week 102 to ensure sufficient group size for meaningful interpretation of the data. Kaplan-Meier survival curves generated by the FDA statistical reviewer are shown below.

Male rat



Female rat

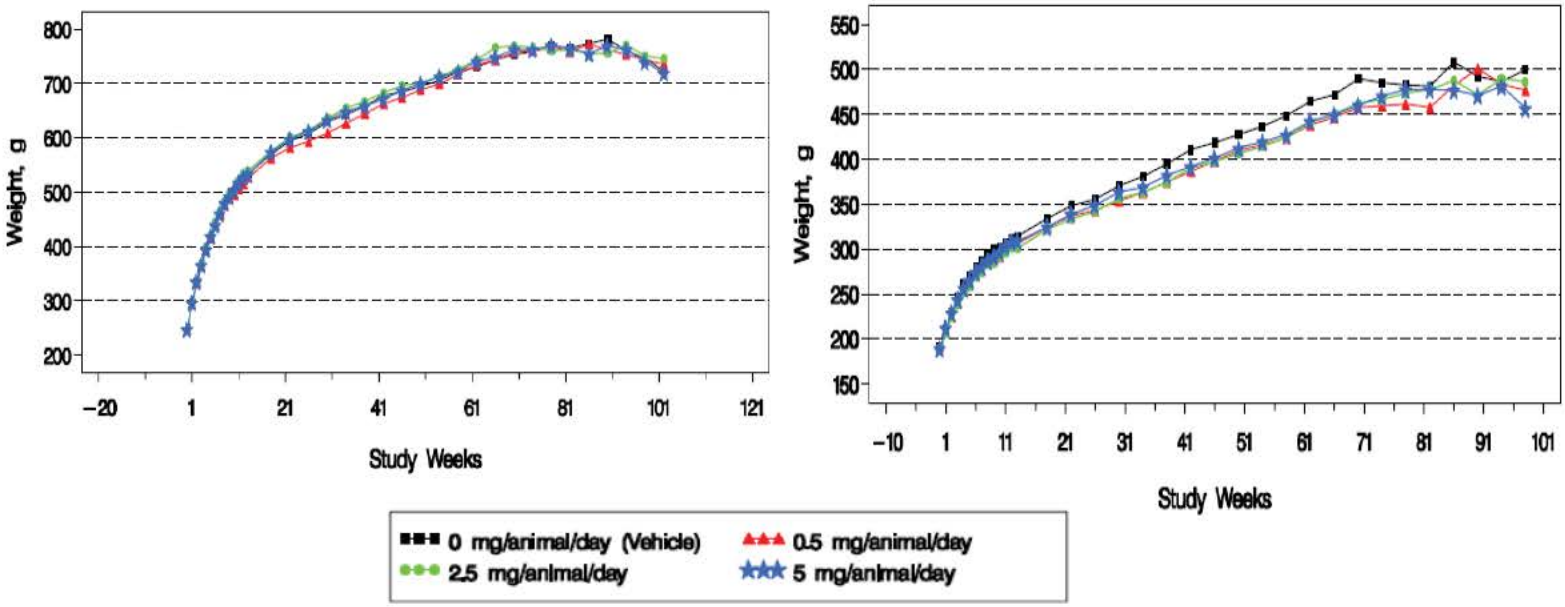


Clinical Signs

All animals were observed for morbidity daily. Detailed clinical examination was performed weekly. There were no treatment-related clinical signs.

Body Weights

There was no treatment-related effect on males at any dose. In treated females, there was a trend for lower body weight for all treatment groups, although the decrease was significant for only the mid-dose group for weeks 4-9 and week 13.



Feed Consumption

No treatment-related findings in males. For females, a trend for lower food consumption, occasionally reaching statistical significance.

Ophthalmology:

Conducted pretest and at termination. There were no treatment-related findings.

Gross Pathology

There were no treatment-related macroscopic findings.

Histopathology

Peer Review: Yes

Neoplastic
The statistical reviewer noted a significant pairwise comparison at the high dose for incidence of benign cortical adenoma in males, and uterine stromal polyps in females. However, these did not show a significant dose-response relationship, and therefore, were not considered to be positive findings. There were other sporadic findings, but overall there were no treatment-related findings in males or females.

Non-Neoplastic
There were no treatment-related nonneoplastic findings. A detailed microscopic examination of the nasal instillation site (four nose sections), trachea, and lungs revealed no biologically significant differences in types or incidence of lesions between control and treated males and females.

Toxicokinetics

Blood samples were collected from 5 non-fasted animals/sex/group at 3, 6, 12, and ~19 months. Samples were collected 15 minutes post-dose.

Mean Plasma PT-141 Concentration, 15 Minutes Postdose				
Males	3-Months ng/mL (SEM)	6-Months ng/mL (SEM)	12-Months ng/mL (SEM)	19-Months ng/mL (SEM)
Group 2	2.62 (1.61)	2.37 (1.73)	4.45 (1.89)	3.30 (0.98)
Group 3	34.8 (10.0)	13.6 (6.74)	23.9 (9.65)	13.5 (6.22)
Group 4	245 (67.0)	31.3 (10.7)	58.1 (18.3)	19.0 (5.70)
Females				
Group 2	11.4 (2.10)	0.54 (0.54)	15.9 (5.05)	3.30 (2.11)
Group 3	127 (66.1)	5.06 (1.97)	12.8 (3.41)	3.30 (0.62)
Group 4	178 (53.3)	34.3 (12.2)	47.1 (15.6)	28.9 (13.8)

For the treated groups, plasma concentrations generally increased with increasing dose. Exposure decreased between 3 and 6 months, was similar at 6 and 12 months, and again was lower at 19 months. No toxicokinetic profiling was conducted; however, the single time point of sample collection at each interval demonstrated exposure to PT-141 throughout the course of this study.

Dosing Solution Analysis

All dosing solution results were within 10% of the nominal concentration when analyzed.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Three studies were conducted to evaluate fertility and early embryonic development. One study was conducted in female mice by the subcutaneous route. One study was conducted in male mice by the subcutaneous route, and another study was conducted in the male rat by the intranasal route. Because this is a female indication, the female mouse study is presented first, followed by the two studies in male rodents.

Study title: PT-141: Study of female fertility and embryo-fetal development in mice.	
Study no.:	996-026
Study report location:	Application 210557 - Sequence 0002 - Study 996-026
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 06, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, Batch 6AC, purity >95%, peptide content (b) (4)%

Key Study Findings

No effect of treatment with bremelanotide was noted in fertility indices, uterine implantation data, gravid uterine weights, fetal body weights, fetal sex ratios, or fetal external, visceral, and skeletal examinations.

The maternal LOAEL was 30 mg/kg/day based on a dose-related increase in the incidence of females with evidence of irritation at the injection sites, including sparse hair at all treatment levels and scabbing in the high dose animals.

The NOEL for both female fertility and developmental toxicity was 150 mg/kg/day, the highest dose evaluated.

No TK measurements were done for this study, but TK data was obtained from pregnant mice at the same doses in PPD study 996-032 (TK study PL-53). Using measurements taken on the first day of dosing, at the low dose of 30 mg/kg/d, $AUC_{0\text{-}inf}$ was 31194 ng.hr/mL, which is 113X the human therapeutic AUC. At the high dose of 150 mg/kg/d, $AUC_{0\text{-}inf}$ was 176379 ng.hr/mL and the MOE was 639X based on AUC.

Methods	
Doses:	0, 0, 30, 75, and 150 mg/kg/d (two control groups)
Dose justification:	Doses were based on range-finding study 996-013 in which animals were dosed at 30, 75, 150, and 300 mg/kg/d from GD6-15.
Frequency of dosing:	daily
Dose volume:	4 mL/kg
Route of administration:	subcutaneous
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Mouse / B6C3F1/Crl
Number/Sex/Group:	30 F/group
Satellite group:	No TK (refer to study PL-53 for TK data obtained at the same doses)
Study design:	Animals were dosed 14 days prior to mating through GD15
Deviation from study protocol:	None that affected outcome

Observations and Results

Mortality

One mouse each in the 30, 75, and 150 mg/kg/day groups died during the study. In addition, one mouse each in the vehicle control 1, 30, and 150 mg/kg/day groups was euthanized in extremis. Clinical observations and macroscopic findings were unremarkable and the mortality of mice in these groups was considered unrelated to treatment.

Clinical Signs

Examined daily. Treatment-related irritation at the injection site was observed in all treatment groups.

Body Weight / Feed Consumption

Maternal body weights, body weight change, food consumption, and organ weights were unaffected.

Toxicokinetics

Not done

Dosing Solution Analysis

The mean values of the PT-141 concentrations ranged from 90.9 to 101.7% of the nominal concentrations.

Necropsy

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

The mating indices for the treated and both controls groups was 100%. The % fertility and fecundity indices for controls 1 and 2 and for the 30, 75 and 150 mg/kg/day groups were 96.6, 93.3, 80.6, 86.7 and 83.3, respectively. Thus, while treated groups were all lower than controls, the differences were not statistically significant. The mean copulatory interval in the treated groups ranged from 2.0 to 2.8 days compared to about 2.8 in the controls.

Uterine and ovarian examinations: The total number of GD17 pregnancies in the control 1 and control 2 and the three drug-treated groups were 24, 27, 19, 23 and 24, respectively. Two animals each in control group 1 and the low dose group, and one animal in the mid dose group delivered prior to GD17. The number of corpora lutea, uterine implantations, viable fetuses, resorptions, preimplantation loss, and postimplantation loss for the treated groups were comparable to controls.

Daily Dose (mg/kg)	0 (Control 1)	0 (Control 2)	30	75	150
Mean No. Days Prior to Mating	3.1	2.6	2.8	2.0	2.2
No. of Pregnant Females	28	28	24	26	25
No. Aborted or with Total Resorption of Litter	0	0	0	0	0
Mean No. Corpora Lutea	11.4	11.6	11.3	11.5	11.8
Mean No. Implantations	11.0	11.1	10.8	10.8	11.3
Mean % Preimplantation Loss	3.41	3.85	4.08	5.92	4.37
Mean No. Viable Fetuses	10.1	10.4	10.0	10.1	10.8
Mean % Postimplantation Loss	7.53	6.46	8.99	6.32	6.16

Fetal data:

Body weights: Average fetal body weights by sex or both sexes combined in all treated groups were comparable to controls and unaffected by treatment.

Sex ratios: Fetal sex ratios were similar among treated groups and comparable to controls.

The number of litters with malformations of any kind (6) reached significance at the mid-dose (26.1% vs 0% in controls). However, no individual malformation was found to be dose-dependent.

Daily Dose (mg/kg)	0 (Control 1)	0 (Control 2)	30	75	150
Total (external, visceral, and skeletal) Malformations (mean)					
No. Litters (%)	0	1	3	6*	1
No. Fetuses (%)	0	1	3	6	1

External examination:

- One fetus in the low dose (30 mg/kg) had omphalocele,
- One fetus each in the mid (75 mg/kg) and high (150 mg/kg) had exencephaly, and one dead fetus in the mid dose group had exencephaly.
- One fetus from a dam that delivered early in the 30 mg/kg dose group had malrotated hindlimbs.

  Note: Even though no malformations were noted in the control fetuses, the sponsor considered these findings unrelated to treatment because of the low incidence and not being dose-dependent. The sponsor did not provide historical control ranges specific to this study, but after consulting a CD1 mouse database from Charles River Laboratories, malformations appear to be within the historical control range.

Visceral examination:
No fetal visceral observations or developmental variations were observed in any group. In the mid-dose group one fetus had a small kidney which was considered spurious and unrelated to treatment.

Skeletal examination:
Skeletal malformation involving misshapen neural arches were reported in one and four litters in the 30 and 75 mg/kg/day dose groups, respectively. In each litter one fetus was affected. The litter incidence was 1/19 (5.3%) and 4/23 (17.4%) and fetal incidence was 1/92 (1.1%) and 4/118 (3.4%) for the 30 and 75 mg/k groups, respectively. This malformation was significant at the mid-dose (17.4%) but was not observed in the controls or the high dose group and therefore not considered related to treatment. In addition, one litter with one fetus each from the 75 and 150 mg/kg dose groups had several skull malformations (misshapen frontal bone, absent interparietal bone, misshapen parietal bone, misshapen squamosal and absent supraoccipital bone). Because the incidence was not dose-related, the sponsor considered these not treatment-related.

Study title: PT-141: study to evaluate functional effects on male fertility in mice via subcutaneous administration. This study was conducted by MPI research to replace Redfield study 060-020 Protocol 2016-001 titled "Intranasal fertility and general reproduction toxicity study of PT141 in male rats", to obtain data with increased exposure through SC administration.	
Study no.:	996-011
Study report location:	Application 210557 - Sequence 0002 - Study 996-011
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Feb 19, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, Batch #10ABI, >95%; peptide content (b) (4) %

Key Study Findings

Reproductive performance: No treatment-related effect was seen on male reproductive indices (mating, fertility, and fecundity). Sperm evaluation: No treatment related effect was reported from sperm evaluation.

The NOEL for parental (males) toxicity was 15 mg/kg/day based on clinical findings of tremors and lower reproductive organ weights at 30 and 75 mg/kg/day.

The NOEL for reproductive and fertility effects was 75 mg/kg/day, the highest dose tested.

Methods	
Doses:	0,0,15, 30, 75 mg/kg
Frequency of dosing:	Daily
Dose volume:	4 mL/kg
Route of administration:	Subcutaneous
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Mouse / B6C3F1/Crl:BR
Number/Sex/Group:	30/sex/dose
Satellite group:	None
Study design:	Males were dosed 28 d prior to mating until euthanasia. Females were not treated. Males and females were euthanized on GD 14.
Deviation from study protocol:	None that affected outcome

Observations and Results

Mortality

There was no treatment-related mortality.

Clinical Signs

Males were examined daily and females were examined weekly.

Treatment-related tremors were observed in 36 and 73% of the animals given 30 and 75 mg/kg/day doses, respectively. Tremors were observed with the highest frequency on the first and second days of treatment and then declined in frequency and were not evident by d5.

Scabbing: Beginning on day 15 and continued throughout the treatment period an increase in sparse hair and scabbing were observed in 5 male animals in the high dose group. These findings were attributed to test article irritation at the injection site.

Body Weight / Feed Consumption

There were sporadic, statistically significant, increases in male body weights in all treated groups. The increase in body weight correlated with increase in food consumption but was not considered toxicologically significant.

Toxicokinetics

Not done

Dosing Solution Analysis

All test article solutions used for dosing were within specifications (± 10%) except for the 3.75 mg/mL concentration during Week 3 that was 118.4% and the 7.50 mg/mL concentration during Week 2 that was 85.5% of nominal.

Necropsy

Terminal body weights for the treated males were statistically increased in comparison to controls consistent with increased weights seen during the in-life portion of this study. Treatment-related statistically decreased reproductive organ weights were evident at the mid and high dose groups. Epididymides, seminal vesicles, and testes weights relative to body weight were statistically decreased about 11%, 12%, and 7%, respectively, at the high dose. Relative epididymides weights were also statistically decreased about 12% at the mid dose. These decreases in relative weights may be a result of the statistically increased terminal body weights in these groups, although there were instances of decreased absolute organ weights that did not achieve statistical significance.

Reviewer notes that the decrease in relative weights of testes and seminal vesicles may suggest an effect on pituitary-gonadal axis or a direct effect on gonadal tissues, which are known to express melanocortin receptors.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Male reproductive performance:
No treatment-related effect was seen on male reproductive indices (mating, fertility, and fecundity). Male mating indices (Number mated/Number paired) for the treated groups and both controls was 100%. Male fertility indices (Number impregnating a female/Number paired) and fecundity indices (Number impregnating a female/Number with evidence of mating) for the treated groups were also comparable to controls. Fertility and fecundity indices for the treated males ranged from 86.7 to 96. 7%. Male fertility and fecundity indices for the Group 1 and 2 controls were 93.3% and 93.1 %, respectively. Copulatory interval (i.e., days-to-mating, see Table 11) for the treated groups was comparable to controls. The mean copulatory interval in the treated groups ranged from 1.7 to 2.3 days compared to about 2.0 days in the controls.

Sperm evaluation:
No treatment related effect was reported from sperm evaluation. Sperm motility in the treated groups ranged from 80.7 to 82.2% and was comparable to controls at 81.5 to 83.2% in groups 1 and 2, respectively. Total caudal epididymal sperm concentrations and sperm concentrations per gram tissues in the treated groups were comparable to controls. The percent of abnormal sperm was similar or lower than controls in all treated groups.

Females:
Uterine and ovarian examination: There were total of 28 and 27 GD14 pregnancies in control group 1 and 2, respectively. The corresponding numbers for the 15, 30 and 75 mg/kg/day PT-141 treated groups were 29, 29, and 26, respectively. No effect of treatment was evident from GD14 uterine implantation data. The number of corpora lutea, uterine implantations, viable embryos, resorptions, preimplantation loss, and post implantation loss for the treated groups were comparable to controls.

The following study is a non-pivotal study, conducted in the male rat by the intranasal route. This study was conducted early in development during the time that BMT was being evaluated for treatment in males.

Study title: Intranasal fertility and general reproduction toxicity study of PT-141 in male rats	
Study no.:	2016-001
Study report location:	Application 210557 - Sequence 0002 - Study 2016-001
Conducting laboratory and location:	(b) (4)
Date of study initiation:	20 March, 2000
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Batch #535'068 (sponsor's notation); purity >95%, peptide content (b) (4)%

Key Study Findings

There were no treatment-related effects on mating and fertility parameters, caudal epididymal sperm motility, average sperm count and sperm morphology. There were also no treatment-related effects on Caesarean-section or litter parameters.

The NOEL for general and reproductive toxicity of PT-141 in male rats was 5 mg/kg/day, the highest dose tested. No TK was performed, but by the intranasal route, absorption is very low. Reviewer estimates that exposures in this study did not exceed the human therapeutic dose.

Methods	
Doses:	0, 0.100, 0.750, and 5 mg/kg Dosing was based on a 28-day toxicity study
Frequency of dosing:	Daily
Dose volume:	0.25 mL/kg (divided between the nostrils)
Route of administration:	Intranasal
Formulation/Vehicle:	0.9% saline
Species/Strain:	Rat / Crl:CD (SD)IGS BR VAF/Plus
Number/Sex/Group:	20 males/group
Satellite group:	none
Study design:	Dosing of males began 28 days before cohabitation through a 21-day cohabitation period. Males were sacrificed at the end of the cohabitation period. Females were sacrificed on GD 13.
Deviation from study protocol:	None that affected outcome.

Observations and Results

Mortality

There was no treatment-related mortality.

Clinical Signs

Males were examined before and 60 minutes after dosing. There were no treatment-related clinical signs.

Body Weight / Feed Consumption

Body weight: body weights and body weight gains were unaffected by treatment.
Food consumption: relative feed consumption (g/kg body weight) was significantly higher during day 15 to 22 for - the 750 and 5000 ug/kg/day groups. We note an error in the study report narrative for food consumption result: tabular data lists the dose levels correctly but the text lists the dose levels incorrectly.

Toxicokinetics

Not done

Dosing Solution Analysis

Low dose: -14.9%,
Mid dose: -12.2%
High dose: -6.5%

The formulations for group 2 and 3 were outside of the acceptable limit (±10% error).
Formulation analysis located in Appendix A of Appendix G.

Necropsy

After completion of the cohabitation period, male rats were sacrificed and a gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The following organs were individually weighed: right testis, left testis, left epididymis (whole and cauda), right epididymis, seminal vesicles (with and without fluid) and prostate. A portion of the left cauda epididymis was used for evaluation of cauda epididymal sperm count, viability and morphology. The left vas deferens was used for sperm motility evaluation.

On GD 13, female rats with a confirmed date of mating, and 13 days after completion of the full 21-day cohabitation period, female rats without a confirmed date of mating were sacrificed, Caesarean-sectioned and gross necropsy of the thoracic, abdominal and pelvic viscera was performed. The number of corpora lutea in each ovary was recorded. The uterus of each rat was excised and examined for pregnancy, the number and distribution of implantation sites and viable and nonviable embryos. Placentae were examined.

Results: Terminal body weights, organ weights and organ weight ratios to terminal body weight were comparable among the four groups.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

There was no effect on mating and fertility parameters.

Dosage group Dosage (ug/kg/day)	I 0	II 100	III 1000	IV 5000
Rat in cohabitation	20	20	20	20
Days in cohabitation	2.9	2.4	2.7	3.4
Rats that mated	20	20	19	19
Fertility index	20/20 (100%)	18/20 (90%)	17/19 (90%)	19/19 (100%)

Sperm evaluation: Caudal epididymal sperm motility and average sperm count were unaffected by PT-141 administration as shown in table below:

Dosage group Dosage (ug/kg/day)	1 0	I100	III 1000	IV 5000
Rats tested	20	20	20	20
Sperm count	80.8	74.8	73.2	76.5
Density[a]	621.3	616.5	564.0	593.5
Number motile sperm	64.6	86.0	76.3	67.0
Number nonmotile sperm	19.1	29.8	23.8	21.2
% motile sperm	75.8	75.4	76.0	78.0

[a] Average number of sperms/gram of caudal epididymal tissue (x 1,000,000)

Caesarean-sectioning observations were based on 20 (100.0%), 18 (90.0%), 17 (85.0%) and 19 (95.0%) pregnant rats with one or more live conceptuses in the four respective dosage groups. No Caesarean-sectioning or litter parameters were affected by administration of dosages of the test article as high as 5 mg/kg/day to males mated to untreated females (data not shown here).

9.2 Embryonic Fetal Development

The effect of bremelanotide on embryofetal development (EFD) was studied in 8 studies in mice, rats, rabbits, and dogs. The rabbit was found not suitable for reprotox testing due to maternal and developmental toxicity. The studies listed in the table below are summarized in order to report significant findings. The sponsor has chosen to use the studies in the mouse and dog by the sc route to support labeling and are fully reviewed below. Selected findings from the other studies are discussed to inform an understanding of toxicity.

Study	Species	Route	Dose (mg/kg/d)	Duration	Results
996-013*	Mouse	SC	30, 75, 150, 300 (Range finding)	GD6-15	Maternal = 150 mkd Developmental = 300 mkd
996-022	Rat	IV	0.25, 1, 2, 2.5 (Range finding)	GD6-17	80% mortality at the high dose Maternal NOEL = 2 mkd Developmental NOEL = 2 mkd
996-029*	Rat	IV	0.25, 1, 1.5 (2)	GD6-17	Mortality at 2 mkg / dose adjustment Maternal NOEL = 1 mkd Developmental NOEL = 1.5 mkd
996-014*	Rabbit NZW	SC	15, 30, 75, 150 (Range finding)	GD6-12 Terminated on GD13	Maternal toxicity at all doses (inappetance, weight loss) No findings for embryotoxicity
996-015	Rabbit NZW and DB	SC	0.3, 1, 3 Range finding	various	No NOEL determined for NZW DB slightly more tolerant
966-025*	Rabbit DB	SC	0.03, 0.1, 0.3, 1 (Range finding)	GD7-18	Severe maternal and developmental toxicity at all doses
996-031*	Dog	SC	2, 20 (Range finding)	GD18-35	Maternal LOEL = 2 mg/kg Developmental NOEL = 2 mg/kg based on post-implantation loss
996-033	Dog	SC	2, 8, 20	GD18-35	Maternal LOEL = 2 mg/kg Developmental NOEL not set based on increased post-implantation loss at all doses

*previously reviewed by Dr. Raheja

MOUSE

Study title: PT-141: Range-finding study for effects on embryo-fetal development in mice.	
Study no.:	Study # 996-013
Study report location:	Application 210557 - Sequence 0002 - Study 996-013
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 12, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, 6AB2, purity >97%, peptide content (b) (4) %

Key Study Findings

Maternal toxicity was minor, consisting of scabbing at the injection site and a transient reduction in food consumption with slightly reduced body weight. There were no treatment related findings on embryo-fetal development.

- The maternal NOEL was 30 mg/kg/day (82X MRHD based on body surface area) based on decreased body weight gain and lower food consumption seen during GD6-9.
- The maternal NOAEL was 150 mg/kg/day based on injection site scabbing at the highest dose.
- The NOEL for developmental toxicity was 300 mg/kg/day (818X based on BSA), the highest dose tested. It is not known whether PT-141 crosses the placenta, so fetal exposure is unknown.

Note: This study was designed as a range finding study and is not considered definitive because the number of animals tested per dose does not meet the criteria of a full study (25/dose).

Methods	
Doses:	0, 30, 75, 150, or 300 mg/kg/d
Frequency of dosing:	daily
Dose volume:	4 mL/kg
Route of administration:	subcutaneous
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Mouse / B6C3F1/Crl: BR
Number/Sex/Group:	10
Satellite groups:	none
Study design:	Mated females dosed from GD6-GD15
Deviation from study protocol:	None that affected conclusions

Observations and Results

Mortality

One animal in the 75 mg/kg/day group was found dead on GD 13. It was found to have a hemorrhage in the thoracic cavity and was not considered not drug-related.

Clinical Signs

Injection site scabbing was noted at the injection site at ≥ 75 mg/kg/d.
Note: No tremors were reported as observed in male fertility study described above even though doses were higher than used in the male fertility study.

Body Weight / Feed Consumption

Food consumption and body weight: An acute and transient dose-dependent decrease in food consumption with a trend towards a decrease in maternal body weight gain over GD 6-9 was reported at ≥ 75 mg/kg/d.

Toxicokinetics

Not done.

Dosing Solution Analysis

Dosing formulations were within specs (+/- 10%).

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Uterine and ovarian examination: There was no effect of PT-141 on number of corpora lutea, uterine implantations, viable fetuses, resorptions, preimplantation loss, or postimplantation loss. Fetal body weights and fetal sex ratios were also not affected by treatment with PT-141.

Offspring (Malformations, Variations, etc.)

Malformations: There was one fetus with a meningocele at the low dose and one case of exencephaly and absent eyelids at the 75 mg dose. There were no treatment-related external malformations at the 150 and 300 mg/kg/d doses.

RAT

Range-finding study for effects of pt-141 on embryo-fetal development in rats

Study	Species	Route	Dose (mg/kg/d)	Duration	Results (Sponsor)
996-022 (GLP)	SD rat	IV	0, 0.25*, 1, 2, 2.5 N=5/group	GD6-17	80% mortality at the high dose Maternal NOEL = 2 mkd Developmental NOEL = 2 mkd

* The mean concentration for the 0.25 mg/kg/day group at Week 2 was 74.9% (based on re-analysis) resulting in the animals being administered a dose level of approximately 0.19 mg/kg/day during Week 2. All other concentrations were considered acceptable and within the ±10% specifications.

There was significant mortality in the high dose group. Eighty percent (4/5) of the animals died during the treatment period between GD7 to 12. All other rats in the treated and control groups survived to terminal euthanasia on GD20.

Treatment-related clinical observations were noted in all rats in the 2.5 mg/kg/day group. These observations were noted in one or more rats and consisted of decreased activity, ataxia, difficulty breathing, prostration, vocalization, and convulsions. All other rats were normal throughout the study period.

Maternal body weights, body weight gain, and food consumption in the treated groups were comparable to controls.

No maternal macroscopic observations were noted in any treated or control rat.

No effect of treatment with bremelanotide was noted in uterine implantation data, gravid uterine data, fetal body weights, or fetal external examinations.

- The maternal iv NOEL was 2.0 mg/kg/day based on significant clinical findings and mortality in the 2.5 mg/kg/day group.
- No maternal or developmental toxicity was noted at 0.25, 1.0, or 2.0 mg/kg/day, resulting in a developmental toxicity NOEL of 2.0 mg/kg/day.
- Based on these results, a high-dose level of 2.0 mg/kg/day was selected for the definitive developmental toxicity study.

Study title: Study for effects of PT-141 on embryo-fetal development in rats.	
Study no.:	996-029
Study report location:	Application 210557 - Sequence 0002 - Study 996-029
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11/15/05
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, 6AC1, purity > 96%, peptide content (b) (4) %

Key Study Findings

There was ~30% mortality at 2 mg/kg/d.

In the dams, there were dose-dependent and treatment duration-related increases in ACTH and corticosterone levels that were not explained.

Uterine parameters were unaffected by treatment. The overall incidence of litters containing fetuses with malformations (external, visceral and skeletal) in the treated groups was comparable to controls.

TK: Although systemic exposure was demonstrated, it was very inconsistent and could not be used to calculate MOE. Using data from study #91-051, a 1 mg/kg iv dose in the rat leads to an AUC of 275 ng.hr//mL, which is equivalent to the human therapeutic exposure of 276 ng.hr/mL.

- The NOEL for maternal toxicity was 1.0 mg/kg/day based on one death, lower gestational body weight, body weight gain, and food consumption and higher levels of ACTH and corticosterone at the 1.5 mg/kg/day level.
- The NOEL for developmental toxicity was 1.5 mg/kg/day, the highest dose level tested.

Methods	
Doses:	Initial: 0.25, 1.0, 1.5 and 2.0 mg/kg/d The 2.0 dose group was adjusted downward due to mortality. Final: 0.25, 1.0, 1.5 mg/kg/d
Frequency of dosing:	daily
Dose volume:	1 mL/kg
Route of administration:	intravenous
Formulation/Vehicle:	0.9% NaCl solution
Species/Strain:	Rats/Crl:CD (SD)IGS BR
Number/Sex/Group:	25/group main study
Satellite groups:	10/group for TK
Study design:	Dosing was on GD 6-17
Deviation from study protocol:	None significant

Group assignment		
Group #	Dose level (mg/kg/day)	# of time-matted female rats
Main study		
1	0	25
2	0.25	25
3	1.0	25
4	1.5[a]	32[c]
Toxicokinetic		
5	0.25	10[b]
6	1.0	10[b]
7	1.5[a]	10[b]
8	0	6

a Due to death of 7 animals in the main study 2.0 mg/kg/day group on the first and second day of dosing, dose level was lowered to 1.5 mg/kg/day.
b One additional animal was assigned as an extra to be used if mortality occurred prior to completion of blood collection. These animals were euthanized and discarded following completion of the final blood collection.
c Includes the 7 animals replaced on study.

Observations and Results

Mortality

Seven animals in the 2.0 mg/kg/day died during GD 6 and 7.

Clinical Signs

Animals that died exhibited ataxia, breathing abnormalities, low carriage, and splayed hind limbs.

Body Weight

Body weight in the high dose group (1.5 mg/kg/day) was significantly lower than controls on GD 9, 18, and 20. Also body weight gain in this group was significantly lower over intervals GD6-18, 6-20, and 0-20. Gestation body weight and body weight gain in the low and mid dose groups were comparable to controls.

Feed Consumption

Food consumption in treated groups was comparable to controls except for GD6 -9 in the high dose group, which was significantly lower.

Clinical pathology:
There were no effects on electrolytes or glucose levels.
Mean ACTH and corticosterone exhibited dose-dependent increases on Day 6 and 17 at 1.5 mg/kg/day, but were statistically significant only on GD 17, suggesting treatment duration effect.

Endpoint	Study interval	0 mg/kg/day	0.25 mg/kg/day	1.0 mg/kg/day	1.5 mg/kg/day
ACTH (pg/ml)	GD 6	2201.0	2653.9	3111.8	3407.3
	GD 17	1655.0	2121.2	2758.2	3085.2[a]
Corticosterone (ng/ml)	GD 6	273.3	446.8	433.1	492.7
	GD 17	261.0	441.3	525.7	646.7[a]

[a] Significantly different from control $p<0.05$

Toxicokinetics

The sponsor stated that a TK modeling report for the data was not generated. A large number of samples were diluted due to insufficient sample volume, leading to plasma concentrations below LLOQ of the assay (< 5 ng/ml) for many of the samples. Although analysis demonstrated test article exposure in the treated animals, the number of "not reportable" sample results as well as high level of variability of the remaining data prevented proper TK modeling.

Dosing Solution Analysis

Dose formulations ranged from 92.0 - 104.3 for the Week 1 preparations, 86.8 - 101.1 for Week 2, and 99.1 - 116.2 for Week 3. Initial results for the Week 3, 1.0, and 1.5 mg/kg/day dose levels were low at 83.7% and 85.1%, respectively. The dose preparations were adjusted based on these results (prior to reinjection results being available) and animals at the 1.0 and 1.5 mg/kg/day level were dosed with these adjusted dose solutions. The adjusted dose solution analysis results were high at 116.2% and 111.4% for the 1.0 and 1.5 mg/kg/day groups, respectively. Therefore, during Week 3, animals in the 1.0 and 1.5 mg/kg/day groups received dose levels of approximately 1.2 and 1.7 mg/kg/day, respectively.

Necropsy

There were no macroscopic findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The pregnancy index was 100%. No effect of treatment was evident from uterine implantation data. The gravid uterine weight was about 9% lower and the adjusted final body weight was significantly lower in the 1.5 mg/kg/day group and correlated with the lower body weight and body weight gain seen throughout the gestation period. The adjusted weight change (GD0-20) was also significantly lower in the 0.25 mg/kg/day group in comparison to controls.

Offspring (Malformations, Variations, etc.)

No effect of treatment with PT-141 on fetal body weights, sex ratio, external, visceral, or skeletal evaluations was observed.

One fetus in the 1.5 mg/kg/day group was observed with hydrocephaly, but as no other fetuses exhibited this malformation and as the incidence was within our historical control range it was considered unrelated to treatment.

RABBIT

Three studies were conducted in the rabbit in an effort to define a dose-range that would allow determination of a NOAEL for embryofetal toxicity. The effort was not successful. Two strains of rabbits, NZW and Dutch Belted were tested in both the pregnant and non-pregnant state. The limiting toxicity was reduced food consumption leading to reduced body weight. However, there was also direct mortality that occurred within 24 hours of dosing that was unexplained. In addition, there may have been a direct effect of bremelanotide on maintenance of pregnancy; a firm conclusion could not be reached due to the confounding effects of inappetance. The three studies that were conducted are summarized below in order to convey the types and severity of toxicity and to compare the range of exposure to other species.

996-014	Rabbit	SC	15, 30, 75, 150 (Range finding)	GD6-12 Terminated on GD13	Maternal toxicity at all doses
996-015	Rabbit NZW and DB	SC	0.3, 1, 3 Range finding	various	No NOEL determined for NZW DB slightly more tolerant
966-025	Rabbit DB	SC	0.03, 0.1, 0.3, 1 (Range finding)	GD7-18	Maternal and developmental toxicity at all doses

PT-141: Range-finding study for effects on embryo-fetal development in rabbits (NZW)
Study #996-014. GLP. Conducted by (b) (4)
Doses: 0, 15, 30, 75, 150 mg/kg/d. N=5/sex/group. Rabbits were injected subcutaneously from GD 6-12. Dose volume = 1 ml/kg. Vehicle, 2.5% glycerin in sterile water. Blood was collected via the jugular vein of all animals at 0.5, 1, 2, 4, and 8 hours post dose on GD 6 for TK.

Results:
Beginning on the 2nd day of dosing, there was reduced food consumption (up to 90%) and reduced body weight (8-16%) in all treated groups without a dose-relationship. Other sporadic clinical findings were: decreased activity, rapid breathing, dilated pupils, anogenital region discolored red, and brown or red material in the pan.

One high dose female was found dead on the 2nd day of dosing. Due to declining health of all the animals, the study was terminated prematurely on gestation day 13 and each female was necropsied. Uterine examinations were conducted and all developmental parameters (corpora lutea, implantation sites, normally developing implants, resorptions, preimplantation loss, and postimplantation loss) for the treated groups were found to be comparable to controls. However, because the study was terminated on GD 13, developmental toxicity could not be determined.

Toxicokinetics: There was a dose-related increase in systemic exposure as shown in table 2 below. At the low dose, the AUC of 26030 ng.hr/mL is 94X the AUC of 276 ng.hr/mL for the therapeutic dose of 1.75 mg in women.

Parameter	Gr 2 (15mg/kg/day)	Gr 3 (30mg/kg/day)	Gr. 4 (75 mg/kg/day)	Gr 5 (150 mg/kg/day)
Tmax (hr)	0.9 +/- 0.1	0.8 +/- 0.1	1.0 +/- 0.0	2.4 +/- 0.7
Cmax (ng/ml)	11,288 +/- 1,244	28,533 +/- 2,124	71,249 +/- 7,023	108,728 +/- 22,351
AUC 0-8 (ng.hr/ml)	25,647+/- 5,015	73,556 +/- 13,001	208,968 +/- 30,840	467,026 +/- 74,544
AUC o-inf (ng.hr/ml)	26,030 +/- 5,274	74,948 +/- 13,558	214,030 +/- 31,909	475,631 +/- 74,600

Table from Dr. Raheja's review. Data from pp 87-91 of the study report.

Following the failure of the range-finding study, a Tcon was held with P/T on 1-20-05 to discuss whether EFD studies should be continued in the rabbit. It was agreed that another study would be conducted at a lower dose range to determine tolerability. The Division agreed that if an acceptable dose range could not be found, the sponsor could conduct an EFD study in the rat by the IV route. In a second Tcon on 2-22-05, P/T recommended, and the sponsor agreed, to conduct the following studies to explain the hypersensitivity of rabbits to PT-141:

- immunotoxicity studies in the rabbit
- delayed sensitization study in guinea pigs.
- metabolism studies using hepatic and skin microsomal preparations to explain species differences in severity of toxicity by the SC route

Study 996-015 was a non-GLP study designed to determine the MTD of bremelanotide in two rabbit strains by sc administration. Dose-ranging was conducted in both non-mated and mated NZW and Dutch Belted rabbits. Excerpts from the sponsor's narrative as given in the Toxicology Written Summary are given below to convey the types of toxicities observed.

Initially, 3 non-pregnant NZW rabbits were dosed subcutaneously with 0.3 mg/kg/day, but 2 of the 3 died within a few hours of dosing. The sponsor then switched strains and tested the same dose on non-pregnant Dutch Belted (DB) rabbits. This dose was tolerated for 5 days with moderate toxicity (reduced activity, rapid breathing). Food consumption was reduced for several days (about 51% from predose levels, resulting in a slight bodyweight loss) but rebounded. The sc dose level was then increased to 1.0 mg/kg/day for the next 7 days, and again food consumption was reduced by about 77% from predose levels with a concurrent loss in bodyweight. At study termination (Day 12), the rabbits were consuming the supplemental food and about half the normal amount of pelleted diet.

To assess developmental toxicity, 3 time-mated DB rabbits received **1.0 mg/kg/day** bremelanotide sc from GD7-12. Clinical observations noted during the first few days of treatment were decreased activity, prostration, ataxia, rapid breathing, and salivation but largely resolved by GD13. Feed consumption was reduced throughout. There was a notable decrease (about 90% in comparison to predose levels) in pelleted food consumption, but animals occasionally ate the supplemental food (carrots and broccoli) provided. The **dose level was increased to 3.0 mg/kg/day** beginning on GD13 through GD18. Again, pelleted food consumption was reduced in comparison to predose levels (about 86%) during the treatment period. Rabbits lost weight throughout the treatment period at both the 1.0 and 3.0 mg/kg/day dose levels. Following completion of the treatment period, 2 of the 3 rabbits exhibited an increase in food intake with concurrent bodyweight gain.

Complete necropsies and uterine examinations were conducted on GD29. No maternal macroscopic findings were noted at necropsy. Uterine examination showed no visible evidence of implantation sites following staining with 10% ammonium sulfide solution, and therefore the rabbits were most likely never pregnant.

As a follow-up, an additional 3 time-mated DB rabbits were assigned to study. They were dosed sc at **1.0 mg/kg/day** from GD6-18. These rabbits exhibited similar clinical observations, reduced food consumption, and lower bodyweights as seen in the previous group. Food intake and bodyweight gain recovered in 2/3 animals following cessation of treatment. At necropsy on GD29, no maternal macroscopic findings were noted at necropsy. Once again, uterine examination results indicated that these rabbits had never been pregnant.

Finally, to determine if bremelanotide at a dose level of **1.0 mg/kg/day** sc was having an effect on implantation, 6 additional time-mated DB rabbits were assigned to study. Three rabbits were dosed beginning on GD6 (early implantation period) and continued on treatment until GD18, and 3 were dosed beginning on GD8 (postimplantation) and dosed to GD18. One rabbit from the GD6-18 group died following 2 days of treatment, and 2 rabbits from the GD8-18 group died following the first dose.

All 3 remaining rabbits were pregnant with normally developing implants. At necropsy, one of these rabbits had black foci (possibly melanosis) on the glandular and nonglandular stomach. The 3 surviving rabbits exhibited reduced consumption of the pelleted feed (near zero consumption), and bodyweight loss throughout the study. One rabbit in the GD6-18 group died on GD18. At uterine examination, this rabbit had **2 resorbing fetuses in utero**. Complete necropsies and uterine examinations were conducted on GD24 for the 2 surviving rabbits. No

macroscopic findings were noted at necropsy. The 1 surviving GD 6 to 18 rabbit was determined not to be pregnant following staining with 10% ammonium sulfide solution, and the one surviving GD8-18 rabbit was pregnant **with 5 resorbing fetuses in utero**.

Summary: In this dose-range finding study of bremelanotide administered sc to NZW and DB non-pregnant and DB pregnant rabbits, a root cause for the marked reduction in food consumption was not determined. Strain differences were evident in the effects of bremelanotide in rabbits. Due to the high mortality rate observed in the non-pregnant NZW rabbits in comparison to the non-pregnant DB rabbits, at a very low dose level (0.3 mg/kg/day), this strain was considered unacceptable for further toxicity testing.

The non-pregnant DB rabbits were better able to tolerate the sc administration of bremelanotide at dose levels to 3.0 mg/kg/day, but still exhibited severe reductions in food consumption. Pregnant DB rabbits were more tolerant to bremelanotide administration than were NZW rabbits, but they still showed **80% mortality at a dose of 1.0 mg/kg/day**. The conclusive result is that sc administration of bremelanotide has a greater effect on food consumption in rabbits than in any other studied species (dogs, mice, and rats).

TK values for the DB rabbits at 1 mg/kg were: Cmax 595 ng/mL, $AUC_{0\text{-}inf}$ = 671 ng.hr/mL, Tmax = 0.3 hr (p 47 of the study report). Plasma values were not measurable at 4 hrs post-dosing. This AUC is 2.4X the AUC of 276 ng.hr/mL at the therapeutic dose.

Study 996-025 continued the range-finding efforts at doses of 0.03, 0.1, 0.3, and 1.0 mg/kg/day sc. N=5 time-mated female Dutch Belted rabbits/dose group. Animals were treated on GD7-18.

No rabbits died on study, but one rabbit in the 0.3 mg/kg/day group was euthanized in extremis on GD23 due to continued inappetence and loss of body weight. Clinical signs of decreased activity (initial day of treatment, GD7) were observed in all treatment groups. Rapid breathing was noted in a few of the rabbits in the 0.3 and 1.0 mg/kg/day groups and ataxia was noted in a few animals in the 1.0 mg/kg/day group, also on GD7. Mean body weight, body weight change, and food consumption were lower throughout the treatment period in all treated groups. No adverse effects were noted in the maternal clinical chemistry parameters, macroscopic findings, or organ weights evaluated.

> Dr. Raheja's notes on this study:
> Clinical chemistry: On GD7, potassium and calcium at all dose levels, chloride at 0.03 and 0.1 mg/kg/day and phosphorus at 0.03, 0.3 and 1.0 mg/kg/day, were statistically decreased relative to controls. These changes were not dose-related and were not observed on GD18 and sponsor considered them not to be treatment-related. Glucose levels were also significantly increased in treated groups compared to controls on GD7. On GD18 globulins were significantly increased in all groups except the high dose group.

Endpoint on GD 7	0 mg/kg/day (control)	0.03 mg/kg/day	0.1 mg/kg/day	0.3 mg/kg/day	1.0 mg/kg/day
Potassium meq/L	5.64	4.24[b]	3.90[b]	4.04[b]	4.22[b]
Chloride meq/L	105.8	101.4[a]	101.6[a]	102.8	104.8
Calcium mg/dL	14.60	13.40[b]	13.14[b]	13.20[b]	13.32[b]
Phosphorus mg/dL	5.82	4.86[b]	5.30	4.68[b]	4.60[b]
Glucose mg/dL	131.8	206.0[a]	208.6[a]	222.6[b]	190.8
Globulin (g/dL)on GD 18	1.50	1.84[a]	1.86[a]	1.94[b]	1.74

a=p,0.05 compared to control b= p,0.01 compared to control Values are mean of 5.

Organ weights: Adrenal weights (absolute, and relative to BW and BrW) were significantly increased compared to controls at 0.1, 0.3 and 1.0 mg/kg/day (~1.5X at the high dose). Kidney weights (relative to BW) were increased in the 0.1, 0.3 and 1.0 mg/kg/day groups (1.2X max). Also increased at the high dose were liver (~1.5X max relative to BW) and lung weights (~1.5X max relative to BrW). Histopathology was not carried out to determine if there were corresponding changes.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

The pregnancy index was 100%, 60%, 40%, 40%, and 20% in the 0, 0.03, 0.1, 0.3, and 1.0 mg/kg/day group, respectively. One rabbit in each of the treated groups had litters comprised of all resorptions, and 1 rabbit aborted in the 0.3 mg/kg/day group. There were very few litters available for evaluation at GD 28 in the treatment groups due to the low pregnancy index and the number of litters with all resorptions.

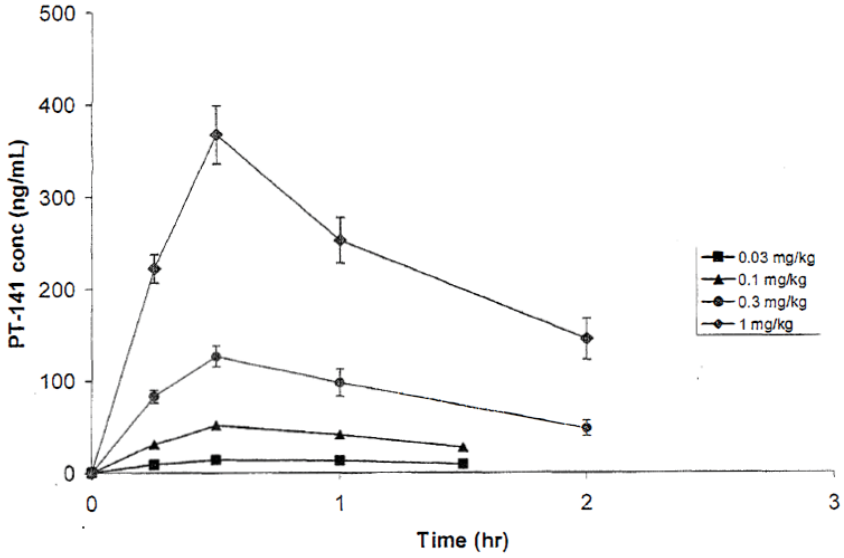
The mean preimplantation and postimplantation loss was high (22% to 100%) in the few remaining litters, leaving very few fetuses for evaluation. The low pregnancy index in the treated group rabbits (all dose levels) coupled with the presence of a few litters comprised entirely of resorptions was considered indicative of a treatment-related response. These changes might have been reflective of a direct effect of treatment on implantation and/or survival of the embryos/fetuses early in gestation or indirectly from adverse effects on food consumption and compromised nutrition status of the does. The sponsor considered that the latter was more likely since higher doses of bremelanotide (15 to 150 mg/kg/day) delivered to NZW rabbits in an earlier dose range-finding study (996-014) had similar effects on food consumption, but did not impact the number of normally developing fetuses through GD 13, at which time the study was terminated due to maternal inappetence.

Mean fetal body weights appeared to be unaffected by sc treatment with bremelanotide, but a clear determination could not be made due to the limited number of fetuses available for evaluation. **No fetal external malformations or developmental variations were observed in any fetuses from a treated rabbit.**

A maternal NOEL for sc bremelanotide to DB rabbits was not determined, as all treatment groups exhibited at least 1 of the following: treatment-related clinical findings (decreased activity, ataxia, and/or rapid breathing), reduced food consumption, lower body weight and body weight gain, and low pregnancy indices. **Likewise, a developmental NOEL was not determined due to an increase in preimplantation and postimplantation loss and low number of litters and fetuses available for evaluation.**

TK results are presented in Section 2.6.5-4-12 under PL-47 or in the study report under Appendix J. The Cmax and AUC increased in a dose-related manner. Cmax averaged 15, 52, 133 and 368 ng/ml and AUC averaged 16, 55, 166 and 456 ng.hr/ml at SC doses of 0.03, 0.1, 0.3 and 1.0 mg/kg/day, respectively. The lowest dose is 0.09 or 9% of the therapeutic AUC of 179 ng.hr/mL. Tmax was 0.5 – 0.6 hours. Sponsor's figure is shown below (p149).

Plasma Concentrations of PT-141 in Time-Mated Dutch Belted Rabbits on Gestation Day 18



DOG

The range-finding study (unaudited draft report) was reviewed by Dr. Raheja who recommended the following comment be sent to the sponsor: " We have reviewed the findings of the pilot range-finding developmental toxicity study in dogs administered PT-141 subcutaneously and concur that the doses proposed for the definitive study are adequate and acceptable." The range finding study is summarized briefly below.

Study 966-031: PT-141: **Pilot study** for effects on embryo-fetal development in dogs. Time-mated female dogs (N=3/g) were dosed daily at 0, 2 or 20 mg/kg sc from GD18 through GD 35. All surviving animals were euthanized on GD57. Conducted in 2005 at (b) (4) GLP + QA. TK was conducted and reported under study #PL-50.

Observations and Results

Mortality

There was no mortality.

Clinical Signs

Clinical observations of repetitive yawning and/or stretching, inappetance and black discolored hair were observed in the treated groups and were considered treatment related.

Body Weight / Feed Consumption

All animals including the controls tended to lose weight during the treatment period, however, weight loss was 2-fold greater in the 20 mg/kg dose group and correlated with lower food intake. Following completion of treatment, all animals gained weight and were similar to controls by termination on GD57.

Toxicokinetics

Blood samples were collected from each female at designated time points on GD18 and 35. Exposure was proportional to dose. There was no apparent accumulation; AUC declined by ~25-35% over the course of the study. Sponsor's tables located on p 152 of the study report.

Table 1a - Toxicokinetics of PT-141 in Time-Mated Beagle Dogs on **Gestation Day 18** Following Subcutaneous Dosing at 2 or 20 mg/kg

	2 mg/kg	20 mg/kg
T_{max} (hr)	1.0 ± 0.0	1.0 ± 0.0
C_{max} (ng/mL)	3,213 ± 770	40,783 ± 6,564
AUC_{0-8} (ng.hr/mL)	7,489 ± 978	86,624 ± 11,039
$AUC_{0-\infty}$ (ng.hr/mL)	7,556 ± 985	87,082 ± 11,031

Table 1b - Toxicokinetics of PT-141 in Time-Mated Beagle Dogs on **Gestation Day 35** Following Subcutaneous Dosing at 2 or 20 mg/kg

	2 mg/kg	20 mg/kg
T_{max} (hr)	0.8 ± 0.2	0.5 ± 0.0
C_{max} (ng/mL)	2,043 ± 258	41,450 ± 2,533
AUC_{0-8} (ng.hr/mL)	4,899 ± 1,141	64,279 ± 8,533
$AUC_{0-\infty}$ (ng.hr/mL)	4,977 ± 1,105	64,321 ± 8,545

Dosing Solution Analysis

Concentration analysis of the dose solutions used on study was conducted weekly. Percent recoveries ranged from 97.0% to 103.4%.

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Pregnancy index was 100% for both treated groups and 66.7% for the control group. One female in the control group was not pregnant and one female in the 20 mg/kg group had all fetuses resorbed, thus leaving 2, 3 and 2 females with viable fetuses for evaluation on GD 57.

Gravid uterine weights, adjusted GD 57 body weights, and adjusted body weight gains (Day 0-57) in the treatment groups were comparable to controls.

Uterine implantation data and fetal sex ratio were comparable in the 2 mg/kg dose group and the controls and unaffected by treatment.

In the 20 mg group:

- Preimplantation loss was 27.6% compared to 7.14% in the control group. The increase was attributed to one female with 42.9% preimplantation loss.
- Post-implantation loss was also high (46.43%) in comparison to controls (8.33%) and was attributed to one female that had all fetuses resorbed.
- Litter size was reduced in comparison to controls (3.3 vs 5.5 pups).

- Fetal sex ratio (# of males/litter) was increased (83.3%) compared to 61.7% for the controls.
- Mean male fetal body weights were 10% lower than controls in the 2 and 20 mg/kg/day groups, however mean fetal body weights of females were unaffected.

Offspring (Malformations, Variations, etc.)

External:

No external malformations or variations were observed in any fetuses in the control or treated groups.

Visceral:

A total of 3 fetuses from 2 litters in the 2 mg/kg/day group were noted with visceral malformations (absent kidney and ureter, malpositioned common carotid artery and discontinuous interventricular septum).

One fetus in each of the 2 and 20 mg/kg/day groups was observed with visceral variation of common carotid and subclavian artery arising from the innominate.

All fetuses in the control and treated groups were observed with edematous tissue surrounding the head and were classified as a variation.

Skeletal:

A skeletal malformation of discontinuous ribs was observed in one fetus from both the control and 2 mg/kg/day group litters and one additional fetus in the 2 mg/kg group was reported with fused ribs. No skeletal malformation were reported in the 20 mg/kg/day group.

Conclusions:

The **maternal LOEL** was set at 2 mg/kg/day based on clinical findings of stereotypic behavior (stretching and yawning), inappetance, discolored hair, and low body weight and body weight gain. Using TK data from GD18, the MOE is 27 based on AUC.

The sponsor's **developmental NOEL** was set at 20 mg/kg/day. However, Dr. Raheja disagreed and set the developmental NOEL at 2 mg/kg/d based on pre and post- implantation losses as well as the visceral and skeletal malformations observed in the treated groups. Even though the findings were not dose-related and were based on limited observations, this reviewer concurs that 2 mg/kg/day is the more conservative developmental NOEL.

Definitive EFD study in the dog.

Study title: Bremelanotide (PT-141): Study for effects on embryo-fetal development in dogs	
Study no.:	966-033
Study report location:	Application 210557 - Sequence 0002 - Study 996-033
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 1, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, 6AC1, purity >96%, Peptide content (b) (4) %

Key Study Findings

The maternal LOEL was 2 mg/kg/day based on clinical findings of stereotypic behavior (stretching, yawning, etc.), inappetance, and lower gestation body weight gain predominately observed during the treatment period (GD18-35). In addition, excessive shedding and discolored hair (black) were evident beginning later in the treatment period (approximately GD33) and persisting through to termination.

The sponsor's developmental NOEL was considered 20 mg/kg/day, the highest dose level evaluated. However, based on increased pre- and post-implantation loss in all treated groups, the reviewer feels that no developmental NOEL can be set.

Methods	
Doses:	0, 2, 8, 20 mg/kg/d*
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	subcutaneous
Formulation/Vehicle:	2.5% glycerin in sterile water
Species/Strain:	Dog / Beagle ages 13-44 months
Number/Sex/Group:	8
Satellite groups:	none
Study design:	Timed mated female animals were treated from GD18-35 and euthanized on GD57.
Deviation from study protocol:	None that affected outcome

*These are the same doses that were tested in the chronic toxicity dog study #966-003.

Observations and Results

Mortality

There was no mortality.

Clinical Signs

Treatment-related clinical findings of stereotypic behavior (stretching, yawning, etc.), inappetance, excessive shedding, and black discolored hair were observed at all doses.

Body Weight / Feed Consumption

Lower body weight gain was observed in all treated groups during the dosing period and correlated with lower food consumption. Body weight was reduced by ~9% in the low and high dose groups at the end of dosing, and by ~6% in the mid-dose group. Following completion of the dosing period, animals resumed normal eating behavior and body weight gain values for the treated animals were similar to controls at termination on GD57.

Toxicokinetics

Plasma samples were collected on GD18 and 35 and were similar at the two timepoints. Mean T_{max} (0.7-1.0 hrs) was unaffected by dose level and did not change following multiple sc doses. Plasma exposure was dose-related on GD18 and 35, with a slight increase in C_{max} and a slight decrease in $AUC_{0-\infty}$ following repeated dosing. Based on AUC averaged across the two timepoints, exposures were approximately 17X, 85X, and 274X the human therapeutic exposure of 276 ng.hr/mL.

	Daily Dose (mg/kg/day)		
	2.0	8.0	20.0
C_{max} (ng/mL)			
Gestation Day 18	1,988	9,923	32,275
Gestation Day 35	1,849	13,060	35,222
AUC_{0-8} (ng·hr/mL)			
Gestation Day 18	4,621	23,192	75,365
Gestation Day 35	4,285	22,432	60,845
$AUC_{0-\infty}$ (ng·hr/mL)			
Gestation Day 18	4,650	23,330	75,706
Gestation Day 35	4,328	22,467	60,921

Data from sponsor's tables on p 227 of the study report.

Dosing Solution Analysis

Stability analysis of the low and high concentrations at 14 and 30 days was conducted and percent recoveries ranged from 85.6-101.2%. Concentration analysis of the dose solutions used on study was conducted weekly. Percent recoveries ranged from 86.7-103.2%.

Necropsy

No test article-related maternal macroscopic findings were observed in the treated animals.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

- The pregnancy index was 87.5, 62.5, and 87.5% in the 2, 8, and 20 mg/kg/day groups and was comparable to controls at 75.0%.
- Preimplantation and postimplantation loss was slightly higher in the treated groups in comparison to controls, but differences were not statistically significant or dose-dependent. Reviewer notes that the low number of animals evaluated make it difficult to establish statistical significance for any changes that might occur.
- Likewise, all other uterine implantation data (number of corpora lutea), implantation sites, viable fetuses, litter size, and number of resorptions) and fetal sex ratios were similar to controls and unaffected by treatment.
- No effect of treatment was evident on gravid uterine weights, adjusted GD57 body weight, and adjusted body weight gains (GD 6-57) in the treated groups.

Daily Dose (mg/kg/day)	0 (Control)	2.0	8.0	20.0
No. Evaluated	8	8	8	8
No. Pregnant	6	7	5	7
No. Died or Sacrificed Moribund	0	0	0	0
No. Aborted or with Total Resorption of Litter	0	0	0	0
Mean No. Corpora Lutea	6.8	8.0	9.4	8.0
Mean No. Implantations	6.7	6.7	8.2	6.4
Mean % Preimplantation Loss	2.08	14.38	11.31	17.66

	Daily Dose (mg/kg/day)			
	0 (Control)	2.0	8.0	20.0
Evaluation of Litters				
Litters: No. Litters Evaluated	6	7	5	7
No. Fetuses Evaluated	39	44	35	41
Mean No. Female Dogs with All Resorptions	0.2	0.4	1.2	0.6
Mean No. Viable Fetuses	6.5	6.3	7.0	5.9
Mean Nonviable Fetuses (no. per dog)	0	0	0	0
Mean % Postimplantation Loss	2.08	7.30	15.36	10.71

Offspring (Malformations, Variations, etc.)

The sponsor indicates that no effect of treatment with PT-141 was evident from fetal body weight or fetal external, visceral, or skeletal evaluations. Reviewer disagrees about fetal body weight, noting that body weight was reduced 12% for both males and females combined at the high dose. Reviewer also notes that the low number of litters evaluated make it difficult to establish statistical significance for any changes that might occur.

	Daily Dose (mg/kg/day)			
	0 (Control)	2.0	8.0	20.0
Mean Fetal Body Weight (g)				
Males	217.89	204.95	209.03	199.35
Females	211.81	194.98	205.59	177.06
Males + Females	214.36	202.47	211.25	189.06

9.3 Prenatal and Postnatal Development

Study title: PT-141: A Pre- and Postnatal Developmental Toxicity Study, Including Maternal Function and Toxicokinetics, in B6C3F1 Mice	
Study no.:	996-032
Study report location:	Application 210557 - Sequence 0002 - Study 996-032
Conducting laboratory and location:	(b) (4)
Date of study initiation:	27 March 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PT-141, 6AC1, purity >96%, peptide content (b) (4) %

Key Study Findings

No treatment-related mortality was observed in the F0 females or F2 generation animals. A treatment-related decrease in F1 pup survival was observed during LD0-4 where nursing F0 female mice were being treated at 150 mg/kg/day; however, this decrease in survival did not persist after LD 4.

No treatment-related macroscopic findings were observed in the F0 females or F1 and F2 generation mice.

Treatment-related clinical findings of tremors were seen in a few F0 females during the first 3 days of dosing (GD6-8) at the high dose. Other effects at this dose level included lower body weights, body weight gain, and food consumption early in lactation (LD0-14). Reproductive performance of the F0 female mice was unaffected.

In the F1 generation, treatment-related effects consisted of clinical findings (decreased activity, thin appearance, and patches of white hair), lower body weights (lactation and postweaning), and a delay in development (eye opening, vaginal opening, and preputial separation) at all dose levels. In addition, lower food consumption was evident postweaning (Weeks 1 to 8) for F1 pups from F0 female mice dosed at 75 and 150 mg/kg/day. There were no behavioral findings (motor activity, learning and memory) and reproductive performance was unaffected at any dose.

In the F2 generation from the high dose group, treatment-related lower body weights were noted during lactation.

The NOEL for maternal toxicity was 75 mg/kg/day based on clinical findings (tremors), lower body weight, body weight gain, and food consumption at 150 mg/kg/day.

The NOEL for reproductive performance of the F0 generation females was 150 mg/kg/day, the highest level evaluated.

A NOEL for growth and development of the F1 generation mice was not achieved since treatment-related effects were noted in the F1 generation mice at all doses. The NOEL for behavior and reproductive performance was >150 mg/kg/d.

The NOEL for growth and development of the F2 mice was 75 mg/kg/day based on lower pup body weights observed at 150 mg/kg/day on LD4-10.

Exposures in this study were approximately 118, 327, and 702X the human therapeutic exposure based on AUC averaged for GD6 and GD15 at the low, mid, and high dose respectively.

Methods	
Doses:	0,0,30, 75, 150 mg/kg/d
Frequency of dosing:	Daily
Dose volume:	4 mL/kg
Route of administration:	subcutaneous
Formulation/Vehicle:	2.5% Glycerin in sterile water
Species/Strain:	Mouse/B6C3F1/Crl: BR
Number/Sex/Group:	30 F/group
Satellite groups:	60 F/dosed group and 10 F/control group for TK TK samples were taken from half the animals per group on GD6 and half on GD15 at 0.25, 0.5, 1, 3, and 8 hours postdose. Control TK samples were collected at 0.5 hours postdose. On LD28, samples were collected from the main study treated groups and vehicle control group 1 at the same timepoints.
Study design:	Animals were dosed from GD6 through LD 28* (implantation through weaning). *The F1 offspring were potentially exposed to PT-141 in utero and as neonates during the lactation period but were not dosed directly. **Litters Culled on** Day 4
Deviation from study protocol:	None that affected outcomes

Observations and Results

F_0 Dams	
Survival:	One F0 female from the low dose group was found dead on LD17. No cause of death was determined.
Clinical signs:	Tremors were sporadically observed in 7 animals during the first 3 days of dosing at the high dose. There was scabbing and sparse hair in all groups at the injection site. There were no treatment-related macroscopic observations.
Body weight:	Gestation body weights and body weight gain in the treated groups were comparable to controls and unaffected by treatment. However, during lactation (LD 0-14), mean body weights were lower in the high dose group. Body weight gain during this period for this group was comparable to controls and final weights were slightly above controls.
Feed consumption:	Early in the lactation period (LD 4-7) food consumption was significantly lower in the treated groups (24-28% lower at the high dose). This was consistent with lower body weight and body weight gain during this time and was considered indicative of a treatment-related response. Food consumption after LD 7 was not analyzed due to an increased incidence in food spillage, which necessitated exclusion of data for a large number of animals in all groups.
Necropsy observation:	There were no treatment related macroscopic observations
Dosing Solution Analysis	Average test article concentrations for the formulations were determined for Weeks 1, 3, and 6. The mean values of the test article concentrations at 7.5, 18.75, and 37.5 mg/mL ranged from 92.7-101.8% and were within the acceptable specified range (± 10% of nominal). Stability: the test article is stable as a solution for at least 30 days (b) (4) Study Number 996-007).

Parturition data:
The number of F0 females delivering litters was 22, 26, 27, 28, and 26 in the Vehicle Control 1, Vehicle Control 2, 30, 75, and 150 mg/kg/day groups, respectively. Likewise, the fertility indices were 76.7%, 86.7%, 90.0%, 93.3%, and 86.7%.

The mean number of pups (live plus dead)/litter on LD0 in the treated groups ranged from 9.04-10.37 and was comparable to vehicle controls 1 and 2 (10.04 and 10.05, respectively). Gestation Length and Stillborn Indices in the treated groups were comparable to controls and unaffected by treatment.

	Daily Dose (mg/kg)				
	0 (Control 1)	0 (Control 2)	30	75	150
F_0 Female Mice: Toxicity	30	30	30	30	30
No. Pregnant	23	26	27	28	26
No. Died or Sacrificed Moribund	0	0	1	0	0
No. Delivering Pups	22	26	27	28	26
Gestation Body Weight[a] (g)	28.90	29.31	28.45	28.51	27.61[c]
Lactation Body Weight[b] (g)	28.18	29.25[d]	30.45[c]	30.57[c]	30.41[c]
Gestation Food Consumption[e] (g/mouse/day)	7.0	7.6	6.9	7.2	6.7
Lactation Food Consumption[f] (g/mouse/day)	14.8	15.7	12.7	11.9[d]	11.3[c]

a Lactation Day 0 (end of gestation)
b Lactation Day 28
c Significantly different from Control 1; ($p < 0.01$)
d Significantly different from Control 1; ($p < 0.05$)
e Gestation Day 0 to 17.
f Lactation Day 4 to 7.
g From birth to weaning

Toxicokinetics: A dose-proportional increase in Cmax and $AUC_{0-\infty}$ was observed at all three study intervals. Mean Tmax was unaffected by dose level but occurred earlier on LD 28 compared to GD 6 and 15. Exposures in this study were approximately 118, 326, and 615X the human therapeutic exposure based on AUC.

Daily Dose (mg/kg)	0 (Control 1)	0 (Control 2)	30	75	150
F_0 Female Mice: Toxicokinetics (mean) (Study PL-53)	10	-	60	60	60
Gestation Day 6					
t_{max} (hour)	-	-	1.0	1.0	1.0
C_{max} (ng/mL)	-	-	17,575	31,132	56,540
AUC_{0-8} (ng·hr/mL)	-	-	31,187	76,977	176,095
$AUC_{0-\infty}$ (ng·hr/mL)	-	-	31,194	76,990	176,379
Gestation Day 15					
t_{max} (hr)	-	-	0.5	1.0	1.0
C_{max} (ng/mL)	-	-	24,135	59,842	109,727
AUC_{0-8} (ng·hr/mL)	-	-	34,469	103,781	210,683
$AUC_{0-\infty}$ (ng·hr/mL)	-	-	34,470	103,784	210,750
Lactation Day 28					
t_{max} (hr)	-	-	0.3	0.5	0.3
C_{max} (ng/mL)	-	-	22,134	55,737	104,560
AUC_{0-8} (ng·hr/mL)	-	-	32,226	89,644	121,670
$AUC_{0-\infty}$ (ng·hr/mL))	-	-	32,268	89,659	122,746

F1 generation:
Observations of F1 mice included clinical observations, body weight, and food consumption during the pre- and post-mating periods, gestation, and lactation. The mated F1 female mice were allowed to give birth. Observations of the offspring (F2) included survival at birth through LD10, individual pup body weights, sex determination, and gross abnormalities.

Necropsies were conducted on subsets of F1 male mice at birth, while F1 female mice and surviving F2 pups were subjected to a complete necropsy on LD10.

F_1 Generation	
Survival:	The viability index (mean % pups surviving LD0-4) was reduced at the high dose. Values were 94.67% and 97.27% for the vehicle controls, and 92.65, 90.76, and 79.59% in the 30, 75, and 150 mg/kg dose groups. The Lactation Index (mean %pups post-cull to LD28) was unaffected by treatment. F1 pup sex ratios were unaffected by treatment. Post weaning, during the F1 growth and evaluation period, one control male and 2 males in the mid-dose group died. No cause of death was determined.
Clinical signs:	Decreased activity and thin appearance; localized areas of white discolored hair.
Body weight:	There were lower body weights in all treated groups during preweaning and postweaning periods. The decrease in pup body weights was less evident at birth with weights ranging from 4-7% lower than controls. However, this difference increased markedly LD 4-28, ranging from 10-27% lower than controls. Mean F1 pup body weights continued to be significantly lower postweaning (LD 35) and ranged from 6-15% lower than controls. These lower F1 pup body weights during lactation in the treated groups were not dose-responsive but were considered treatment related.

F_1 Generation	
Feed consumption:	Postweaning, during the premating period, food consumption in males was lower in the two highest dose groups. Likewise, premating food consumption in females at 75 and 150 mg/kg/day was lower in comparison to controls, but unlike in the males, these values were less likely to be statistically significant. These differences were considered related to treatment with PT-141. Food consumption during subsequent gestation and lactation were considered similar among treated and control groups.
Physical development:	Mean age at eye opening was statistically greater in all treated groups and averaged 15.9 to 16.1 days in comparison to Control 1 and 2 at 14.7 and 14.8 days, respectively. The delay in eye opening was indicative of developmental retardation and was consistent with the lower body weight of these pups. Righting reflex was unaffected as was pinna detachment.
Sexual maturation: Onset of vaginal opening in females and preputial separation in males	Mean age at preputial separation was greater in the treated groups and in most instances was statistically significant. Vaginal opening was also delayed, but this delay was only significant at the low dose. However, body weight on the day sexual maturation was achieved for both males and females was lower in comparison to controls and in most instances statistically significant. These lower body weights and delay in maturation are suggestive of developmental retardation, however this delay in maturation did not impact reproductive performance or fertility of the F1 generation.
Neurological assessment:	Auditory response was unaffected by treatment. Motor activity in the treated pups (male and female) was generally comparable to controls. Learning and memory as determined from passive avoidance testing were unaffected by treatment.
Reproduction:	There was no effect of treatment on reproductive performance or fertility of the F1 animals. Mating indices among the treated groups and controls were 100%. Fertility and Fecundity indices in the treated groups ranged from 83.3-86.7% and were comparable to the 80-90% in controls. The mean number of days-to-mating (Copulatory Interval) in the treated groups was unaffected by treatment. The number of F1 females delivering litters, the mean number of pups (live plus dead)/litter on LD 0, gestation length, stillborn indices, and mean litter size on LD 4, 7 and 10 in the treated F1 pups were unaffected by treatment.
Macroscopic findings.	No treatment-related macroscopic observations were noted in F1 pups (stillborn, died on study, culled on LD 4, and LD 35 scheduled euthanasia) at necropsy.
Other:	

Sponsor's tables with parameters from the F1 generation, preweaning, postweaning, and premating, are shown below.

Mean Duration of Gestation (days)	18.09	18.04	18.11	18.11	18.15
Daily Dose (mg/kg)	**0 (Control 1)**	**0 (Control 2)**	**30**	**75**	**150**
F1 Litters: (Preweaning)					
No. Litters Evaluated	22	26	27	28	26
Mean No. Pups/Litter	10.05	10.04	10.37	9.71	9.04
Mean No. Liveborn Pups/Litter	10.05	9.96	10.33	9.64	8.92
No. of Litters with Stillborn Pups	0	2	1	2	3
Postnatal Survival to Day 4	9.50	9.65	9.52	8.68	8.13[d]
Postnatal Survival to Weaning (Day 28)	7.59	7.19	7.27	6.75	6.70
Pup (M+F) Body Weights at Birth (g)	1.28	1.30	1.21[d]	1.23[e]	1.21[e]
Pup (M+F) Body Weights at Weaning (g)	13.92	14.15	12.49[e]	11.55[e]	11.49[e]
Pup Sex Ratios (%Male)	39.73	51.93[d]	49.13	45.89	49.92
Pup Clinical Signs					
No. Mice	221	258	279	270	231
Activity decreased	1	4	23	27	28
Skin cold to touch	0	0	5	8	14
Breathing shallow	0	1	3	4	10
Thin	1	7	14	19	26
Hair discolored, white, abdominal region	0	0	23	23	28
Hair discolored, white, cranial region	0	0	40	34	29
Hair sparse, cranial region	0	3	9	14	20
Physical Development					
Eye Opening (days)	14.7	14.8	15.9[e]	16.0[e]	16.1[e]
Air Drop Righting Reflex (days)	16.1	16.0	16.1	16.2[d]	16.1
F1 Male Mice: (Postweaning)					
No. Evaluated Postweaning per Litter	30	30	30	30	30
No. Died or Sacrificed Moribund	0	1	0	2	0
Clinical Observations					
Hair discolored, white, cranial region	0	0	9	5	7
Necropsy Observations	-	-	-	-	-
Mean Body Weight (g)	25.99	26.64	24.13[e]	23.65[e]	23.94[e]
Mean Food Consumption (g) (Week 7 to 8)	5.1	5.4	5.3	4.8	4.9
Preputial Separation					
Preputial Separation (days)	37.0	38.0[d]	39.0[e]	39.8[e]	40.4[e]
Body Weight on Day of Preputial Separation (	20.4	20.9	18.9[e]	17.9[e]	18.4[e]
Motor Activity	-	-	-	-	-
Learning and Memory	-	-	-	-	-
Mean No. Days Prior to Mating	2.0	2.4	2.5	2.3	1.9
No. of Male Mice that Mated	30	30	30	29	30
No. of Fertile Male Mice	24	27	26	25	25
F1 Female Mice: (Postweaning)					
No. Evaluated Postweaning	24	27	26	25	24
No. Died or Sacrificed Moribund	0	0	0	0	0
Clinical Observations					
Hair discolored, white, cranial region	0	0	6	7	5
Necropsy Observations	-	-	-	-	-
Premating Body Weight (g) (Week 8)	23.29	23.44	21.81[e]	21.87[e]	20.77[e]
Gestation Body Weight (g) (GD 17)	38.85	38.30	**Daily Dose (mg/kg)**	36.52	35.31[e]
Lactation Body Weight (g) (LD 10)	32.85	31.28	31.76	29.72[e]	29.36[e]

	0 (Control 1)	0 (Control 2)	30	75	150
Premating Food Consumption (g/mouse/day) (Week 7 to 8)	5.1	5.1	4.7	5.2	4.5
Gestation Food Consumption (g/mouse/day) (GD 0 to 17)	6.7	6.3	6.1	6.2	5.8[d]
Vaginal Opening					
Mean Age of Vaginal Opening (days)	37.9	37.6	40.2	40.0	39.9
Body Weight on Day of Vaginal Opening (g)	16.5	16.9	15.9	15.8	15.4[d]
Motor Activity	-	-	-	-	-
Learning and Memory	-	-	-	-	-
Mean No. Days Prior to Mating	2.0	2.4	2.5	2.3	1.9
No. of Female Mice Sperm-Positive	27	27	30	29	28
No. of Pregnant Female Mice	24	27	26	25	25

F_2 Generation	
Survival:	F2 pup survival LD 0-4 and LD 0-10 was similar among all groups and unaffected by treatment. The Viability Index (mean % pups surviving LD 0-4) was 96%, 83%, and 97% in the 30, 75, and 150 mg/kg/day groups, respectively, and was comparable to controls (95% and 82% in Vehicle Control 1 and 2, respectively). Similarly, the lactation index (mean % pups surviving LD 4-10) was 95%, 99%, and 97% in the 30, 75, and 150 mg/kg/day groups, respectively, and was comparable to controls (98% and 99% in Vehicle Control 1 and 2).
Body weight:	Mean F2 pup body weights in the treated groups at birth (LD 0), were similar to controls and unaffected by treatment. However, on LD 4, 7, and 10, pup weights were lower (3-10%) at the high dose and considered to be treatment-related.
Macroscopic evaluation:	No treatment-related findings.
Male/Female ratio:	F2 pup sex ratios were unaffected by treatment.
Clinical findings:	None significant.

	Daily Dose (mg/kg)				
	0 (Control 1)	0 (Control 2)	30	75	150
F_2 Litters:					
Duration of Gestation (days)	18.81	19.04	19.00	19.04	18.91
No. Pups Born per Litter	7.92	7.59	7.77	6.84	7.46
Mean No. Live Pups/Litter	7.83	7.52	7.69	6.60	7.29
No. of Litter with Stillborn Pups	2	1	2	2	2
No. Stillborn Pups/Litter	0.08	0.07	0.08	0.24	0.17
Body Weights (M+F) at Birth (g)	1.36	1.39	1.38	1.42	1.35
Body Weights (M+F) at Day 10 (g)	5.75	5.58	5.59	5.83	5.19[d]
Sex Ratio at Birth (% Male Mice)	49.75	59.32	50.52	53.65	43.32
	-	-	-	-	-

a Lactation Day 0 (end of gestation)
b Lactation Day 28
c Significantly different from Control 1; ($p < 0.01$)
d Significantly different from Control 1; ($p < 0.05$).
e Gestation Day 0 to 17
f Lactation Day 4 to 7
g From birth to weaning.

10 Special Toxicology Studies

Immunotoxicity: In vitro studies for immunotoxicity were conducted. A risk assessment for immunotoxicity was made by OPQ reviewers and found to be low.

Abuse potential: In vivo studies for abuse potential were conducted in the rat. A risk assessment of abuse potential was made by the Controlled Substances Division and found to be negligible.

11 Integrated Summary and Safety Evaluation

Summaries of the data from reproductive toxicity studies were prepared for memos the senior reviewers and are given below.

	Mouse (SC)	Rat (IV)	Rabbit (SC)	Beagle Dog (SC)
Gestation length (d)	18-22	21-23	31-32	63
Dam mortality	--	+	+	-
Fertility index	reduced at all doses but not sig	NA	NA	NA
Preimplanation loss	--	--	+	+ (but not treatment related)
Postimplantation loss	--	--	+	+
Pup viability	+ reduced at the high dose	--	Too few to assess	--
Pup body weight	+ reduced in all groups	--	Too few to assess	+ (slight)
Malformations	-- None treatment related	--	Too few to assess	None

Gestation in the B6C3F1/crl mouse is 18-22 days; average litter size 7
Average litter size in the Beagle dog was 6-7

Overall conclusions from the pivotal studies:

In the mouse:

- There was no evidence for an effect on fertility.
- There was no evidence for teratogenicity.
- There was no evidence of embryofetal toxicity through organogenesis (GD15). There was, however, evidence of reduced pup viability and developmental delays if dosing continued through parturition and weaning. This was probably due to reduced food consumption and weight gain in the dams.
- Exposures were >100X the human therapeutic dose

In the dog:

- There was no evidence for teratogenicity.
- There was some evidence for embryofetal toxicity (postimplantation loss)
- Exposures were >10X the human therapeutic dose

A nonpivotal study in the rat that achieved exposures 1-2X the therapeutic dose supports the finding that there is no teratogenicity, and no embryotoxicity through organogenesis.

Pivotal reprotox studies: all by the SC route

Species	Duration of dosing	Doses mg/kg/d MOEs	# dose	Significant findings	Developmental NOEL (mg/kg/d)
Mouse Seg 1	14 days prior to mating through GD15	30, 75, 150 113, 278, 639*	30	No effect on maternal or fetal body weights Malformations: Exencephaly: 2@75; 1@150 Omphalocele: 1@30	150
Dog Seg 2	GD18-35 (2.5-5 wks)	2, 8, 20 17, 85, 274	8	No malformations	Not set due to elevated post-implantation loss
Mouse Seg 2/3**	GD6-LD28	30, 75, 150 113, 278, 639	30	No malformations Reduced weight and delayed development	None set

*Mouse MOEs based on $AUC_{0\text{-}inf}$ obtained on GD6 from the Mouse Seg 2/3 study
** Standard Seg 3 design in the rodent is GD16-LD21

Nonpivotal reprotox studies Segment 2 EFD (range-finding)

Rat was intolerant of sc dosing and was dosed intravenously; all others dosed subcutaneously

Species	Duration of dosing	Doses mg/kg/d MOEs	# dose	Significant findings	Developmental NOEL (mg/kg/d)
Mouse	GD6-15	30, 75, 150, 300 113, 278, 639, no data	10	Exencephaly 1@75 Meningocele 1@30	
Rat	GD6-17	0.25, 1, 2, 2.5 No data, 1.3, 2.5, no data	5	Maternal mortality; no fetal malformations	
Rat	GD6-17	0.25, 1, 1.5 (adjusted downward from 2 due to maternal mortality)	25	Maternal mortality: Pups: Gastroschisis 1@0.25 Hydrocephaly 1@1.5	1.5
Rabbit NZW	GD6-12 terminated on GD13	15, 30, 75, 150	5	Severe maternal toxicity	
Rabbit NZW and DB	Various	0.3, 1, 3	3-6	Severe maternal toxicity	
Rabbit DB	GD7-18	0.03, 0.1, 0.3, 1	5	Severe maternal toxicity	
Dog	GD18-35	2, 20 113, 639	3	None	

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Drug mechanism related to indication

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PT-141, a cyclic heptapeptide melanocortin analog, was evaluated following intranasal administration in healthy male subjects and in Viagra-responsive erectile dysfunction (ED) patients. Erectile response was assessed by RigiScant in healthy subjects without visual sexual stimulation (VSS) and in Viagras-responsive ED patients with VSS. In healthy subjects, mean Cmax and AUC(0–t) increased in a dose-dependent manner. Median Tmax was 0.50 h and mean t1/2 ranged from 1.85 to 2.09 h. In both studies, an erectile response induced by PT-141 administration was statistically significant, compared to placebo, at doses greater than 7 mg, with the onset of the first erection occurring in approximately 30 min. PT-141 was safely administered and well tolerated in both studies. A maximum-tolerated dose was not identified. Flushing and nausea were the most common adverse events reported in both studies and no clinically significant changes in vital signs, laboratory tests, ECGs, or physical exams were observed. Based upon its erectogenic potential and tolerability profile, PT-141 is a promising candidate for further evaluation as a treatment for male ED.

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Although more work is needed to further dissect this pathway, recent observations that MC4 receptors are located in cells of the sympathetic nervous system in the hypothalamus — which are areas also involved in feeding control and autonomic control of the brainstem and spinal cord — provide possible points of actions for central MC4 receptor control of sympathetic outflow to the periphery. Moreover, local injections of ACTH into the rostral ventrolateral medulla (RVL M) increase efferent sympathetic discharge and cause an increase of blood pressure by an effect that is probably mediated by MC4 receptors.

Melanocortins and autonomic functions

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alpha-MSH regulates important physiological functions including energy homeostasis and inflammation. Potent analogs of alpha-MSH, [Nle4, d-Phe7]-α-MSH (NDP- α -MSH) and melanotan-II (MT-II), are widely used in pharmacological studies, but the hemodynamic effects associated with their systemic administration have not been thoroughly examined. Therefore, we investigated the hemodynamic actions of these compounds in anesthetized and conscious C57Bl/6N mice using peripheral routes of administration. NDP- α -MSH and MT-II induced mild changes in blood pressure and heart rate in anesthetized mice compared to the effects observed in conscious mice, suggesting that anesthesia distorts the hemodynamic actions of α -MSH analogs. In conscious mice, NDP- α -MSH and MT-II increased blood pressure and heart rate in a dose-dependent manner, but the tachycardic effect was more prominent than the pressor effect. Pretreatment with the melanocortin (MC) 3/4 receptor antagonist SHU9119 abolished these hemodynamic effects. Furthermore, the blockade of β1-adrenoceptors with metoprolol prevented the pressor effect and partly the tachycardic action of α -MSH analogs, while the ganglionic blocker hexamethonium abrogated completely the difference in heart rate between vehicle and α -MSH treatments. These findings suggest that the pressor effect is primarily caused by augmentation of cardiac sympathetic activity, but the tachycardic effect seems to involve withdrawal of vagal tone in addition to sympathetic activation. In conclusion, the present results indicate that systemic administration of alpha-MSH analogs elevates blood pressure and heart rate via activation of MC3/4 receptor pathways. These effects and the consequent increase in cardiac workload should be taken into account when using alpha-MSH analogs via peripheral routes of administration.

Wikberg, JE and F Mutulis. Targeting melanocortin receptors: an approach to treat weight disorders and sexual dysfunction. Nat Rev Drug Discov 7(4):307-323. 2008.

Although more work is needed to further dissect this pathway, recent observations that MC4 receptors are located in cells of the sympathetic nervous system in the hypothalamus — which are areas also involved in feeding control and autonomic control of the brainstem and spinal cord — provide possible points of actions for central MC4 receptor control of sympathetic outflow to the periphery. Moreover, local injections of ACTH into the rostral ventrolateral medulla (RVL M) increase efferent sympathetic discharge and cause an increase of blood pressure by an effect that is probably mediated by MC4 receptors.

ADME

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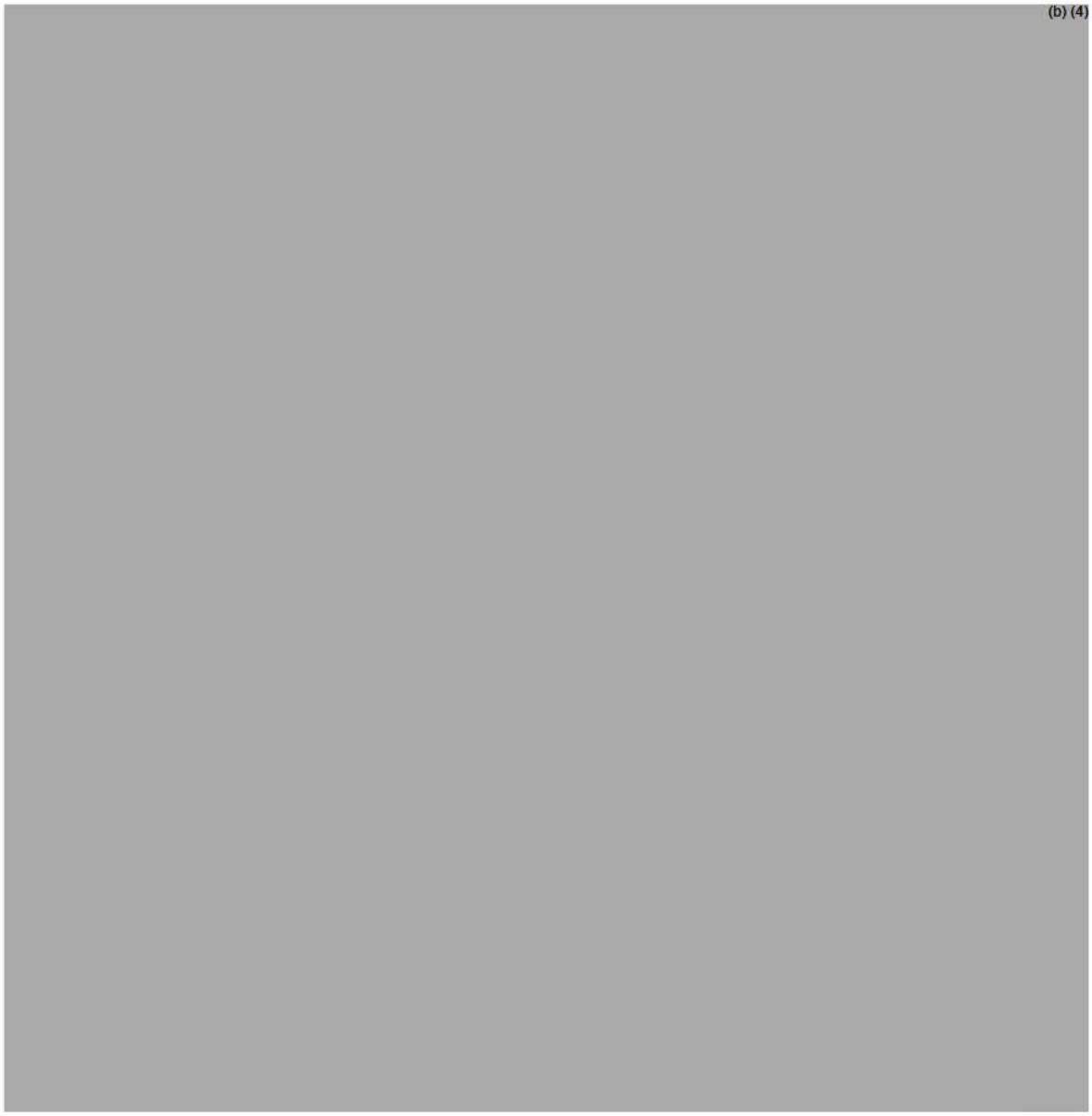
12 Appendix/Attachments

Solubility information from Study 996-013 under section 4.2.3.5.2 – reprotox.



Executive CAC Meeting Minutes

Date of meeting: 5/28/2013

Committee: David Jacoboson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D. OND IO, Member
Tim Robison, Ph.D., DPARP, Alternate Member
Lynnda Reid, Ph.D., DBRUP, Supervisor
Krishan Raheja, D.V.M., Ph.D., DBRUP, Presenting Reviewer
Author of the Draft: Krishan L. Raheja

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND 61,706
Drug name: Bremelanotide (PT-141)
Sponsor: Palatin Technologies Inc. Cedar Brook Dr. Cranbury, NJ 08512

Background information: Bremelanotide, a cyclic heptapeptide, is a melanocortin-4-receptor agonist indicated for the treatment of erectile dysfunction in men. It is not mutagenic when tested in vitro in the Ames and chromosomal aberration assays and in vivo in the mouse micronucleus test.

Rat carcinogenicity study: In this study with Sprague Dawley IGS CrlBR rats, four treatment groups having 60 rats/sex were administered Bremelanotide at dose levels of 0, 0.5, 2.5 and 5.0 mg/animal/day in a volume of 25 uL by the intranasal route of administration. The highest dose was the maximum feasible dose based on drug solubility and volume of administration. Vehicle was 2.5% glycerin in sterile water. There was no treatment effect on survival, body weight or food consumption. The primary cause of death was attributed to pituitary tumors in both control and drug-treated male and female rats. There were no statistically significant treatment-related tumor findings. The only tumor that had a noticeable numerically increased incidence in the high group was uterine polyps in the high-dose females when compared to control females. The systemic exposure was very variable with the high-dose resulting in systemic Cmax 2 – 3 fold higher than systemic exposures with the human therapeutic dose in men.

Mouse carcinogenicity study: In this study four groups having 60 B6C3F1 CRL:BR mice/sex/group were administered dose levels of 0, 3, 9, and 15 mg/kg/day by the subcutaneous route of administration. Vehicle was 2.5% glycerin in sterile water. An additional 18 mice/sex/group were used for TK evaluation. The highest dose was the maximum tolerated dose and resulted in 75 to 100 fold higher systemic exposures when compared to systemic exposures in men at the proposed human therapeutic dose. Exposures were less variable by the SC route compared to the intranasal route of

administration. Treatment did not affect mortality, body weight, or food consumption. There were no statistically significant macroscopic findings. In male mice, the penis was extended in one control and 7 high-dose animals, respectively. There were no significant treatment-related neoplastic or non-neoplastic findings.

Executive CAC Recommendations and Conclusions

For the rat study

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee notes that for statistically significant or otherwise remarkable findings in the high-dose group, the sponsor should have looked at the affected tissues in all of the dosed groups.

- The Committee concurred that there were no drug-related neoplasms.

For mouse study

- The Committee concurred that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug –related neoplasms.

David Jocobson-Kram, Ph.D
Chair, Executive CAC

cc:\
/Division File, Division of Bone, Reproductive & Urologic Products
/Lynnda Reid, Supervisor , Division of Bone, Reproductive & Urologic Products
/Krishan L. Raheja, Division of Bone, reproductive & Urologic Products.
/Freshnie Deguia, Division of Bone, Reproductive & Urologic Products
Adele Seifried, OND IO

Immunogenicity Review Memo for IND Submissions

IND number:	64119
Serial:	0129 (eCTD sequence number)
CDER Receipt Date:	8/17/2017
From:	Susan Kirshner
Product:	Bremelanotide
Indication:	Hypoactive Sexual Desire Disorder in Premenopausal Women
Route of Administration:	s.c.
Dose Regimen:	As desired
Sponsor:	Palatin
Clinical Division:	Division of Bone, Reproductive, and Urologic Products
IND Phase:	Pre-NDA
Review Date:	10/13/2017

Recommendation:
The Sponsor should provide an immunogenicity risk assessment for the product. The assessment should include analysis of the likelihood that the product is immunogenic supported by data from assessments such as in silico and, if indicated from the in silico results, in vitro assessments.

Comment to the Sponsor:
In your NDA submission you should provide a risk assessment of the immunogenicity of bremelanotide because peptides as short as 7 – 8 amino acids can be immunogenic. Bremalanotide shares sequence homology with the endogenous human peptide hormone alfa-melanocyte-stimulating hormone (α-MSH). Therefore, there is a risk that anti-bremalanotide antibodies could cross-react with and inhibit the function of α-MSH. In your NDA submission provide an assessment of the risk that anti-bremalanotide antibodies will form in treated subjects and the potential impacts of anti-bremalanotide antibodies on product safety and efficacy. Support your risk assessment with in silico and, if indicated by the in silico results, in vitro data.

Review:
OBP was consulted on the need for immunogenicity data in an NDA for bremalanotide to treat hypoactive sexual desire disorder. Bremalanotide is a heptomeric analog of the tridecapeptide hormone α-MSH and shares sequence homology of 4 amino acids.

Bremalanotide: Ac – Nle – cyclo (Asp – His – [^{14}C]D-Phe – Arg – Trp – Lys – OH) [Sequence from Sponsor's IND]
α-MSH: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 [Sawyer TK et al. 1989. Peptides, Vol 11:351 – 357]

α-MSH is involved in melanogenesis, feeding, energy homeostasis, sexual activity, and ischemia protection. Because peptides as short as 7 – 8 amino acids can induce immune responses and because bremalanotide is not a native human sequence is it likely that anti-drug antibodies may develop to

this product. Over 50% of bremalanotide sequence is shared with endogenous α-MSH, therefore there is some risk that anti-bremalanotide antibodies may cross-react with human α-MSH. Due to the late stage of development for this product it seems most reasonable to ask the sponsor to provide a risk assessment supported by in silico and, if indicated by the in silico results, in vitro data in their NDA. The need for additional immunogenicity data may be evaluated during review of an NDA. OBP recommends that assessment of bremalanotide immunogenicity be incorporated into future clinical trials.

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/s/

SUSAN L KIRSHNER
11/09/2017

16 pages of CSS review after this page is withheld to avoid duplication. The same CSS review is included in the OtherR

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/s/

LESLIE C MCKINNEY
04/09/2019 11:45:23 AM

MUKESH SUMMAN
04/09/2019 12:10:37 PM
Nonclinical recommends AP

Memorandum

To:

NDA#	DARRTS SDN	EDR#	Document Type	Letter Date	Received Date
210557	44	0044	Protocol Amendment V4.0	1-31-19	1-31-19

Through: Christina Chang, M.D., M.P.H., Team Leader, DBRUP

From: Marcea Whitaker, M.D., Medical Officer, DBRUP

Date: **February 1, 2019**

Re: **Bremelanotide for HSDD**
Ambulatory Blood Pressure Monitoring Study

Sponsor: **AMAG**

Background: Bremelanotide (BMT) is a synthetic melanocortin agonist being developed as an as-needed (potentially daily) treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. NDA 210557 was submitted on March 23, 2018, with an original PDUFA goal date of March 23, 2019. The goal date was extended to June 23, 2019 based on the need for an ambulatory blood pressure monitoring (ABPM) study pre-approval.

The Applicant submitted the initial ABPM study protocol AMAG-BMT-HSDD-101 on November 20, 2018, entitled, "An Open-Label Bremelanotide (BMT) Treatment Period Followed by a Placebo-controlled, Double-blind, Parallel Arm Randomized Withdrawal Study to Evaluate the Effects of Daily Dosing of BMT on Blood Pressure in Premenopausal Females. Amendments to the protocol were submitted on January 10, 2019, and January 25, 2019 for versions 2.0 and 3.0, respectively.

Current submission:
The sponsor now submits Amendment 3 for version 4.0 (dated January 28, 2019).

The major changes to the protocol include:

- Change in enrollment target: Increase the total number of subjects to be enrolled (sample size) from 140 to up to 150. The targeted number of controlled hypertensive subjects was increased to 30 subjects although the percentage of total subjects (up to 20%) was unchanged. The targeted number of completers through Day 8 was updated to be approximately 127 subjects (total of healthy and controlled hypertensives). The discontinuation rate was revised from 9% to

approximately 15%. This change was made in order to permit greater flexibility in the enrollment of study subjects.

- Hypertensive Status: the definition of controlled hypertension was modified to permit use of to 3 anti-hypertension medications based on the 8th Joint National Committee treatment guidelines.
- Other minor changes added clarity or correct errors
    - Clarification language has been added to specify entry criteria (Inclusion #5 and Exclusion #1)
    - Corrections to minor errors/consistency in
        - Start time for ABPM (approximately 1 hour prior to dosing)
        - Timing of clinical laboratory assessments and drug screening conducted as part of study entry criteria (corrected to Day -2)
        - Timing of physical examinations (corrected to Screening & Day 17/EOS throughout protocol)

Reviewer's comment: The changes are acceptable.

Recommended regulatory action: None.

Marcea B. Whitaker, M.D.
Medical Officer
Division of Bone, Reproductive and Urologic Products

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/s/

MARCEA B WHITAKER
02/04/2019 05:19:32 PM

CHRISTINA Y CHANG
02/04/2019 05:56:23 PM

Memorandum

To:

NDA	DARRTS SDN	EDR#	Document Type	Letter Date	Received Date
210557	43	0043	Protocol Amendment v3.0; SAP v3.0	1-25-19	1-25-19

Through: Christina Chang, M.D., M.P.H., Team Leader, DBRUP

From: Marcea Whitaker, M.D., Medical Officer, DBRUP

Date: **January 27, 2019**

Re: **bremelanotide for HSDD**

Sponsor: **AMAG**

Background: Bremelanotide (BMT) is a synthetic melanocortin agonist being developed as an as-needed (potentially daily) treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. NDA 210557 was submitted on March 23, 2018, with an original PDUFA goal date of March 23, 2019. The goal date was extended to June 23, 2019 based on the need for an ambulatory blood pressure monitoring (ABPM) study pre-approval.

The Applicant submitted the initial ABPM study protocol AMAG-BMT-HSDD-101 on November 20, 2018. Following review of version 2.0, the Division sent two information requests, dated January 14 and 17, 2019.

Current submission:
In response to the Information requests, the Applicant has submitted an amended version of the protocol entitled "An Open-Label Bremelanotide (BMT) Treatment Period Followed by a Placebo-Controlled, Double-Blind, Parallel Line Randomized Withdrawal Study to Evaluate the Effects of Daily Dosing of BMT on Blood Pressure in Premenopausal Females." The current submission includes a revised protocol version 3.0 and the current statistical analysis plan.

The sponsor agrees to:

1. Prohibit NSAIDs throughout the duration of the study.
2. Provide changes from baseline with 95% confidence intervals for SBP, DBP, mean arterial pressure (MAP), and heart rate (HR) for each time point for all 24 hours of ABPM monitoring periods from the open-label and randomized withdrawal periods of study.

3. Use the upper bound of a two-sided 95% confidence interval to rule out a 4 mmHg increase in daytime SBP.

Conclusion: The sponsor has agreed to all Division requests and all changes are acceptable. No further comments are required.

Marcea B. Whitaker, M.D.
Medical Officer
Division of Bone, Reproductive and Urologic Products

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/s/

MARCEA B WHITAKER
01/28/2019 12:50:33 PM

CHRISTINA Y CHANG
01/28/2019 12:52:37 PM

Division of Bone, Reproductive, and Urologic Products (DBRUP)
Clinical Review

NDA 210557 SD 37 11/20/18
AMAG Pharmaceuticals, Inc.
Bremelanotide subcutaneous injection for hypoactive sexual desire disorder
Protocol AMAG-BMT-HSDD-101 version 1.0 dated 11/16/2018

Introduction and Background:

Bremelanotide (BMT) is a synthetic melanocortin agonist being developed as an as-needed (potentially daily) treatment for hypoactive sexual desire disorder (HSDD) in premenopausal women. NDA 210557 was submitted on March 23, 2018, with a PDUFA goal date of March 23, 2019. Review of information in the associated IND (64119) by DBRUP and the Division of Cardiovascular and Renal Products (DCRP) identified increases in systolic and diastolic blood pressures (BPs) with repeat doses of BMT (approximately 4 mmHg, with effect lasting at least four hours). Given the relationship between elevations in BP and adverse cardiovascular (CV) outcomes, there is concern that BMT use may increase the risk of CV events in women, if it is approved. DBRUP recommended that an ambulatory blood pressure monitoring (ABPM) study be conducted to characterize the extent and duration of the BP elevations in March 2017[1] and again at the pre-NDA meeting.[2]

DBRUP and DCRP's review of data included in the application has confirmed BP elevations associated with BMT use. In a teleconference on November 7, 2018, the applicant was notified that an ABPM study is necessary to demonstrate the benefit of BMT can outweigh the risks. The Applicant submitted an ABPM study protocol on November 20, 2018, for FDA comment, aiming to initiate the study as soon as feasible. On December 13, 2018, the review clock was extended by three months to yield a new PDUFA goal date of June 23, 2019.

DCRP, the clinical pharmacology review team and the biostatistics review team are also reviewing the protocol.

Protocol Review:

1. **Title:** An Open-Label Bremelanotide (BMT) Treatment Period Followed by a Placebo-controlled, Double-blind, Parallel Arm Randomized Withdrawal Study to Evaluate the Effects of Daily Dosing of BMT on Blood Pressure in Premenopausal Females

2. **Design:** This is a Phase 1, two-center, single-blind, open-label, single-arm study to evaluate daily administration of BMT 1.75 mg SC for 8 days, followed by randomized (1:1), placebo-controlled withdrawal, stratified by hypertensive status for an additional 8 days. Ambulatory blood pressure monitoring (24 hour) will be conducted on Day -1 (following placebo injection to provide time-matched baseline reading), Day 8 and Day 16. At least 20% of the subjects are to have controlled hypertension (defined as having ≤ 2 antihypertensive

[1] Advice letter dated March 3, 2017, recommending an ABPM study.
[2] Pre-NDA meeting held on September 18, 2017; final meeting minutes dated October 17, 2017.

medications). BMI 18-35 kg/m^2. A total of 80 premenopausal women aged 18-55 years will be enrolled for the open-label phase of the study to ensure at least 30 completers per group in the second, randomized withdrawal phase of the study.

3. **Objectives**:

Primary: To investigate the magnitude and duration of effect of blood pressure (BP) and heart rate (HR) changes using 24-hour ambulatory blood pressure monitoring (ABPM) following repeated daily administration of BMT in premenopausal female subjects.

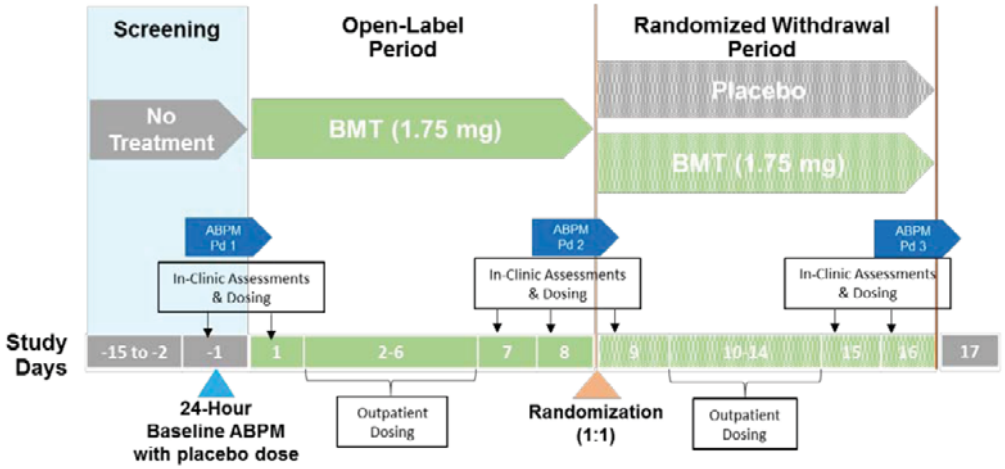
Secondary:

- To investigate the persistence or withdrawal of BP and HR effects following the administration of daily doses of BMT compared to placebo in premenopausal female subjects.
- To evaluate the overall safety and tolerability of BMT after sequential, daily doses in premenopausal female subjects.

Exploratory objective: Assess the pharmacokinetic (PK) results from the end of the Open-Label period and the Double-Blind Randomized treatment period relative to the time-matched changes in BP.

4. **Study Design and Conduct:** Following the screening period, subjects will be confined for 2 hours on Days 1, 8 and 16. Subjects will be instructed on how to use the autoinjector on Day -1. Subjects will self-administer the first dose of single-blind placebo as well as subsequent clinic doses of BMT under staff supervision between 07:00 and 10:00 (Day 1; Days 8 and 16, respectively). All other doses will be self-administered at home between 07:00 and 10:00. Subjects will complete a dosing diary each day (including date, time, and injection site location [abdomen or thigh]). Subjects also return to the clinic on Days 7 and 15, one day prior to ABPM, for supervised study drug administration.

Figure 1 Study Schematic



Abbreviations: ABPM=ambulatory blood pressure monitoring; BMT=bremelanotide.

Screening includes medical history, 12-lead ECG, physical exam, vital signs, serology, clinical laboratory testing, urine screen (drugs, cotinine, alcohol), and serum pregnancy test.

Diet/Activity: Subjects are to refrain from strenuous activity during the study. Subjects are to continue their normal diet with no changes within 14 days of study participation. No over-the-counter (OTC)/nutritional/dietary supplements are allowed within 7 days of the first dose of study drug; no prescription medications are allowed within 14 days prior to first study drug except anti-hypertensives and anti-glycemics for maintenance therapy. No tobacco or nicotine containing products or alcohol are allowed during ABPM periods. Other exclusions include: no blood donations within 3 months, no illicit drugs within 12 months, and no testosterone within 6 months (for implant or injection) or 7 days (for oral). Additional exclusions include CNS active drugs (3 months), MAOIs/immunizations, etc. (for at least 30 days).

Reviewer's comment: There is no mention of whether sexual activity is permissible during the ABPM days.

Pharmacokinetics/pharmacodynamics (PK/PD): PK parameters include Cmax, Tmax, terminal rate constant, half-life, AUC_{last}, AUC_{inf}, AUC_{Extrap}, C_{last}, and T_{last}. PK blood samples will be drawn (on Days 8 and 16) at 0.5-hour pre-dose and 0.5, 1.0, 1.5, 2.0 hours post-dose. A back up PK sample will also be collected. On PK blood draw days, breakfast will given at least 1 hour prior to dosing.

The Applicant also submitted a PK simulation study report, using clinical data from Study PT-141-56, a Phase 1 PK study in 36 healthy premenopausal women to evaluate safety and bioavailability of BMT 1.75 mg injection.[3] In Study 56, subjects received up to three doses of 1.75 mg BMT, with the washout period of 48 hours between doses. Based on a simulation of multiple-dose BMT plasma concentration-vs-time curves, the sponsor predicts minimal BMT accumulation for the 1.75 mg daily subcutaneous dosing regimen (given the short half-life of BMT [2.7 hours ± 0.56 hours (mean ± standard deviation)]. The simulation study examined several parameters, including Cmax, AUCs, and accumulation index); the results indicated that the mean accumulation would be less than 1%. The Applicant concludes that the predicted BMT plasma concentrations for Day 8 would be the same as those predicted for Day 16.

The PD effect (blood pressure) peaks within 4 hours after dosing and returns to baseline approximately 8-12 hours following dosing.

Blood pressure measurement:
Manual BPs will be obtained on Days 1, 8, 16, as shown in Table below.

[3] Study report for Study PT-141-56 was included in the original NDA submission.

Table 1. Schedule of Vital Signs Measurements (During Clinic Confinement Only)

Time point	Blood pressure mmHg	Pulse Beats/min	Temperature °C	Respiration rate Breaths/min	Pulse oximetry (SpO_2) %
Screening	X	X	X	X	X
0.5 hours pre-dose	X	X			
0.5 hours post-dose	X	X			
1.0 hours post-dose	X	X			
1.5 hours post-dose	X	X			
2.0 hours post-dose	X	X	X	X	

Source: Table 4, page 33 of 54 in the protocol.

ABPM will be conducted by a central core laboratory. The manual for ABPM equipment and settings is separate from the protocol. All ABPMs will start 1 hour prior to dosing. The final ABPM will complete 2 hours after Day 17 dose (26 hours and will allow documentation of 2 consecutive doses of BMT.

Reviewer's comment: The Applicant did not provide documentation detailing the ABPM equipment and settings.

5. Safety:

Subjects will be monitored for any AEs from the first dose through the end of the study.

Subjects will be instructed not to dose more than once per 24-hour period. Unblinding will be allowed in an emergency or if expedited reporting is required. Subjects should bring all used/unused autoinjectors to the clinic on Day 7 and Day 15, respectively, for drug accountability. Separate sets of kits will be dispensed for the open-label phase and the randomized withdrawal phase. End of study procedures include physical exam, ECG, clinical laboratory tests, and serum pregnancy.

6. Endpoints

Primary Endpoint: Change from baseline in 24-hour BP and heart rate following 8 days of BMT treatment during the open-label period.

Secondary Endpoints:

- Change from baseline in 24-hour BP and heart rate following 8 days of study drug treatment with BMT compared to placebo during the double-blind (randomized withdrawal) period.
- Adverse events, including SAEs, ECG, and clinical laboratory tests

7. Inclusion/Exclusion criteria

Inclusion criteria

All volunteers must satisfy the following criteria for study participation:

1. Has provided written informed consent prior to the start of any study-specific procedures.

2. Is female, 18 to 55 years of age (inclusive), and premenopausal as defined by the modified STRAW criteria (specifically, Stage -5 [menses variable to regular] through Stage -1 [≥ 2 skipped cycles and an interval of amenorrhea ≥ 60 days]. Postmenopausal females, designated by having amenorrhea for ≥ 12 months, are not eligible for this study.
3. Is neither pregnant nor breastfeeding at Screening.
4. Has a body mass index (BMI) between 18 and 35 kg/m2 (inclusive) and weighs at least 50 kg.
5. Be in good general health and free from clinically significant medical or psychiatric illness or disease (as determined by medical/surgical history, physical examination, weight, 12-lead ECG, and clinical laboratory tests).
6. Has vital signs at screening within the following ranges (measured in a sitting position after at least 5 minutes of rest):
   - SBP ≥90 and ≤140 mmHg,
   - DBP ≥50 and ≤90 mmHg, and
   - HR ≥40 and ≤100 beats per minute (bpm).

   (Note: If vital signs are out of range, the Investigator may obtain one additional reading, within 1 hour.)
7. Has a 12-lead ECG consistent with normal cardiac conduction and function at Screening, including: pulse rate between 45 and 100 bpm, QTcF interval ≤450 ms, QRS interval <120 ms, PR interval <220 ms, and morphology consistent with healthy cardiac conduction and function
8. Has clinical chemistry, hematology, and complete urinalysis (fasted for at least 10 hours) results at Screening and Day –1 within the reference range for the testing laboratory unless the out-of-range results are deemed not clinically significant by the Investigator.
9. Has a negative urine drug screen result at Screening and on Day –1.
10. Must be using acceptable contraception or be surgically sterile [i.e. had a bilateral tubal ligation or hysterectomy at least 6 months prior to the first dose of study medication]. All contraception should have had stable, continuous use for at least the past 3 months.
11. Is willing and able to remain in the study unit as required and return for outpatient visits as scheduled including any necessary repeat analyses.

Exclusion criteria

1. Has a history of or current clinically significant medical illness including (but not limited to) pulmonary, cardiovascular [stable controlled hypertension is not excluded], coagulation disorders, gastrointestinal, immunologic, endocrine [stable thyroid hormone replacement therapy as well as moderately controlled diabetes defined as HbA1c <8% are not excluded], neurologic, psychiatric, or thromboembolic disease, metabolic disturbances, or any other current physical condition that the Investigator considers should exclude the participant, or that could interfere with the interpretation of the study results.
2. Has any clinically significant medical condition, physical examination finding, ECG abnormality, or clinically significant abnormal value for hematology, serology, clinical chemistry, or urinalysis at Screening or at admission to the study center, as deemed appropriate by the Investigator.

3. Has any of the following (subject may rescreen once for failure to meet criteria at initial Screening):
    a. History or current diagnosis of uncontrolled hypertension defined as:
        i. Two sequential assessments (approximately 4 minutes apart and no more than 15 minutes apart, after being seated quietly for at least 5 minutes prior to the first reading) at levels above 140 mmHg SBP or 90 mmHg DBP. Subjects who meet either of these criteria at two separate visits at least 24 hours apart will be excluded from study participation and advised to consult their primary care physician for follow-up.
        ii. Treatment for hypertension that has been changed at least once in the 4 weeks before Screening.
4. If diagnosed with diabetes, does not meet criteria for moderately controlled glycemia (HbA1c ≤8.0%).
5. History or presence of malignancy within the past 5 years, with the exception of adequately treated localized skin cancer (basal cell or squamous cell carcinoma), which is allowed.
6. Currently suffers from clinically significant systemic allergic disease, or has a history of significant drug allergies, including, but not limited to the following:
    a. A history of anaphylactic reaction
    b. Allergic reaction due to any drug that led to significant morbidity
    c. Known hypersensitivity to any component of the formulation of BMT
7. Has donated blood or had an acute loss of blood (>500 mL) during the 3 months before study drug administration, or intends to donate blood or blood products within 3 months after the completion of the study.
8. Has had an acute, clinically significant illness within 30 days prior to Day 1, or has had a recent febrile illness with an abnormal body temperature for at least 72 hours before dosing on Day 1.
9. Has a history (within the past 12 months before Screening) of drug abuse (defined as any illicit drug use), a history of alcohol abuse (defined as alcohol consumption exceeding 14 units per week), a positive test for drugs of abuse at Screening or upon admittance to the testing facility (Day -1), or is unwilling to abstain from alcohol and drugs of abuse throughout the study.
10. Has ever received BMT in a previous clinical study or has used any investigational compound and/or an experimental medical device within 3 months before study drug administration.
11. Intends to become pregnant before, during, or within 3 months after receiving the last dose of study drug, or intends to donate ova during such time period.
12. Has inadequate venous access for the required blood draws for the study.
13. Is unable to meet or perform study requirements (eg, collection of urine due to urinary incontinence) or has a known or suspected inability to comply with the study protocol.
14. Is an immediate family member of the Investigator or an employee of the study center with direct involvement in the proposed study or other studies under the direction of the Investigator or study center, is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling), or is another person who may consent under duress.

15. Is unwilling or too anxious to receive and self-administer the study SC injections, at the Investigator's discretion.

8. **Statistical considerations:** The protocol mentions a separate statistical analysis plan (SAP) that would include PK analysis details. The SAP was not included in the submission.

DCARP comments (preliminary):

1) We are in agreement with what the sponsor proposes in this comprehensive protocol.
2) We defer to Clinical Pharmacology Division on whether the sponsor has characterized the PK/PD of bremelanotide appropriately, and to confirm that there is essentially no accumulation.
3) Regarding the to-be-enrolled population, we note that at least 20% of subjects that will have controlled hypertension, and diabetics are now allowed in the trial. However, this remains a relatively low risk population. It will be important that the enrolled population reflect the overall CV risk of the to-be-marketed-to population.

Clinical pharmacology team comments (preliminary):

1) The overall study design is acceptable. PK sampling scheme in the protocol seems appropriate. We do not expect any PK accumulation of BMT upon once daily dosing. Nonetheless, current PK sampling scheme allows us to catch some signals if there is any BMT accumulation.
2) Simulation of BMT PK in the clinical-info-amendment is also reasonable.

Conclusion and Recommendations:

The proposed protocol appears adequate. We believe the sponsor has enrolled a population that is consistent with HSDD, which are generally healthy subjects. If approved, BMT will be used in higher risk subjects, including such subjects in the current protocol; however, findings from this study may not answer the long-term CV risk question in the higher-risk subjects.

1. Clarify if sexual activity is permitted on ABPM days. We recommend that subjects abstain from sexual activity (as they would be with other strenuous activities) during the study period.
2. Consider extending the Day 16 ABPM two additional hours to better cover the pharmacodynamic (PD) window for blood pressure effects.
3. Provide the Statistical Analysis Plan for FDA review.

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/s/

MARCEA B WHITAKER
12/21/2018

CHRISTINA Y CHANG
12/21/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	210557
Drug Name:	Bremelanotide
Indication:	Treatment of hypoactive sexual desire disorder (HSDD)
Study number:	BMT-117
Applicant:	Palatin Technologies, Inc.
Date(s):	Consult received date: May 3, 2018 Completion date: Aug 27, 2018
Review Priority:	Standard
Biometrics Division:	DBVI
Statistical Reviewer:	Anna Sun, Ph.D., Mathematical Statistician, OB/DBVI
Concurring Reviewers:	Qianyu Dang, Ph.D., Lead Mathematical Statistician, OB/DBVI Yi Tsong, Ph.D., Division Director, OB/DBVI
Medical Division:	Control Substance Staff
The CSS Team:	Katherine Bonson, Ph.D., Pharmacologist, CDER/OCD/CSS
Project Manager:	Sandra Saltz, Project Manager, CSS

Keywords: *Crossover design, Drug abuse potential study, Self-reported endpoint, Multiple endpoints*

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1. Executive Summary

Study BMT-117 was a randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of BMT administered by subcutaneous (SC) injection, compared to phentermine PO (by mouth) and placebo in nondependent, recreational stimulant users.

The primary objective of this trial was to evaluate the abuse potential of single subcutaneous (SC) doses of bremelanotide (BMT) compared to phentermine and placebo in healthy, recreational stimulant users.

The Maximum effect (Emax) on the bipolar Drug Liking visual analog scale (VAS) was the primary pharmacodynamic endpoint.

The treatment comparisons to assess the abuse potential of BMT included the following:

- Each dose of phentermine versus placebo (study validity)
- Each dose of BMT versus placebo (absolute abuse potential)
- Each dose of BMT versus each dose of phentermine (relative abuse potential)

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Good Effects, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The mean difference was statistically significant for the comparisons between Phentermine 90 mg and placebo (P-value=0.0227). For the Phentermine 45 mg compared with placebo, the mean difference in Emax was not statistically significant (P-value=0.1556), however, the study was designed and conducted based on the recommendations in the draft guidance on the Assessment of Abuse Potential of Drugs (Jan 2010), thus, the study was not powered with an adequate sample size to perform this post-hoc analysis, which should be considered in the interpretation of this result.

- For the relative abuse potential tests: All 3 BMT doses were associated with significantly lower effects than the positive controls on the primary endpoint and secondary endpoints of Good Effects, Take Drug Again and Overall Drug Liking (P value <0.01), indicating that subjects liked the positive controls significantly more than BMT.

- For the absolute abuse potential test: For the primary PD endpoint Drug Liking, all 3 BMT doses versus placebo were statistically significant (P value<0.01), the results showed that all 3 BMT doses were similar to placebo. For the secondary endpoints, except for Good Effect VAS, all 3 BMT doses versus placebo were statistically significant (P value<0.01), showing that all 3 BMT doses were similar to placebo.
  Overall, BMT produced abuse-related responses that were not significantly different than placebo.

2. Review Report on Study BMT-117

2.1 Introduction

Abnormalities of female sexual function are relatively common, reported to occur in up to 40% of American females. Subjects may experience difficulties with sexual desire, sexual arousal, dyspareunia (pain during intercourse), or difficulty achieving orgasm. These disorders are commonly characterized by the general term "female sexual dysfunction" (FSD).

Abnormalities of female sexual desire or arousal, occurring as an acquired condition reflecting loss of prior usual function, not associated with depression or relationship dysfunction and accompanied by distress have been characterized as hypoactive sexual desire disorder (HSDD) and female sexual arousal disorder (FSAD). The present BMT development program focuses on premenopausal females with HSDD with or without arousal difficulties.

Bremelanotide (BMT) is a cyclic heptapeptide melanocortin analog that is being developed for the treatment of HSDD. Results from primary activity studies showed BMT to be a high-affinity ligand and agonist for melanocortin receptors (MCR), including MC1R, MC3R, and MC4R.

Bremelanotide is a new molecular entity (NME) that demonstrates central nervous system (CNS) effects. Thus far in the clinical development of BMT, there has been little to no evidence to suggest abuse potential or stimulant-like activity in humans (ie, few if any reports of potential abuse- or stimulant-related adverse events (AEs) such as euphoric mood, psychomotor hyperactivity, feeling jittery, etc). This study of the abuse potential of BMT was conducted to fulfill a requirement of the US Food and Drug Administration (FDA) guidance, related to the assessment of potential abuse of a new drug, including NMEs, that affect the CNS.

2.1.1 Objectives of the study

The primary objective of this trial was to evaluate the abuse potential of single subcutaneous (SC) doses of bremelanotide (BMT) compared to phentermine and placebo in healthy, recreational stimulant users.

The secondary objectives of the trial were:

- To evaluate the safety and tolerability of SC dosed BMT in healthy, recreational stimulant users.

- To evaluate the pharmacokinetics (PK) of SC dosed BMT in healthy, recreational stimulant users.

2.1.2 Study design

The design was a randomized, double-blind, placebo- and active-controlled crossover study to evaluate the abuse potential of BMT administered by subcutaneous (SC) injection, compared to phentermine PO (by mouth) and placebo in nondependent, recreational stimulant users. Subjects participated in an outpatient medical Screening Phase (Visit 1); inpatient Qualification Phase (Visit 2); inpatient, 6-period Treatment Phase (Visits 3 to 8); and an outpatient safety Follow-up Phase (Visit 9).

Within 28 days after the Screening Visit, eligible subjects were admitted to the clinical research unit (CRU) on the day prior to dosing (Day –1) in the Qualification Phase. The Qualification Phase comprised a Drug Discrimination Test, in which subjects received phentermine 60 mg or matching placebo in a randomized, double-blind, crossover manner on Day 1 and Day 3, with each drug administration separated by approximately 48 hours. Pharmacodynamic (PD) assessments were performed to evaluate whether subjects could discriminate between phentermine and placebo, show positive subjective effects of phentermine, and safely tolerate phentermine.

Subjects who passed the Drug Discrimination Test were eligible for the Treatment Phase. The washout period between the last study drug administration in the Qualification Phase and the first study drug administration in the Treatment Phase was a minimum of 96 hours (± 4 hours) and a maximum of 30 days. The washout period between each treatment period in the Treatment Phase was a minimum of 5 days.

The Treatment Phase consisted of 6 treatment periods with drug administration on Day 1 of each period. Prior to first dosing in the Treatment Phase, subjects were randomized into 1 of 6 treatment sequences according to a 6×6 Williams square.

For Treatment Period 1, subjects remained in the CRU until approximately 24 hours post-dose (Day 2). There was a minimum 92-hour washout period and a maximum of 30 days between the last drug administration in the Qualification Phase and the first drug administration in the Treatment Phase. For Treatment Periods 2 to 6, subjects were admitted to the CRU on the day prior to drug administration (Day -1) and remained resident until approximately 24 hours post-dose (Day 2). Subjects could be required to remain in the clinic longer at the discretion of the Investigator.

Subjects received a single dose of the following 6 treatments, administered via SC injection in the abdomen (BMT, placebo) and by PO (phentermine and placebo), in a randomized, double-blind, double-dummy, crossover manner following an overnight fast:

Treatment A: BMT 1.75 mg (1 active SC injection + 2 placebo SC injections + 3 placebo PO capsules)

Treatment B: BMT 3.5 mg (2 active SC injections + 1 placebo SC injection + 3 placebo PO capsules)

Treatment C: BMT 5.25 mg (3 active SC injections + 3 placebo PO capsules)

Treatment D: Phentermine 45 mg (3 placebo SC injections + 3 × 15 mg phentermine PO capsules)

Treatment E: Phentermine 90 mg (3 placebo SC injections + 3 × 30 mg phentermine PO capsules)

Treatment F: Placebo (3 placebo SC injections + 3 placebo PO capsules)

Following the washout period after the final treatment period subjects were discharged from the CRU after laboratory assessments (hematology, chemistry, coagulation) urinalysis, and electrocardiogram [ECG]). Subjects returned for a Follow-up Visit within 3 to 7 days after discharge from the final treatment period and underwent final assessments.

Pharmacodynamic Endpoints:

The Maximum effect (Emax) on the bipolar Drug Liking visual analog scale (VAS) was the primary pharmacodynamic endpoint.

The secondary pharmacodynamic endpoints were as follows:

Drug Liking VAS: maximum effect at any dose (EmaxD), minimum effect (Emin), and time-averaged area under the effect curve to 24 hours postdose (TA_AUE); Overall Drug Liking VAS: Emax/Emin; Take Drug Again VAS: Emax; Good, Bad, and Any Effects VAS, Alertness/Drowsiness VAS, and Agitation/Relaxation VAS: Emax and TA_AUE for all; Drug Similarity VAS: score at 12 hours post-dose.

2.1.3 Number of subjects:

Up to 50 healthy male and female nondependent, nontreatment-seeking, recreational stimulant users were planned to be included in the study to ensure that a minimum of 30 subjects, approximately 50% of whom were female, would complete the planned treatments.

2.1.4 Pharmacodynamic Statistical Methodology used in Sponsor's analyses

Pharmacodynamic values at each time point were summarized by treatment using descriptive statistics and presented graphically. A mixed effects model for a crossover study was used to compare PD endpoints (eg, Emax, Emin, TA_AUE) between treatments. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, and subject nested within treatment sequence as random effect. Baseline (predose) measurement was included as a covariate, where applicable. If the carryover effect was found to be non-significant at the 25% level, then the term was dropped from the model. The residuals from the mixed effects model were investigated for normality using the Shapiro Wilk W-test.

If the probability value was $\geqslant 0.01$ and the residuals appear relatively unskewed and moderately symmetric, all PD parameters were analyzed as having a normal distribution and the results of the mixed effects model was reported. LS means, the difference between the means, and corresponding 95% confidence intervals (CIs) were provided for the treatment comparisons. No adjustments were made for multiplicity.

If the probability value was < 0.01 or the residuals appear to be severely non-normal in distribution, then the paired differences between treatments was graphically assessed for normality. If the distribution of the paired differences appears to be relatively unskewed and moderately symmetric, then parameters were analyzed using paired t-tests. Means, the difference between the means, and corresponding 95% CIs will be provided for the treatment comparisons. No adjustments will be made for multiplicity. If the probability value is < 0.01 or the residuals appear to be severely non-normal in distribution and the paired differences between treatments do not graphically appear to follow a normal distribution, then parameters were analyzed non-parametrically using Friedman's test (with subject as a stratification variable) for the overall treatment effect and the differences between treatments were compared using Wilcoxon signed-rank tests. Medians, the difference between the medians, and corresponding p-values were provided for the treatment comparisons. No adjustments were made for multiplicity.

Analyses comparing Drug Liking VAS EmaxD for phentermine versus placebo, BMT versus. placebo, and BMT versus phentermine was performed using the Completer population. A similar SAS mixed effects linear model procedure was used to construct ANOVA models. The model included terms for treatment, period, and sequence as fixed effects, and subject nested within sequence as a random effect. LS means, the difference between the means, and corresponding 95% CIs were provided for the study drug comparisons. The treatment comparisons to assess the abuse potential of BMT included the following:

- Each dose of phentermine versus placebo (study validity)
- Each dose of BMT versus placebo (absolute abuse potential)
- Each dose of BMT versus each dose of phentermine (relative abuse potential)

2.1.5 Sponsor's Pharmacodynamic Conclusions

- No human abuse potential of BMT was demonstrated in this study of recreational drug users at doses up to 3 multiples higher than the therapeutic dose of BMT 1.75 mg.
- Phentermine was demonstrated to be significantly different than placebo for drug liking, establishing the validity of the positive control.
- For Drug Liking Emax, BMT resulted in clinically meaningful reductions in abuse related responses that were statistically significantly smaller than phentermine.
- For Drug Liking Emax, BMT produced abuse-related responses that were not significantly different than placebo.
- Three euphoria-like events were reported with the use of BMT, but were not considered to be a signal of abuse potential as the euphoria was not experienced with all BMT dose levels by these subjects or consistently associated with the highest dose used by any of the subjects.
- A dose proportionality in serum concentration profile was seen and confirmed appropriate exposure with 3.5 and 5.25 mg BMT to assess abuse potential for subjects (recreational drug users) in this study.

2.2 Data Location

The analysis datasets are located at

\\CDSESUB1\evsprod\NDA210557\0011\m5\datasets\bmt-117\analysis\adam\datasets

2.3 Reviewer's Assessment

All analyses were conducted from the stand point of the pharmacodynamics analysis.

2.3.1 Descriptive Statistics

The descriptive statistics of E_{max} for the primary PD endpoint Drug Liking, and secondary PD endpoints: Good Effects, Overall Drug Liking and Take Drug Again are provided in Table 1. E_{max}

is calculated as the maximum effect in the first 24 hours in the review's analysis. Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q1), median, the third quartile (Q3), and maximum of E_{max} for the six treatments in the study.

Table 1. E_{max} Descriptive Statistics for Drug Liking, Good Effects, Overall Drug Liking and Take Drug Again, PD population (N=36)

Parameter	Treatment	Mean	Std Dev	Min	Q1	Median	Q3	Max
Drug Liking	A: BMT 1.75 mg	53.81	6.09	50.00	50.00	50.00	57.00	69.00
	B: BMT 3.5 mg	56.06	8.37	50.00	50.00	51.00	62.00	79.00
	C: BMT 5.25 mg	54.67	8.42	50.00	50.00	50.00	54.50	77.00
	D: Phentermine 45 mg	71.33	14.35	50.00	60.00	69.00	82.50	100.00
	E: Phentermine 90 mg	73.78	16.09	41.00	64.00	71.00	86.00	100.00
	F: Placebo	53.81	8.53	50.00	50.00	50.00	51.00	89.00
Good Effects	A: BMT 1.75 mg	11.56	16.65	0.00	0.00	2.50	21.50	67.00
	B: BMT 3.5 mg	19.25	24.76	0.00	0.00	12.00	28.00	100.00
	C: BMT 5.25 mg	20.81	24.81	0.00	0.00	10.00	35.50	100.00
	D: Phentermine 45 mg	43.58	29.75	0.00	20.00	39.00	72.00	89.00
	E: Phentermine 90 mg	50.25	32.93	0.00	24.00	44.00	78.50	100.00
	F: Placebo	6.47	17.21	0.00	0.00	0.00	5.00	90.00
Overall Drug Liking	A: BMT 1.75 mg	43.67	21.65	0.00	45.00	50.00	57.50	71.00
	B: BMT 3.5 mg	41.36	22.18	0.00	26.00	48.50	54.50	80.00
	C: BMT 5.25 mg	36.28	20.62	0.00	22.50	40.50	50.00	78.00
	D: Phentermine 45 mg	68.03	18.11	21.00	57.00	66.50	80.50	98.00
	E: Phentermine 90 mg	62.44	25.52	2.00	50.00	69.00	81.00	100.00
	F: Placebo	50.94	3.71	40.00	50.00	50.00	50.00	61.00
Take Drug Again	A: BMT 1.75 mg	42.28	21.49	0.00	39.00	50.00	50.00	77.00
	B: BMT 3.5 mg	36.47	23.07	0.00	21.00	36.50	50.00	71.00
	C: BMT 5.25 mg	30.81	21.96	0.00	11.00	35.00	48.50	75.00
	D: Phentermine 45 mg	66.67	19.67	23.00	50.00	65.50	78.50	100.00
	E: Phentermine 90 mg	63.92	30.39	0.00	46.00	71.50	85.50	100.00
	F: Placebo	50.58	3.58	37.00	50.00	50.00	50.00	61.00

From Table 1, mean Drug Liking VAS Emax values for BMT 3.5 mg and BMT 5.25 were only slightly greater than those of placebo, mean value of BMT 1.75 has same mean of placebo. Mean Emax with Phentermine 45 mg and Phentermine 90 mg were markedly higher ($\geqslant$ 15 points compared to placebo and all doses of BMT). Median Drug Liking VAS Emax values for three BMT doses were also lower, comparing with median scores with Phentermine 45 mg and Phentermine 90 mg.

For Good Effects VAS, Emax scores remained relatively low with placebo (6.47) and were higher for Phentermine 45 mg, followed by Phentermine 90 mg. In contrast, three doses of BMT scores were numerically higher than those of placebo, but lower than those of the positive controls.

For Overall Drug Liking VAS and Take Drug Again VAS, mean Emax scores for placebo were neutral (~50), while scores for Phentermine 45 mg and Phentermine 90 mg were higher (>60). In contrast, mean Overall Drug Liking VAS Emax scores and Take Drug Again VAS Emax scores for all 3 BMT doses were lower than those of placebo.

Figure 1. Mean Drug Liking VAS Scores over time (Completer Population, N=36)

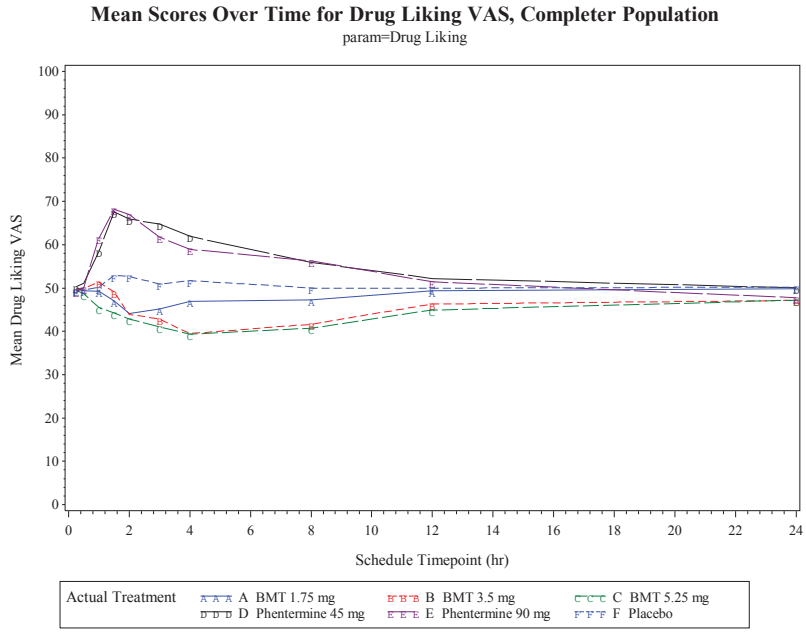


Figure 1 shows the mean drug liking VAS over time, mean scores for placebo remained neutral (~50) at all timepoints, Phentermine 45 mg and Phentermine 90 mg reached a higher maximum(~68) at hour 1.8, and all three doses of BMT had lower mean score than placebo for the first 12 hours. There were no differences in these treatment effects after hour 12.

Figure 2. Mean Good Effects VAS Scores over time (Completer Population, N=36)

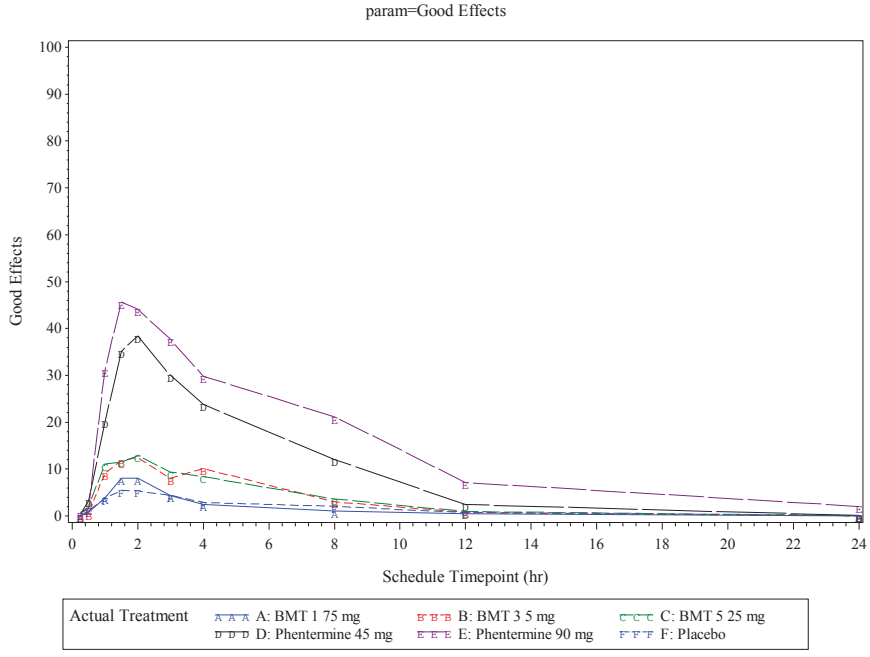


Figure 2 presented the Mean Good Effects VAS scores over time. Mean scores for placebo and three doses of BMT remained <10 at all timepoints. In contrast, mean Good Effects VAS scores

with Phentermine 45 mg increased up to 40 at 2 hours post-dose, and Phentermine 90 mg reached mean scores up to 46 at hour 1.8.

Individual E_{max} scores are displayed by subject for all treatments from Figure 3 to Figure 6, each row represents one patient with 6 treatments, the darker color means the more like. We can compare the E_{max} score for each patient at different treatment. The heatmaps show general more like for Phentermine 45 mg and Phentermine 90 mg comparing with three doses of BMT. For Drug Liking VAS, some subjects had high placebo response, there were 6 out of 36 (17%) subjects had placebo response >60.

Figure 3. Heatmap for Emax of Drug Liking VAS by treatment

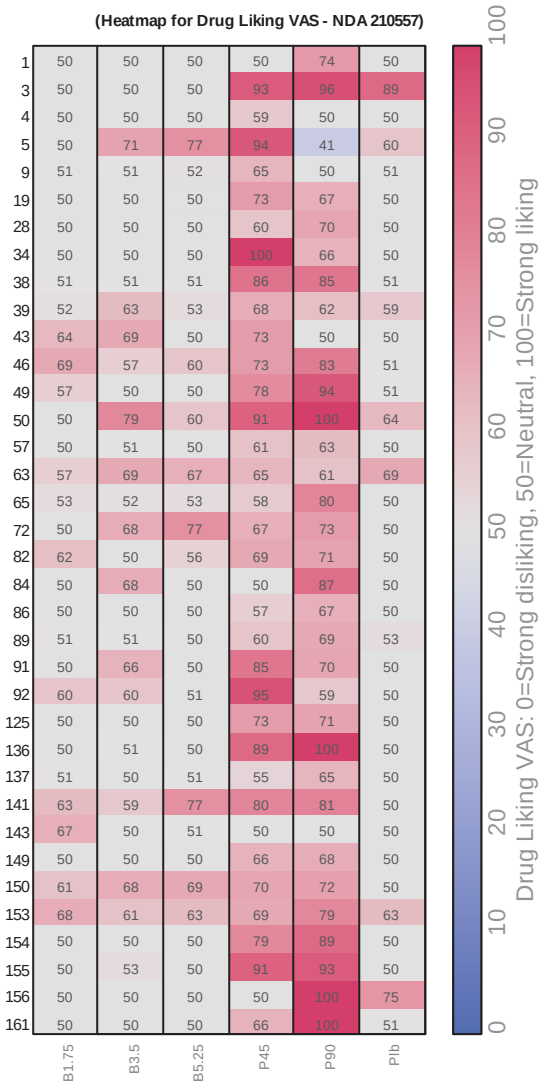


Figure 4. Heatmap for Emax of Good Effects VAS by treatment

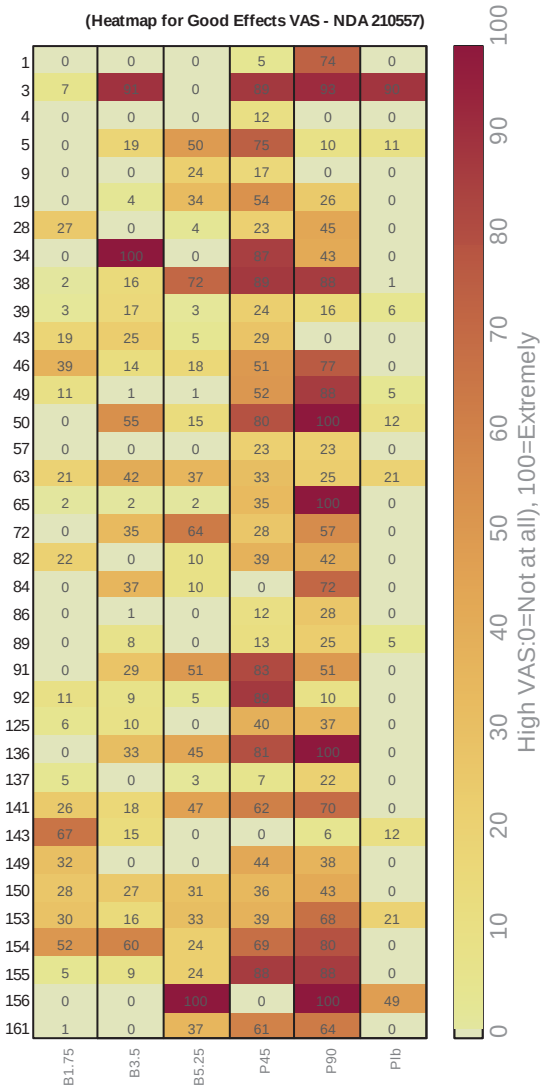


Figure 5. Heatmap for Emax of Overall Drug Liking VAS by treatment

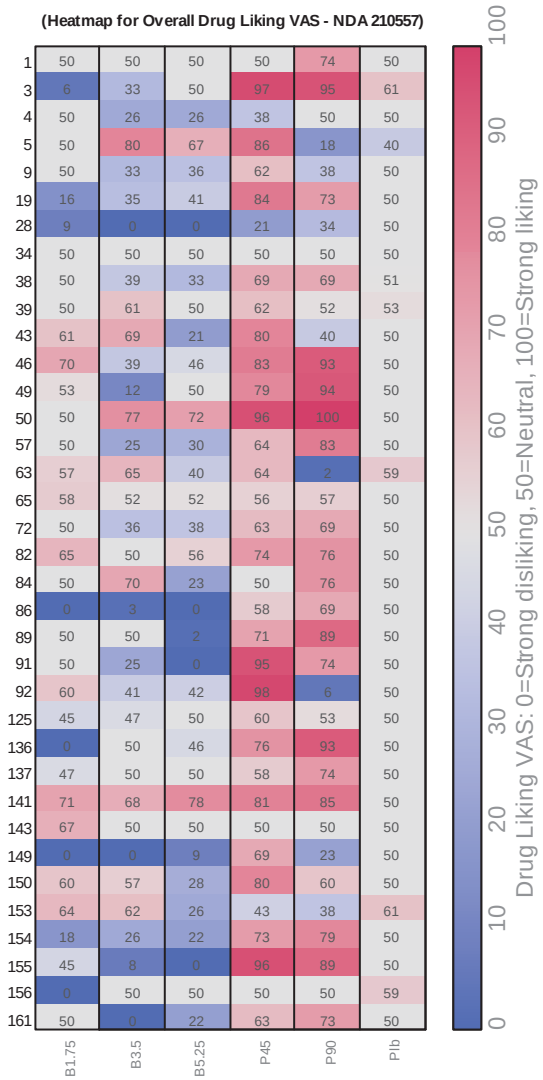
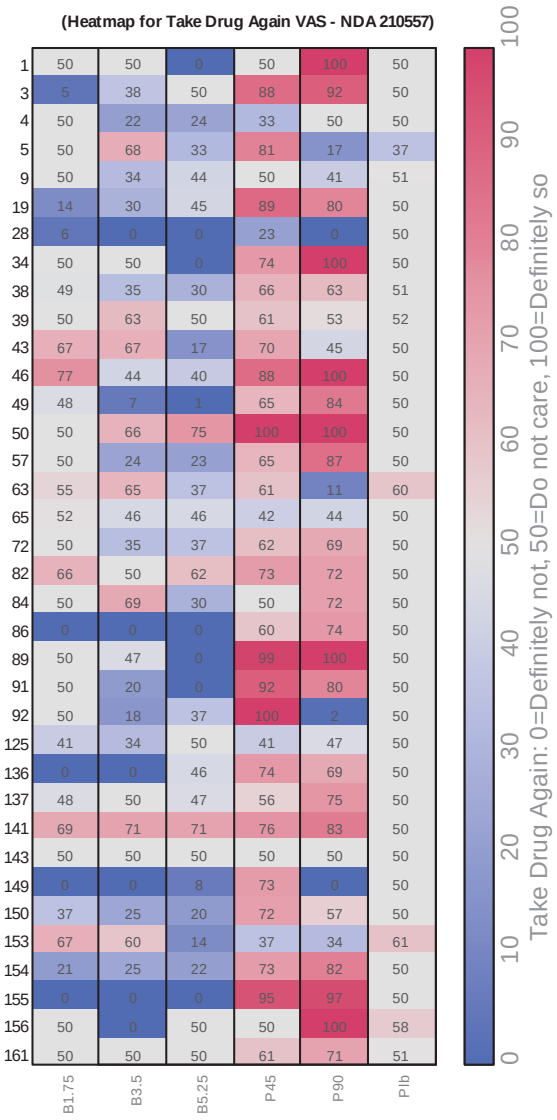


Figure 6. Heatmap for Emax of Take Drug Again VAS by treatment



2.3.2 Statistical Analysis

The statistical analysis of a HAP study should address whether:

• The known drug of abuse (positive control) produces reliable abuse-related responses compared to placebo.

• The test drug produces abuse- related responses that are smaller than the positive control.

• The test drug produces abuse- related responses that are similar as placebo.

To address these issues, the following hypotheses should be tested:

1. Validation test: Comparison between Positive Control and placebo

For study validity purpose, the primary endpoint, Emax for Drug Liking VAS, will be compared between each of the positive controls (Phentermine 45 mg and Phentermine 90 mg) and placebo. Each comparison will assess the null hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is less than or equal to 15 against the alternative hypothesis that the mean difference in Drug Liking Emax between the positive control and placebo is greater than 15. The hypothesis can be expressed as:

$$H_0: \mu_C - \mu_P \leq 15 \text{ versus } H_a: \mu_C - \mu_P > 15$$

where μ_C is the mean for the positive controls (Phentermine 45 mg and Phentermine 90 mg), and μ_P is the mean for placebo. If the treatment difference is statistically significant and the lower confidence limit for the difference exceeds 15, then validity is established for the study.

2. Relative abuse potential test: Comparison between positive controls and test drug

Comparison between the positive controls (Phentermine 45 mg and Phentermine 90 mg), and the test drug (BMT) can be expressed as (where μ_T is the mean for the BMT dose):

$$H_0: \mu_C - \mu_T \leq 0 \text{ versus } H_a: \mu_C - \mu_T > 0$$

3. Absolute abuse potential test: Comparisons between test drug and placebo

The hypothesis for comparisons between each dose of the test drug, BMT, and placebo will be:

$$H_0: \mu_T - \mu_P \geq 11 \text{ versus } H_a: \mu_T - \mu_P < 11$$

The primary endpoint and key secondary endpoints will be analyzed using a mixed-effect model if the distribution of the residuals is normally distributed. The model will include treatment, period, sequence, as fixed effects, and subject as a random effect. If this criterion is not met, each paired difference will be investigated for normality using the Shapiro-Wilk W-test. If the p-value for the distribution of the paired difference is $\geqslant$ 0.05 or the distribution is quite symmetric (skewness between -0.5 and 0.5), a paired t-test will be used. Means, SE, and one-sided 95% CIs for treatment differences will be presented. P-values will be provided for the contrasts from the paired t-tests. If the paired differences are not normally distributed and quite symmetric, pairwise treatment comparisons will be assessed using the sign test. The median, first and third quartiles,

1-sided 95% CI, and the p-value for the paired difference will be presented. In this study, the normality assumption tests were met for all PD endpoints.

Table 2 summaries the results of Comparison of Drug Liking VAS Emax for the three tests.

Table 2. Comparison of Drug Liking VAS Emax – Primary endpoint, Completer Population

Treatments	LS Mean	StdE	Lower	Upper
A: BMT 1.75 mg	53.73	1.86	50.06	57.39
B: BMT 3.5 mg	55.77	1.86	52.11	59.44
C: BMT 5.25 mg	54.55	1.86	50.89	58.22
D: Phentermine 45 mg	71.07	1.86	67.40	74.73
E: Phentermine 90 mg	73.54	1.86	69.87	77.21
F: Placebo	53.56	1.86	49.89	57.23

Contrasts	**LS Mean**	**StdE**	**P-value**	**Lower**	**Upper**
Positive Controls vs. Placebo (Trial Validity, H_0: $\mu_C - \mu_P \leq 15$)					
D: Phentermine 45 mg vs. F: Placebo	17.51	2.47	0.1556	13.42	Infty
E: Phentermine 90 mg vs. F: Placebo	19.98	2.47	0.0227	15.89	Infty
BMT vs. Positive Controls (Relative Abuse Potential, H_0: $\mu_C - \mu_T \leq 0$)					
A: BMT 1.75 mg vs D: Phentermine 45 mg	17.34	2.47	<.0001	13.25	Infty
B: BMT 3.5 mg vs D: Phentermine 45 mg	15.29	2.47	<.0001	11.21	Infty
C: BMT 5.25 mg vs D: Phentermine 45 mg	16.51	2.47	<.0001	12.43	Infty
A: BMT 1.75 mg vs E: Phentermine 90 mg	19.81	2.47	<.0001	15.73	Infty
B: BMT 3.5 mg vs E: Phentermine 90 mg	17.77	2.47	<.0001	13.68	Infty
C: BMT 5.25 mg vs E: Phentermine 90 mg	18.99	2.47	<.0001	14.90	Infty
BMT vs. Placebo (Absolute Abuse Potential, H_0: $\mu_T - \mu_P \geq 11$)					
A: BMT 1.75 mg vs F: Placebo	0.17	2.47	<.0001	-Infty	4.25
B: BMT 3.5 mg vs F: Placebo	2.21	2.47	0.0002	-Infty	6.30
C: BMT 5.25 mgvs F: Placebo	0.99	2.47	<.0001	-Infty	5.08

Table 2 presents, for Drug Liking:

- The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The null hypothesis was defined as a mean difference in Drug Liking Emax of ⩽ 15 points between treatments. The mean difference was statistically significant for the comparisons between Phentermine 90 mg and placebo. For the Phentermine 45 mg compared with placebo, the mean difference in Emax was not statistically significant (P-value=0.1556); therefore, the criteria for study validity was not met. However, the study was designed and conducted based on the recommendations in the draft guidance on the Assessment of Abuse Potential of Drugs (Jan 2010), thus, the study was not powered with an adequate sample size to perform this post-hoc analysis, which should be considered in the interpretation of this result.

- The relative abuse potential of BMT was evaluated by the comparison of Drug Liking Emax scores of each positive control (Phentermine 45 mg and Phentermine 90 mg) versus each dose of BMT. The null hypothesis was defined as a mean difference in Drug Liking Emax of $\leqslant 0$. All 3 BMT doses showed significantly lower Drug Liking VAS Emax scores compared with Phentermine 45 mg and Phentermine 90 mg ($p < 0.01$), indicating that subjects liked the positive controls significantly more than BMT.

- The absolute abuse potential of BMT was evaluated by the comparison of Drug Liking Emax between BMT and placebo. The null hypothesis was defined as a mean difference in Drug Liking Emax of $\geqslant$ 11 points. If the null hypothesis was not rejected, then the results supported that the treatments were not similar. The comparisons of all 3 BMT doses versus placebo were statistically significant (P value<0.01). The results showed that all 3 BMT doses were similar to placebo.

Table 3. Comparison of Good Effect VAS Emax – Completer Population

Treatments	LS Mean	StdE	Lower	Upper
A: BMT 1.75 mg	11.05	4.23	2.71	19.39
B: BMT 3.5 mg	18.18	4.23	9.84	26.52
C: BMT 5.25 mg	20.47	4.23	12.13	28.81
D: Phentermine 45 mg	42.95	4.23	34.61	51.29
E: Phentermine 90 mg	49.75	4.23	41.41	58.09
F: Placebo	5.86	4.23	-2.48	14.20

Contrasts	LS Mean	StdE	P-value	Lower	Upper
BMT vs. Positive Controls (Relative Abuse Potential, H0: μC - μT≤ 0)					
A: BMT 1.75 mg vs D: Phentermine 45 mg	31.90	5.39	<.0001	22.99	Infty
B: BMT 3.5 mg vs D: Phentermine 45 mg	24.77	5.38	<.0001	15.88	Infty
C: BMT 5.25 mg vs D: Phentermine 45 mg	22.48	5.38	<.0001	13.58	Infty
A: BMT 1.75 mg vs E: Phentermine 90 mg	38.70	5.38	<.0001	29.81	Infty
B: BMT 3.5 mg vs E: Phentermine 90 mg	31.57	5.39	<.0001	22.66	Infty
C: BMT 5.25 mg vs E: Phentermine 90 mg	29.28	5.38	<.0001	20.39	Infty
BMT vs. Placebo (Absolute Abuse Potential, H0: μT - μP ≥ 11)					
A: BMT 1.75 mg vs F: Placebo	5.19	5.38	0.1410	-Infty	14.09
B: BMT 3.5 mg vs F: Placebo	12.32	5.38	0.5972	-Infty	21.22
C: BMT 5.25 mgvs F: Placebo	14.61	5.39	0.7481	-Infty	23.52

Table 3 shows that for Good Effects VAS:

- All 3 BMT doses showed significantly lower Good Effect VAS Emax scores compared with Phentermine 45 mg and Phentermine 90 mg ($p < 0.01$), indicating that subjects liked the positive controls significantly more than BMT.

- The comparisons of all 3 BMT doses versus placebo were not statistically significant (P value>0.05). The results showed that all 3 BMT doses were not similar to placebo.

Table 4. Comparison of Overall Drug Liking VAS Emax, Completer Population

Treatments	LS Mean	StdE	Lower	Upper
A: BMT 1.75 mg	43.49	3.35	36.87	50.10
B: BMT 3.5 mg	40.78	3.35	34.16	47.39
C: BMT 5.25 mg	35.74	3.35	29.13	42.36
D: Phentermine 45 mg	67.45	3.35	60.84	74.07
E: Phentermine 90 mg	62.03	3.35	55.42	68.65
F: Placebo	50.80	3.35	44.18	57.41

Contrasts	LS Mean	StdE	P-value	Lower	Upper
BMT vs. Positive Controls (Relative Abuse Potential, H_0: $\mu_C - \mu_T \leq 0$)					
A: BMT 1.75 mg vs D: Phentermine 45 mg	23.96	4.38	<.0001	16.72	Infty
B: BMT 3.5 mg vs D: Phentermine 45 mg	26.67	4.37	<.0001	19.45	Infty
C: BMT 5.25 mg vs D: Phentermine 45 mg	31.71	4.38	<.0001	24.48	Infty
A: BMT 1.75 mg vs E: Phentermine 90 mg	18.55	4.37	<.0001	11.32	Infty
B: BMT 3.5 mg vs E: Phentermine 90 mg	21.25	4.38	<.0001	14.01	Infty
C: BMT 5.25 mg vs E: Phentermine 90 mg	26.29	4.37	<.0001	19.06	Infty
BMT vs. Placebo (Absolute Abuse Potential, H_0: $\mu_T - \mu_P \geq 11$)					
A: BMT 1.75 mg vs F: Placebo	-7.31	4.38	<.0001	-Infty	-0.08
B: BMT 3.5 mg vs F: Placebo	-10.02	4.37	<.0001	-Infty	-2.79
C: BMT 5.25 mgvs F: Placebo	-15.06	4.38	<.0001	-Infty	-7.82

Table 4 shows that for Overall Drug Liking VAS:

- All 3 BMT doses showed significantly lower Overall Drug Liking VAS Emax scores compared with Phentermine 45 mg and Phentermine 90 mg ($p < 0.01$), indicating that subjects liked the positive controls significantly more than BMT.

- The comparisons of all 3 BMT doses versus placebo were statistically significant (P value<0.01). The results showed that all 3 BMT doses were similar to those for placebo.

Table 5. Comparison of Take Drug Again VAS Emax, Completer Population

Treatments	LS Mean	StdE	Lower	Upper
A: BMT 1.75 mg	41.84	3.55	34.83	48.86
B: BMT 3.5 mg	35.70	3.55	28.69	42.72
C: BMT 5.25 mg	29.96	3.55	22.94	36.97
D: Phentermine 45 mg	65.78	3.55	58.77	72.80
E: Phentermine 90 mg	63.30	3.55	56.29	70.31
F: Placebo	50.24	3.55	43.23	57.26

Contrasts	LS Mean	StdE	P-value	Lower	Upper
BMT vs. Positive Controls (Relative Abuse Potential, H_0: $\mu_C - \mu_T \leq 0$)					
A: BMT 1.75 mg vs D: Phentermine 45 mg	23.94	4.75	<.0001	16.08	Infty
B: BMT 3.5 mg vs D: Phentermine 45 mg	30.08	4.74	<.0001	22.23	Infty
C: BMT 5.25 mg vs D: Phentermine 45 mg	35.83	4.75	<.0001	27.97	Infty
A: BMT 1.75 mg vs E: Phentermine 90 mg	21.46	4.74	<.0001	13.61	Infty
B: BMT 3.5 mg vs E: Phentermine 90 mg	27.60	4.75	<.0001	19.74	Infty
C: BMT 5.25 mg vs E: Phentermine 90 mg	33.35	4.74	<.0001	25.50	Infty
BMT vs. Placebo (Absolute Abuse Potential, H_0: $\mu_T - \mu_P \geq 11$)					
A: BMT 1.75 mg vs F: Placebo	-8.40	4.75	<.0001	-Infty	-0.55
B: BMT 3.5 mg vs F: Placebo	-14.54	4.74	<.0001	-Infty	-6.69
C: BMT 5.25 mg vs F: Placebo	-20.29	4.75	<.0001	-Infty	-12.42

Table 5 shows that for Take Drug Again VAS:

- All 3 BMT doses showed significantly lower Take Drug Again VAS Emax scores compared with Phentermine 45 mg and Phentermine 90 mg ($p < 0.01$), indicating that subjects liked the positive controls significantly more than BMT.

- The comparisons of all 3 BMT doses versus placebo were statistically significant (P value<0.01). The results showed that all 3 BMT doses were similar to those for placebo.

3. Conclusions

The primary objective of this trial was to evaluate the abuse potential of single subcutaneous (SC) doses of bremelanotide (BMT) compared to phentermine and placebo in healthy, recreational stimulant users.

The reviewer analyzed the primary PD endpoint Drug Liking, and the secondary PD endpoints: Good Effects, Take Drug Again and Overall Drug Liking. The results from the statistical reviewer's analyses establish that:

- The validity of the study was determined from the comparison of Drug Liking Emax between each positive control and placebo. The mean difference was statistically significant for the comparisons between Phentermine 90 mg and placebo (P-value=0.0227). For the Phentermine 45 mg compared with placebo, the mean difference in Emax was not statistically significant (P-value=0.1556), however, the study was designed and conducted based on the recommendations in the draft guidance on the Assessment of Abuse Potential of Drugs (Jan 2010), thus, the study was not powered with an adequate sample size to perform this post-hoc analysis, which should be considered in the interpretation of this result.

- For the relative abuse potential tests: All 3 BMT doses were associated with significantly lower effects than the positive controls on the primary endpoint and secondary endpoints of

Good Effects, Take Drug Again and Overall Drug Liking (P value <0.01), indicating that subjects liked the positive controls significantly more than BMT.

- For the absolute abuse potential test: For the primary PD endpoint Drug Liking, all 3 BMT doses versus placebo were statistically significant (P value<0.01), the results showed that all 3 BMT doses were similar to placebo. For the secondary endpoints, except for Good Effect VAS, all 3 BMT doses versus placebo were statistically significant (P value<0.01), showing that all 3 BMT doses were similar to placebo.
  Overall, BMT produced abuse-related responses that were not significantly different than placebo.

4. References

1) Guidance for Industry: Assessment of Abuse Potential for Drugs (January 2017) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

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/s/

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