

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208700Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 208700 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Lutathera Established/Proper Name: lutetium Lu 177 dotatate Dosage Form: 370 MBq/mL (10 mCi/mL) in single-dose vial		Applicant: Advanced Accelerator Applications USA, Inc. (AAA) Agent for Applicant (if applicable):
RPM: Nataliya Fesenko		Division: DOP2
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <ul style="list-style-type: none"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) <p>Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is Resubmission Class 2: January 26, 2018 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> Lutathera has previously been reviewed under the original NDA submission that was submitted on 04-27-16 under rolling review with Priority Review Designation. FDA issued a Complete Response issued 12/19/2016
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1: New Molecular Entity (confirmed with OPQ 1-23-2018)
(confirm chemical classification at time of approval)

- Fast Track granted 4/21/15 under IND 022719 Rx-to-OTC full switch
 Rolling Review (see comment below) Rx-to-OTC partial switch
 Orphan drug designation Direct-to-OTC
 Breakthrough Therapy designation

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

Under the original NDA, first review cycle, the NDA was granted a Priority Review Designation and was under Rolling Review. This application is a Class 2 Resubmission (under 6 months review).

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified Form submitted 5/18/16 under the first review cycle. No form was submitted under the second review cycle. <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) (link)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees (link)	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) -Approval Letter with final labeling issued 01-26-18 -Complete Response letter without labeling issued 12-19-16
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 1-24-18: FDA edits in track-changes format, in response to Applicant's label received on 1-24-18
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included Original labeling submitted with Resubmission 07-26-17
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included Revised Vial label, Container label, and Lead Pot labelling received 1/22/18
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	2nd cycle: Conditionally Acceptable Letter issued 1-9-18 Proprietary Name Review Uploaded 01-08-18 1st cycle: Conditionally Acceptable Letter issued 5-27-16 Proprietary Name Review Uploaded 5-26-16 04-05-16 IND 077219 Proprietary

<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews</i>) 	<p>name review.</p> <p>RPM: 1st Cycle: Review uploaded 6-22-16</p> <p>DMEPA: 2nd cycle: 01-22-18 TL concurrence 1-22-18 12-26-17 TL concurrence 12-26-17 11-9-17 TL concurrence 11-13-17; 1st cycle: Review uploaded 8-22-16 TL concurrence 8-22-16</p> <p>DRISK: N/A</p> <p>OPDP: 2nd Review cycle: Review uploaded 12-04-17 1st cycle: Pre-Decisional Consult Memo uploaded 11-21-16</p> <p>SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None DPMH review uploaded 2nd cycle: 12-21-17 1st cycle: 11-8-16</p>
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee 	<p>Completed 6-22-16 for 1st review cycle</p> <p><input checked="" type="checkbox"/> Not a (b)(2)</p>
<ul style="list-style-type: none"> ❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>) 	<p><input checked="" type="checkbox"/> Completed 01-25-2018 (Do not include)</p>
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC. If PeRC review not necessary, explain: <u>This product in this proposed indication was granted orphan drug designation on 5/21/15 (Designation # 02-2710)</u> 	<p>N/A</p>
<ul style="list-style-type: none"> ▪ Breakthrough Therapy Designation 	<p>N/A</p>
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s)</i>) 	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<p><i>and not the meeting minutes)</i></p> <p><i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i></p>	
<ul style="list-style-type: none"> ▪ <i>Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)</i> 	<p>01-24-18 Clinical, DMEPA IR 1-24-18 FDA modified labeling to include additional revisions to PI 01-23-18 Clinical IR 1-22-18 FDA modified labeling to include additional revisions to PI 1-19-18 FDA modified labeling to include additional revisions to PI 1-17-18 Clinical, DMIP IR 1-12-18 FDA modified labeling to include additional revisions to PI 1-10-18 Clinical (PMC) IR 1-5-18 Clinical (PMR) IR 12-27-17 Clinical IR 12-27-17 DMEPA (carton and Container) IR 12-19-17 FDA modified labeling to include additional revisions to PI 12-18-17 Clinical (PMR/PMC Communication) 12-5-17 Clinical IR 11-17-17 DMEPA (Carton and Container) IR 11-17-17 FDA modified labeling to include additional revisions to PI 11-16-17 Statistics IR 11-14-17 Clinical IR 11-14-17 Acknowledge Proprietary Name letter 11-13-17 Clinical Pharmacology IR 11-8-17 Clinical & Stat IR 11-7-17 Midcycle Communication, letter uploaded 1-16-18 11-6-17 Midcycle Agenda 10-27-17 Statistics IR 10-24-17 Statistics IR 10-23-17 (1) Clinical IR 10-23-17 (2) Clinical IR 10-11-17 (1) Clinical IR 10-11-17 (2) Clinical IR 10-10-17 Statistics IR 10-3-17 Clinical Pharmacology 10-2-17 Clinical IR 9-28-17 Clinical IR 9-21-17 Clinical IR 9-20-17 Clinical IR 9-14-17 OSI IR 8-31-17 Clinical IR 8-25-17 Clinical Pharmacology IR 8-25-17 Acknowledge Class 2 Resubmission letter</p>

	<p>8-23-17 Clinical Pharmacology IR 8-17-17 Statistics IR 8-14-17 Clinical IR 6-23-17 Stats IR, <i>uploaded 6-26-17</i> 6-13-17 Clinical IR 6-7-17 Statistics IR</p> <p>Outgoing Communications under first review cycle:</p> <p>2-10-17 Type A Meeting, Meeting <i>Minutes uploaded 2-13-17</i> 11-21-16 Discipline Review letter 9-19-16 CMC IR 8-16-16 CMC IR 8-12-16 Clinical Pharmacology IR 8-2-16 Mid-Cycle Communication, <i>letter uploaded 8-4-16</i> 7-28-16 CMC IR 7-21-16 CMC IR 7-18-16 Clinical IR, <i>uploaded 7-25-16</i> 7-13-16 OSI F/U IR 7-11-16 OSI IR 7-7-16 Clinical/Stats IR 7-7-16 Stats F/U IR 7-5-16 Stats IR 6-30-16 General Correspondence 6-23-16 No Filing Issues Identified Letter with Clinical Pharmacology IR & Labeling Comments 6-21-16 Stats/Clinical IR 6-10-16 Stats IR 6-9-16 Clinical IR 6-9-16 Stats F/U IR 6-6-16 Clinical Pharmacology IR 6-3-16 Clinical/OSI IR 6-1-16 Stats IR 5-24-16 OSI IR 5-23-16 OSI IR 5-18-16 CMC IR sent via fax 5-17-16 Form 3542a IR 5-16-16 OSI IR 5-5-16 IRT/QT IR 5-2-16 NDA Acknowledgement Letter 4-18-16 Pre-sub Acknowledgement Letter <i>uploaded in DARRTS</i></p>
<p>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</p>	<p>01-18-18 TCON with Applicant (PI revisions), <i>minutes uploaded 01-19-18</i> 1-10-18 Wrap-up Meeting, <i>minutes uploaded 1-17-18</i> 01-03-18 Monthly Internal Team Meeting, <i>minutes uploaded 01-17-</i></p>

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12-18-17 Internal labeling meeting #9, *minutes uploaded 01-02-18*
11-13-17 Internal labeling meeting #7, *minutes uploaded 01-04-18*
11-08-17 Internal labeling meeting #5, *minutes uploaded 01-04-18*
11-08-17 Internal labeling meeting #6, *minutes uploaded 1-04-18*
11-08-17 Internal labeling meeting #4, *minutes uploaded 1-04-18*
11-07-17 Internal labeling meeting #3, *minutes uploaded 11-07-17*
11-06-17 Agenda for Mid-Cycle Communication to Applicant
11-03-17 Labeling meeting, *minutes uploaded 11-07-17*
10-30-17 Internal Midcycle Summary Meeting, *summary minutes uploaded 11/21/17*
10-11-17 Applicant TCON (Manufacturing Facilities) held, *internal minutes uploaded 01-04-18*
10-02-17 Internal Team Meeting #1
08-24-17 TCON with Applicant (clin pharm), *minutes uploaded 08-31-2017*
08-17-17 Planning meeting, *summary minutes uploaded 09-22-17*
11-21-16 OPDP Pre-Decisional Consult Memo
11-20-16 DRISK Deferral Review Memo
11-8-16 DPMH consult memo
10-26-16 TCON with Applicant-re CR, *uploaded 10-27-16*
10-23-17 Internal Team Meeting #2, *minutes uploaded 1-16-18*
10-21-16 TCON with Applicant, *minutes uploaded 10-24-16*
9-12-16 Delay in review completion memo by CDTL
8-18-16 DMIP consult review memo
8-11-16 TCON with Applicant, *minutes uploaded 8-15-16*
7-27-16 Internal Mid-Cycle Summary Meeting, *summary minutes uploaded 8-10-16*
7-12-16 TCON with Applicant, *summary minutes uploaded 7-13-16*
6-30-16 TCON with Applicant, *summary minutes uploaded 7-6-16*
6-23-16 Priority Review

	<p>Designation Memo 6-8-16 Filing meeting, <i>minutes uploaded 6-10-16</i> 5-17-16 Planning meeting, <i>summary minutes uploaded 5-18-16</i></p>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 1-10-18 Wrap Up Meeting, <i>minutes uploaded 1-17-18</i>
<ul style="list-style-type: none"> Pre-NDA/BLA or BPD Type 4 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 2-10-17 Type A Meeting, <i>minutes uploaded 2-13-17</i> 3-14-16 Type B/pre-NDA Meeting under IND 077219, <i>minutes uploaded 3-17-16</i>
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 3-8-11 (IND 077219; sponsor: BioSynthema, Inc.)
<ul style="list-style-type: none"> Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 3-2-16 (1 st cycle), October 30, 2017 (2 nd cycle)
<ul style="list-style-type: none"> Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> Not held
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	5-22-17 Type B Guidance under IND 077219, <i>minutes uploaded 6-8-17</i> 5-18-17 Type C Guidance Written responses Only under IND 077213 11-24-15 Type C Advice under IND 077213, <i>minutes uploaded 12-3-15</i> 8-27-15 Type C Guidance under IND 077213, <i>minutes uploaded 9-2-15</i>

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	2 nd cycle: OD signed multidisciplinary review on 01-25-18. 1 st cycle: OD signed multidisciplinary review on 12-19-16.
Division Director Summary Review (<i>indicate date for each review</i>)	2 nd cycle: DD Clinical Addendum 1-25-18 DD signed DARRTS memo 01-04-18; multidisciplinary review signed on 01-25-18. 1 st cycle: DD signed DARRTS memo 12-6-16; multidisciplinary review signed on 12-16-16.
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	2 nd cycle: CDTL signed multidisciplinary review on 01-24-18. 1 st cycle: CDTL signed multidisciplinary review on 12-16-16.
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> 2 PMRs, 1 PMC, uploaded 1-24-18
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 12-15-17; Clinical and Clinical Team Leader signed concurrence in multidisciplinary review on 01-24-18 1 st cycle: No separate review; DARRTS memo signed 11-22-16; Clinical and Clinical Team Leader signed concurrence in multidisciplinary review on 12-16-16.
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	2 nd cycle: No separate review; DARRTS memo signed 12-15-2017; Clinical and Clinical Team Leader signed concurrence in multidisciplinary review on 01-24-18. 1 st cycle: No separate review; DARRTS memo signed 11-22-16; Clinical and Clinical Team Leader signed concurrence in multidisciplinary review on 12-15-16.

<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> 	<p>2nd Review Cycle: See Sections 8.1.1 (page 70) and 8.1.3 (page 90) of Multidisciplinary review</p> <p>1st Review cycle: Financial Disclosure review in Clinical/Statistical section of multidisciplinary review (section 7.2.2., 13.2).</p>
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>⁵ 	<input type="checkbox"/> None 2 nd cycle: CDER, Division of Medical Imaging Products/ Clinical Review uploaded 10-6-17 1 st cycle: CDER/ Division of Medical Imaging Products/ Clinical Review 8-18-16
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	<input checked="" type="checkbox"/> None <input checked="" type="checkbox"/> None <input type="checkbox"/> None 2 nd Cycle: Review uploaded 12-8-17; TL concurrence 12/10/17 1 st cycle: Review uploaded 11-20-16; TL concurrence 11-20-16
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i> 	1 st cycle: 1-24-17 Letters to Investigators (2) 2 nd Review cycle: 10-7-16 OSI Summary Review 8-19-16 Letters to Investigators (2)

⁵For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Microbiology <input checked="" type="checkbox"/> None	
• Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 01-04-18. Signed concurrence in multidisciplinary review on 01-24-18 1 st cycle: No separate review; DARRTS memo signed 11-22-16. Signed concurrence in multidisciplinary review on 12/16/16.
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 01-03-18. Signed concurrence in multidisciplinary review on 01-24-18 1 st cycle: No separate review; DARRTS memo signed 11-22-16. Signed concurrence in multidisciplinary review on 12-15-16.
Statistical Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 01-03-18. Signed concurrence in multidisciplinary review on 01-24-18 1 st cycle: No separate review; DARRTS memo signed 11-22-16. Signed concurrence in multidisciplinary review on 12-15-16.

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 12-08-17. Signed concurrence in multidisciplinary review on 01-24-18. 1 st cycle: No separate review; DARRTS memo signed 11-21-16. Signed concurrence in multidisciplinary review on 12-16-16.
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 12-08-17. Signed concurrence in multidisciplinary review on 12-24-18. 1 st cycle: No separate review; DARRTS memo signed 11-21*16. Signed concurrence in multidisciplinary review on 12-15-16.
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 2 nd cycle: No separate review; DARRTS memo signed 12-08-17. Signed concurrence in multidisciplinary review on 12-24-18. 1 st cycle: DARRTS memo signed 11-21-16. Signed concurrence in multidisciplinary review on 12-15-16.
	QT IRT Review uploaded 7-7-16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Pharmacology/Toxicology Discipline Reviews 	
<ul style="list-style-type: none"> • ADP/T Review(s) <i>(indicate date for each review)</i> 	<p><input checked="" type="checkbox"/> 2nd cycle: No separate review; DARRTS memo signed 12-14-17. Signed concurrence in multidisciplinary review on 01-24-18</p> <p>1st cycle: No separate review; DARRTS memo signed 11/14/16. Signed concurrence in multidisciplinary review on 12/16/16.</p>
<ul style="list-style-type: none"> • Supervisory Review(s) <i>(indicate date for each review)</i> 	<p><input checked="" type="checkbox"/> 2nd cycle: No separate review; DARRTS memo signed 12-14-17. Signed concurrence in multidisciplinary review on 01-24-18</p> <p>1st cycle: No separate review; DARRTS memo signed 11-14-16. Signed concurrence in multidisciplinary review on 12-15-16.</p>
<ul style="list-style-type: none"> • Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> 	<p>2nd cycle: No separate review; DARRTS memo signed 12-14-17. Signed concurrence in multidisciplinary review on 12-24-18.</p> <p>1st cycle: DARRTS Memo signed 11-14-16; signed concurrence in multidisciplinary review on 12-15-16.</p>
<ul style="list-style-type: none"> ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i> 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i> 	<p><input checked="" type="checkbox"/> No carc</p>
<ul style="list-style-type: none"> ❖ ECAC/CAC report/memo of meeting 	<p><input checked="" type="checkbox"/> None Included in P/T review, page</p>
<ul style="list-style-type: none"> ❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i> 	<p><input checked="" type="checkbox"/> None requested</p>

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
<ul style="list-style-type: none"> • Tertiary review (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2 nd cycle: OPQ Integrated Quality Assessment final Review Date: 12-13-17 1 st cycle: Primary, secondary and tertiary joint review – final tertiary signature 11-22-2016
<ul style="list-style-type: none"> • Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2 nd cycle: OPQ Integrated Quality Assessment final Review Date: 12-13-17 1 st cycle: Primary, secondary and tertiary joint review – final signature 11-22-2016
<ul style="list-style-type: none"> • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> 2 nd cycle: OPQ Integrated Quality Assessment final Review Date: 12-13-17 1 st cycle: Microbiology review 11-14-16; CMC TL review 11-18-16 Microbiology & CMC: Approval
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	2 nd cycle: 12-13-17 see OPQ Integrated Quality Assessment final review. 1 st cycle: 11-22-16 see page 31 of the Product Quality review (Executive Summary)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
<p><input checked="" type="checkbox"/> Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</i>)</p>	<p><input checked="" type="checkbox"/> Acceptable Re-evaluation date: 2nd cycle: 12-13-17 No re-inspection needed (see page 3,4 of the OPQ Integrated Quality Assessment final review. 1st cycle: Withhold recommendation - 11-10-16 (Facilities reviewer) and 11-14-16 (Facilities TL) <input type="checkbox"/> Not applicable</p>

Day of Approval Activities

<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(Notify CDER OND IO)</i> N/A
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> N/A <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> 2 nd cycle: Courtesy copy of approval letter sent to applicant via email on 01-26-18. 1 st cycle: Courtesy copy of CR letter sent to applicant via email on 12/19/16.
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> 01-26-18
<p>Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name</p>	<input checked="" type="checkbox"/> 2 nd cycle: Proprietary name is acceptable 1-04-18 1 st cycle: Done – Note: Proprietary name conditionally accepted via memo dated 5-13-16.
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	01-26-18
<ul style="list-style-type: none"> ❖ Take Action Package (if in paper) down to Document Room for scanning within two business days 	01-30-18



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 24, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-30]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-30] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Thursday, January 25, 2018**

We refer to your January 19, 2018 submission that contains a Draft [REDACTED] (b) (4).
[REDACTED] The following are comments and recommendations [REDACTED] (b) (4) for your consideration.

[REDACTED] (b) (4)

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
01/24/2018

Fesenko, Nataliya

From: Fesenko, Nataliya
Sent: Wednesday, January 24, 2018 4:47 PM
To: 'Victor Paulus'
Cc: Myers, Claire; 'Gabrielle Bravoco'
Subject: NDA 208700 Proposed labeling - Response requested 5PM EST Thursday, January 25, 2018
Attachments: NDA_208700_Label_to_AAA_01_24_2018.docx

Importance: High

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked. **Please accept the tracked changes that you agree with.** If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by 5PM EST Thursday, January 25, 2018, or sooner, if possible, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov



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/s/

NATALIYA N FESENKO
01/24/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 23, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-29]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-23] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on January 24, 2018**

Please refer to Section 2.5 of the proposed PI. Provide further clarification regarding the administration procedure.

Section 2.5 currently reads as below (note yellow highlights), (b) (4)

[Redacted]

For the bullet that states (b) (4):

[Redacted]

Administration Instructions

- Insert a 2.5 cm, 20 gauge needle (short needle) into the LUTATHERA vial and connect via a catheter to 500 mL 0.9% sterile sodium chloride solution (used to transport LUTATHERA during the infusion). Ensure that the short needle does not touch the LUTATHERA solution in the vial and do not connect this short needle directly to the patient. Do not allow sodium chloride solution to flow into the LUTATHERA vial prior to the initiation of the LUTATHERA infusion and do not inject LUTATHERA directly into the sodium chloride solution.
- Insert a second needle that is 9 cm, 18 gauge (long needle) into the LUTATHERA vial ensuring that this long needle touches and is secured to the bottom of the LUTATHERA vial

during the entire infusion. Connect the long needle to the patient by an intravenous catheter that is prefilled with 0.9% sterile sodium chloride and that is used exclusively for the LUTATHERA infusion into the patient.

- Use a clamp or pump to regulate the flow of the sodium chloride solution (b) (4)
- (b) (4) Do not administer LUTATHERA as an intravenous bolus.
- During the infusion, ensure that the level of solution in the LUTATHERA vial remains constant (b) (4)
- Disconnect the vial from the long needle line and clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Follow the infusion with an intravenous flush of 25 mL of 0.9% sterile sodium chloride.
- Dispose of any unused medicinal product or waste material in accordance with local and federal laws.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
01/23/2018

Fesenko, Nataliya

From: Fesenko, Nataliya
Sent: Monday, January 22, 2018 4:19 PM
To: Victor Paulus
Cc: Myers, Claire; Gabrielle Bravoco
Subject: NDA 208700 Proposed labeling - Response requested by EOB Tuesday, January 23, 2018
Attachments: NDA_208700_Label_to_AAA_01_22_2018.docx

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked. **Please accept ALL the tracked changes that you agree with.** If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by EOB Tuesday, January 23, 2018, or sooner if possible, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov

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/s/

NATALIYA N FESENKO
01/22/2018

Fesenko, Nataliya

From: Fesenko, Nataliya
Sent: Friday, January 19, 2018 2:48 PM
To: Victor Paulus
Cc: Myers, Claire; 'Gabrielle Bravoco'
Subject: NDA 208700 Proposed labeling - Response requested 5PM EST Monday, January 22, 2018
Attachments: NDA_208700_Label_to_AAA_01-19-2018.docx

Importance: High

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked. Please accept the tracked changes that you agree with. If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by EOB Monday, January 22, 2018, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov



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NATALIYA N FESENKO
01/19/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 18, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Applicant Teleconference re: Lutathera labeling

FDA Attendees

Steven Lemery, M.D., M.H.S., Associate Director, DOP2/OHOP
Suzanne Demko, PA-C., Clinical Team Leader (CDTL)
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead, ONDQA
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA
Chi-Ming (Alice) Tu, DMEPA Team Leader
Ann Marie Trentacosti, Medical Officer, OMPT/CDER/OND
Cynthia Welsh, M.D., Division of Medical Imaging, DMIP
Janine Stewart, DMEPA Reviewer
Danielle Harris, DMEPA Reviewer
Nataliya Fesenko, Pharm. D., Regulatory Health Project Manager, DOP2
Kellie Reece, Ph.D., Regulatory Health Project Manager, DOP2
Claire Myers, Ph.D., Sr. Regulatory Health Project Manager, DOP2

Advanced Accelerator Applications USA, Inc. (AAA) Attendees

(b) (4)

Maurizio Mariani, M.D., Ph.D., Head of Preclinical Research
Val Nassiri, R.Ph., Director, Medical Affairs
Debora Barton, M.D., Head of Medical Affairs
Claude Hariton, Ph.D., D.Sc., Global Head of R&D
Jack Erion, Ph.D., VP R&D
Francesco DePaolo, Ph.D., Head of Lutathera Manufacture and development
Victor Paulus, Ph.D., Global Head, Regulatory Affairs

Background

AAA submitted the last versions of proposed carton and container labels and PI on January 3, 2018, and January 16, 2018, respectively. In addition, a draft Instruction Brochure was provided by AAA via email, that describes instructions for LUTATHERA infusion preparation and administration. The purpose of this teleconference was to discuss the applicant-proposed Package Insert Section 2. DOSAGE AND ADMINISTRATION, and carton and container labels.

Summary

- FDA stated that AAA's proposed method of LUTATHERA administration as described in AAA's January 16, 2018 response to FDA's January 10, 2018 information request, was acceptable. FDA stated acceptability was based on AAA's justification provided in the NDA.

- AAA stated that this method of LUTATHERA administration was utilized in ERASMUS, the NETTER-1 trial, and expanded access program. LUTATHERA has been administered to over 1,000 patients.
- FDA stated that the proposed method of LUTATHERA administration is unique and may have potential for medication errors and asked AAA if there were any medication errors reported with LUTATHERA administration.
- AAA stated that there were no episodes of misadministration using the technique utilized in the clinical studies and expanded access. AAA stated that the administration procedures were designed to minimize radiation exposure as the drug stays in the shielded vial.
- All radiopharmaceuticals are unique and have variable administration schedules and techniques. Use of lead pigs and tongs are typical.
- It is common for drug companies to submit brochures to a radiopharmacist outside of the label.
- Personnel that specialize in the radiopharmaceutical field are used to the idiosyncrasies that arise.
- Radiopharmaceuticals have limited distribution only to physicians that have met the requirements for an NRC license.
- FDA will update Section 2.5 of the labeling with more detailed instructions. AAA can propose alternative language after FDA sends the labeling to AAA on Friday.
- FDA agreed that the product should NOT be diluted in a bag of saline. The product should stay in the original vial to minimize radiation exposure to staff.
- AAA will submit a draft (b) (4) of LUTATHERA.
- AAA agreed to revise the carton and container labels to match the PI.

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/s/

NATALIYA N FESENKO
01/19/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 17, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-28]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-28] by **5PM Eastern Time on January 18, 2018.**

Please send via overnight mail to the address below, two sets of the following: empty or placebo samples of the Lutathera vial, the lead pot, and the administration tubing that you state should be used for Lutathera administration.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2383
10903 New Hampshire Avenue
Silver Spring, Maryland

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/s/

NATALIYA N FESENKO
01/17/2018

Fesenko, Nataliya

Subject: FW: NDA 208700 Proposed labeling - Response requested 5PM EST Tuesday, January 16, 2018
Attachments: NDA_208700_Label_to_AAA_01-12-2018.docx
Importance: High

From: Fesenko, Nataliya
Sent: Friday, January 12, 2018 1:20 PM
To: Victor Paulus <victor.paulus@adacap.com>
Cc: Fesenko, Nataliya <Nataliya.Fesenko@fda.hhs.gov>; Myers, Claire <Claire.Myers@fda.hhs.gov>
Subject: NDA 208700 Proposed labeling - Response requested 5PM EST Tuesday, January 16, 2018
Importance: High

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked. Please accept the tracked changes that you agree with. If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by **EOB Tuesday, 01/16/18**, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov



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/s/

NATALIYA N FESENKO
01/12/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 10, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-27]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-27] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Thursday, January 11, 2018**

The review team inadvertently omitted sending one additional post-marketing commitment request. Given that OS is immature, we believe it is important to obtain the final results for OS. Note that this would be a PMC rather than a PMR.

Please indicate whether you are in agreement with the language and **provide a proposed date for the submission of the FSR.**

Submit the final clinical report and datasets at the time of the final analysis for overall survival (OS) for Trial NETTER-1, entitled “A Multicentre, stratified, open, randomized, comparator-controlled, parallel-group phase III study comparing treatment with ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate to Octreotide LAR in Patients with Inoperable, Progressive, Somatostin Receptor Positive, Midgut Carcinoid Tumors”, to revise product labeling with mature OS data.

Final Report Submission: **XX, XX, XXXX (Proposed Date)**

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products

APPEARS THIS WAY ON ORIGINAL

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/s/

NATALIYA N FESENKO
01/10/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 10, 2018
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Wrap-up Internal Team Meeting

NDA: 208700
Applicant: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial

Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults.

Attendees:

Steven Lemery, Suzanne Demko, Huanyu Chen (Jade), Kun He, Hong Zhao, Mei-Yean Chen, Eldon Leutzinger, Whitney Helms, Nataliya Fesenko

Meeting Summary:

1. The team discussed multidisciplinary review status; it is ready to be sent to the OD/ADRA.
2. The team reviewed Action template and determined what sections are applicable for this NDA.
3. RPM Fesenko reviewed milestone dates.
4. The team discussed proposed labeling revisions for all sections (proposed PI received from AAA on 12/22/2017).

Action items:

1. RPM Fesenko will follow-up with DMIP regarding the proposed label revisions to sections 11.
2. RPM Fesenko will review the proposed PI and send it to Applicant on 01/11/2018.
3. RPM Fesenko will forward Multidisciplinary review to continue working on finalizing the multidisciplinary review to OD/ADRA.

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/s/

NATALIYA N FESENKO
01/17/2018



NDA 208700

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue
Suite 6902
New York, NY 10118

ATTENTION: Victor G. Paulus, Ph.D.
Global Head, Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received July 26, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutetium Lu 177 Dotatate Injection, 370 MBq/mL.

We also refer to your correspondence, dated and received November 8, 2017, requesting a review of your proposed proprietary name, Lutathera.

We have completed our review of the proposed proprietary name, Lutathera and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 8, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022,
(<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact, Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Nataliya Fesenko, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/09/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 5, 2018
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-26]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-26] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Monday, January 8, 2018**

Please refer to your submission dated December 12, 2017, in response to our letter, dated December 18, 2017, containing your post-marketing requirements (PMRs) proposal. We also acknowledge the receipt of your response to information request [IR-25], received on January 3, 2018, containing justification of assumptions for the design of the PASS study.

Regarding the proposed PMR milestone dates:

- Analysis Plan: June 2018
- Descriptive interim report 1, including a Study progress report: September 2021
- Descriptive interim report 2, including a Study progress report: September 2024
- Final report of study results: December 2025

Since the final report will be submitted in 2025, the second interim report in September 2024 is not needed. Limit to one interim safety report.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
01/05/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 8, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #4

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees:

Carol Broadnax, Mei-Yean Chen, Nataliya Fesenko, Jeanne Fourie Zirkelbach, Brian Furmanski, Ruthann Giusti, Jeongmi Kim, Janine Stewart, Steven Lemery, Christos Mastroyannis, Claire Myers, Kelie Reece, Cynthia Welsh

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 2 Dosage and Administration
- 7 Drug Interactions
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

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/s/

NATALIYA N FESENKO
01/04/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 8, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #5

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Carol Broadnax, Connie Cheng, Nataliya Fesenko, Latonia Ford, Ruthann Giusti, Steven Lemery, Claire Myers, Janine Stewart

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 6 Adverse Reactions

(b) (4)

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/s/

NATALIYA N FESENKO
01/04/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 8, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #6

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Carol Broadnax, Mei-Yean Cheng, Connie Cheng, Nataliya Fesenko, Latonia Ford, Ruthann Giusti, Christos Mastroyannis, Tamara Johnson, Steven Lemery, Claire Myers, Kelie Reece, Janine Stewart

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 4 Contraindications
- 5 Warnings and Precautions
- 17 Patient Counseling Information

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/s/

NATALIYA N FESENKO
01/04/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 3, 2018
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of January Internal Team Meeting

NDA: 208700
Applicant: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial

Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults.

Attendees:

Steven Lemery, Suzanne Demko, Huanyu (Jade) Chen, Hong Zhao, Brian Furmanski, Mei-Yean Chen, Stacy Shord, Nataliya Fesenko, Claire Myers

Meeting Summary:

1. The team discussed multidisciplinary review status, and final sign-off process. Primary, secondary, and CDTL reviews are complete. Reviewer memos were uploaded into DARRTS.
2. The team discussed proposed labeling revisions for all sections (proposed PI received from AAA on 12/22/2017).

Action items:

1. Follow-up with CMC and DMIP regarding the proposed label revisions to sections 11 and 16.
2. Request OPQ's input concerning a nomenclature issue in PI.
3. Team will continue working on finalizing the multidisciplinary review, and the action letter.

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/s/

NATALIYA N FESENKO
01/17/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 27, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-24]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-24] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, January 3, 2018**

General Comments (Container Label and Carton Labeling)

1. Remove the (b) (4) statement, (b) (4) on the proposed container label (vial) and carton labeling (leadpot).
2. Revise the strength and dose statements to consistent units of measurement across all labels and labeling. We recommend using the units of measurement MBq followed by mCi in parenthesis. We remind you to revise the proposed Prescribing Information for consistency.
3. Revise the dosage form statement, (b) (4) to read "Injection" (i.e., Lutathera (lutetium Lu 177 dotatate injection)).
4. Revise the statement "For intravenous infusion" to read "For Intravenous Infusion (b) (4)" in mixed case letters. We recommend this (b) (4)
5. Revise and relocate the statement "Single-Dose Vial" to appear underneath the (b) (4) statement and to read, "Single-Dose Vial. Discard Unused Portion".
6. Add a "Usual Dose" statement on the side panel of the container label and carton Labeling to read "Usual dose: See Prescribing Information" in accordance with 21 CFR 201.55.

7. Ensure the radioactive warning symbol is accurate in shape and color, as is commonly seen in the US among drug products with radioactivity.

Container Label (Vial)

8. Revise the container label so activity at calibration time, lot number, and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed to optimize the clarity and the order of important product information on the Principal Display Panel (PDP). The example layout below demonstrates our recommendation only (Please note, the example need not be replicated with respect to size, spacing, color, etc.).



Carton Labeling (Leadpot)

9. Consider removing the statement (b) (4) This statement clutters the label and does not appear necessary (b) (4)
(b) (4)
10. Consider providing perforated leadpot label with duplicate product information for use in the radiopharmacy. This would provide ease of use for verification and documentation by the radiopharmacy.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
12/27/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 27, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-25]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-25] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, January 3, 2018**

Re: Assumptions for the design of the PASS study:

Please provide justification for the assumption of 1-2% incidence of second primary malignancies of between 1-2% of 5 years of follow-up. Provide justification for the underlying assumption that the median time of onset for these events is within 5 years and that the incidence rate remains constant over time. Alternatively, design the trial to allow for a longer duration of follow-up on an adequate number of patients to assess the likely risk out to ten years.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
12/27/2017

Fesenko, Nataliya

From: Fesenko, Nataliya
Sent: Tuesday, December 19, 2017 4:40 PM
To: Victor Paulus
Cc: Fesenko, Nataliya; Myers, Claire
Subject: NDA 208700 Proposed labeling - Response requested 5PM EST Tuesday, December 26, 2017
Attachments: NDA_208700_Label_to_AAA_12-19-2017.docx

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked (if you are using Word 2016, please view in "All Markup"). Please accept the tracked changes that you agree with. If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by EOB Tuesday, December 26, 2017, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov



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NATALIYA N FESENKO
12/19/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 18, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700, Advanced Accelerator Applications USA, Inc.: Proposed
PMC/PMR Language

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lutetium Lu 177 dotatate, 370 MBq/mL solution for infusion.

Please note that additional post-marketing requirement (PMR) and post-marketing commitment (PMC) proposals may be forthcoming while your application is under review. Provide your agreement and your proposed scheduled milestone dates to the below proposals. We remind you to use due diligence in proposing timelines for completion of these trials.

In addition, please note that final language will be included in the action letter. We are requesting that you respond to our proposal by close of business on December 22, 2017.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

1. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risk of renal failure with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

Proposed PMR Milestone Dates:
Final Analysis Plan: June, 2018

Interim Safety Report: June, 2023
Final Report: June, 2028

2. Submit cumulative, integrated safety analyses after 5 and after 10 years of follow-up of patients from an adequate number of clinical trials to identify and characterize the risks of myelodysplastic syndrome and acute leukemia with Lutathera; include incidence rates, time to onset, predisposing factors and outcomes. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

Proposed PMR Milestone Dates:

Final Analysis Plan: June, 2018
Interim Safety Report: June, 2023
Final Report: June, 2028

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf>
- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review*
https://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4143B1_06_Tab-13.pdf
- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf>.
- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf>

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

If you have any questions, call me, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
12/18/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 18, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #9

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Brian Furmanski, Carol Broadnax, Suzanne Demko, Whitney Helms, Connie Cheng, Nataliya Fesenko, Stacy Shord, Ruthann Giusti, Steven Lemery, Christos Mastroiannis, Eldon Leutzinger, Hong Zhao, Ann Marie Trentacosti, Latonia Ford, Tamara Johnson, Cindy Welsh, Latonia Ford

Meeting Summary:

FDA's proposed labeling revisions were discussed for all sections.

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/s/

NATALIYA N FESENKO
01/02/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 11, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #8

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (lutetium Lu 177 dotatate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Brian Furmanski, Carol Broadnax, Suzanne Demko, Whitney Helms, Connie Cheng, Mei-Yean Chen, Huanyu Chen (Jade), Kun He, Nataliya Fesenko, Stacy Shord, Ruthann Giusti, Steven Lemery, Christos Mastroyannis, Claire Myers, Janine Stewart

Meeting Summary:

AAA submitted an updated version of the label on December 01, 2017. FDA's proposed labeling revisions were discussed for all sections.

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/s/

NATALIYA N FESENKO
01/02/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: December 5, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-23]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-23] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Tuesday, December 5, 2017**

Clarify whether the 599 patients enrolled between March 2007 and December 2012 in the second data collection (after the data cut-off date of January 2010) were graded for response using SWOG criteria and converted to RECIST or graded using RECIST criteria.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
12/05/2017

Fesenko, Nataliya

From: Fesenko, Nataliya
Sent: Friday, November 17, 2017 3:42 PM
To: Victor Paulus
Cc: Fesenko, Nataliya
Subject: NDA 208700 Proposed labeling - Response requested 5PM EST Friday, December 1, 2017
Attachments: NDA_208700_Label_to_AAA_11-17-2017.docx

Importance: High

Hello Dr. Paulus,

Please find attached the FDA's draft proposed labeling for NDA 208700. Our changes are tracked (if you are using Word 2016, please view in "All Markup"). Please accept the tracked changes that you agree with. If you would like to propose alternative language, please do so using tracked changes.

Please send us back an updated version of the label in Word format via email to me (Nataliya.Fesenko@fda.hhs.gov) by **EOB Friday, 12/01/17**, followed by formal submission to the NDA. If you do not accept all of our changes, please send both a redline and clean version of the label.

Please confirm receipt.

Thanks,
Nataliya

Nataliya Fesenko, Pharm.D., R.Ph.
Regulatory Health Project Manager

Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Center for Drug Evaluation & Research (CDER)
U.S. Food and Drug Administration
Office phone: 240-402-6376
Fax: 301-796-9849
Nataliya.Fesenko@fda.hhs.gov



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NATALIYA N FESENKO
11/17/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 17, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-22]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-22] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, December 1, 2017**




General Comments

1. Revise the dosage form statement, (b) (4) to read “Injection” (i.e., Lutathera (lutetium Lu 177 dotatate injection).
2. Revise the statement (b) (4) to read “For Intravenous Infusion (b) (4) (b) (4)” in mixed case letters. FDA recommends this (b) (4)
3. Remove the “Rx Only” statement from the yellow “Caution: Radioactive Materials” warning symbol since the “Rx Only” statement already appears adjacent to the product information.
4. Provide justification or revise for consistent unit of measurement across all labeling to improve dosing instructions. FDA notes inconsistent units of measurement when comparing the container labels and carton labeling (MBq, and mCi) to the Dosage and Administration section (GBq) of the PI. Inconsistent units of measurement for dosing increase the risk of wrong dose medication errors.
5. Consider adding the United States Distributor address to the container label and carton labeling to provide readily available US contact information for this product.
6. As proposed, the last two digits of the NDC numbers for the lead shielded carton labeling and the shipping carton labeling each have a different number. The lead

shielded carton labeling and the shipping carton labeling each provide one vial of Lutathera. Therefore, having two different NDC numbers for the carton labeling could cause confusion when ordering the product and when verifying product selection prior to dispensing. Revise the NDC numbers so that the last two digits which indicate the commercial package size are the same between the lead shielded carton labeling and the shipping carton labeling (i.e., 69488-003-01).

Container Label

7. Remove the (b) (4) statement, (b) (4) from the container and carton labels. This (b) (4) statement (b) (4) may cause confusion and medication errors.
8. Remove the (b) (4) statement, (b) (4) from the container and carton labels. This (b) (4) statement (b) (4) may cause confusion and medication errors.
9. Revise the container label so activity, production time, lot and expiration date information, which are critical for the use of the proposed drug product, are prominently displayed on the Principal Display Panel (PDP). This may be achieved by relocating other information to the side panel. Example layout below demonstrates our recommendation only (not to size, spacing, color, etc.). Also, ensure barcode placement (horizontal vs. vertical) can be easily scanned.

PDP	Side Panel
NDC# 69488-003-01	Rx only statement
Lutathera (lutetium Lu 177 dotatate injection)	Usual dosage: See Prescribing Information
Activity: _____ MBq (_____ mCi)	Storage and shelf life
Total Volume _____ mL	Warning statement
Concentration _____ MBq/mL (_____ mCi/mL)	Manufactured by information
End of Production Time: _____ Date: _____	 
Lot number _____	
Exp. date _____ Exp. time _____	 US contact information, such as distributor
For Intravenous Infusion After Dilution.	
Single-dose vial. Discard unused portion.	

Carton Labeling

10. Revise and relocate the statement (b) (4) to appear underneath the (b) (4) statement and to read, “Single-Dose Vial. Discard Unused Portion”.

11. To make the label appear less crowded, [REDACTED] (b) (4) [REDACTED] provide only the name of the manufacturer and the city, state and country. The full manufacturer contact information appears in the Prescribing Information.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
11/17/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 16, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-21]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-21] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Monday, November 20, 2017**

FDA performed the derivations on the attached page to get baseline metastatic disease in liver. Confirm that there are 100% patients with baseline metastatic disease in the liver per IRC target lesion assessment.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
11/16/2017



NDA 208700

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue
Suite 6902
New York, NY 10118

ATTENTION: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received July 26, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutetium Lu 177 Dotatate Injection, 370 MBq/mL.

We acknowledge receipt of your correspondence, dated and received November 8, 2017, requesting a review of your proposed proprietary name, Lutathera.

The user fee goal date to review your proposed proprietary name is February 6, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (301) 796-4901. For any other information regarding this application, contact Nataliya Fesenko, Regulatory Project Manager, in the Office of New Drugs at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Latonia Ford, MBA, BSN, RN
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LATONIA M FORD
11/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 14, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-20]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-20] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, November 15, 2017**

Please provide information on how to identify patients in the NETTER-1 study who have liver metastases. Is this information considered to be complete? Is there any variable captured in the database which can be used to quantitate the burden of metastatic disease in the liver?

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
11/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 13, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-19]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-19] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, November 15, 2017.**

- Provide an updated ADL database with creatinine clearance calculation estimated by Cockcroft-Gault equation using actual body weight and by Cockcroft-Gault equation using ideal body weight for all timepoints and patients in both NETTER-1 and Erasmus trials.
- Define the upper limit of normal for bilirubin AST, ALT, and serum creatinine in the NETTER-1 and Erasmus trials.
- Provide additional information to support and propose estimates based on US nuclear regulatory commission guidelines (8.39): Radiation can be detected in the urine up to **XX** days following LUTATHERA administration. (b) (4) minimize radiation exposure to patients, medical personnel, and household contacts consistent with institutional good radiation safety practices and patient management procedures. Prolonged elimination of lutetium Lu 177 (b) (4) in the urine is expected, however, based on the half-life of lutetium 177 and terminal half-life of lutetium Lu 177 (b) (4), greater than **XX**% will be eliminated within **XX** (weeks/days) after administration of LUTATHERA.
- Provide the location for the data to support the following labeling claim: (b) (4)

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
11/13/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 13, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #7

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA 0 -Tyr 3 -Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Brian Furmanski, Carol Broadnax, Denise Johnson-Lyles, Connie Cheng, Mei-Yean Chen, Huanyu Chen (Jade), Nataliya Fesenko, Stacy Shord, Ruthann Giusti, Tamara Johnson, Steven Lemery, Claire Myers, Kelie Reece, Janine Stewart

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 2.3 Premedication and Concomitant Medications
- 5 Warnings and Precautions
- 6.1 Clinical Trials Experience
- 7. Drug Interactions
- 8 Use in Specific Populations
- 17 Patient Counseling Information
Highlights of Prescribing Information

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/s/

NATALIYA N FESENKO
11/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 8, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-18]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-18] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Monday, November 13, 2017**

1. Address the information requests included in the mid-cycle communication agenda sent to you on November 6, 2017, with the exception of 3.b., as it was determined that a teleconference is no longer needed.

In addition, we have the following items that were mentioned during the November 7, 2017 mid-cycle teleconference but which were not included in the agenda.

2. Complete the attached table "Efficacy Results in Study NETTER-1".
3. Clarify how male patients were monitored for infertility and whether patients with decreased sperm counts and/or decreased inhibin-B with concomitant increase in FSH have been reported in the clinical trials database following Lutathera treatment. If so, provide case narratives with details concerning the identification, reversibility and duration of these events.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Table 1 Efficacy Results in Study NETTER-1

	Lutathera N=116	Octreotide LAR N=113
PFS by IRC (Mid-Cycle IR 3.e.i)		
Events (%)		
Progressive Disease, n (%)		
Death, n (%)		
Median in months (95% CI)		
Hazard ratio (95% CI) ^a		
P-Value ^b		
PFS by IRC (Mid-Cycle IR 3.e.ii)		
Events (%)		
Progressive Disease, n (%)		
Death, n (%)		
Median in months (95% CI)		
Hazard ratio (95% CI) ^a		
P-Value ^b		
PFS by IRC (Mid-Cycle IR 3.e.iii)		
Events (%)		
Progressive Disease, n (%)		
Death, n (%)		
Median in months (95% CI)		
Hazard ratio (95% CI) ^a		
P-Value ^b		
OS (Updated) (Mid-Cycle IR 3.f)		
Deaths (%)		
Median in months (95% CI)		
Hazard ratio* (95% CI) ^a		
P-Value ^{b,d}		
Objective Response Rate (ORR) by IRC (Mid-Cycle IR 3.g)		
ORR, % (95% CI)		
Complete response rate, n (%)		
Partial response rate, n (%)		
P-Value ^c		
Duration of Response, median in months (95% CI) (Mid-Cycle IR 3.h.)		

a: Hazard ratio (Lutathera compared to Octreotide LAR) based on the unstratified Cox model
b: Unstratified log rank test; c: Fisher's Exact test; NR: Not reached; NE: Not evaluable

Figure 2 K-M Curves for PFS in Study NETTER-1 (Mid-Cycle IR 3.e.i)

Figure 2 K-M Curves for PFS in Study NETTER-1 (Mid-Cycle IR 3.e.ii)

Figure 3 K-M Curves for PFS in Study NETTER-1 (Mid-Cycle IR 3.e.iii)

Figure 3 K-M Curves for Updated OS in Study NETTER-1 (Mid-Cycle IR 3.f)

Please provide related SAS code to validate your analysis results.

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/s/

NATALIYA N FESENKO
11/08/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 7, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #3

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: Carol Broadnax, Suzanne Demko, Elizabeth Everhart, Nataliya Fesenko, Ruthann Giusti, Kun He, Huanyu (Jade) Chen, Christos Mastroyannis, Tamara Johnson, Ann Marie Trentacosti, Cynthia Welsh, Denise Johnson-Lyles, Steven Lemery, Claire Myers, Kelie Reece

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 1 Indications and Usage
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 14 Clinical Studies

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/s/

NATALIYA N FESENKO
11/07/2017



NDA 208700

MID-CYCLE COMMUNICATION

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for for Lutathera (^{177}Lu -DOTA⁰-Tyr3-Octreotate, USAN - lutetium Lu 177 dotatate) 370 MBq/mL solution for infusion.

We also refer to the teleconference between representatives of your firm and the FDA on November 7, 2017. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me, at (240)-402-6376.

Sincerely,

{See appended electronic signature page}

Nataliya Fesenko, Pharm. D., R.Ph.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: November 7, 2017, 1:00 PM – 2:00 PM

Application Number: NDA 208700

Product Name: Lutathera (^{177}Lu -DOTA⁰-Tyr3-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Meeting Chair: Suzanne Demko, PA-C

Meeting Recorder: Nataliya Fesenko, Pharm.D.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S., Associate Director, DOP2/OHOP
Ruthann Giusti, M.D., Clinical Reviewer, DOP2/OHOP
Kun He, Ph.D., Statistical Associate Division Director, DBV/OB
Huanyu Chen (Jade), Ph.D., Statistical Reviewer, DBV/OB
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPV
Brian Furmanski, Pharm, D., Clinical Pharmacology Reviewer, OCP/DCPV
Elizabeth Everhart, DRISK Team Leader
Latonia Ford, Safety Regulatory Project Manager, OSE/PMS
Janine Stewart, DMEPA Reviewer
Cindy Welsh, M.D., Clinical Reviewer, DMIP
Kelie Reece, Ph.D., Regulatory Project Manager, DOP2/OHOP
Nataliya Fesenko, Pharm, D., Regulatory Project Manager, DOP2/OHOP
Claire Myers, Ph.D., Senior Regulatory Project Manager, DOP2/OHOP
Jeongmi Kim, Visiting Fellow, DOP1/OHOP

APPLICANT ATTENDEES

Debora Barton, M.D., Vice President and Head of Oncology
Stefano Buono, Chief Executive Officer
Jack Erion, Ph.D., Vice President R&D USA
Claude Hariton, Ph.D., D.Sc., Global Head Research & Development
Maurizio Mariani, M.D., Ph.D., DABT, Head Pre-Clinical Development
Victor Paulus, Ph.D., Head, Global Regulatory Affairs
Paola Santoro, Ph.D., Senior Clinical Project Manager

(b) (4) now Clinical Consultant
Thomas Thevenet, PharmD, Clinical Development Manager
(b) (4) CEO (b) (4)

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical

- a. FDA continues to have internal discussions regarding whether to expand the indication to include patients with non-midgut somatostatin-receptor-positive tumors based on data from the ERASMUS trial. Independently-reviewed images (e.g., on response rate based on RECIST) may be necessary to accurately describe the treatment effect in product labeling for these patients.
- b. The proposed label includes a Warning (Section 5.7) for neuroendocrine hormonal crises; however, FDA could not confirm the occurrence of these events in the application. Refer to information request 3.a. below.
- c. AAA will need to resolve discrepancies between AAA's and FDA's analyses of adverse events reported in Table 7. Refer to information request 3.b. below.
- d. Hepatotoxicity has been included in Section 5.3 of the proposed label; however, the risk of such events has not been adequately characterized. Refer to information request 3.c. below.
- e. We note that of the 59 patients treated with ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate who developed thrombocytopenia, only 6 patients recovered to baseline platelet counts during follow-up. Therefore, the time to platelet recovery reported in section 6.2 of the label may be misleading. Refer to information request 3.d. below.
- f. (b) (4)
Please see our information request 3.e. below.

Statistics

- g. There may be inconsistencies in the assessments of PFS, OS, ORR, and DoR. Refer to information requests 3.f. – 3.i. below.

Clinical Pharmacology

No significant issues have been identified to date.

Nonclinical

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

- a. Provide a summary of adverse events of neuroendocrine hormonal crises which occurred with $^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$ in the clinical trials database. Include case narratives as well as events related to $^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$ or similar compounds reported in the literature. Alternatively, provide a link to the place in the submission in which these events are described.
- b. We request a separate teleconference with your statistical team to clarify how the values in Table 7 were derived.
- c. Please provide an assessment of hepatotoxicity as defined by Riff and colleagues (Clin Nucl Med 2015; 40: 845-850) as related to the burden of metastatic disease in the liver to assess whether patients in the NETTER-01 trial with extensive liver involvement were at increased risk of hepatotoxicity following treatment with Lutathera.
- d. Provide an assessment of the degree of persistent thrombocytopenia in patients treated with Lutathera who developed thrombocytopenia but failed to recover to baseline and propose revised labeling to adequately describe this outcome.
- e. Clarify how male patients were monitored for infertility and whether patients with decreased sperm counts and/or decreased inhibin-B with concomitant increase in FSH have been reported in the clinical trials database following Lutathera treatment. If so, provide case narratives with details concerning the identification, reversibility and duration of these events.
- f. Reanalyze the PFS per IRC assessment using the date of randomization as starting time defining PFS based on the ITT population. Perform three analyses separately using the new calculated PFS time with the following three censoring rules:
 - i. as defined in the SAP

Mid-Cycle Communication

- ii. as defined in the SAP but use $2*12+1$ weeks (175 days) as 2 continues missing threshold
- iii. a PFS event should be assessed if a patient had disease progression or death regardless of whether the patient had missing scheduled visits, treatment discontinuation for toxicity, or new anticancer treatment started without progression

In addition, the date used in the censoring rule should not be imputed or replaced by the date of data cut-off.

- g. Reanalyze OS using the date of randomization as the starting time defining OS based on the ITT population. For alive patients, the date of last know alive date should not be replaced by the efficacy cut-off date.
- h. Provide ORR results based on the ITT population since the analysis based on the measurable disease population is a subgroup analysis.
- i. Provide duration of response results using the same censoring rules for PFS.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time. There is currently no need for a REMS; however, in the NDA, please provide the specific information that AAA will plan to communicate to all patients based on NRC requirements (and how this information will be communicated).

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

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/s/

NATALIYA N FESENKO
01/16/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 6, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700: Agenda for Mid-Cycle Communication

Meeting Date and Time: November 7, 2017, 1:00 PM – 2:00 PM
Application Number: NDA 208700
Product Name: Lutathera (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults
Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)
Meeting Chair: Suzanne Demko, PA-C
Meeting Recorder: Nataliya Fesenko, Pharm.D.

FDA ATTENDEES (tentative)

Steven Lemery, M.D., M.H.S., Associate Director, DOP2/OHOP
Suzanne Demko, PA-C, Clinical Team Leader, DOP2/OHOP
Ruthann Giusti, M.D., Clinical Reviewer, DOP2/OHOP
Kun He, Ph.D., Statistical Associate Division Director, DBV/OB
Huanyu Chen (Jade), Ph.D., Statistical Reviewer, DBV/OB
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, OCP/DCPV
Brian Furmanski, Pharm, D., Clinical Pharmacology Reviewer, OCP/DCPV
Whitney Helms, Ph.D., Nonclinical Team Leader, DHOT/OHOP
Anwar Goheer, Ph.D., Nonclinical Reviewer, DHOT/OHOP
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead, ONDQA
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA
Krishnakali Ghosh, Ph.D., Facilities, OPQ/OPF

APPLICANT ATTENDEES

TBD

1.0 INTRODUCTIONS AND INTRODUCTORY COMMENTS

2.0 SIGNIFICANT REVIEW ISSUES

Clinical

- a. FDA continues to have internal discussions regarding whether to expand the indication to include patients with non-midgut somatostatin-receptor-positive tumors based on data from the ERASMUS trial. Independently-reviewed images (e.g., on response rate based on RECIST) may be necessary to accurately describe the treatment effect in product labeling for these patients.
- b. The proposed label includes a Warning (Section 5.7) for neuroendocrine hormonal crises; however, FDA could not confirm the occurrence of these events in the application. Refer to information request 3.a. below.
- c. AAA will need to resolve discrepancies between AAA's and FDA's analyses of adverse events reported in Table 7. Refer to information request 3.b. below.
- d. Hepatotoxicity has been included in Section 5.3 of the proposed label; however, the risk of such events has not been adequately characterized. Refer to information request 3.c. below.
- e. We note that of the 59 patients treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$ who developed thrombocytopenia, only 6 patients recovered to baseline platelet counts during follow-up. Therefore, the time to platelet recovery reported in section 6.2 of the label may be misleading. Refer to information request 3.d. below.

Statistics

- f. There may be inconsistencies in the assessments of PFS, OS, ORR, and DoR. Refer to information requests 3.e. – 3.h. below.

Clinical Pharmacology

No significant issues have been identified to date.

Nonclinical

No significant issues have been identified to date.

3.0 INFORMATION REQUESTS

- a. Provide a summary of adverse events of neuroendocrine hormonal crises which occurred with $^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$ in the clinical trials database. Include case narratives as well as events related to $^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$ or similar compounds reported in the literature. Alternatively, provide a link to the place in the submission in which these events are described.
- b. We request a separate teleconference with your statistical team to clarify how the values in Table 7 were derived.

- c. Please provide an assessment of hepatotoxicity as defined by Riff and colleagues (Clin Nucl Med 2015; 40: 845-850) as related to the burden of metastatic disease in the liver to assess whether patients in the NETTER-01 trial with extensive liver involvement were at increased risk of hepatotoxicity following treatment with Lutathera.
- d. Provide an assessment of the degree of persistent thrombocytopenia in patients treated with Lutathera who developed thrombocytopenia but failed to recover to baseline and propose revised labeling to adequately describe this outcome.
- e. Reanalyze the PFS per IRC assessment using the date of randomization as starting time defining PFS based on the ITT population. Perform three analyses separately using the new calculated PFS time with the following three censoring rules:
 - i. as defined in the SAP
 - ii. as defined in the SAP but use 2*12+1 weeks (175 days) as 2 continues missing threshold
 - iii. a PFS event should be assessed if a patient had disease progression or death regardless of whether the patient had missing scheduled visits, treatment discontinuation for toxicity, or new anticancer treatment started without progression

In addition, the date used in the censoring rule should not be imputed or replaced by the date of data cut-off.

- f. Reanalyze OS using the date of randomization as the starting time defining OS based on the ITT population. For living patients, the last know alive date should not be replaced by the efficacy cut-off date.
- g. Provide ORR results based on the ITT population since the analysis based on the measurable disease population is a subgroup analysis.
- h. Provide duration of response results using the same censoring rules for PFS.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

There are no major safety concerns identified at this time. There is currently no need for a REMS; however, in the NDA, please provide the specific information that AAA will plan to communicate to all patients based on NRC requirements (and how this information will be communicated).

5.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an advisory committee meeting.

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/s/

NATALIYA N FESENKO
11/06/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 6, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Internal Labeling Meeting #1

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees: John Amartei, Carol Broadnax, Suzanne Demko, Elizabeth Everhart, Nataliya Fesenko, Latonia Ford, Ruthann Giusti, Denise Johnson-Lyles, Steven Lemery, Eldon Leutzinger, Claire Myers, Janine Stewart

Meeting Summary:

FDA's proposed labeling revisions were discussed for the following sections:

- 3 Dosage Forms and Strengths
- 11 Description
- 16 How Supplied/Storage and Handling
- Carton and container labels

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/s/

NATALIYA N FESENKO
11/07/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 30, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of October Internal Midcycle Meeting

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA 0 -Tyr 3 -Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial

Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees:

Steven Lemery, Patricia Keegan, Suzanne Demko, Ruthann Giusti, Kun He, Huanyu Chen (Jade), Hong Zhao, Brian Furmanski, Whitney Helms, Anwar Goheer, Steven Kinsley, Eldon Leutzinger, Elizabeth Everhart, Mei-Yean Chen, Stacy Shord, Carole Broadnax, Cindy Welsh, Denise Johnson-Lyles, Janine Stewart, Jinzhong Liu, Krishna Gosh, Latonia Ford, Peter Waldron, Tamara Johnson, Nataliya Fesenko, Claire Myers

Meeting Summary:

1. Clinical, statistical, and clinical pharmacology teams presented their review updates.
2. Nonclinical and OMPQ/facilities teams had no new information to present at this time.
3. The team discussed the need for a Mid-Cycle Communication, as this resubmission is not subject to PDUFA V, and agreed to hold a post-mid-cycle teleconference with the Applicant on November 7, 2017.

Action items:

1. The assigned RPM, Dr. Fesenko will set up a teleconference with AAA to convey the deficiencies identified to date.

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/s/

NATALIYA N FESENKO
11/21/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 27, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-17]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-17] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Tuesday, October 31, 2017**

1. Provide the meaning of VISIT which is classified as "Eligibility", "Eligibility 1", or "Eligibility 2"
2. Provide the meaning of EPOCH which is classified as "RUN- IN" and "SCREENING"
3. Explain how to capture baseline tumor or lesion related information in TR and TU domains per IRC assessment.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/27/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October, 24, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-16]

Advanced Accelerator Applications USA, Inc.
 Attention: Victor Paulus, Ph.D.
 Global Head, Regulatory Affairs
 350 Fifth Avenue, Suite 6902
 New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-16] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Thursday, October 26, 2017**

- There were 98 (45%) patients with at least 15 days, and 17 patients with at least 30 days delayed first treatment post randomization, which were mainly in the experimental arm (see details in below SAS output). Provide reasoning and analyses addressing the impact caused by the imbalanced delayed first treatment to evaluate the accuracy of the PFS results.

As least 15 days delayed treatment post randomization.

LU	83	84.69	83	84.69
OCTREOTI	15	15.31	98	100.00

As least 30 days delayed treatment post randomization.

USUBJID	TRT01P	RANDDT	TRTSDT	DIFFRS
NETTER1-IT04-001	OCTREOTI	06SEP2012	11OCT2012	35
NETTER1-UK01-009	LU	19MAR2014	24APR2014	36
NETTER1-UK01-010	LU	17JUL2014	28AUG2014	42
NETTER1-US01-011	LU	23JAN2015	26FEB2015	34
NETTER1-US05-003	LU	21JUN2013	28AUG2013	68
NETTER1-US05-005	LU	02AUG2013	18SEP2013	47
NETTER1-US07-003	LU	20DEC2013	23JAN2014	34
NETTER1-US07-006	LU	21FEB2014	09APR2014	47
NETTER1-US08-003	LU	03APR2014	08MAY2014	35

NETTER1-US08-005	LU	28MAY2014	23JUL2014	56
NETTER1-US08-007	LU	08SEP2014	10DEC2014	93
NETTER1-US08-015	LU	18NOV2014	06MAR2015	108
NETTER1-US10-003	LU	24MAR2014	30APR2014	37
NETTER1-US13-029	LU	10DEC2013	17JAN2014	38
NETTER1-US14-001	LU	24JUN2013	06NOV2013	135
NETTER1-US14-004	LU	23AUG2013	10OCT2013	48
NETTER1-US14-010	LU	16JAN2014	26FEB2014	41

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/24/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 23, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-14]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-14] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, October 25, 2017**

For the Erasmus trial:

1. Clarify whether there was a unique, stand-alone clinical protocol under which patients were enrolled and treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.
2. Provide an English translation of the Informed Consent Document used to consent patients prior to 2002.
3. Clarify how the subset of 51 Dutch patients were selected from the larger set of 98 Dutch patients with progressive midgut NEC for review by the Independent Radiology Review Committee.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/23/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 23, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-15]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-15] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, October 25, 2017**

This is a follow-up to our information request [IR-12], dated October 11, 2017.

- Clarify the definition used to determine the time to platelet recovery.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/23/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 23, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of October Internal Team Meeting

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial

Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees:

Steven Lemery, Suzanne Demko, Ruthann Giusti, Kun He, Huanyu Chen (Jade), Brian Furmanski, Whitney Helms, Anwar Goheer, John Amartey, Krishnakali Ghosh, Mei-Yean Chen, Carolyn McCloskey, Cindy Welsh, Nataliya Fesenko, Claire Myers

Meeting Summary:

1. Disciplines presented review updates; reviews are ongoing and on schedule.
2. RPM Nataliya Fesenko reviewed milestone dates and deliverables, and consult requests.

Action items:

1. Team will continue working on their reviews and will prepare for the mid-cycle meeting.

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/s/

NATALIYA N FESENKO
01/16/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 11, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-12]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-12] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, October 18, 2017**

We acknowledge your October 6, 2017 response to our [IR-09] dated October 2, 2017 and have the following clarifications and additional requests concerning section 6.1 (Clinical Trials Experience) of your proposed US Package Insert:

1. For all safety analyses, including laboratory analyses, patient DE-01-003 who received no Lutathera should be classified with the Octreotide LAR control group. (All efficacy analysis should be conducted with the intent-to-treat study population).
2. Tables 7 and 8 should be re-titled as follows and the content of the table revised accordingly:

a. Table 7:  (b) (4)

¹National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

b. Table 8:  (b) (4)

¹National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03

3. For Tables 7 and 8, round all percent values to a whole number.
4. Delete (b) (4) from Table 7 as these are more accurately reported in table 8 based on actual laboratory monitoring.

(b) (4)

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/11/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 11, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-13]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-13] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Thursday, October 12, 2017**

 (b) (4)
If summary

information concerning this safety information has been provided to the NDA, provide the location of this information.

If this information has not been formally submitted to the NDA, provide a summary of exposure and adverse events reported to AAA under these programs. Also provide adverse event reports concerning deaths, serious adverse events and adverse events of special interest reported under these programs.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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NATALIYA N FESENKO
10/11/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 11, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Applicant Teleconference re: Manufacturing Facilities

FDA Attendees:

Steven Lemery, M.D., M.H.S., Associate Director, DOP2
Ghosh, Krishnakali, Ph.D., Facility Reviewer, OPQ/OPF/DIA/BIII
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA - API/DP/Process
Danae Christodoulou, Application Branch Chief, OPQ/ONDP/DNDPII/BVI
Eric Duffy, Division Director, OPQ/ONDP/DNDPII
Ruthann Giusti, M.D., Clinical Reviewer, Medical Officer, DOP2
Nataliya Fesenko, Pharm. D., Regulatory Health Project Manager, DOP2
Kelie Reece, Ph.D., Regulatory Health Project Manager, DOP2

Advanced Accelerator Applications USA, Inc. (AAA) Attendees:

Beth Lakey, D.Ph., Manager Regulatory Affairs
Stefano Buono, CEO
James Cook, COO AAA US
Philippe Dass, Pharm.D., Global Pharmaceutical Coordinator, QP
Francesco DiPaolo Ph.D., Lutathera Production Expert
Bill Diamantopoulos, Pharm.D., Facility Manager
Paul Bigio, Quality Assurance Manager
Victor Paulus, Ph.D., Head, Regulatory Affairs

Summary:

The FDA Facility and Product Quality teams requested this teleconference with AAA to discuss the addition of Millburn NJ manufacturing facility.

On August 29, 2017, under IND 077219, AAA submitted information for the addition of a new manufacturing site in Millburn, New Jersey, ¹⁷⁷Lu-DOTA0-Tyr³-Octreotate manufacturing site, in order to supply investigational product, ¹⁷⁷Lu-DOTA0-Tyr³-Octreotate, strictly for use in Protocol AAA-177Lu-03, an intermediate-size, expanded access program (EAP)
<\\cdsesub1\evsprod\ind077219\0087\ml\us\I2-cover-letter\eap-cover-letter-millburn-addition.pdf>

On September 14, 2017, FDA sent an information request to AAA requesting that they confirm the Millburn, NJ manufacturing facility was ready for FDA inspection. On September 18, 2017, AAA responded and stated that the facility was not ready for an FDA pre-approval inspection. AAA stated that they plan to have the facility inspection ready in the first quarter of 2018, as part of a future supplement to their NDA.

During the teleconference FDA asked AAA to elaborate why the Millburn facility was not ready for a pre-approval inspection and to identify what, if any GMP elements were lacking.

AAA explained that the Millburn facility was compliant with Phase 3 GMP requirements for clinical trials and that two manufacturing lines are fully qualified and functional for manufacturing. However, AAA stated that the facility is not ready for the rigor of a pre-approval inspection for all the manufacturing lines as was done at the Italy manufacturing facilities. The data for QA in Millburn are complete with most data having been submitted with the August 29, 2017, amendment to IND 077219. AAA stated that while all Quality Systems were in place, and data have been generated and reviewed, the necessary reports are not yet finalized and ready for inspection.

FDA reiterated that Millburn facility needs to be inspected as soon as possible as there is no inspectional history available for this site. FDA noted some of the essential elements that are required for a new site inspection for the aseptic manufacturing of sterile drugs.

[REDACTED] (b) (4)

FDA inquired about the Nuclear Regulatory Commission (NRC) license status. AAA responded that the firm obtained Radioactive Materials License in the state of NJ.

AAA and FDA discussed importation and shipping challenges of Lutathera for the Expanded Access Program (EAP).

AAA acknowledged the Millburn manufacturing facility **will only supply** investigational product for use in the EAP. [REDACTED] (b) (4)

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/s/

NATALIYA N FESENKO
01/04/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 10, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-11]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-11] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, October 13, 2017**

Provide SAS program(s) with adequate documentation used for QoL analyses in the CSR V2 Section 11.4.1.5.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/10/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 3, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-10]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-10] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, October 13, 2017**

In order for FDA to reanalyze the pharmacokinetic data in the Erasmus and NETTER-1 studies, provide a time order dataset with the following columns for each study:

- | | | | |
|----|--|----|----------------------------|
| 1 | subject ID | 16 | sample type urine |
| 2 | dose ng/ml | 17 | amino acid sol |
| 3 | administered activity (GBq) | 18 | age |
| 4 | peptide specific activity (GBq/ μ g) | 19 | weight |
| 5 | nominal time | 20 | gender |
| 6 | actual time | 21 | bilirubin |
| 7 | time since first dose | 22 | Alanine Aminotransferase |
| 8 | concentration ng/ml | 23 | Aspartate Aminotransferase |
| 9 | concentration kBq/mL | 24 | Lactate Dehydrogenase |
| 10 | concentration percent activity | 25 | Basophils |
| 11 | concentration sample counts | 26 | Eosinophils |
| 12 | calibration factor | 27 | Hematocrit |
| 13 | baseline creatinine clearance | 28 | Hemoglobin |
| 14 | creatinine clearance | 29 | Lymphocytes |
| 15 | sample type blood | 30 | Urea Nitrogen |
| | | 31 | Visit |

Refer to the PC dataset submitted under Module 5.3.5.1 on April 28, 2016 and the abbreviated example below for the general structure of a PC dataset. Please request a teleconference with FDA if further clarification is needed.

StudyID	USUBJID	Sample	Time since first dose Col Time	Nominal Col Time (h)	Conc ng/ml	Conc kBq/mL	Amino Acid sol	Etc...
Netter-1	1	Blood	0.31	0.25	5.11	237.6	Vamin-18	.
.
.
.
Netter-1	1	Blood	26.5	24	37.86	1456.7	Vamin-18	.
Netter-1	1	Urine	0.31	0.25	0.1	0.7	Vamin-18	.
.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
10/03/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 2, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-09]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-09] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, October 6, 2017**

1. We refer to Table 7 in the proposed US Package Insert for Lutathera. Provide a revised version of this table showing the frequency of all adverse reactions CTCAE Grades 1-4 occurring on or within 30 days following treatment, regardless of attribution, and which occur in excess in the Lutathera arm. Include in the table only adverse reactions for which the between arm difference (all grades) is greater than or equal to 5% or for which the between arm difference (Grades 3-4) is greater than or equal to 2%.
2. Re-code patient DE03-001 who was randomized to receive Lutathera but received only Octreotide LAR with the Octreotide LAR control patients.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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NATALIYA N FESENKO
10/02/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 2, 2017
From: Nataliya Fesenko, Pharm.D., DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of October Internal Team Meeting

NDA: 208700
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)
Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 ml single-dose vial
Submitted and Received: July 26, 2017
PDUFA Date: January 26, 2018

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumours in adults.

Attendees:

Steven Lemery, Suzanne Demko, Ruthann Giusti, Kun He, Huanyu Chen (Jade), Wentao Fu, Brian Furmanski, Whitney Helms, Anwar Goheer, John Amartey, Danae Christodoulou, Krishnakali Ghosh, Janine Stewart, Mei-Yean Chen, Carolyn McCloskey, Connie Cheng, Cindy Welsh, Nataliya Fesenko, Claire Myers, Kelie Reece

Meeting Summary:

1. Disciplines presented review updates; reviews are ongoing and on schedule.
2. RPM Fesenko reviewed milestone dates and deliverables, and consult requests.
3. The team discussed OHOP multidisciplinary (“Unireview”) review process.
4. OMPQ/facilities team expressed the need for further discussions with AAA to ensure manufacturing capabilities and facility licensing.

Action Items:

1. RPM Fesenko will set up a teleconference with AAA to discuss manufacturing capabilities and facility licensing.

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/s/

NATALIYA N FESENKO
01/16/2018



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 28, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-08]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-08] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, October 6, 2017**

We refer to Table 11-51 on Page 137 of 232 of the Clinical Study Report for the NETTER-1 trial. Provide revised tables demonstrating the completeness of health-related quality of life measurements. Provide a separate table for

- (1) patients completing the EORTC QLQ-30 questionnaire,
- (2) patients completing the QLQ-G.I.NET21 questionnaire, and
- (3) patients completing both questionnaires.

Modify the format of Table 11-51 to indicate the total number of patients in each study arm on study at each time point, the total number of patients in each study arm completing questionnaire(s) at each time point, and the percentage of eligible patients in each study arm who completed questionnaire(s) at each time point.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
09/28/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 21, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-07]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-07] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, September 22, 2017.**

After reviewing the Case Report Forms, we are unable to confirm the dose(s) of ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate reported in the ADEX file to have been administered to the patients listed below. Clarify how the doses entered as ACTDOSE into the ADEX file were confirmed.

SUBJID	EXSEQ	EXSTDTC	EXDOSE	EXDOSU	MEASACTI	MEASRACT	ACTDOSE
ES01-007	1	2014-11-06T12:30	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
ES01-007	2	2015-01-08T12:15	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
ES01-008	1	2015-04-15T00:00	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
IT05-004	1	2013-10-09T15:35	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
IT05-004	2	2013-12-04T15:24	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
IT05-004	3	2014-02-12T15:22	. GBq	According to protocol (7.4 GBq, 200 mCi)			7.4
UK06-003*	1	2014-01-30T09:40	7.9 GBq	According to protocol (7.4 GBq, 200 mCi)	7.99	0.09	7.9
UK06-003*	2	2014-03-27T10:15	7.934 GBq	According to protocol (7.4 GBq, 200 mCi)	8.03	0.096	7.934
UK06-003*	3	2014-05-20T10:15	7.934 GBq	According to protocol (7.4 GBq, 200 mCi)	8.03	0.096	7.934
UK06-003*	4	2014-07-18T09:45	8 GBq	According to protocol (7.4 GBq, 200 mCi)	8.1	0.1	8

*The CRF for this patient does not record that ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate was administered.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
09/21/2017

From: Biable, Missiratch (Mimi)
To: "[Victor Paulus](#)"
Cc: [Beth Lakey \(beth.lakey@adacap.com\)](mailto:beth.lakey@adacap.com); [Fesenko, Nataliya](#)
Subject: NDA 208700: Clinical Information Request -- Response Required
Date: Wednesday, September 20, 2017 2:08:00 PM
Importance: High

Dear Victor,

On behalf of your RPM, Nataliya Fesenko, please respond to the following clinical information request **as soon as possible**:

We note that patient NETTER1-DE03-001 is identified as part of the safety population, however, a review of the case report form for this patient indicates that this patient did not receive any administrations of 177Lu-DOTA0-Tyr3-Octreotate. Why is this patient included in the safety population?

If you have any questions, please contact me and kindly respond to confirm receipt of this communication.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
09/20/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 14, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-05]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-05] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Monday, September 18, 2017**

We refer to your letter dated August 29, 2017, submitted to IND 077219, regarding the addition of Millburn, NJ manufacturing facility. Submit an updated 356h form for NDA 208700 that includes the Millburn, NJ manufacturing facility. In the cover letter, state that investigational product will be shipped to the clinical sites from this new facility. In addition, confirm the Millburn, NJ manufacturing facility's readiness for FDA inspection.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
09/14/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 31, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-04]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please respond to the following information request [IR-04] via email to me (Nataliya.Fesenko@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Thursday, September 7, 2017**

State whether the overall response data from Dutch patients in the EMC trial was centrally reviewed for all tumor sites or only for the midgut carcinoid tumors.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
08/31/2017



NDA 208700

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

We acknowledge receipt on July 26, 2017, of your July 26, 2017, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera ($^{177}\text{Lu-DOTA}^0\text{-Tyr3-Octreotate}$, USAN - lutetium Lu 177 dotatate) 370 MBq/mL solution for infusion.

We consider this a complete, class 2 response to our December 19, 2016, action letter. Therefore, the user fee goal date is January 26, 2018.

If you have any questions, call Nataliya Fesenko, Pharm.D., Regulatory Health Project Manager, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Monica Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

MONICA L HUGHES
08/25/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 25, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-03 clarification]

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Global Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

The purpose of this clarification to [IR-03] is to provide the revised deadline below. (The same three items were originally sent on August 23, 2017.)

Please respond to the following information request [IR-03] via email to me (Nataliya.Fesenko@fda.hhs.gov), copying (Claire.Myers@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Monday, August 28, 2017**

1. During the review of the PC dataset, the FDA noted that the time at which the samples were collected (actual and nominal) is absent from the dataset. Was the revised summary of clinical pharmacology derived from the dataset submitted to the FDA?
 - a. Provide updated PC datasets with the actual and nominal times at which plasma PK samples were collected for both Erasmus and NETTER-1 studies.
 - b. Confirm with the updated dataset that the values reported in the summary of clinical pharmacology are accurate.
2. Submit the SAS transports files for all datasets used in analysis of intrinsic and/or extrinsic factors on ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate dosimetry. Provide a description of each data item in a define file and mode codes or control streams and output listings.
3. Provide a point-by-point breakdown of how each deficiency identified by the FDA in the Complete Response Letter was addressed by AAA.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

CLAIRE E MYERS
08/25/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 24, 2017
From: Claire Myers, Ph.D., on behalf of Nataliya Fesenko, Pharm.D., R.Ph.,
DOP2/OHOP/CDER
Subject: NDA 208700: Minutes of Applicant Teleconference re: Clinical Pharmacology
[IR-03]

FDA Attendees:

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer
Claire Myers, Ph.D., Sr. Regulatory Health Project Manager

Applicant Attendees:

From Advanced Accelerator Applications USA, Inc. (AAA)

Stefano Buono, CEO

Daniela Chicco, Ph.D., Preclinical

Jack Erion, Ph.D., VP, R&D

Beth Lakey, D.Ph., Manager, Regulatory Affairs

Lauren Maynard, Statistician

Maurizio Mariani, M.D., Ph.D., DABT, Head of Preclinical Development

Victor Paulus, Ph.D., Regulatory Affairs

Paola Santoro, Ph.D., Director, Clinical Development

Thomas Thevenet, Clinical Development Manager and Statistician

From (b) (4)

(b) (4) President (b) (4) and Consulting Statistician for AAA

Summary:

During a teleconference on August 24, 2017, which was requested by FDA, AAA and FDA discussed information request [IR-03] (sent August 23, 2017) regarding potential issues within the resubmitted application. AAA provided the location of the PK sample collection time in the supplemental PC (SUPPC) dataset. AAA also provided the location of the dataset for the evaluation of intrinsic and/or extrinsic factors of 177Lu-DOTA0-Tyr3-Octreotate. AAA agreed to provide a detail roadmap regarding the location of the PK sample collection time and mode codes or control streams and output listings for the evaluation of intrinsic and/or extrinsic factors of 177Lu-DOTA0-Tyr3-Octreotate. At FDA's request, AAA agreed to provide a point-by-point breakdown of how they addressed each deficiency identified by the FDA in the Complete Response Letter.

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/s/

NATALIYA N FESENKO
08/31/2017

Reece, Kelie

From: Reece, Kelie
Sent: Wednesday, August 23, 2017 11:03 AM
To: 'beth.lakey@adacap.com'
Cc: 'victor.paulus@adacap.com'; Myers, Claire
Subject: NDA 208700: Clinical Pharmacology Information Request; in preparation for 8/24/17 teleconference

Dear Dr. Lakey,

In preparation for the **Thursday, August 24, 2017** teleconference, please respond to the following Clinical Pharmacology Information Request via email to Claire.Myers@fda.hhs.gov (cc Kelie.Reece@fda.hhs.gov), including an itemized response, followed by formal submission to your IND.

1. During the review of the PC dataset, the FDA noted that the time at which the samples were collected (actual and nominal) is absent from the dataset. Was the revised summary of clinical pharmacology derived from the dataset submitted to the FDA?
 - a. Provide updated PC datasets with the actual and nominal times at which plasma PK samples were collected for both Erasmus and NETTER-1 studies.
 - b. Confirm with the updated dataset that the values reported in the summary of clinical pharmacology are accurate.
2. Submit the SAS transports files for all datasets used in analysis of intrinsic and/or extrinsic factors on 177Lu-DOTA0-Tyr3-Octreotate dosimetry. Provide a description of each data item in a define file and mode codes or control streams and output listings.
3. Provide a point-by-point breakdown of how each deficiency identified by the FDA in the Complete Response Letter was addressed by AAA.

Please confirm receipt.

Thank you,
Kelie

Kelie Reece, Ph.D.

Regulatory Health Project Manager

**Center for Drug Evaluation and Research
Office of Hematology & Oncology Products
Division of Oncology Products 2
U.S. Food and Drug Administration**

Tel: 240-402-6397

Fax: 301-796-9849

Kelie.Reece@fda.hhs.gov



 Follow [@FDAOncology](https://twitter.com/FDAOncology) on Twitter

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/s/

KELIE M REECE
08/23/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 17, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-02]

Advanced Accelerator Applications USA, Inc.
Attention: Beth Lakey, R.Ph.
Manager, Regulatory Affairs - US
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Ms. Lakey:

Please respond to the following information request [IR-02] via email to me (Nataliya.Fesenko@fda.hhs.gov, copying Claire.Myers@fda.hhs.gov), followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Friday, September 1, 2017**

AAA did not address below statistical comments as stated in the FDA's Complete Response Letter dated on the October 21, 2016:

- As required per 21 CFR 314.50, provide safety and efficacy subgroup analyses for gender, age, and racial subgroups. Also provide subgroup analyses based on stratification factors and any other important disease characteristics.
- Provide DSMB meeting minutes from the NETTER and ERASMUS trials.
- Provide all necessary SAS programs, SAS macro, SAS format library, and adequate documents in order to duplicate the analysis datasets derivation from the raw dataset and the analysis results in the CSR and USPI.

Hence, please provide the following:

1. Provide the SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets.

2. Provide the SAS programs with adequate document(s) used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs. Specifically, provide SAS programs and overview of SAS programs for Tables 14.1.1.1, 14.1.1.4, 14.1.2.1.1, 14.1.2.2.1, 14.1.2.3.1, 14.1.2.4.1, 14.1.2.5.1, 14.1.2.6.1, 14.1.2.7.1, 14.1.2.8.1, 14.1.2.9.1, 14.1.2.10.1, 14.1.2.13.1, 14.1.2.14.1, 14.1.2.15.1, 14.1.2.16.1, 14.1.2.17.1, 14.1.2.18.1, 14.1.2.19.1, 14.1.3.1.1, 14.1.3.2.1, 14.1.3.3.1, 14.2.1.1.1-14.2.1.16, 14.2.2.1.1, 14.2.2.1.3, 14.2.2.1.4, 14.2.2.2.1, 14.2.2.2.3, 14.2.3.1, 14.2.3.2, 14.2.3.3, 14.2.3.4, 14.2.3.5, 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.5.1, 14.2.9.1, and 14.2.9.2.
3. Provide subgroup analyses for efficacy and safety endpoints by race, age, and gender.
4. For NETTER study, provide DSMB meeting minutes which were held on the following dates:
 - 26-Jun-2013 (administrative meeting)
 - 11-Nov-2013 (10% of Lutathera administrations)
 - 23-Jan-2014 (25% of Lutathera administrations)
 - 28-Apr-2014 (25% of anticipated PFS events)
 - 11-Aug-2014 (50% of Lutathera administrations)
 - 16-Oct-2014 (50% of anticipated PFS events)
 - 26-Feb-2015 (75% of anticipated PFS events)
 - 24-Jun-2015 (just prior to 100% anticipated PFS events)The DSMB chairman's memo or report were found for the above-listed DSMB meetings in the Module 1 meeting folder except for the one held on June 24, 2015. Instead, the reviewer found DSMB meeting minutes for a meeting held on October 28, 2016.
5. Please clarify how many planned and unplanned PFS and OS analyses AAA had conducted for NETTER study. The O'Brien-Fleming boundary should be used to get a valid alpha allocation for PFS and OS (except FDA required OS analysis) analyses between multiple planned and unplanned looks.
6. Provide DSMB meeting minutes from the ERASMUS trials.
7. Provide supportive PFS analysis which uses the same censoring rules as Table 11-18 except treating no documented PDs as PD events. In the summary of analysis results table, provide reasons for events (death and PD), and censored. Related data and SAS program(s) should be provided to help the reviewer to duplicate this analysis results.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

CLAIRE E MYERS
08/17/2017

Planning Meeting Minutes
August 17, 2017

NDA: 208700 - 505 (b)(1) New Molecular Entity, Class 2 Resubmission
Product: Lutathera (177Lu-DOTA0-Tyr3-Octreotate) solution for intravenous infusion; 370 MBq/mL, 30 mL single-dose vial
Submission Date: July 26, 2017
Received Date: July 26, 2017
PDUFA goal: **January 26, 2018**
Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)

Proposed Indication: Treatment of somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut and hindgut, neuroendocrine tumors in adults.

Attendees:

Steven Lemery, M.D., M.H.S., Associate Director, DOP2 (Signatory)
Suzanne Demko, PA-C, Clinical Team Leader (CDTL)
Ruthann Giusti, M.D., Medical Officer (DOP 2), Clinical Reviewer
Monica Hughes, M.S., CPMS, DOP2
Kun He, Ph.D., Statistics Team Leader
Huanyu (Jade) Chen, Ph.D., Statistics Reviewer
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Brian Furmanski, Pharm, D., Clinical Pharmacology Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader
Steven Kinsley, Ph.D., ONDQA, Regulatory Business Process Manager (RBPM)
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead (ATL)
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA
Mei-Yean Chen, Pharm.D., DRISK reviewer
Giang Ho, Clinical Pharmacology intern
Claire Meyers, Ph.D., Regulatory Health Project Manager
Kelie Reece, Ph.D., Regulatory Health Project Manager

Additional team members not available for this meeting:

Anwar Goheer, Ph.D., Nonclinical Reviewer
Nataliya Fesenko, Pharm.D., R.Ph., Regulatory Health Project Manager
Krishnakali Ghosh, Ph.D., Facilities
Elizabeth Everhart, DRISK Team Leader

Discussion Summary:

The following is a high-level summary of the internal discussion that occurred during this planning meeting; including, the overall review team's goals/timelines, meetings to be scheduled, and consults to be requested to assist DOP2 with the overall review of this resubmission.

- Core disciplines discussed whether the submission is a complete response addressing all the deficiencies in the complete response letter. Consensus: **Yes, this is a complete response to our December 19, 2016 letter.**
- This was confirmed to be a Class 2 resubmission.

- Core Discipline's Overview/Initial Impressions of the Resubmission:
 - **Clinical** (Discipline-specific comments appeared in the CR letter):
 - There is some concern about data provenance (tumor measurements). The specific concern related to the observation that one patient listed in the treatment arm was noted not to have received LU-177-Octreotate. Two patients were noted to have imputed doses and one patient noted to have doses that were not confirmed in the CRF.
 - There are still some missing safety data (e.g., labs). Labs appeared to be reported in the analysis file ADLB in inconsistent units and values missing.
 - CRF/narrative links appear to have been corrected
 - Overall, the completeness and quality of the data is an improvement over the original submission; most organizational issues appear to have been addressed.
 - **Statistics** (Discipline specific comments appeared in the CR letter):
 - There are some concerns, initial concerns will be addressed via an upcoming Information Request (IR); these issued are expected to be resolvable. **Post-meeting addendum:** [IR-02] was sent 8/17/17, received 8/31/17.
 - **Facilities** (Discipline specific comments appeared in the CR letter):
 - Facilities reviewer noted before this meeting that no re-inspection is needed of the 3 international manufacturing sites that had OAI 483 citations in the previous review cycle, and noted that all issues appear to have been satisfactorily addressed.
 - Note: Inspection may be needed for the new manufacturing facility in New Jersey, included as part of this complete response. **Post-meeting addendum:** AAA confirmed that the new facility is used only for expanded access program (IND 077219). It is not ready for FDA inspection at this time.
 - **Clin Pharm** (Discipline specific comments appeared in the CR letter): Most issues appear to have been addressed. Clin Pharm requested an ad hoc applicant teleconference to discuss issues identified, prior to sending a formal IR. **Post-meeting addendum:** teleconference took place on August 24, 2017
 - **Nonclinical:** (No Discipline specific comments appeared in the CR letter): Confirmed that there are no new review issues; review was completed in previous cycle.
 - **CMC:** (No Discipline specific comments appeared in the CR letter): No changes expected; review was completed in previous review cycle.
- Regarding the Class 2 Acknowledgement letter to be sent to the applicant by Day 30, CPMS/RPM requested additional regulatory advice from the OHOP ADRA whether to note any milestones not completed during the first PDUFA V review cycle. **Post-meeting addendum:** CPMS confirmed that this resubmission is not subject to PDUFA V and therefore, does not need to include timing of our proposed PMR/PMC or labeling comments to the applicant.
- The OHOP Unireview format will be used. To avoid time-consuming re-formatting close to the deadline, it will be important to communicate style and formatting guidelines to the authors before they begin work in the unireview template (will follow OCE template/milestones).

- The team discussed whether we would issue an ASCO Burst and/or a Press Release. These decisions were deferred until the Divisions next administrative rounds meeting with the OHOP Office Director.
- The team discussed overall timelines and internal review goals over the next six months, and the impact of fall/winter staff schedule. The team will plan accordingly.
- The team agreed to hold monthly team meetings, as needed, and every-two-week standing applicant/RPM teleconferences which disciplines may join as needed to clarify IRs, etc.; these meetings may be shortened or canceled if not needed.
- The team agreed to hold an internal mid-cycle meeting. **Post-meeting addendum:** an ad hoc teleconference with AAA will be scheduled after internal mid-cycle meeting, if needed.
- The team agreed to hold separate PMR/PMC meeting(s) close to the end of the review cycle.
- For labeling meetings, it was agreed to begin with the sections/disciplines that were not affected by any changes in this review cycle (e.g., we will begin with Nonclinical and CMC-related sections)
- The team agreed it would be beneficial to seek the advice of Special Government Employees (SGEs) during this review cycle , DOP2 will follow internal standard practices and hopes to clear both an SGE and a patient advocate.
- The following consults will be needed to assist with the review of this resubmission: OPDP, OSE (regarding various subconsults, discuss with OSE: DMEPA, DRISK, DPV, and DEPI), Facility/OMPQ.
- Still to be determined whether the following consults are needed: OSI (RPM to follow up), Microbiology (Eldon to follow up), SEALD, Division of Medical Imaging
- The following consults will **NOT** be needed: DPMH, QT/IRT.

Post-meeting addendum

- Determined that pharmacometrics review is not required for this resubmission (per Hong Zhao's email 9/14/17);
- Determined that no additional inspections will be needed for this submission, since no significant findings were noted regarding data integrity or subject safety in the original submission (per email from Susan Thompson on 9/6/17)
- Product Quality Microbiology does not need to review (per Eldon Leutzinger's email 09/19/17)

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/s/

NATALIYA N FESENKO
09/22/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 14, 2017
From: Nataliya Fesenko, Pharm.D., R.Ph., DOP2/OHOP/CDER
Subject: NDA 208700 Information Request [IR-01]

Advanced Accelerator Applications USA, Inc.
Attention: Beth Lakey, R.Ph.
Manager, Regulatory Affairs - US
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Ms. Lakey:

Please respond to the following information request [IR-01] via email to me (Nataliya.Fesenko@fda.hhs.gov), copying Claire.Myers@fda.hhs.gov, followed by a formal submission to your NDA.

Response due: **5PM Eastern Time on Wednesday, August 16, 2017.**

1. Revise Table 19, “Erasmus study – results comparison between 2012 and 2015 CSR – Dutch progressive midgut carcinoid tumors” (Page 52 of 76, Module 2) of the Summary of Clinical Efficacy, limiting the analysis of the OR assessed in the EMC2012 (Independent Reviewer and Independent Reviewer/Computer) to the 38 patients with scans available for review.

Please confirm receipt.

Thanks,
Nataliya

Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATALIYA N FESENKO
08/14/2017

From: [Mehta, Shubhangi](#)
To: ["Victor Paulus"; Beth Lakey](#)
Cc: [Fesenko, Nataliya](#)
Subject: RE: NDA 208700: Statistical Comments
Date: Friday, June 23, 2017 2:55:32 PM
Importance: High

Good afternoon Victor,

Please refer to your New Drug Application (NDA) 208700 submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera[®] (177Lu-DOTA0-Tyr3-Octreotate).

The Statistical Reviewer has the following comments, which in addition to the agreed-upon items during our June 12, 2017, teleconference, we would like for you to address for the NETTER-1 CSR in your formal NDA resubmission.

Comments:

1. In general, more than one missed assessment visit will be defined as an assessment visit not occurring within 2 times the length between two per protocol assessment visits + 1 week (175 days instead of 210 days). Provide PFS sensitivity analysis based on 175 days difference to derive 2 continuous missing.
2. In the time to event dataset, please included the following censoring rules related variables: date of new anti-cancer therapy, date of new anti-chemotherapy, date of new anti-radiotherapy, date of new oncology surgery, last adequately assessed before PD, last adequately assessed PD before 2 continuous missing tumor assessments, last adequately assessed PD before discontinuation, date of PD, date of death, and censoring reasons. If any of these variables is not applicable, please clarify.
3. Provide the SAS program, analysis results (mean, STD, median, range, log rank test P- value) and the potential reasoning for the imbalance in the time to scheduled tumor assessment analysis (+/-1 week of scheduled visit) per INV assessment.
4. In the analysis result table(s) for PFS primary and sensitivity analyses, please provide number (%) of censoring for listed reasons, and number (%) of PFS events (classified by PD and death) by treatment arms, per IRC and INV assessments.

Kindly respond to confirm receipt of this communication.

I have copied Nataliya Fesenko on this communication, who will be the Regulatory Health Project Manager for this NDA moving forward.

If you have any questions, please contact Nataliya.

Regards,

Gina

Shubhangi (Gina) Mehta, PharmD
Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
shubhangi.mehta@fda.hhs.gov
Phone: 301-796-7910
Fax: 301-796-9849

From: Victor Paulus [mailto:victor.paulus@adacap.com]
Sent: Wednesday, June 21, 2017 2:19 PM
To: Mehta, Shubhangi
Cc: Beth Lakey
Subject: Re: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond

Hi Gina,

My managment would like to have the resubmission pass the gateway on Friday 30 June.

If you can provide me with comments ASAP I might be able to provide guidance that could improve our documentation and may even be able to influence the timetable.

In my past I have frequently dealt with "submit by the end of the year or else". This is a little different but the concept is still the same.

Thank you!!

Victor

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From: "Mehta, Shubhangi" <Shubhangi.Mehta@fda.hhs.gov>
Date: Wednesday, June 21, 2017 at 12:38 PM
To: victor paulus <victor.paulus@adacap.com>
Cc: Beth Lakey <beth.lakey@adacap.com>
Subject: RE: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond

Good Afternoon Victor,

Thank you for your responses. The reviewers have no further comments to your responses to our information requests.

Please formally submit your email responses and attachments from June 12 and June 16, 2017 to NDA 208700.

In addition, we might have additional comments pertaining to your planned NDA resubmission. If you do not hear back from me in the next week, please feel free to give me a call for an update.

Thank you,

Gina

Shubhangi (Gina) Mehta, PharmD

Regulatory Health Project Manager

FDA/CDER/OND/OHOP/DOP2

shubhangi.mehta@fda.hhs.gov

Phone: 301-796-7910

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]

Sent: Monday, June 19, 2017 3:02 PM

To: Mehta, Shubhangi

Cc: Beth Lakey

Subject: Re: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond

Hi Gina,

With the information contained in the email sent on Friday, below, we feel that all questions posed in the IR from the Division and the follow-up question have been addressed.

However, I have learned over the years that company and Agency opinions can differ. I wonder if our responses satisfactorily address the FDA concerns or if additional dialog is needed?

All the best,

Victor

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sender immediately and destroy the original message, any attachments thereto and all copies.

From: victor paulus <victor.paulus@adacap.com>
Date: Friday, June 16, 2017 at 2:09 PM
To: "Mehta, Shubhangi" <Shubhangi.Mehta@fda.hhs.gov>
Cc: Beth Lakey <beth.lakey@adacap.com>
Subject: Re: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond

Dear Gina,

The response to the FDA request for clarity regarding radiology reviewers (below):

We confirm that all the independent radiology reviewers were blinded to the local radiology reading as well as to the treatment assignment of patients in the trial. The imaging reading process is explained in detail in the Imaging Charter (Appendix III of the SAP, see section 3.5.2.1- attached to this email).

There is no use of any supportive clinical information in the central read. Information on local assessment (PD, SD, PR or CR) is given to the IRC QC person only, without detailed information on which lesions have been identified as target by the investigational site. Data on specific lesions are reported in the clinical eCRF of the main study, but central readers do not have access to the eCRF.

Also accompanying this email in order to address and close open discussion items from our teleconference on 12 June are "adtte2_imputation_20170616_clean" which presents data of the main PFS analysis for patients whose date of start of new anti-cancer therapy during long-term follow-up (ADDTHDT) were imputed due to partial dates in concomitant medication SDTM data (CM.CMSTDTC) (IRC assessment - ADTTE2 dataset), the aatte2 dataset and the Rules for PFS Derivation.

Should you have any questions please let me know and it is my sincere hope that the weekend is fantastic for all.

All the best,

Victor

Victor G. Paulus, PhD

Head, Global Regulatory Affairs
Advanced Accelerator Applications
The Empire State Building
350 Fifth Avenue, Suite 6902
69th Floor
New York, NY 10118

tel. 212.235.2391

www.adacap.com

NASDAQ: AAAP

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From: "Mehta, Shubhangi" <Shubhangi.Mehta@fda.hhs.gov>

Date: Tuesday, June 13, 2017 at 12:49 PM

To: victor paulus <victor.paulus@adacap.com>

Cc: Beth Lakey <beth.lakey@adacap.com>

Subject: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond

Dear Victor,

Please refer to your New Drug Application (NDA) 208700 submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera® (177Lu-DOTA-OTyr3-Octreotate).

Please also refer to your May 8, 2017 submission containing datasets for the NETTER-1 study which is intended to be included in the NDA resubmission. Additionally, reference is made to statistical comments addressed to AAA on June 7, 2017 and to the teleconference held between FDA and AAA on June 12, 2017 to discuss these comments.

The clinical reviewer has the following additional clinical information request:

Please provide additional clarification concerning your response to our question 7:

You stated in your response:

"...as described in the protocol, SAP and Imaging Charter, all the medical imaging examinations performed were generated by the site radiologists and evaluated using RECIST v 1.1. The examinations were sent for central real-time assessment to the IRC, as soon as obtained. As part of the protocol real-time assessment process, Investigators scanned the patients locally and sent the images to the IRC. The immediate local assessment was mentioned to the IRC and the IRC decided to adjudicate or not based on that immediate local assessment..."

This description appears to be inconsistent with the description of the assessment of the primary endpoint, progression-free survival (PFS) by central, blinded, real-time IRC (Independent Review Committee) assessment (Protocol N^o AAA-III-01/FINAL version 1.0, November, 14th, 2011; page 53).

Please clarify whether the independent radiology reviewers were blinded to the local radiology reading as well as to the treatment assignment of patients in the trial and provide the Independent Review Committee Charter or a link to the Charter, if this is contained in the original NDA submission.

Please contact me if you have any questions and kindly respond to confirm receipt of this email.

Regards,

Gina

Shubhangi (Gina) Mehta, PharmD
Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
shubhangi.mehta@fda.hhs.gov

Phone: 301-796-7910

Fax: 301-796-9849

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/s/

SHUBHANGI H MEHTA
06/26/2017

From: [Mehta, Shubhangi](#)
To: "Victor Paulus"
Cc: ["beth.lakey@adacap.com"](mailto:beth.lakey@adacap.com)
Subject: NDA 208700: Statistical Comments: Clinical Information Request: Please Respond
Date: Tuesday, June 13, 2017 12:49:02 PM
Importance: High

Dear Victor,

Please refer to your New Drug Application (NDA) 208700 submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera® (177Lu-DOTA-OTyr3-Octreotate).

Please also refer to your May 8, 2017 submission containing datasets for the NETTER-1 study which is intended to be included in the NDA resubmission. Additionally, reference is made to statistical comments addressed to AAA on June 7, 2017 and to the teleconference held between FDA and AAA on June 12, 2017 to discuss these comments.

The clinical reviewer has the following additional clinical information request:

Please provide additional clarification concerning your response to our question 7:

You stated in your response:

"...as described in the protocol, SAP and Imaging Charter, all the medical imaging examinations performed were generated by the site radiologists and evaluated using RECIST v 1.1. The examinations were central for central real-time assessment to the IRC, as soon as obtained. As part of the protocol real-time assessment process, Investigators scanned the patients locally and sent the images to the IRC. ***The immediate local assessment was mentioned to the IRC and the IRC decided to adjudicate or not based on that immediate local assessment...***"

This description appears to be inconsistent with the description of the assessment of the primary endpoint, progression-free survival (PFS) by ***central, blinded, real-time IRC (Independent Review Committee) assessment*** (Protocol N° AAA-III-01/FINAL version 1.0, November, 14th, 2011; page 53).

Please clarify whether the independent radiology reviewers were blinded to the local radiology reading as well as to the treatment assignment of patients in the trial and provide the Independent Review Committee Charter or a link to the Charter, if this is contained in the original NDA submission.

Please contact me if you have any questions and kindly respond to confirm receipt of this email.

Regards,

Gina

Shubhangi (Gina) Mehta, PharmD

Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Food and Drug Administration
shubhangi.mehta@fda.hhs.gov
Phone: 301-796-7910
Fax: 301-796-9849

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/s/

SHUBHANGI H MEHTA
06/13/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 7, 2017
From: Shubhangi (Gina) Mehta, Regulatory Health Project Manager –
CDER/OHOP/DOP2
Subject: **NDA 208700** – Advanced Accelerator Applications USA Inc.
Statistical Comments

Advanced Accelerator Applications USA Inc.
Attn: Victor Paulus, PhD
Head of Regulatory Affairs
The Empire Building
350 5th Ave 69th Floor, Suite 6902
New York, New York 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 506(b) of the Federal Food, Drug, and Cosmetic Act for “Lutathera ($^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$).”

Reference is also made to your May 8, 2017 submission containing datasets for the NETTER-1 study which is intended to be included in the NDA resubmission.

The Statistical Reviewer has the following comments for discussion at our teleconference scheduled for June 12, 2017 at 1:30 pm EST:

1. Please update the annotated Case Report Form (CRF). The submitted CRF is a blank CRF.
2. Please clarify the number of patients in the full analysis set (FAS) or intent to treat (ITT) population and provide a summary of discordance between previous and future submissions.

(b) (4)

Table 11-1 Number of patients randomized and per population




(b) (4)

N: number of patients in a group; Source data: [Table 14.1.1.1](#)


3. In the Analysis Data Reviewers Guide (ADRG) Section 3.6, the following date was imputed:



(b) (4)

- a. Please note, the above imputations  (b) (4) which is not acceptable. For handling missing tumor assessments in the analysis of PFS, please refer to Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, found at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>.
- b. The time to event endpoint analysis results based on imputed date may be provided as supportive analysis. Under this case, you should provide flag variables for imputed date of randomization, death, last known alive date, progress disease, loss of follow up, discontinue, new anti-cancer therapy (procedure or therapy other than study treatment), and tumor assessment.

4. Update variables  (b) (4) In the ADAM define.xml file,  (b) (4)



5. In the SDTM domain, some mandatory variables are missing. For example, in the SDTM/DM domain, variables (b) (4) are missing. Please refer to CDISC guidance document to check the availability of mandatory variables in the entire submission, found at https://www.cdisc.org/system/files/members/standard/foundational/sdtm/study_data_tabulation_model_v1_4.pdf
6. FDA has concerns with missing values in the submitted submission. For example, there are (b) (4)% missing value in the visitday and (b) (4)% in the visitdy, which is highly related to PFS derivation. If there are a lot of missing values in the essential variables, please provide details in the define file.
7. In the STD.M.TU domain: please double check your data set and provide details on

a. Why most of the tumor assessment records are missing?

Method of Identification

TUMETHOD	Frequency	Percent	Cumulative Frequency	Cumulative Percent
CT SCAN	(b) (4)	(b) (4)	(b) (4)	(b) (4)
MRI	(b) (4)	(b) (4)	(b) (4)	(b) (4)
OCTREOSCAN	(b) (4)	(b) (4)	(b) (4)	(b) (4)
OTHER	(b) (4)	(b) (4)	(b) (4)	(b) (4)

b. Is this TU data limited to IRC results only?

If yes, please confirm that there are only (b) (4)% of the TU records for investigator assessment. Please note, PFS per investig or assessment should be provided as one of the supportive analyses.

If no, please clarify the relationship between variable (b) (4) ; (c) (4)

- c. Please confirm that only (b) (4) ((b) (4)%) out of (b) (4) observations are post treatment records.

(b) (4)

- d. Please explain (b) (4)

(b) (4)

(b) (4)

8. In the STDM.TR domain: please double check your data set and provide details on the following:

- a. (b) (4)

(b) (4)

- b. In variable TRTEST, provide absolute change from NADIR in sum of diameter, percent change from baseline in sum of diameter, longest diameter, and sum of longest diameter for target lesion, area and sum of area fir target nodal.
- c. Please confirm that there is no equivocal new lesion progression in the RS domain.

9. In the SDTM.PR domain, the procedure data only included (b) (4) which is inconsistent (b) (4). Please verify that your data is accurate. In general, PR data has (b) (4) records (b) (4)

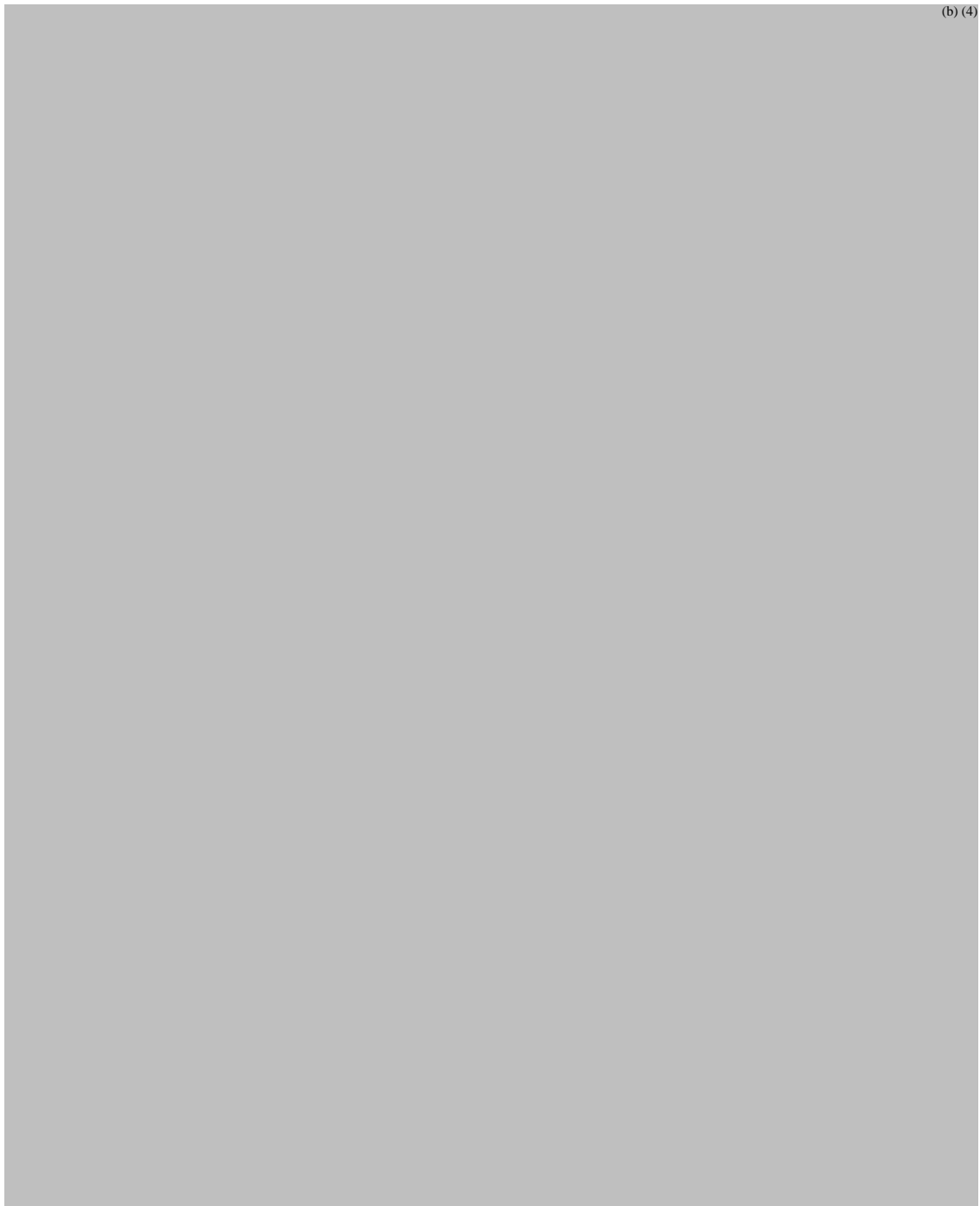


10. Due to missing values in the linked variable, provide details on how to merge the XX domain to SUPPXX domain in your data submission. For example, in the RS domain, the review identified:



11. FDA recommends AAA to reduce the length of variables to some reasonable length. Per FDA’s conformance guidance section 3.3.4, the length of variable names, descriptive labels, and dataset labels should not exceed the maximum permissible number of characters of 8, 40, and 40, respectively. Please refer to the Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Standardized Study Data, found at:
<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>.

For example, to run a simple proc means of age, the reviewer got the following 3 pages of results in SAS, which is really inconvenient.



(b) (4)

The following is an example of variables in ADSL which should be modified in the future data submission.

Alphabetic List of Variables and Attributes

(b) (4)

If you have any questions, please contact me at shubhangi.mehta@fda.hhs.gov or at (301) 796-7910.

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/s/

SHUBHANGI H MEHTA
06/07/2017



IND 077219

MEETING MINUTES

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for 177Lu-DOTA⁰-Tyr³-Octreotate.

We also refer to your April 24, 2017, correspondence, received April 24, 2017, requesting a meeting [REDACTED] (b) (4)

[REDACTED] We further refer to our electronic mail (email) dated April 27, 2017, in which we informed you that the meeting package was sufficient to permit FDA responses to and discussion of your Questions 1. b) and 1. c) but insufficient to provide a response to Question 1.a) regarding [REDACTED] (b) (4) the ongoing intermediate-size expanded access trial, Protocol AAA-177Lu-03, entitled "Expanded Access Protocol for Therapeutic Use of 177Lu-DOTA⁰-Tyr³-Octreotate in Patients with Inoperable, Somatostatin Receptor Positive, Midgut Carcinoid Tumors, Progressive Under Somatostatin Analogue Therapy."

In order to permit a substantive discussion of Question 1. a), we informed you that a meeting package providing chemistry, manufacturing, and controls (CMC) information [REDACTED] (b) (4) [REDACTED] and a description of proposed revisions to Protocol AAA-177Lu-03 should be submitted to your IND.

We also refer to the teleconference between representatives of your firm and the FDA on May 22, 2017. The purpose of the meeting was to discuss your [REDACTED] (b) (4) [REDACTED] NDA.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Shubhangi (Gina) Mehta, PharmD
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: May 22, 2017, 3:00 PM to 4:00 PM

Meeting Location: Teleconference – Dial-Information: (b) (4) **no PIN**

Application Number: IND 077219

Product Name: (b) (4)

Indication: (b) (4)

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Meeting Chair: Patricia Keegan, MD
Meeting Recorder: Shubhangi (Gina) Mehta, PharmD

FDA ATTENDEES

Patricia Keegan, MD, Division Director
Steven Lemery, MD, Associate Division Director
Suzanne Demko, PA-C, Clinical Team Leader
Denise Casey, MD, Clinical Reviewer
Whitney Helms, PhD, Nonclinical Team Leader
John Amartey, PhD, CMC Reviewer
Hong Zhao, PhD, Clinical Pharmacology Team Leader
Brian Furmanski, PhD, Clinical Pharmacology Reviewer
Shubhangi (Gina) Mehta, PharmD, Regulatory Health Project Manager
Norma Griffin, Lead Regulatory Health Project Manager

SPONSOR ATTENDEES

Debora Barton, MD, Vice President and Head of Oncology
Stefano Buono, Chief Executive Officer

Jack Erion, PhD, Vice President R&D USA
Claude Hariton, PhD, DSc, Global Head Research & Development
Maurizio Mariani, MD, PhD, DABT, Head Pre-Clinical Development
Victor Paulus, PhD, Head, Global Regulatory Affairs
Paola Santoro, PhD, Senior Clinical Project Manager
Maribel Lopera Sierra, MD, Chief Medical Officer
Thomas Thevenet, PharmD, Clinical Development Manager

BACKGROUND

Proposed Indication

[REDACTED] (b) (4)

Regulatory

On April 24, 2017, AAA submitted a Type A meeting request and meeting briefing package. The stated purpose of the meeting was [REDACTED] (b) (4). [REDACTED] FDA confirmed in an electronic mail (email) dated April 27, 2017, that the meeting package contained sufficient information only for questions 1. b) and 1.c). FDA also advised AAA to submit the necessary CMC information [REDACTED] (b) (4) [REDACTED] (b) (4) and proposed revisions to the protocol formally to IND 077219 with a separate meeting request for discussion of Question 1.a).

(b) (4)

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ISSUES REQUIRING FURTHER DISCUSSION

N/A

ACTION ITEMS

N/A

ATTACHMENTS AND HANDOUTS

N/A

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/s/

SHUBHANGI H MEHTA
06/08/2017



IND 077219

**MEETING REQUEST-
WRITTEN RESPONSES**

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Ph.D.
Head, Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu -DOTA-0-Tyr3-Octreotate.

We also refer to your submission dated March 8, 2017, containing a request for a Type C meeting.

The purpose of the requested meeting was to discuss the addition of a new manufacturing site in Millburn, New Jersey in order to supply ^{177}Lu -DOTA-0-Tyr3-Octreotate for use in the ongoing intermediate-size, expanded access program, Protocol AAA- ^{177}Lu -03, and to discuss proposed modification to Protocol AAA- ^{177}Lu -03. As communicated in the telephone conversation between Susan Truitt, Regulatory Health Project Manager, and you on March 10, 2017, we determined that you should submit a separate meeting request for your meeting request question 4 regarding (b) (4) the NDA.

Further reference is made to our Meeting Granted letter dated March 13, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 19, 2017, background package.

If you have any questions, call me at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Susan Truitt, B.A., R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: 077219

Product Name: ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate

Indication: Somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc.

Regulatory Pathway: 505(b)(1)

BACKGROUND

Regulatory

Advanced Accelerator Applications USA, Inc. (AAA) submitted a request for a Type C meeting on March 8, 2017. The purpose of the meeting was to the addition of a new manufacturing site in Millburn, New Jersey in order to supply ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate for use in Protocol AAA-¹⁷⁷Lu-03, an intermediate-size, expanded access program (EAP) and to discuss proposed modification to Protocol AAA-¹⁷⁷Lu-03. As communicated in the telephone conversation between Susan Truitt, Regulatory Health Project Manager, and AAA on March 10, 2017, FDA determined that AAA should submit a separate meeting request for their meeting request question 4 regarding [REDACTED] (b) (4) the NDA.

According to AAA, ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate is distributed by AAA in Europe under Compassionate Use Programs and in the United States under IND 77219. In France, in addition to the Patient Use Program, a Compassionate Use Program was approved by the French Health Agency (the ANSM) in April 2015, and started in June 2015.

FDA received the electronic meeting background package on April 19, 2017.

Clinical

The safety and efficacy of ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate was evaluated in the NETTER-1 trial for the treatment of patients with somatostatin receptor-positive, midgut neuroendocrine The

NETTER-1 trial provided the primary efficacy data in support of NDA 208700, submitted on April 28, 2016.

On January 27, 2016, AAA submitted an intermediate-size access trial Protocol AAA-¹⁷⁷Lu-03, entitled "Expanded Access Protocol for Therapeutic Use of ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate in Patients with Inoperable, Somatostatin Receptor Positive, Midgut Carcinoid Tumors, Progressive Under Somatostatin Analogue Therapy." The EAP is limited to patients who were treated on the NETTER-1 trial at clinical sites in the U.S. upon closure of the NETTER-1 trial in advance of the submission of the NDA. AAA now proposes to revise the eligibility criteria to include patients with non-midgut carcinoid NETs and to open the EAP at additional sites in the U.S. (i.e., sites that did not participate in the NETTER-1 trial).

SPONSOR QUESTIONS AND FDA RESPONSES

Chemistry, Manufacturing and Controls/Facilities (AAA Question 3)

1.

(b) (4)
[Redacted]
We intend to use
product manufactured at this facility to supply the EAP (b) (4)
[Redacted]

(b) (4)
[Redacted]
Does the FDA concur with this approach?

FDA Response: From a CMC/quality perspective, the proposed approach appears reasonable. (b) (4)
[Redacted]

From a quality microbiology perspective, FDA recommends that the resubmitted NDA contain complete information for the new facility (b) (4)
[Redacted] In particular, information should be provided related to a full description of the manufacturing process and sterilization of the drug product, container closure system, drug product release specification, including the (b) (4) testing criteria, and stability/storage conditions, as well as all of the sterilization validation information for production of the drug product at the additional manufacturing site.

(b) (4)

Clinical (AAA Questions 1 and 2)

2. With the postponement of the PDUFA date for LUTATHERA and the NDA resubmission as planned, AAA is proposing to continue and expand the current access programs in Europe and in the United States. To date, 62 patients have received at least one dose of LUTATHERA as part of the EAP in the United States. *While still considered an intermediate sized EAP, would the Agency support additional clinical sites and possibly smaller hospitals to be part of the program, if the nuclear medicine department is appropriately qualified?*

FDA Response: FDA has no objection to amending Protocol AAA-¹⁷⁷Lu-03 to permit enrollment of patients at additional clinical sites, provided that AAA has determined that such sites are adequately equipped and qualified to safely administer ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate.

3. The compassionate use programs in Europe include pulmonary NETs. In the US, there are many centers with patients with NETs who do not meet the inclusion criteria for the EAP, *would the Agency support amending the inclusion criteria of the protocol to include all NETs?*

FDA Response: Yes. FDA agrees that it would be reasonable to amend the inclusion criteria for ¹⁷⁷Lu-DOTA-0-Tyr3-Octreotate to permit enrollment of patients with metastasized or locally advanced, inoperable NETs arising at sites other than midgut and that have progressive disease during or after treatment with somatostatin analogues.

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/s/

SUSAN B TRUITT
05/18/2017



NDA 208700

MEETING MINUTES

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate), injection for intravenous infusion, 370 MBq/mL single-use vial.

We also refer to the teleconference between representatives of your firm and the FDA on February 10, 2017. The purpose of the teleconference was to discuss specific items presented in the Complete Response Letter (CRL), detail the planned response, provide an overview of response timing, discuss the Expanded Access Program and review [REDACTED] (b) (4) [REDACTED] the NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-3656.

Sincerely,
{See appended electronic signature page}

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: NDA - Other

Meeting Date and Time: February 10, 2017, 11:00 a.m. – 12:00 p.m. ET
Meeting Location: Teleconference (AAA Email Request of February 7, 2017)

Application Number: NDA 208700
Product Name: LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate)
Indication: Treatment of [REDACTED] (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut, in adults.

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Susan Truitt, R.N., M.S.

FDA ATTENDEES

Steven Lemery, M.D., M.H.S., Clinical Team Leader
Suzanne Demko, PA-C, Clinical Team Leader
Joohee Sul, M.D., Clinical Reviewer
Ruthann Giusti, M.D., Clinical Reviewer
Denise Casey, M.D., Clinical Reviewer
Kun He, Ph.D., Statistical Team Leader
Huanyu (Jade) Chen, Ph.D., Statistical Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer
Susan Truitt, R.N., M.S., Regulatory Health Project Manager
Shubhangi Mehta, Pharm.D., Regulatory Health Project Manager

SPONSOR ATTENDEES

Debora Barton, M.D., Vice President and Head of Oncology
Stefano Buono, Chief Executive Officer
Jack Erion, PhD, Vice President Research and Development USA

Claude Hariton, PhD, DSc, Global Head Research and Development
Beth Lakey, R.Ph., Manager, Regulatory Affairs
Maurizio Mariani, MD, Ph.D., DABT, Head Pre-Clinical Development
Victor Paulus, Ph.D., Head, Regulatory Affairs
Paola Santoro, Ph.D., Senior Clinical Project Manager
Maribel Lopera Sierra, M.D., Chief Medical Officer
Thomas Thevenet, Pharm.D, Clinical Development Manager
(b) (4) Chief Executive Officer (b) (4)

BACKGROUND

Regulatory

FDA issued a Discipline Review (DR) letter to AAA on November 21, 2016, communicating deficiencies and comments regarding the Clinical, Statistical, and Clinical Pharmacology sections of the AAA New Drug Application (NDA) 208700. On December 19, 2016, FDA issued an NDA 208700 Complete Response (CR) letter to AAA. The CR letter stated that after review of the application, FDA could not approve the application in its present form. The CR letter described FDA's reasons for this action and, where possible, recommendations to address the issues.

On January 9, 2016, AAA submitted a Type A meeting request and briefing package to discuss specific items presented in the CR letter, detail the planned response, provide an overview of response timing, discuss the Expanded Access Program and review (b) (4) the NDA. AAA also stated that their intent for the meeting is to address those items for which AAA seeks additional clarity or which are not described in either the DR or CR letters.

FDA sent Preliminary Comments to AAA on February 3, 2017. AAA requested a teleconference instead of the originally scheduled face-to-face meeting in a February 7, 2017, email, and FDA replied via email on February 7, 2017, that this request was acceptable.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical/Statistical

Interim Lock Procedure

1. *Is this procedure acceptable to the Agency?*

FDA Response:

FDA understands the term "database lock" to represent a pivotal milestone in the clinical trial that determines the scope of data to be reviewed and the timelines for data analysis and reporting. Locking of a database is done after review and query resolution are complete, and a determination has been made that the database is ready for analysis. FDA expects that data will continue to be updated in the database as the study continues with

the understanding that all data prior to the original data cut-off date of June 30, 2016, will not be modified once it is locked.

In addition to AAA's proposed efficacy clinical data cut-off date of July 24, 2015, provide data and analysis results for updated overall survival (OS) using a clinical data cut-off date of June 30, 2016, or later.

AAA February 7, 2017, Email Response: AAA requested discussion of question 1 during the teleconference.

Discussion During the Teleconference: AAA stated that they would provide the requested OS analysis for regulatory purposes. FDA confirmed that this would be an administrative look at the data for regulatory purposes only and not considered one of the pre-specified analyses of OS as described in the statistical analysis plan (SAP) (i.e., a statistical alpha penalty would not be needed for the final OS analysis).

Imaging

2. Per AAA, subsequent to FDA and EMA inspections, AAA has become aware of the need to correct several scans used in the progression free survival (PFS) analysis previously submitted to the Agencies, as well as add previously omitted scans. *Does the Agency agree with the above proposal?*

FDA Response: The plan to submit an updated, complete, and corrected tumor imaging assessment dataset to be used for the primary analysis of progression free survival (PFS) as previously described in the statistical analysis plan (SAP) and the NETTER-1 protocol is acceptable, provided that changes to the original imaging datasets are documented and submitted to FDA for review.

In the resubmission, include an audit trail that lists the changes that were made and the reasons for the changes.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Safety Summary: Expanded Access Program (EAP), Compassionate Use, and Other Safety Data

3. AAA plans to [REDACTED] (b) (4)
[REDACTED] Does the Agency accept the submission [REDACTED] (b) (4)
[REDACTED] to respond to the request of a safety update?

FDA Response: The proposal [REDACTED] (b) (4)
[REDACTED] of a safety update for the data in the NDA is not acceptable. The safety update submitted to NDA 208700 for LUTATHERA will include a safety report as well as an Integrated Analysis of Safety (IAS) and any new safety

information related to LUTATHERA that may reasonably affect the contraindications, warnings and precautions, or adverse reactions sections in the draft labeling. Furthermore, the safety update should be submitted in the same format as the integrated summary and include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event.

AAA February 7, 2017, Email Response: AAA requested discussion of question 3 during the teleconference.

Discussion During the Teleconference: AAA asked if it would be acceptable to submit safety data from the Expanded Access (EA) program separately and not integrated as part of the integrated safety analysis in Section 5.3.5.3 (ISS). FDA agreed with this approach.

FDA asked about how data would be identified from patients enrolled into a clinical trial and then subsequently enrolled under the EA program. FDA requested that AAA flag these patients in the integrated dataset. AAA stated that they would include this flag.

AAA confirmed they used the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) for the pharmacovigilance database, but used the prior version for clinical trials. AAA stated that only 5 SAEs have been reported to date in the EA program. AAA clarified that no cases of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) have been identified under the EA program.

AAA stated that they are acting on every point in the CR letter.

4. By the implementation of Safety Data Exchanges Agreements, AAA receives the DSUR from other sponsors for more comprehensive safety information on the product. All DSURs are included into the drafting of the main LUTATHERA DSUR which will be provided to the Agency. *Does the agency wish to receive the DSURs from other sponsors as well?*

FDA Response: Include safety data from all clinical studies of LUTATHERA in the primary DSUR for LUTATHERA. The DSUR for LUTATHERA is submitted to the primary IND 077219 and questions related to the Expanded Access Program or DSUR should be submitted to IND 077219 for 177Lu-DOTA0-Tyr3-Octreotate for discussion.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

5. In the European Compassionate Use Program, AAA estimates the number of patients (b) (4) at the end of November (see table below). In the United States, 42 patients have received at least one dose between the initiation of the Expanded Access Program (July 2016) and 1 January 2016. *Is the presentation of the information (b) (4) acceptable for the Agency?*

FDA Response: Questions related to the Expanded Access Program should be submitted to IND 077219 for 177Lu-DOTA0-Tyr3-Octreotate for discussion. Please provide clarification regarding what information AAA expects to submit in the NDA resubmission. Refer to FDA's response in item 3 above.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

6. In response to the FDA requests, the Sponsor will provide narratives for patients who experienced a serious adverse event regardless of its causality, an adverse event which led to treatment discontinuation, or death due to any cause during treatment phase, as well as patients who experienced adverse events of special interest (as described in Protocol N° AAA-III-01, version 4.1, June 5, 2014, section 8.7 Adverse Events of Special Interest: hematotoxicity, secondary hematological malignancies, nephrotoxicity, cardiovascular events).

The narratives will be provided for the aforementioned patients who were randomized to the experimental arm.

- a. *Does the agency require narratives to be written for patients who developed other non-hematological malignancies?*
- b. *Does the agency require narratives to be written for patients experiencing events described above but randomized to the control arm?*
- c. *Are there any other group of patients the Agency will require narratives to be written?*

FDA Response: Provide the required narratives for all patients enrolled on the NETTER-1 study, including from patients who develop adverse events of special interest or serious adverse events (as defined in section 8.2 of the NETTER-1 protocol, version 4.1, June 5, 2014). Development of a non-hematological malignancy meets the criteria for "...important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition..." as described in section 8.2 of the NETTER-1 protocol; therefore, these narratives should be included. During the review of the NDA, please be prepared to submit any additional narratives (including from patients who did not receive LUTATHERA) upon request.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Test Dataset

7. *Would the Agency agree on the principle that a test submission of a draft electronic data package be conducted prior to the official resubmission of the complete final data package, in order to check the full technical compliance and reviewability status of the new structure and content the Sponsor offers?*

FDA Response: AAA may submit a test data package which should include a define file prior to the official submission of the completed data package for FDA review. Clearly label the test dataset as such in the submission and provide an accompanying cover letter. Notify the Regulatory Health Project Manager (RPM) that the test submission is to be submitted, so other relevant internal FDA staff can be alerted.

Ensure that the datasets have undergone appropriate quality control before submission. FDA's preliminary high-level review of data in a test data package should not be considered an assurance that the datasets are acceptable for review in the NDA.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Expanded Access Program

8. *With the postponement of the PDUFA date for LUTATHERA and the NDA resubmission as planned, AAA is proposing to continue and expand the current access programs in Europe and in the United States. To date, 42 patients have received at least one dose of LUTATHERA as part of the EAP in the United States. While still considered an intermediate sized EAP, would the Agency support additional clinical sites and possibly smaller hospitals, if the nuclear medicine department is appropriately qualified?*

FDA Response: Questions related to the Expanded Access Program should be submitted to IND 077219 for 177Lu-DOTA0-Tyr3-Octreotate for discussion; however, the addition of appropriate clinical sites to the expanded access protocol conducted in the US would be acceptable. A final determination will be made after review of a protocol amendment submitted to IND 077219.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

9. *The compassionate use programs in Europe include pulmonary NETs. In the US, there are many centers with patients with NETs who do not meet the inclusion criteria for the EAP, would the Agency support amending the inclusion criteria of the protocol to include all NETs?*

FDA Response: Questions related to the Expanded Access Program should be submitted to IND 077219 for 177Lu-DOTA0-Tyr3-Octreotate for discussion. Modifications to the eligibility criteria for the expanded access protocol conducted in the US in order to allow enrollment of patients with diseases other than midgut neuroendocrine tumors may be acceptable; however, a final determination will be made after review of a protocol amendment submitted to IND 077219.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

(b) (4)

10. The Sponsor would like to discuss with the Agency:

(b) (4)

FDA Response: Questions related to the Expanded Access Program (b) (4) are outside the scope of a Type A meeting and should be submitted to IND 077219 for ¹⁷⁷Lu-DOTA0-Tyr3-Octreotate for discussion.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

Clinical Pharmacology

11. Typically, dosimetry assessments are based on radioactivity concentration data derived from regions of interests in scintigraphic images. In this case, the rawest measurement would be expressed as counts per pixel (or counts per region of interest), before normalization to percent injected activity (%IA). In the Erasmus MC Phase I/II study, most of the raw data derived from scintigraphs was recorded by the investigators only as %IA, so pixel count data is not available.

Therefore, for the next submission the Sponsor proposes to provide an SDTM dataset for the NETTER-1 dosimetry sub-study which includes both the raw pixel count data, as well as the %IA time-course data; and a SDTM dataset for the Erasmus MC dosimetry sub-study which includes only %IA time-course data. *Is this approach acceptable to the Agency?*

FDA Response: Yes; however, provide both the raw pixel count data, as well as the %IA time-course data for patients in which this data exists from the Erasmus MC dosimetry sub-study.

AAA February 7, 2017, Email Response: AAA acknowledged the Division's feedback and indicated that no further discussion is necessary.

ISSUES REQUIRING FURTHER DISCUSSION

N/A

ACTION ITEMS

N/A

ATTACHMENTS AND HANDOUTS

N/A

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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/s/

SUSAN B TRUITT
02/13/2017



NDA 208700

DISCIPLINE REVIEW LETTER

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated April 27, 2016, received April 28, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion, 370 MBq/mL, single-use vial. We also refer to your amendments dated October 18 and 19, 2016.

Our reviews of the Clinical, Statistical, and Clinical Pharmacology sections of your submissions are complete, and we have identified the following deficiencies:

- *The data are not acceptable because they do not conform to standards that enable FDA review;*

Clinical and Statistical Comments

1. The data used to generate the Clinical Study Report (CSR) and tables, listings, and figures (TLFs) differ from the data submitted to FDA for review. In order for FDA to confirm findings of safety and effectiveness for ^{177}Lu -DOTA⁰-Tyr³-Octreotate, and to verify data proposed for product labeling, submit the primary cleaned and verified data that are used to generate the CSR and TLFs in a format that is acceptable for FDA review. Specifically submit the following:
 - a. Datasets from all studies submitted with the NDA that are used to generate the information intended to support the safety and effectiveness of ^{177}Lu -DOTA⁰-Tyr³-Octreotate;
 - b. CSRs and TLFs for each study submitted with the NDA generated using the same datasets submitted to FDA for review;

- c. Integrated Summaries of Safety (ISS) and Efficacy (ISE) generated using the same datasets submitted to FDA for review.
2. Under 21 CFR §§ 314.101(d) (1),(2), (4)-(9) and FDA MAPP 6025.4, the application does not contain an accurate and complete English translation of the data submission. Please refer to FDA MAPP 6025.4, available at: <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtoxicology/cder/manualofpoliciesprocedures/ucm370948.htm>.
3. The study data do not provide sufficient information to understand the provenance of the data (i.e., traceability of the analysis results back to the annotated case report form [aCRF]). Traceability permits an understanding of the relationships among the analysis results (tables, listings, and figures in the study report), analysis datasets, tabulation datasets, and source data. Please refer to the “Study Data Technical Conformance Guide: Technical Specifications Document,” available at: <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>.
4. The data submitted contain errors, are inconsistent, and are incomplete. Ensure that the raw data used to generate all datasets have been audited for completeness, missing data points, and errors up to the time of database lock. Minimize missing data, and provide acceptable explanations for any data that are missing.
5. Case narratives for patients who experienced adverse events of special interest are not included in the NDA. For all clinical studies submitted in support of the NDA, provide narratives of all adverse events of special interest (AEOSI) in addition to narratives for patient deaths and serious adverse events (SAEs). Specifically, provide narratives for AEOSI related to hematologic and renal toxicity.
6. Case narratives are incomplete and are not consistent with case report forms (CRFs). Ensure that the narratives for patient deaths, SAEs, and AEOSI submitted to the NDA accurately reflect the information in the CRFs. Furthermore, ensure that all narratives summarize the nature and intensity of the event (i.e., grade), document the circumstances that may have led to its occurrence, describe the subsequent management and final outcome of the event, and provide a causality assessment.
7. Adverse event (AE) datasets do not contain terms for all levels of the MedDRA hierarchy. For all clinical studies submitted to the NDA, provide datasets for AEs to include all levels of the MedDRA Hierarchy: System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lower Level Term (LLT).

8. Summary table groupings for AEs are not informative. For all clinical studies submitted to the NDA, provide summary tables of AEs grouped by SOC, PT, and grade, rather than grouping PTs together under HLTs.
- *The datasets are not acceptable because they are incomplete, inconsistent, and contain specific errors;*

Clinical, Statistical and Clinical Pharmacology Comments

9. The datasets submitted in the original NDA application and the revised datasets submitted as amendments on October 18 and 19, 2016, contain significant and widespread deficiencies to the degree that the datasets cannot be used to confirm the safety and effectiveness of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. Regulations in 21 CFR Part 11 require all datasets submitted in electronic format to provide an accurate and complete copy of the data suitable for inspection, review, and archiving. Therefore, address the following specific deficiencies for all datasets to be submitted to the NDA:
 - a. The datasets are not organized in a standard fashion that allows reviewers to open, understand, and compare data across datasets. For example, there is no “Unique Subject ID” (USUBJID) provided in the datasets to allow comparison of information across datasets, and most character columns use internal or special formats. Submit datasets using a consistent framework for organizing study data, including standard names for variables without the use of internal formats. We strongly recommend use of the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standards for tabulations data and the CDISC Analysis Data Model (ADaM) standard for analysis data.
 - b. The datasets do not use consistent controlled terminology across datasets. Controlled standard terminology is critical to allow comparison of data across datasets and for data exchange. Submit revised datasets and supporting documents using consistent controlled terminology standards (e.g., CDISC Controlled Terminology, MedDRA).
 - c. The define files associated with the datasets are generally inadequate and erroneous and do not allow reviewers to understand the variables and derivations in the datasets. For example, define files are missing metadata and there are inconsistencies between output variables and the assigned code. Submit complete and accurate define files that allow reviewers to interpret the information in the datasets.
 - d. There are a number of missing definitions for variables in the following specific datasets: fdaclinpharmreqbaselab, supppp, and supppc. Provide definitions for all variables in all clinical pharmacology datasets.

- e. There are missing unique subject ID, study ID, and domain in the following specific datasets: fdaclinpharmreqbaselab, pktp, zdtp (Netter), zllesion, zltp, zporgan, zdparm, and zdtp (Erasmus). Provide these variables in all clinical pharmacology datasets.
- f. There are missing lab values for a number of specific patients (e.g., CrCl values were missing for IT06-007, US05-015, US11-024, US11-025, and US11-026) in the fdaclinpharmreqbaselab dataset. Additionally, patient information is missing for a number of patients, which is not shown in the missing-forms-04oct2016 pdf file. Provide these variables in all clinical pharmacology datasets and correct missing data forms as appropriate.
- g. There is missing dosing information for a number of patients (e.g., tdosemci) in the fdaclinpharmreqbaselab dataset, while organ radiation exposure and blood concentrations (Cmax, AUC) are provided for those patients. Provide dosing information for all patients or explain any missing information.
- h. There are inconsistent definitions between datasets, e.g., A indicates treatment in fdaclinpharmreqbaselab dataset, but AO is listed as treated in the PK sub study in the summpat dataset. Also, summpat lists 17 patients in the PK sub study, while 20 patients are listed in fdaclinpharmreqbaselab. Provide consistent definitions and patient numbers, or explain why the discrepancies are correct and acceptable.
- i. We are unable to reproduce derived values because baseline values are missing for a number of patients in the fdaclinpharmreqbaselab dataset. Provide baseline values for all patients in all datasets or explain why the discrepancies are correct and acceptable.
- j. IDVAR and IDVARAL columns contain duplicate information in the datasets supppc and supppp. Explain.
- k. There are missing lab parameters and organ exposures in the requested datasets, e.g., fdaclinpharmreqbaselab, in the Erasmus PK study folder. Provide this data or justify why it cannot be provided.
- l. There are inconsistent doses recorded across datasets, e.g., for patient BE01-002: 7.541 GBq in fdaclinpharmreqbaselab and 7.274 GBq for pktp datasets. Provide consistent data across datasets or justify why the different doses provided are correct.
- m. The explanation is missing for why the calibration factor ^{(b) (4)} is used in the gamma detection of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate for the following specific patients: DE01-006, DE01-009, DE01-010, and DE01-014 in the

pktp dataset, as other patients in this dataset have a calibration factor ranging from (b) (4). Provide an explanation for this difference.

- n. We are unable to confirm certain derived values in the Clinical Pharmacology datasets for the Erasmus trial pp, pc, supppc, and supppp, as the following variables were not provided: sampled, timefadm, measurdt, bloodvol, sampvol, collvol, countval, countvau, activcon, pepticon, activity, percia, and percumia. Provide all relevant variables in all datasets.
 - o. The appropriate analyses were not performed for patient ID NETTER-1-UK06-003 in the pp and supppp datasets. Provide the analysis.
 - p. Conversion of GBq to a vweight-based dose (e.g., µg) administered to patients was not provided for the Erasmus and Netter-1 studies. Provide the weight-based dose for all patients in the Erasmus and Netter-1 studies.
- *The datasets are not acceptable because they contain technical issues that preclude review.*

Statistical Comments

10. Study data contained in the electronic submissions were not in a format that FDA can process, review, and archive. Currently, FDA can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog). Please refer to the FDA Guidance for Industry entitled “Providing Regulatory Submissions In Electronic Format — Standardized Study Data and Data Standards Catalog,” available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334>, and
<http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>.
11. The encoding system used to generate the datasets (utf-8 Unicode) results in reading errors. Use the default SAS coding system, wlatin1 (i.e., western world encoding).
12. The revised datasets submitted on October 18 and 19, 2016, were submitted in an unacceptable exchange file format. Although the initial datasets submitted on April 28, 2016, used .xpt as the file extension, the revised datasets used the .sas7bdat file extension, which is not in compliance with FDA requirements for submission of electronic datasets. Submit all datasets in a format that is accessible using the JMP program for data analysis; i.e., electronic datasets in SAS System XPORT transport format, with all SAS transport files in the non-compressed .xpt file format.

We are providing these comments to you in accordance with our commitment to do so during the telephone conference held with you on October 26, 2016, and, to the extent possible, having completed our review of your entire application in order to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change.

Finally, we have determined that the deficiencies identified herein preclude discussion of labeling changes and postmarketing requirements/commitments at this time.

If you have any questions, call Susan Truitt, Regulatory Health Project Manager, at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Suzanne Demko, PA-C
Cross Discipline Team Leader
Division of Oncology Products 2
Center for Drug Evaluation and Research

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/s/

SUZANNE G DEMKO
11/21/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 26, 2016

Application Number: NDA 208700

Product Name: Lutathera


Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (“AAA”)

Purpose: Ensure AAA understands FDA Complete Response (CR) decision, or option for AAA to withdraw application, regarding inadequate dataset submission requirements

FDA Participants

Patricia Keegan, Division Director
Steven Lemery, Clinical Team Leader/Acting Associate Director
Suzanne Demko, Clinical Team Leader
Joohee Sul, Clinical Reviewer
Huanyu (Jade) Chen, Statistics Reviewer
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader
Brian Furmanski, Clinical Pharmacology Reviewer
Susan Truitt, Regulatory Health Project Manager

AAA Participants

Debora Barton, Vice President, Oncology
Gerard Ber, Chief Operating Officer
Fanny Bonnet-Eymard, Manager, Regulatory Affairs
Stefan Buono, Chief Executive Officer
 (b) (4)
Carlos Chanquia Delprato, Head, Clinical Development
Jack Erion, Vice President, Research and Development
Claude Hariton, Global Head, Research and Development
Beth Lakey, Manager, Regulatory Affairs
Maurizio Mariani, Head, Pre-Clinical Development
Victor Paulus, Head, Global Regulatory Affairs
Izabela Rejdych, Associate Director, Global Regulatory Affairs
Maribel Lopera Sierra, Chief Medical Officer
Paola Santoro, Senior Clinical Study Manager
Thomas Thevenet, Clinical Development Manager

BACKGROUND:

After reviewing AAA's submissions of the revised datasets received on October 18 and 19, 2016, the FDA review team determined that the datasets contained significant and widespread deficiencies; therefore, the Division had a teleconference with AAA on October 21, 2016, to convey the deficiencies and discuss potential options moving forward.

Based on the October 21, 2016 teleconference between FDA and AAA, AAA agreed to another teleconference with FDA on October 26, 2016, to confirm their understanding of the potential next step; i.e.,

- FDA will take an action on the NDA and issue a complete response (CR) that will enumerate the deficiencies and the information needed to correct them; or,
- AAA has the option of withdrawing their application and re-submitting at a later date once all deficiencies had been corrected.

DISCUSSION:

FDA stated that the purpose of the teleconference was to allow AAA to ask follow-up questions or request clarification of the issues discussed during the teleconference on October 21, 2016.

Victor Paulus indicated that their team has been fully briefed on the deficiencies identified in the NDA, and asked if any additional deficiencies have been identified since the October 21, 2016, teleconference.

FDA stated that additional deficiencies may be identified as there are ongoing review activities related to the NDA (e.g., facilities inspections); however, at this time the major deficiencies identified are related to the datasets.

AAA confirmed their understanding of dataset deficiencies and stated they will make every effort to reduce future delays. AAA stated that they now have a "forensic statistician" who has identified similar issues as described by FDA and who will continue to evaluate the datasets. AAA also asked about the timing for the FDA's CR letter.

FDA stated that Discipline Review (DR) letters outlining the deficiencies will be issued while the CR action is being completed, so that AAA will have an FDA assessment of the major findings. FDA will issue the CR letter after completion of all inspections with related reports.

AAA stated that the DR letters will be very helpful, and that they are contemplating re-submitting datasets as a major amendment to reduce delay. FDA indicated that the October re-submission of data might have been considered a major amendment if the data had been adequate to begin a review; however, there is not enough time in the review cycle to permit another opportunity to correct the deficiencies in the datasets, and re-submission of data. AAA confirmed their understanding.

FDA committed to working closely with AAA to address specific issues that will need to be addressed in any future submission, and reiterated that datasets must be executable in an FDA-approved format, and include correct variable names used consistently across datasets.

AAA had the following additional questions.

- 1) AAA stated they may at this point consider submission of data in CDISC format for expediency; would a Type A meeting request be possible to discuss this and other issues?

FDA response: Yes.

- 2) Is it necessary that the data from the ERASMUS study be structured similarly to NETTER?

FDA Response: FDA would need to discuss this internally; however, ultimately the decision on the format for ERASMUS data depends on how AAA would like to use the data to support their application.

- 3) AAA requested guidance on the timing of re-submission of the application materials.

FDA Response: This should be discussed at a Type A meeting, and FDA will need to first issue the DR letters.

- 4) AAA stated they were unaware of significant CMC issues, and asked if there were any to communicate at this time.

FDA Response: The facility inspections are ongoing; therefore, FDA will await final inspection reports before communicating any issues.

AAA reiterated their commitment to this application and apologized for the inconvenience regarding the deficient datasets.

FDA confirmed that the FDA team will work with AAA to resolve issues and move forward as appropriate. FDA stated that time is required to issue DR letters and subsequently a CR letter; then further discussion about revised timelines will occur.

AAA stated they will identify database deficiencies and questions regarding structure/analyses.

ACTION ITEMS:

- AAA will be in contact with FDA regarding any other questions.
- FDA will issue DR letters, followed by a CR letter after all inspections are complete.

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/s/

SUSAN B TRUITT
10/27/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 21, 2016

Application Number: NDA 208700

Product Name: Lutathera


Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (“AAA”)

Subject: Discuss issues related to AAA’s required dataset submission received via the eCTD gateway on October 18 and 19, 2016, and related emails. EDR Link is: <\\CDSESUB1\evsprod\NDA208700\208700.enx>.

FDA Participants

Patricia Keegan, Division Director
Steven Lemery, Clinical Team Leader/Acting Associate Director
Suzanne Demko, Clinical Team Leader
Joohee Sul, Clinical Reviewer
Kun He, Statistics Team Leader
Huanyu (Jade) Chen, Statistics Reviewer
Jeanne Fourie Zirkelbach, Clinical Pharmacology Reviewer
Brian Furmanski, Clinical Pharmacology Reviewer
Susan Truitt, Regulatory Health Project Manager

Sponsor/Applicant Participants

Izabela Rejdych, Associate Director, Global Regulatory Affairs (facilitated the meeting for AAA on behalf of primary contact Victor Paulus, who could not attend)
Fanny Bonnet-Eymard, Manager, Regulatory Affairs
 (b) (4)
Claude Hariton, Global Head, Research and Development
Beth Lakey, Manager, Regulatory Affairs
Paola Santoro, Senior Clinical Study Manager
Thomas Thevenet, Clinical Development Manager

BACKGROUND:

On August 11, 2016, the Division held a teleconference with AAA to discuss AAA’s August 4, 2016, proposal in response to FDA’s Mid-Cycle Communication and subsequent teleconference requests regarding the sponsor’s dataset submission timeline. During the teleconference, the Division and AAA agreed to the following timeline for submission of revised data to the NDA:

1. AAA will submit the following by October 10, 2016 (60 days from the August 11, 2016 teleconference):

- a. CLINICAL DATA TO BE USED: data from submission (July 24, 2015 clinical cutoff date), with fully cleaned data from the NETTER-1 and ERASMUS clinical trials
- b. ANALYSIS DATA/FORMAT TO BE USED: create the raw and analysis datasets as requested by the FDA with consistent variable names and clear derivation definitions, non-CDISC structure but ready for analysis in SAS and JMP.
- c. DELIVERABLES:
 - A detailed Reviewers Guide including data dictionaries for all variables and derivation paths for all derived variables
 - Raw dataset
 - Analysis datasets

AAA confirmed that they would formally submit these items to their NDA. FDA further clarified that if there are any discrepancies between FDA's and AAA's analyses, FDA will use what FDA runs, unless AAA can prove that their numbers are accurate.

On October 10, 2016, AAA submitted the datasets as agreed upon via electronic mail (email); however, the datasets were not accessible. AAA submitted the required deliverables as formal amendments to their NDA on October 18, 2016. These datasets were accessible; however, multiple deficiencies were identified, including datasets with foreign characters, errors in the variable outputs, and inadequate define files. Therefore, the review team was not able to utilize the provided datasets to begin a review. There were multiple communications sent to AAA to convey the issues identified and AAA was asked to contact the CDER eSub team to assist them with submission of datasets. AAA did address an encoding issue that corrected the foreign characters and resubmitted datasets on October 19, 2016 (SDN 33); however, there continued to be deficiencies with the datasets. The CDER edata team (Ruth Li, Senior Regulatory Analyst) communicated to AAA via email that the sas7bdat file format submitted by AAA was not acceptable and that these files should be converted to SAS XPT V5 format, and referred AAA to the Study Data Technical Conformance Guide, available at: <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>.

After reviewing AAA's formal submissions of the revised datasets received on October 18 and 19, 2016, the FDA review team determined that the datasets contained significant and widespread deficiencies; therefore, the Division requested a teleconference with AAA to convey the deficiencies and discuss potential options for moving forward.

DISCUSSION:

FDA communicated to AAA that the revised datasets submitted on October 18 and 19, 2016 contain significant and widespread deficiencies, to the degree that FDA is not able to utilize the datasets to confirm the safety and efficacy of AAA's product, Lutathera. FDA described the following key deficiencies.

1. The datasets submitted are not in a format that meets FDA requirements for electronic dataset submission; specifically the files are not in .xpt format. Therefore, although the statistical reviewer is able to access the SAS files, other review disciplines are not able to utilize the data sets.
2. The raw datasets in SAS format are not accessible through JMP.
3. There is no “unique subject ID” provided in the dataset to allow comparison across datasets, and of raw and derived datasets.
4. The dataset and variable nomenclature are non-standard, and there are inconsistent variable names across datasets.
5. There are inconsistencies between the output variables assigned to a code compared to what is assigned in the define file.
6. The define files are generally inadequate, with missing metadata.
7. It appears that some data has been incorrectly formatted as there are nonsense values for some variables (e.g. CrCl: (b) (4)).

AAA responded that they are unable to convert their datasets to .xpt format and stated that the problems encountered with the datasets were due to using JMP, as the datasets did not appear to have issues in the SAS format. FDA reminded AAA of their agreement to provide datasets that are executable in JMP. In addition, FDA reiterated that the clinical and clinical pharmacology reviewers are not able to use the SAS format datasets. Furthermore, FDA stated that the deficiencies were not related to formatting issues alone.

FDA stated that given the significant deficiencies, FDA is not able to utilize the revised datasets to confirm the safety and efficacy information submitted in AAA’s NDA for Lutathera. Therefore, FDA has suspended review of the NDA. FDA stated the following actions were potential options for next steps:

- FDA will take an action on the NDA and issue a complete response (CR) that will enumerate the deficiencies and the information needed to correct them.
- FDA also communicated that AAA has the option of withdrawing their application and re-submitting at a later date once all deficiencies had been corrected.

Either option would allow for AAA to work closely with FDA to understand the deficiencies and what is needed to address them. FDA recommended that AAA work with the FDA’s Office of Computational Science for any future submissions.

FDA asked if AAA clearly understood the deficiencies as outlined, to which AAA responded they did. FDA confirmed that AAA should await a formal letter with a list of deficiencies from FDA.

FDA reiterated the following potential actions at this time: 1) The Division will issue a CR letter with a list of deficiencies; or, 2) AAA could withdraw their application and request a Type A meeting for follow up and clarification regarding requirements for a new application submission.

AAA personnel stated that they would need to discuss these options with Victor Paulus (authorized contact) and that AAA plans to reply to the Division on Monday, October 24, 2016.

AAA also stated they are currently working on the CSR; however, the Division advised AAA to stop since the CSR would reflect analyses done with the deficient datasets. AAA confirmed their understanding and agreement.

ACTION ITEMS:

- AAA will contact the DOP2 RPM on or about Monday, October 24, 2016, regarding setting up a brief teleconference to confirm their understanding of the FDA's decision to issue a CR letter or AAA choosing the option to withdraw their application.

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/s/

SUSAN B TRUITT
10/24/2016

From: Steven Kinsley
To: victor.paulus@adacap.com
Cc: Susan Truitt
Subject: NDA 208700 CMC Information Request 9-19-16
Date: September 19, 2016

Dear Victor,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Monday, September 26, 2016.

1. The media fill information provided in the August 5, 2016 information request response is acknowledged. Provide the environmental monitoring results for the 2016 media fill simulations.
2. Regarding sterility testing, it is stated in the August 5, 2016 information request response that the post-release sterility test will be performed to allow final batch release (b) (4). It is also noted that during discussion of the IND 77219 meeting package received July 27, 2015, the sterility testing was proposed to be initiated (b) (4). According to 21CFR211.165, drug product batches may be released prior to completion of sterility testing, provided such testing is completed as soon as possible. Provide the justification for performing the sterility testing within a variable timeframe (b) (4).

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773



Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 9/19/2016 03:08:36PM
GUID: 555cc3bc000836e194b17e8bf695ce5f

MEMORANDUM
NDA 208700

TO: NDA 208700 File
FROM: Suzanne G. Demko, Cross-Discipline TL, DOP2
DATE: September 12, 2016
RE: Delay in Completion and Filing of All Primary Reviews

Primary reviews for this NDA will not be completed or filed by September 28, 2016. This is based on instructions given to all reviewers as a result of identifying significant errors and omissions in the datasets submitted to the NDA. FDA was in discussions with the applicant regarding the dataset issues early in the review cycle and sent multiple IRs to determine if the problems with the submitted datasets could be resolved. They could not. During teleconferences with the applicant on August 4 and 11, 2016, further discussions to resolve the issues took place and an agreement was reached for re-submission of all datasets within 60 days of August 4, 2016. Revised datasets for test purposes were submitted to FDA on August 31, 2016. These test datasets were acceptable for review.

Because of the significant errors and omissions in the datasets submitted with the original NDA, all primary reviewers were directed to cease their primary reviews of the datasets (with the exception of CMC, since all data submitted to the IND for the CMC module were acceptable and reviewable). Since revised datasets will not be submitted to the NDA until October 4, 2016, which is after the September 28, 2016 due date for filing primary reviews, primary reviews will not be completed or filed according to PDUFA goals. Once the new datasets are submitted, FDA will determine if they are reviewable and then, if reviewable, a determination will be made if the submission constitutes a major amendment and the applicant will be advised, if so.

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/s/

SUZANNE G DEMKO
09/12/2016

From: Steven Kinsley
To: victor.paulus@adacap.com
Cc: Susan Truitt
Subject: NDA 208700 CMC Information Request 8-16-16
Date: August 16, 2016

Dear Victor,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, August 26, 2016.

1. In the application (**Section S.2 Manufacture**) you have indicated that the minimum

(b) (4)



for drug

substance manufacturing. Confirm that this would be the case.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,

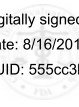
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
240-402-2773



Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 8/16/2016 03:42:41PM
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From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 Clinical Pharmacology Information Request: Response Required
Date: Friday, August 12, 2016 12:14:00 PM

Dear Victor,

Please respond to the following Clinical Pharmacology information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Monday, October 10, 2016**, or sooner if possible, followed by a formal submission to your NDA. When you respond, please also include this information request in the body of your email.

Please submit requested information and ensure that all variables per patient are included or provide justification if data is missing.

Please submit datasets from the following studies or literature and provide justifications if some of these requested datasets are not available.

- i. As stated previously in the Mid-Cycle teleconference, new datasets derived from the raw data for NETTER-1 and ERASMUS studies
- ii. Dataset containing information found in article entitled "Subacute haematotoxicity after PRRT with ¹⁷⁷Lu-DOTA-octreotate: prognostic factors, incidence and course" published in European Journal Nuclear Medicine and Molecular Imaging in 2016.
- iii. Dataset containing information found in article entitled "Renal function affects absorbed dose to the kidneys and haematological toxicity during ¹⁷⁷Lu-DOTATATE treatment" published in European Journal Nuclear Medicine and Molecular Imaging in 2015.
- iv. Dataset containing information found in article entitled "Individualized dosimetry of kidney and bone marrow in patients undergoing ¹⁷⁷Lu-DOTA-octreotate treatment." Journal Nuclear Medicine 2013; 54 (1):33-41.
- v. Any published or unpublished data from patients with creatinine clearance ≤ 40 ml/min who were treated with ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.

Datasets should contain the following information: Unique subject ID, Tumor type/origin, Dose absorbed ((Gy, Gy/GBq) to kidney, liver, spleen, bone and whole body), Metastatic organ, Tumor burden (small, medium, large) Sex, Age, Weight, Height, Serum Creatinine, Creatinine clearance (Cockcroft-Gault (ml/min)), Bilirubin, ALT, AST, Albumin, Chromogranin A, Dose (mg, mCi), White blood cell count (neutrophils, lymphocytes, eosinophils, monocytes, basophils), Hemoglobin, Platelet, if available PK parameters (AUC, Cmax, Cmin).

In addition, provide the results of the following analyses:

- i. association of individual baseline parameters to individual hematological toxicities,

- ii. association of creatinine clearance to the dose absorbed (Gy, Gy/GBq) to individual organs (kidney, liver, spleen, bone and whole body),
- iii. association of individual baseline liver function (bilirubin, AST, ALT) to the dose absorbed (Gy, Gy/GBq) to individual organs (kidney, liver, spleen, bone and whole body),
- iv. association of hematological toxicities to the dose absorbed (Gy, Gy/GBq) to individual organs (kidney, liver, spleen, bone and whole body), and
- v. association of tumor burden (small, medium, large) to individual hematological toxicities.

Based on the analyses from the available data, explore if an appropriate dose reduction recommendation can be generated for patients with renal impairment, in lieu of a potential dedicated post-marketing study (PMR).

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
08/12/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 11, 2016

Application Number: NDA 208700

Product Name: Lutathera

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Subject: Teleconference with sponsor to discuss sponsor's August 4, 2016, proposal in response to FDA's Mid-Cycle Communication and subsequent teleconference requests regarding the sponsor's dataset submission timeline

FDA Participants – Suzanne Demko, Clinical Team Leader/CDTL; Joohee Sul, Clinical Reviewer; Susan Truitt, Regulatory Health Project Manager; Jeanne Fourie-Zirkelbach, Clinical Pharmacology Team Leader; Brian Furmanski, Clinical Pharmacology Reviewer; Christos Mastroyannis, DPMH Reviewer, Denise Johnson-Lyles, DPMH Project Manager; Kirsten Goldberg, OHOP Medical Editor

Sponsor/Applicant Participants

Stefano Buono, CEO
Gerard Ber, COO
Claude Hariton, Head of Research & Development
Jack Erion, VP Research & Development
Paola Santoro, Manager, Clinical Research
Isabelle Gimbert-Chan, Head Pharmaceutical Development
Victor Paulus, Head, Regulatory Affairs
Thomas Thevent, Manager, Clinical Research
Daniela Chicco, Manager, Preclinical

(b) (4) Statistician and Head, (b) (4)
(b) (4) EVP Biostatistics, (b) (4)
(b) (4) COO, (b) (4)
(b) (4) Global Project Leader, (b) (4)

BACKGROUND

Due to extensive email exchanges, the lack of clarity in the applicant's NDA submission regarding datasets and an August 3, 2016, follow up teleconference to the August 2, 2016, Mid-Cycle Communication teleconference, FDA had another follow up teleconference with AAA on August 11, 2016. The purpose was to discuss AAA's most recent August 4, 2016, electronic mail (email) with their proposed dataset submission timeline in response to FDA's Mid-Cycle Communication timeline.

DISCUSSION

1. FDA asked AAA to clarify their August 4, 2016, email with their proposed 30-60-90 day dataset timeline submission plan. AAA clarified that their proposed submission plan was for FDA to consider either the 30, 60 or 90-day plans; i.e., to consider one of those three options.
2. FDA stated that FDA requests that AAA submit all materials specified in their 90-day timeline, but submitted to FDA within 60 days of this August 11, 2016, teleconference. AAA replied that it would not be possible for them to submit all requested materials by 60 days.
3. FDA proposed that AAA submit everything in their 90-day plan, in SAS or JMP format, except the last three bullets in their 90-day plan (see below). FDA further clarified that if there are any discrepancies between FDA's and AAA's analyses, FDA will use what FDA runs, unless AAA can prove that their numbers are accurate.
4. AAA confirmed that they would formally submit the following to their NDA, with the associated due dates. FDA stated that the due dates below are firm, and AAA agreed, further confirming that AAA would provide the requested data for both the ERASMUS and NETTER-1 studies.

Due by October 10, 2016, latest (= 60 days from the August 11, 2016, teleconference):

CLINICAL DATA TO BE USED: data from submission (July 24, 2015 clinical cutoff date), with fully cleaned data

ANALYSIS DATA/FORMAT TO BE USED: create the raw and analysis datasets as requested by the FDA with consistent variable names and clear derivation definitions, non-CDISC structure but ready for analysis in SAS and JMP.

DELIVERABLES:

- A detailed Reviewers Guide including data dictionaries for all variables and derivation paths for all derived variables.
- Raw datasets
- Analysis datasets

Due by November 9, 2016 (= 90 days from the August 11, 2016, teleconference):

- Updated Tables/Figures/Listings
- Updated CSR, both red-lined and clean version, that shows the impact of the updated/cleaned clinical data and matches the TFLs and datasets
- Notations of why any data changes occurred that impact the CSR

5. AAA asked if it would be possible to send a “test” submission to FDA to confirm FDA’s ability to run the data. FDA agreed, requesting that this be formally submitted to the NDA via the electronic Gateway with a cover letter identifying the submission as “test datasets.”
6. FDA’s Clinical Pharmacology reviewer indicated that FDA would send an information request (IR) to AAA soon, to further clarify the analyses to be performed, etc.
7. FDA requested that AAA send their revised proposed submission timeline via email by COB Friday, August 12, 2016, followed by a formal submission to the NDA.

ACTION ITEMS

- AAA will send their revised proposed submission timeline via email to FDA by COB Friday, August 12, 2016, followed by a formal submission to the NDA.
- AAA will formally submit a “test” dataset submission to FDA via the electronic Gateway to confirm FDA’s ability to run the data, with a cover letter identifying the submission as “test datasets.”
- AAA confirmed that they would formally submit the information in their revised plan to their NDA by the 60-day and 90-day timelines as indicated in point 4. above.
- FDA’s Clinical Pharmacology reviewer will send an IR to AAA soon.

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/s/

SUSAN B TRUITT
08/15/2016



NDA 208700

MID-CYCLE COMMUNICATION

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion, 370 MBq/mL single-use vial.

We also refer to the teleconference between representatives of your firm and the FDA on August 2, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: August 2, 2016, 11:00 a.m. – 12:00 p.m. ET
Location: Teleconference

Application Number: NDA 208700
Product Name: Lutathera
Indication: Treatment of patients with (b) (4)
(b) (4) somatostatin receptor positive,
gastroenteropancreatic neuroendocrine tumors (GEP-NETs),
including foregut, midgut and hindgut [neuroendocrine tumors (b) (4)
(b) (4)]

Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA)

Meeting Chair: Suzanne Demko, PA-C.
Meeting Recorder: Susan Truitt, R.N., M.S.

FDA ATTENDEES

Patricia Keegan, M.D., OHOP/DOP2
Suzanne Demko, PA-C., Clinical Team Leader (CDTL), DOP2
Joohee Sul, M.D., Medical Officer (DOP 2), Clinical Reviewer, DOP2
Amy McKee, M.D., Acting Deputy Office Director, OHOP
Susan Truitt, R.N., M.S., Regulatory Health Project Manager, DOP2
Mimi Biable, M.S., Senior Regulatory Health Project Manager, DOP2
Kun He, Ph.D., Statistics Team Leader
Jeanne Fourie-Zirkelbach, Ph.D., Clinical Pharmacology Team Leader (for Hong Zhao)
Brian Furmanski, Pharm. D., Clinical Pharmacology Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader
Anwar Goheer, Ph.D., Nonclinical Reviewer
Jennie Chang, Pharm. D. Associate Director for Labeling
Todd Knepper, Fellow (working with Jennie Chang)
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead (ATL)
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA
Lauren Iacono-Connor, OSI Reviewer
Janine Stewart, DMEPA Reviewer
Latonia Ford, OSE, Safety Regulatory Project Manager
Miriam Dinatale, Acting Team Lead, DPMH (Maternal Health)
Christos Mastroyannis, DPMH Reviewer/Maternal Health MO

Eastern Research Group, Inc. (ERG)
Peggha Khorrami, Independent Assessor

APPLICANT ATTENDEES

AAA

Albert Chau, Statistician
Maribel Lopera Sierra, Chief Medical Officer
Stefano Buono, Chief Executive Officer
Gerard Ber, Chief Operating Officer
Claude Hariton, Head of Research and Development
Jack Erion, Vice President, Research
Paola Santoro, Manager, Clinical Research
Maurizio Mariani, Head of Preclinical Development
Francesco De Palo, Qualified Person
Izabela Rejdych, Associate Director, EU Regulatory Affairs
Isabelle Gimbert-Chan, Head Pharmaceutical Development
Victor Paulus- Head, Regulatory Affairs
Thomas Thevenet, Manager, Clinical Research
Beth Lakey, Manager, Regulatory Affairs
Daniela Chicco, Manager, Preclinical
Camelia Cercel, Manager, Regulatory Affairs
Fanny Bonnet-Eymard, Manager, Regulatory Affairs



1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Significant issues conveyed via email to AAA on July 29, 2016

The application is materially incomplete in that the datasets provided are inaccurate, incomplete, and inconsistent across datasets. Thus, FDA cannot verify the information provided in the clinical study reports nor verify data proposed in the product labeling. In order to address the issues raised below, Advanced Accelerator Applications USA, Inc. (AAA) should do one of the following:

- Submit new clinical and clinical pharmacology datasets containing data that has been verified for accuracy within 30 days of this teleconference. The new datasets should be complete, verified for accuracy against the raw data from each trial as previously agreed in the pre-NDA meeting and subsequent communications, and be in such a format as to allow for use with software such as SAS and JMP. Additionally, a revised Clinical Study Report (CSR) to include any new results should be submitted to the NDA in both red-lined and clean versions.
- Withdraw the application and resubmit with accurate, complete, and reviewable datasets and revised clinical study reports as described in the bullet above.

Discussion during Teleconference

FDA opened the discussion by asking whether AAA had questions or required clarification of any agenda items communicated to AAA via electronic communication (email) on Friday, July 29. FDA reiterated that the application is materially incomplete in that the datasets provided are inaccurate, incomplete, and inconsistent across datasets. Thus, FDA cannot verify the information provided in the clinical study reports nor verify data proposed for product labeling. AAA acknowledged FDA's comments.

FDA and AAA did not conduct any further discussion regarding specific review discipline issues listed; however, the general requirements for the revised datasets were discussed, as summarized below.

- a. FDA stated that the issues related to the datasets included the CDISC SDTM and ADaM datasets, and asked AAA whether they understood the concerns as outlined by FDA, and the options for addressing the issues. AAA stated that they understand the issues overall, but requested some additional clarification regarding the statistical comments.
- b. FDA indicated that the Clinical and Statistics review teams, in particular, are not able to use the datasets provided by AAA, including the revised datasets submitted by AAA in response to FDA information requests. FDA stated that the raw datasets must be cleaned, complete, verified for accuracy against the raw data from each trial and be the same data from which the results in the CSR were

obtained. FDA again confirmed that a revised CSR should be submitted to the NDA in both red-lined “track changes” and clean versions.

- c. AAA requested clarification regarding what is needed to support the datasets. FDA confirmed the need for submission of reviewer guides with defined files that allow for understanding of all headings and variable names in the datasets so that the data can be analyzed. FDA stated that the analysis programs used to generate the tables and the CSR are also required. FDA also stated that given the importance of the drug, FDA is willing to waive the requirement for data in CDISC format as a one-time exception as long as the datasets are submitted in a format that is compatible with FDA review tools.
- d. FDA confirmed that the requirements for the new datasets and supporting materials apply to both the Erasmus and NETTER-1 studies, with a focus on the Dutch patients in the Erasmus study. FDA also stated that the Erasmus data should include information relevant to conducting the Clinical Pharmacology and safety reviews.
- e. FDA asked AAA if they are able to submit the requested new datasets and materials for review as discussed within 30 days of the August 2 teleconference. AAA responded that they will discuss a timeline internally, and will communicate a plan to FDA via teleconference on Wednesday, August 3.
- f. AAA stated that the most significant task will be the resubmission of data, and confirmed *the specific Clinical, Clinical Pharmacology, Statistics and CMC discipline review issues listed below do not require further discussion at this time.*

Clinical – No further discussion

- g. FDA is not able to use the datasets submitted in the NDA to confirm the analyses presented in the clinical study reports (CSR) for NETTER-1 or for the Erasmus Medical Center (EMC) study. The converted SDTM datasets must be able to support the analysis datasets, and the analyses contained in the CSR.
- h. There are errors, inconsistencies and missing values identified in the datasets provided.
- i. The data definition files are incomplete or do not provide sufficient details to describe the variables included in some datasets.

Clinical Pharmacology – No further discussion

- j. FDA could not confirm AAA’s analyses using the clinical pharmacology datasets due to missing patient baseline demographic information in both the NETTER-1 and EMC studies.

- k. The origin of the datasets used to generate the figures in the clinical pharmacology summary and CSR from the EMC studies could not be found.
- l. Define files are not associated with SDTM datasets and do not provide sufficient details to describe the variables.
- m. Data and analyses were not provided to determine the impact of renal dysfunction (decrease in creatinine clearance) on the exposure of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and subsequent association with observed toxicities.

Statistics – No further discussion

- n. The CSR included in the NDA submission was generated using the raw and derived (analysis) data not following standard CDISC format; therefore, the statistical reviewers cannot use the ADaM and STDM datasets submitted on 4/28/2016 (not used for the CSR generation) to obtain results included in the CSR.
- o. New ADaM and SDTM data sets were submitted to FDA on 7/13 and 7/18/2016. However, the reviewers cannot reproduce some results using the new ADaM datasets (for example, variables in Table 10-1, race in Table 10-2, height and weight in Table 11-2, variables in Table 11-11, continuous CgA and 5-HIAA in Table 11-15, PFS local assessment analysis, PFS sensitivity analysis 4, ORR analysis).
- p. The 7/18/2016 submission did not include a define file necessary to conduct analyses using the datasets. For example, FDA could not determine the variables used for the two stratification factors used in the randomization.
- q. Please confirm the following dates and address the following:
 - Clarify the reason why the last patient enrollment date is between the two database cutoff dates.
 - Why were the dates different for the date of first patient randomized and “first patient in?”
 - Were changes made to the SAP (version 2) dated 7/31/2015 compared with the previous versions (and what changes were made)?
 - Did AAA provide a copy of the previous SAPs (i.e., before SAP version 2) in the NDA submission?
 - What was the cutoff date for the analyses in the CSR (i.e., was the date 9/14/2016)?

Study start (first patient randomized)	09/06/2012
First patient in	10/07/2012
Last patient enrollment date	08/06/2015

SAP Version 2	07/31/2015
Study end (database cutoff date for primary analysis)	7/24/2015
Clean rest of data and lock rest with 5 additional death	09/14/2015

Chemistry, Manufacturing and Controls (CMC) – No further discussion

FDA has identified several CMC deficiencies in the application; however, the deficiencies are potentially correctable contingent upon whether FDA's information requests are adequately addressed.

3.0 NEW OR PENDING INFORMATION REQUESTS

Submit new datasets and revised clinical study reports to the NDA **within 30 days** of this teleconference in order to enable a complete review of the application and confirmation of the various trial results. The new datasets should be *complete* and based on the raw data from each trial as previously agreed in the pre-NDA meeting and subsequent communications, and be in such a format as to allow for use with software such as SAS and JMP. Additionally, a revised CSR to include any new results should be submitted to the NDA in both red-lined and clean versions.

Discussion during Teleconference

AAA confirmed they will respond to two recent CMC information requests by the requested due dates and will discuss their plan to address FDA's issues regarding the new datasets/revised clinical study reports in a teleconference with the FDA on August 3, 2016.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

None

5.0 PROPOSED DATE AND FORMAT FOR LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

- Current proposed labeling to AAA: by September 28, 2016
- Current Late Cycle meeting: October 18, 2016

6.0 MISCELLANEOUS/WRAP-UP

FDA would like to discuss the timeline for the submission of new datasets and a revised CSR as described above.

Discussion during Teleconference

AAA stated that their representative would be in contact with the FDA RPM on Wed., August 3, 2016, via teleconference to confirm AAA's response to the above FDA requirements regarding significant issues.

7.0 POST MEETING ADDENDUM

On August 3, 2016, AAA initiated a teleconference with FDA and conveyed that although they will be able to submit much of the required information requested by FDA during the August 2, 2016, Mid-Cycle Communication teleconference within a 30 day window, they will not be able to provide all of it. AAA confirmed that they will submit a written timeline outlining which materials they would be able to submit within 30, 60 and 90 day time frames. AAA committed to providing this document to FDA by Thursday, August 4, or Friday, August 5, at the latest. FDA will review AAA's proposed plan and confirm next steps.

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/s/

SUSAN B TRUITT
08/04/2016



NDA 208700

INFORMATION REQUEST

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Head of Regulatory Affairs
350 Fifth Avenue
Suite 6902
New York, NY 10118

Dear Dr. Paulus,

Please refer to your original New Drug Application received April 28, 2016 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera (^{177}Lu -DOTA0-Tyr3-Octreotate) Injection, Solution, 370 MBq/mL.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response prior to COB Thursday, August 11, 2016.

1. We note that you have presented executed batch records in the Regional Information Section where only IDB $^{177}\text{LuCl}_3$ is used in the manufacturing. Present at least one executed batch record from each of the manufacturing sites and for the two batch sizes ($^{(b)(4)}$ GBq) where MURR is the supplier of the $^{177}\text{LuCl}_3$ used.

If you have any questions, please contact Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Eldon Leutzinger, Ph.D.
Application Team Leader
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Eldon E.
Leutzinger -A

Digitally signed by Eldon E. Leutzinger
-A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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Date: 2016.07.28 13:39:34 -04'00'

MID-CYCLE MEETING MINUTES

Meeting Date: July 27, 2016

NDA: 208700 - 505 (b)(1) New Molecular Entity

Product: Lutathera (¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial

Proposed Proprietary Name: Lutathera
Established Name: Lutetium Lu 177 dotatate

Submission Date: April 28, 2016
Received Date: April 28, 2016 (Final 3rd part, Rolling Submission)

PDUFA Date: December 28, 2016 (Priority)

Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)

Proposed Indication: Treatment of patients with [REDACTED] (b) (4) [REDACTED] somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors [REDACTED] (b) (4)]

The complete application can be accessed via DARRTS (SDN 1-3 and eCTD 0001 – 0003). The clinical development of Lutathera was conducted under IND 077219.

Current Review Team/Collaborators for NDA 208700

Richard Pazdur, Director, OHOP - ATTENDED
Patricia Keegan, M.D., Director, DOP2 - ATTENDED
Steven Lemery, M.D., M.H.S., Acting Associate Director, DOP2 - ATTENDED
Suzanne Demko, PA-C., Clinical Team Leader (CDTL), DOP2 - ATTENDED
Joohee Sul, M.D., Medical Officer (DOP 2), Clinical Reviewer, DOP2 - ATTENDED
Melanie Pierce, CPMS, DOP2
Susan Truitt, R.N., M.S., Regulatory Health Project Manager, DOP2 - ATTENDED
Mimi Biable, M.S., Senior Regulatory Health Project Manager, DOP2 - ATTENDED
Kun He, Ph.D., Statistics Team Leader - ATTENDED
Lan Huang, Ph.D., Statistics Reviewer - ATTENDED
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader - ATTENDED
Brian Furmanski, Pharm. D., Clinical Pharmacology Reviewer - ATTENDED
Shawna Weis, Ph.D., Nonclinical Team Leader (on behalf of Whitney Helms, TL)
Anwar Goheer, Ph.D., Nonclinical Reviewer - ATTENDED

Jennie Chang, Pharm. D. Associate Director for Labeling - ATTENDED
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead (ATL) - ATTENDED
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA - ATTENDED
Erica Pfeiler, Ph.D., Microbiology (TL), ONDQA
Peggy Kriger, Ph.D., Microbiology, ONDQA
Krishnakali Ghosh, Ph.D., Facilities
Steven Kinsley, Ph.D., ONDQA, Regulatory Business Process Manager - ATTENDED
Okpo Eradiri, Biopharmaceutics Team Leader
Banu Zolnik, Biopharmaceutics Reviewer
Lauren Iacono-Connor, OSI Reviewer - ATTENDED
Devi Kozeli, IRT/QT Regulatory Project Manager
Carole Broadnax, OPDP Reviewer - ATTENDED
Steve Bird, DEPI Team Leader
Carolyn McCloskey, DEPI Reviewer
Naomi Redd, DRISK Team Leader
Mei-Yean Chen, DRISK reviewer - ATTENDED
Chi-Ming (Alice) Tu, DMEPA Team Leader
Janine Stewart, DMEPA Reviewer - ATTENDED
Afrouz Nayernama, DPV Team Leader
Peter Waldron, DPV Medical Officer/Reviewer
Latoria Ford, OSE, Safety Regulatory Project Manager - ATTENDED
Miriam Dinatale, Acting DPMH TL (for Tamara Johnson, DPMH TL) - ATTENDED
Christos Mastroyannis, DPMH Reviewer/Maternal Health MO - ATTENDED
Denise Johnson-Lyles, DPMH Regulatory Project Manager - ATTENDED
Cynthia Welsh, DMIP Medical Officer/Reviewer – ATTENDED

Other Attendees

Amanda Walker, Medical Reviewer, DOP1
Abhilasha Nair, Clinical Reviewer, DOP2
Kirsten Goldberg, Medical Editor, OHOP
Lorraine Pelosof, Clinical Reviewer, DOP2
Todd Knepper, Fellow, DOP2 attended the follow up Mid-Cycle meeting on August 2

Agenda:

1. Discipline Review Presentations/Updates – Note: Clinical Safety/Efficacy and Clinical Pharmacology presented during this July 27 meeting.

Note: Due to time constraints, Nonclinical and CMC presented during a 30-minute follow up internal Mid-Cycle meeting on August 2, 2016.

Clinical Safety/Efficacy (20-25 minutes):	Joohee Sul/Lan Huang
Clinical Pharmacology (10 minutes):	Brian Furmanski
Nonclinical (5 minutes):	Anwar Goheer
CMC (5-10 minutes):	John Amartey

2. Discussion of key issues and strategies for resolution (PDUFA V Mid-Cycle) –

The following will be conveyed to AAA during the Mid-Cycle Communication teleconference scheduled for August 2, 2016. Specific review discipline issues related to the incomplete application regarding the datasets will be listed in the agenda.

The application is materially incomplete in that the datasets provided are inaccurate, incomplete, and inconsistent across datasets. Thus FDA cannot verify the information provided in the clinical study reports nor verify data proposed in the product labeling. In order to address the issues raised below, Advanced Accelerator Applications USA, Inc. (AAA) should do one of the following:

- Submit new clinical and clinical pharmacology datasets that contain data that has been verified for accuracy and within 30 days of this teleconference. The new datasets should be *complete*, verified for accuracy against the raw data from each trial as previously agreed in the pre-NDA meeting and subsequent communications, and be in such a format as to allow for use with software such as SAS and JMP. Additionally, a revised CSR to include any new results should be submitted to the NDA in both red-lined and clean versions.
- Withdraw the application and resubmit with accurate, complete, and reviewable datasets and revised clinical study reports as described in the bullet above.

3. Clinical/Statistics: During the course of the review, AAA informed FDA that the clinical study report (CSR) for NETTER-1 was generated using the raw and derived (analysis) data, not the STDM and ADaM datasets submitted for review, resulting in an inability for the reviewers to verify the results in the CSR. Multiple information requests (IR) were issued to AAA in an attempt to reconcile the deficiencies found in the datasets; however, the revised datasets submitted by AAA continued to be inadequate and were not able to be utilized to continue the review of the safety and efficacy data. AAA informed FDA that although raw datasets were available and could be analyzed by the statistics team, these were not compatible with the clinical team's review tools.

4. Labeling Issues – None identified at this time; will follow up during labeling meetings beginning on August 29, 2016 (see schedule below).

5. PMC/PMR and REMS Issues – The team does not have any PMC/PMR and/or REMS issues at this time.

6. Miscellaneous

- a. SGE updates - Scientific and patient representative process in progress.

- b. OSI update (provided after the meeting) - There are two foreign inspections scheduled to begin in (b) (4). (b) (4) scheduled to start (b) (4) and, (b) (4) (b) (4) scheduled to start (b) (4)
- c. QT Consult: Review submitted 7/7/16 - “The sponsor did not propose any clinical QT labeling language. QT-IRT’s proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.” Not discussed during Mid-Cycle meeting.

NDA 208700 Timeline: Submission Date – April 28, 2016

Milestone	8-Month Priority Review Actual/Goal
Acknowledgment Letter	May 12, 2016 [within 14 days] <i>Issued May 2, 2016 (Acknowledge Presubmission issued April 18, 2016)</i>
Applicant Orientation Meeting (AOM) , with Application “Walk Through” meeting prior to AOM **NOTE: <i>Team members please attend AOM meeting on 6/17 in WO 22, room 2205 at 1:00 pm.</i>	Scheduled Fri., June 17, 2016 – 1:00 OHOP Rounds; Application “ Walk Through ” with sponsor 6/17/16, 11:30-12:30, WO 22 rm. 1311
Filing Action Letter – Day 60 (Inform applicant of review designation, filing determination) - <i>Filing Meeting held June 8, 2016.</i>	June 27, 2016 – No Filing Review Issues Identified letter issued June 23, 2016.
Filing Issues Identified (Day 74 Letter) — if not sent in Day 60 letter	July 11, 2016 N/A since 60-day letter sent
Mid-Cycle Internal Meeting	July 27, 2016 [Month 3 = by July 28, 2016]
Mid-Cycle Sponsor Communication (TC) – <i>Send Agenda to Sponsor by 7/29 latest. Minutes within 30 days of TC = by 9/1/16.</i>	August 2, 2016 [Month 3.5 = by August 11, 2016]
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 = <u>by September 28, 2016</u>
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	[Month 5.25 = by October 5, 2016]
Late Cycle Internal Meeting Briefing/background pkg. to sponsor due 2 days before Late Cycle Sponsor meeting, so by Oct. 16 latest	September 30, 2016 [Month 5.25 = by October 5, 2016]
Late Cycle Sponsor Meeting (no Advisory Committee)	October 18, 2016 [Month 6 if <u>no</u> AC (current plan) = by October 28, 2016]
Advisory Committee	N/A
Review Target Due Dates: Primary Review Due <i>Secondary Review Due</i> <i>CDTL Review Due (4 weeks before action)</i> <i>Division Director Review Due (3 weeks before action)</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 = September 28, 2016 Month 5.1 = ~ September 30, 2016 Month 7 = November 30, 2016 3 weeks prior = December 7, 2016 December 28, 2016
Wrap-Up Meeting w/ Safety discussion	November 18, 2016 [5 weeks pre-action = November 23, 2016]
Compile and circulate Action Letter and Action Package	[3 weeks pre-action = December 7, 2016]
FINAL Action Letter Due	December 28, 2016

Labeling Meeting Organization and Scheduling: NME/NDA 208700

Note: Jennie Chang “High Level” TC with Sponsor Held June 30, 2016.

Meeting #	Discipline Attendance Required	Label Section(s) to be discussed	Length of Meeting	Meeting Date/Time/Room (Check Invites)
1 st meeting	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	1 hour	Mon., 8/29/16; 1-2, rm. 3201
2 nd meeting	Clinical, Statistics	1, 14	1 hour	Tues., 8/30/16; 11-12, rm. 2376
3 rd meeting	Clinical Pharmacology, DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 and 6.2 (Immunogenicity)	1.5 hours	Thurs., 9/1/16, 2-3:30, rm. 4201
4 th meeting	Non-clinical, Maternal Health Team (MHT), Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	1.5 hours	Tues., 9/6/16, 12-1:30, rm. 2327
5 th meeting	Clinical	6	1 hour	Thurs., 9/8/16; 1:30-2:30, rm. 2376
6 th meeting	Clinical	4, 5, 2, 17	1.5 hours	Mon., 9/12/16; 1:30-3, rm. 4201
7 th meeting	Initially include all review disciplines (to hold time)	Any items not covered during originally scheduled time	1 hour	Mon., 9/19/16; 12-1, rm. 3201
When PI is substantially complete, send label to applicant, OPDP & Patient Labeling Team.				
8 th Meeting (Schedule 2-3 weeks after labeling sent to applicant-by 9/28)	Review revised labeling from applicant, include all review disciplines and OPDP and PLT		1.5 hours	Fri., 10/14/16; 11-12:30, rm. 3201

Monthly Team Meetings

Date/Time/Room	Notes/Comments
#1: Tues., 8/23/16, 2:30-3:30, rm. 3201	<i>Mimi Biable covering for Susan Truitt (OOO). Other team meetings were held in June, July; Wrap Up is on Nov. 18.</i>
#2: Thurs., 9/22/16, 2:30-3:30, rm. 3201	
#3: Fri., 10/28/16, 11-12, rm. 3201	

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/s/

SUSAN B TRUITT
08/10/2016

From: [Biable, Missiratch \(Mimi\)](#)
To: [Victor Paulus](#)
Cc: [Truitt, Susan](#)
Subject: RE: NDA 208700 - Clinical Information Request: Response Required
Date: Wednesday, July 20, 2016 9:55:56 AM

Dear Victor,

Yes, the request is for the new datasets.

In addition, I want to inform you that the team would like to have a standing weekly teleconference with AAA to facilitate the review of your application.

I am following up with the team to confirm if one is needed for this week. Once Susan is back in the office, she will work with you to reserve the weekly/standing TC.

Feel free to contact me if you have additional questions.

Thanks,
Mimi

From: Victor Paulus [mailto:victor.paulus@adacap.com]
Sent: Wednesday, July 20, 2016 9:00 AM
To: Biable, Missiratch (Mimi)
Cc: Truitt, Susan
Subject: Re: NDA 208700 - Clinical Information Request: Response Required
Importance: High

Hi Mimi,

Could you tell me if, in point 3, the requests for the DFINE file is for the datasets submitted last week?

Thank you!

All the best,

Victor

From: "Biable, Missiratch (Mimi)" <Missiratch.Biable@fda.hhs.gov>
Date: Monday, July 18, 2016 at 10:55 AM
To: victor paulus <victor.paulus@adacap.com>
Cc: "Truitt, Susan" <Susan.Truitt@fda.hhs.gov>
Subject: NDA 208700 - Clinical Information Request: Response Required

Dear Victor,

I am sending the following on behalf of Susan Truitt.

Please respond to the following clinical information request via **email** to me and cc [Susan](#) by **COB ET on Thursday, July 21, 2016**, *or sooner if possible*, followed by a formal submission to your NDA.

1. There are several discrepancies between patient status at end of study and at end of treatment. For example:
 - a. Patient NETTER1-US13-045: The patient is included in the Lutathera treatment arm; however, the patient is described as randomized but not treated. The patient is also described as “SUBJECT OFF TREATMENT AND STUDY, REFUSING LONG-TERM FOLLOW-UP” and off study due to “OTHER: RANDOMIZED DID NOT RECEIVE TREATMENT HAD SAE BEFORE START OF TREATMENT WENT OFF STUDY”. Please explain why this patient was included in the Lutathera arm and not in the “not treated” cohort of patients. Please also provide a rationale for the discrepancies in the data and provide a revised dataset with the correct patient status information.
2. Regarding the ADAE dataset:
 - a. The “AETERM” is captured; however there are several rows with missing values for AELLT, AEDECOD, AEHLT, AEHLGT, AE BOBYSYS. Please provide a complete dataset with all the values included.
 - b. Please provide a rationale for missing AETOXGRN for eighteen AEs.
3. Please provide DEFINE files for all datasets submitted as new variables are included in these datasets that are unknown.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov

Phone: 301-796-0154

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/s/

SUSAN B TRUITT
07/25/2016



NDA 208700

INFORMATION REQUEST

Advanced Accelerator Applications USA, Inc.
Attention: Victor Paulus, Head of Regulatory Affairs
350 Fifth Avenue
Suite 6902
New York, NY 10118

Dear Dr. Paulus,

Please refer to your New Drug Application (NDA) dated March 31, 2016, received April 28, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lutathera (177Lu-DOTA0-Tyr3-Octreotate) Injection, Solution, 370 MBq/mL.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please submit your response by Thursday, August 4, 2016.

IBD drug substance precursor (¹⁷⁷LuCl₃):

1. What is the source (b) (4)
(b) (4)?
2. You h (b) (4)
(b) (4)
(b) (4)
3. Expla (b) (4)
(b) (4)
4. (b) (4)
(b) (4)



5. We noticed that you have not provided any data or information on leachable and extractable of the Lutetium (Lu-177) Chloride Radiopharmaceutical Precursor container closure system. Present information on leachable and extractable of the container closure system.

Drug substance/ product:

6. In section 3.2.P.2, reference is made to DMF II under extractable. Clarify the DMF cited.
7. In the batch analysis data and the batch records presented in the application, the batch identity of the drug substance precursor (b) (4) used is lacking. Provide this information in the batch records as well as in the clinical batches used for the stability studies of the drug product.
8. You have indicated in the dossier that $^{177}\text{LuCl}_3$ is sourced from MURR or IDB and the information presented in the batch analysis table #2. However, the sources of the $^{177}\text{LuCl}_3$ used for manufacture of the pivotal batches for the clinical studies are lacking in the executed batch records. Provide this information in the batch records to facilitate traceability.
9. We note that the peak identification RRT limits reported for the (b) (4) species are inconsistent. Correct these discrepancies in tables 7 and 8 of section P. 5.5.

Microbiology:

10. With respect to (b) (4) the (b) (4) application states (b) (4) Describe the circumstances, if any, under which (b) (4) the drug product is permitted.
11. Regarding the microbiological monitoring of the manufacturing environment, address the following:
 - a) For personnel monitoring, provide the monitoring method and the alert and action levels.
 - b) Provide the frequencies of air, surface and personnel monitoring during routine manufacturing. Specify the (b) (4) conditions after collection of the samples.



- c) Provide a description of the periodic or routine monitoring methods used for yeasts and molds in the manufacturing environment.
 - d) Describe the actions taken when levels are exceeded.
12. The information regarding the media fill simulations in the document 3.2.P.3.5.2.3 (3/31/16) “process-validation.pdf” is acknowledged; however:
- a) Provide the production line, [REDACTED] (b) (4) [REDACTED] (b) (4) for each of the nine media fill simulations noted in Table 2.
 - b) Provide the filling medium and [REDACTED] (b) (4) conditions for the vials.
 - c) Provide results for recent media fill simulations for each of the [REDACTED] (b) (4) [REDACTED] (b) (4) Colleretto Giacosa site.
13. Regarding the actions concerning product when media fills fail, address the following:
- a) Describe all activities that must take place in order to requalify the line after a media fill failure, including the number of runs required.
 - b) Describe the decision making process and personnel involved in determining hold/disposition/release of products potentially affected by a media fill failure.
14. Regarding sterility testing of the drug product:
- a) It is acknowledged that the document “justification-of-specifications.pdf” indicates that the sterility testing [REDACTED] (b) (4) [REDACTED] (b) (4). Indicate when the post-release sterility test will be performed.
 - b) Provide the revised sterility test method and drug product specification.
 - c) Describe the actions taken in the event that a released batch fails sterility testing.
15. Regarding bacterial endotoxins testing of the drug product, the verification reports [REDACTED] (b) (4) and the exhibit batch records are acknowledged.



- a) It is noted that the verification test calculations used what appears to be an (b) (4) (b) (4) Comment and specify whether this will continue for routine testing of the commercial drug product.
- b) Confirm that the release testing of the drug product for bacterial endotoxins will be tested at the Colletterto Giacosa, Italy and Meldola, Italy sites. In addition, confirm that the same bacterial endotoxins methods will be used at all sites.

If you have any questions, please contact, Steven Kinsley, Ph.D. Regulatory Business Process Manager, at (240) 402-2773.

Sincerely,

Eldon Leutzinger, Ph.D.
Application Team Leader
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Eldon E.
Leutzinger -A

Digitally signed by Eldon E.
Leutzinger -A
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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54329, cn=Eldon E. Leutzinger -A
Date: 2016.07.21 15:37:28 -04'00'

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: RE: NDA 208700 - OSI Information Request: Response Required-Follow Up
Date: Wednesday, July 13, 2016 8:03:00 AM

Dear Victor,

Please respond to the following Office of Scientific Investigations (OSI) information request (IR), in follow up to our July 11, 2016 IR, via email to me (Susan.Truitt@fda.hhs.gov) **by noon ET on Thursday, July 14, 2016**, or sooner if possible, followed by a formal submission to your NDA.

The table you provided may be included as an attachment, but the response should explain which datasets were used, and include a definition of the various datasets (e.g. derived datasets=SDTM datasets) and an explanation of all abbreviations.

Please contact me should you have any question(s) and kindly confirm receipt of this communication. I'm also requesting that you please include the initial IR email in any replies.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

-----Original Message-----

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Tuesday, July 12, 2016 4:07 PM
To: Truitt, Susan
Cc: Biable, Missiratch (Mimi)
Subject: RE: NDA 208700 - OSI Information Request: Response Required

Hi Susan,

Please see the attached.

All the best,

Victor

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/s/

SUSAN B TRUITT
07/13/2016

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 12, 2016

Application Number: NDA 208700

Product Name: Lutathera

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc.

Subject: Teleconference with sponsor's statistician to discuss questions regarding datasets and programs

FDA Participants - Joohee Sul/Clinical Reviewer, Lan Huang/Statistics Reviewer, Susan Truitt/Regulatory Health Project Manager

Sponsor/Applicant Participants - Albert Chau/Statistician, Jack Erion/VP, Research and Development, Izabela Reydych/EU Regulatory Affairs Manager, Victor Paulus/Head, Regulatory Affairs

BACKGROUND

Due to extensive email exchanges and the lack of clarity in the applicant's NDA submission regarding datasets and programs, the FDA Statistics reviewer requested a brief teleconference with the applicant's statistician to discuss related questions.

DISCUSSION

1. Review of statistics files/locations submitted to date via email by AAA via email by FDA Statistics reviewer (Lan Huang). All the files (legacy data) were used to generate the CSR submitted to FDA in the original NDA submission.
 - The AAA Statistician (Albert Chau) confirmed there are 66 files in total in the NETTER1_Originalrawdata folder: (1) pdf (annotated CRF file) and 65 SAS data files including the (b)(4)_03aug2015.sas7bdat data file.
 - The derived data files AAA submitted via separate email submissions (on July 11, 2016) were reviewed. AAA confirmed that in their submission they included the data from various countries in data dset_split_lab1.sas7bdat, dset_split_lab2.sas7bdat, dset_split_lab3.sas7bdat, and dset_split_lab4.sas7bdat. It is actually one set of data.
 - The AAA program folder submitted on July 11 was reviewed – programs for analyzing the CRO's raw and derived data (legacy data).
 - FDA emphasized that AAA must provide ADaM/SDTM datasets in their formal submission through the electronic gateway, and the results obtained using the ADaM/SDTM data should be consistent with the CSR included in the NDA submission.

2. Revised SDTM data sent by AAA via email on July 11, 2016 – The AAA statistician stated AAA used SDTM data to create ADaM datasets, and sent the programs for generating SDTM data to ADaM data.
3. The FDA Clinical reviewer asked when AAA plans to submit the ADaM and SDTM data coming through the electronic gateway. AAA stated they will be submitted on July 13, 2016, via eCTD sequence 0021. Per AAA, the new eCTD sequence 0021 contains refreshed SDTM and ADaM data. The AE datasets will also be formally submitted on July 13. The old ADaM and STDM datasets submitted in previous submission (eCTD sequence 0003) should not be used.
4. Efficacy – eCTD sequence 0021 contains 6 SDTM datasets, and 3 ADaM datasets. AAA provided tables generated from the ADaM dataset so the FDA can replicate results from ADaM and use these to confirm a CSR table in the NDA submission. AAA stated that the derived datasets (submitted to FDA through emails and discussed in item 1 above) are consistent with the new ADaM datasets. AAA also included programs for checking the derived legacy datasets and the ADaM datasets.

ACTION ITEMS

- AAA will formally submit eCTD sequence number 0021 via the electronic gateway on July 13, 2016. This will include all of the information sent/specified in the July 11, 2016, email submission to FDA for this sequence number.
- Sequence number 0020 (19 emails submitted on July 11) will be submitted via the electronic gateway on July 12, 2016. The FDA Regulatory Health Project Manager (Susan Truitt) requested in a July 12, 2016, email that AAA submit a brief list of the contents of sequence 0020 due to the 19 emails sent by AAA on July 11, and AAA will provide this.

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/s/

SUSAN B TRUITT
07/13/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - OSI Information Request: Response Required
Date: Monday, July 11, 2016 1:26:00 PM

Dear Victor,

Please respond to the following Office of Scientific Investigations (OSI) information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **noon ET on Tuesday, July 12, 2016**, *or sooner if possible*, followed by a formal submission to your NDA.

OSI requests to know what datasets were used to generate the following PDF files:

1. "netter1_Site Data Listings;" and,
2. "Study AAA-III-01 [netter-1] Subject Data Listings" (aka listing 16.2 Patient data listings).

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
07/11/2016

From: Truitt, Susan
To: "[Victor Paulus](#)"
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Clinical/Statistics Information Request: Response Required
Date: Thursday, July 07, 2016 1:37:00 PM

Dear Victor,

Please respond to the following Clinical/Statistics information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Wednesday, July 13, 2016**, or sooner if possible, followed by a formal submission to your NDA.

1. Regarding the revised ADSL dataset submitted July 1, 2016:

- a. Last visit date: LVISDT (integer) or LVISDTL (text) should not be missing for patients even if the study is ongoing, as this is the date of the last clinical visit on or off study.
- b. Treatment duration in days (TRTDURD) should be for the randomized *treatment* administered (Lutathera vs. high dose octreotide LAR 60 mg). You may derive this from TRTEDT (treatment end date) – TRTSDT (treatment start date) + 1. It should not include the supportive care octreotide LAR 30 mg administered in both arms as information on exposure and doses received should be included in the concomitant medications dataset.
- c. Status at end of study: this should describe the patient's status at the time of the data base cutoff/lock, e.g.: "completed study," "does not meet entrance criteria," "discontinued due to X," "ongoing treatment," "ongoing follow-up phase," etc. For patients not continuing on study drug, the specific reason should be provided. For patients not continuing on the long-term follow-up, the specific reason should be provided.
- d. Please provide withdrawal reason (specified) for certain responses such as "withdrawal by subject," "physician decision," and "other."

2. Regarding the requests for additional information discussed during the teleconference on June 30, 2016:

- a. There are several patients with missing data in the ADSL dataset. Please revise the ADSL to ensure that the following variables are available for all patients in the FAS:
 - i. BMI
 - ii. HEPATIMP
 - iii. RENALIMP
 - iv. OCTUP
- b. The DM dataset describes the following populations:
 - i. LUTATHERA (n=111)
 - ii. LUTATHERA_NON-RANDOMIZED (n=11)
 - iii. Not Assigned (n=71)
 - iv. Not Treated (n=9)
 - v. SANDOSTATIN (n=110)
 - vi. Screen Failure (n=33)

However, this does not reflect the information in the NETTER-1 CSR that describes

screen failures (n=87) or patients who did not receive medication (n=8), etc. Please provide an explanation for these discrepancies.

- c. The DM dataset does not provide specific disposition information such as reason for study drug discontinuation, reason for off study, etc. Please revise the DM dataset to provide the specific disposition for each study patient.
- d. In the IE dataset, there are thirty-three (33) patients with “inclusion/exclusion criteria not met”, but there are eighty-seven (87) screen failures described in the NETTER-1 CSR. Please provide a dataset that includes all screen failures, and the reasons for screen failures.

3. Additional requests for the ADSL dataset:

- a. OCTUP: This variable is in the updated ADSL submitted on 7/1/2016, but counts obtained using the ADSL data are not the same as the counts for tumor update mean score in CSR Table 11-12. Please clarify.
- b. AAA refers to “KI67GRP” in the cover letter submitted on 7/1/2016; however, this variable is not in the ADSL dataset. KI67GR1 is provided in the updated ADSL data submitted on 7/1/2016, and the values of the variable are 1, 2, and 3. Please clarify the meaning of 3.
- c. Provide the following variables in the new ADSL data that you plan to submit by 7/11/2016.
 - i. Tumor uptake score (highest score)
 - ii. Variables for obtaining the reasons for not entering or stopping the long-term follow-up (did the patient enter in the long-term follow-up phase? If no, reason for not entering)
 - iii. Disease stage
 - iv. Prior cancer surgery type (resection, ablation, chemo-embolization)
 - v. Previous cancer treatment (yes, no)
 - vi. Previous cancer treatment type (radiotherapy, radiometabolic therapy, chemotherapy, other). Note that the counts obtained using CHEMFL and RADFL in the current ADSL data are not consistent with the counts shown in CSR Table 11-11.
 - vii. Synaptophysin
 - viii. 5-HIAA
 - ix. Alkaline phosphatase
 - x. CgA (continuous variable)
 - xi. Creatinine clearance

4. Regarding the ADAE dataset, please provide a revised ADAE dataset that includes the following:

- a. Provide the TRTP (planned treatment) for each event, and do not leave blank or missing cells.
- b. Provide an “AE ongoing” flag.
- c. Provide the Study Treatment start date for Lutathera or control arm (60 mg octreotide LAR).
- d. The AEDUR values are not explained in the define file. For example, it is not clear what

- “P12D” refers to. Provide AE duration (AEDUR) and units (e.g. days, weeks) for all AEs.
- e. AE grades are not provided. Please provide AE grades as an integer.
 - f. Provide AE outcomes (AEOUT) describing outcomes such as “fatal,” “not recovered/resolved,” “recovered/resolved,” “recovered/resolved with sequelae,” “recovering/resolving.”
 - g. Provide an AE leading to withdrawal flag and AE leading to study drug discontinuation (for Lutathera or 60 mg octreotide LAR, not for supportive octreotide LAR).
 - h. Provide a death flag (DEATHFL).
 - i. Provide death date (DTHDT) and primary reason for death (DTHREAS).
 - j. The CSR page 139 states *“If the information of an untoward medical occurrence was collected before starting the intake of study medication, this information was listed as a pre-treatment AE during statistical analysis.”* Please confirm that worsening of any baseline AEs were captured in the AE database.

5. Regarding the ADEX dataset, please provide a revised ADEX with the following:

- a. Visit number
- b. Visit date
- c. Delayed study drug administration flag
- d. Interrupted study drug administration flag

6. Additional information requests

- a. Page 134 of the CSR states *“Due to the ongoing cleaning process, at the time of database lock for the primary end-point analysis a small number of AEs were not coded and are therefore missing in the analyses. A list of these AEs sorted by patient ID is given in Section 14.3.5.”* Section 14.3.5 refers to a list of narratives for deaths and serious adverse events. Please provide the list of AEs that were not coded and are missing from the analysis.
- b. Please provide an analysis of concomitant medication use for octreotide LAR 30 mg every 4 weeks in the Lutathera arm and subcutaneous octreotide for rescue administered in the control arm.
- c. In the cover letter submitted on 7/1/2016, AAA stated that *“AAA would like to propose that we submit the revised SDTM and ADaM datasets to include the additional variables required, and provide programs to generate the PFS endpoints in ADaM from the SDTM datasets, in order to help the FDA statistical reviewers to conduct the analyses. AAA would aim to provide these programs and datasets for the efficacy endpoints by 11 July 2016.”* FDA agrees with this proposal and in addition to PFS, please provide programs and datasets for OS and ORR analyses.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager

Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
07/07/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Follow Up Statistics Information Request: Response Required
Date: Thursday, July 07, 2016 7:37:00 AM
Attachments: [NETTER1_OriginalDerivedData.txt](#)
[NETTER1_OriginalRawData.txt](#)

Dear Victor,

Please respond to the following Statistics information request, in follow up to your July 6, 2016 email response, via **email** to me (Susan.Truitt@fda.hhs.gov) by **noon ET on Friday, July 8, 2016**, or sooner if possible, followed by a [formal submission to your NDA](#).

FDA reviewers cannot find any data in the .sas7bdat files in your July 6, 2016, email submission. Two files about data (see the attached files) are included in the submission. *Please check and provide the SAS data.*

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Wednesday, July 06, 2016 2:58 PM
To: Truitt, Susan
Cc: Biable, Missiratch (Mimi)
Subject: Re: NDA 208700 - Statistics Information Request: Response Required
Importance: High

Hi Susan,

The response to the request, below, is attached. The links in the version are not functional.

I spent most of the day email the ESG help desk and our gateway is still not working. Our IT folks will work the the help desk tomorrow to resolve the issue.

All the best,

Victor

From: "Truitt, Susan" <Susan.Truitt@fda.hhs.gov>

Date: Tuesday, July 5, 2016 at 1:18 PM

To: victor paulus <victor.paulus@adacap.com>

Cc: "Biable, Missiratch (Mimi)" <Missiratch.Biable@fda.hhs.gov>

Subject: NDA 208700 - Statistics Information Request: Response Required

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Statistics information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Wednesday, July 6, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Provide the original raw/derived datasets and external data (as .sas7bdat files) from the NETTER-1 study with the associated SAS programs for the CSR generation shown in the data processing flow diagram on page 8 of your attached July 1, 2016, submission, sequence 0018. The FDA statistical reviewers will check the submitted data and will schedule a teleconference with AAA on the define files and following questions about the datasets and programs.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
07/07/2016

From: Truitt, Susan
To: [Victor Paulus](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Statistics Information Request: Response Required
Date: Tuesday, July 05, 2016 1:18:00 PM
Attachments: [cover-letter.pdf](#)
Importance: High

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Statistics information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Wednesday, July 6, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Provide the original raw/derived datasets and external data (as .sas7bdat files) from the NETTER-1 study with the associated SAS programs for the CSR generation shown in the data processing flow diagram on page 8 of your attached July 1, 2016, submission, sequence 0018. The FDA statistical reviewers will check the submitted data and will schedule a teleconference with AAA on the define files and following questions about the datasets and programs.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
07/05/2016

Truitt, Susan

From: Truitt, Susan
Sent: Thursday, June 30, 2016 10:50 AM
To: 'Victor Paulus'; 'mark Ibrahim'
Cc: Biable, Missiratch (Mimi); Chang, Jennie; Trentacosti, Ann Marie
Subject: UPDATE: NDA 208700 Teleconference - Labeling Comments: TC Cancelled

Importance: High

Dear Mark,

Per the phone conversation this morning between Jennie Chang, you and me, the labeling teleconference scheduled for today, June 30, 2016, from 1:00 – 2:00 p.m. is cancelled since AAA does not have any questions about the labeling at this time.

Please let me know if you have any question(s) on this and kindly respond to confirm receipt of this email communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Truitt, Susan
Sent: Tuesday, June 21, 2016 2:30 PM
To: 'Victor Paulus'
Cc: Biable, Missiratch (Mimi)
Subject: RE: NDA 208700 Teleconference - Labeling Comments

Hi Victor,

Thank you for your email with the dial-in information. Yes, you may add AAA participants as appropriate.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Tuesday, June 21, 2016 1:40 PM
To: Truitt, Susan
Cc: Biable, Missiratch (Mimi)
Subject: Re: NDA 208700 Teleconference - Labeling Comments

Hi Susan,

I am on vacation next week but will be available at the time designated. May I add participants on my side as I think necessary?

The dial-in number will be the same as what I had provided for the "walk through" meeting:

From the US: (b) (4) no PIN
From (b) (4): (b) (4) followed by (b) (4)
From Italy: (b) (4) followed by (b) (4)
From the UK (b) (4) followed by (b) (4)

I will try to eliminate the annoying music.

Victor

Confidentiality Note: This email is intended only for the person or entity to which it is addressed and may contain information that is privileged, confidential or otherwise protected from disclosure. Unauthorized use, dissemination, distribution or copying of this email or the information herein or taking any action in reliance on the contents of this email or the information herein, by anyone other than the intended recipient, or an employee or agent responsible for delivering the message to the intended recipient, is strictly prohibited. If you have received this email in error, please notify the sender immediately and destroy the original message, any attachments thereto and all copies.

From: "Truitt, Susan" <Susan.Truitt@fda.hhs.gov>
Date: Tuesday, June 21, 2016 at 1:23 PM
To: victor paulus <victor.paulus@adacap.com>
Cc: "Biabale, Missiratch (Mimi)" <Missiratch.Biabale@fda.hhs.gov>
Subject: NDA 208700 Teleconference - Labeling Comments

Dear Victor,

Our Associate Director for Labeling, Jennie Chang, mentioned to you and your team during the recent NDA 208700 "walk through" meeting that she would like to have a teleconference with you to discuss high-level comments regarding your NDA 208700 labeling draft. She has requested that this teleconference occur towards the end of next week.

The only available time we have for next week is **Thursday, June 30, 1:00 – 2:00 p.m. ET.**

Please confirm your attendance and provide a dial-in number for this teleconference via email to me by COB Thursday, June 23, 2016 at the latest.

Please confirm receipt of this communication and let me know if you have any question(s).

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

Phone: 240-402-3656

Fax: 301-796-9849

Email: susan.truitt@fda.hhs.gov

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MEMORANDUM OF TELECONFERENCE

Teleconference Date: June 30, 2016

Application Number: NDA 208700

Product Name: Lutathera

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc.

Subject: Teleconference with sponsor's data management team to discuss questions regarding datasets

FDA Participants - Joohee Sul/Clinical Reviewer, Brian Furmanski/Clinical Pharmacology Reviewer, Lan Huang/Statistics Reviewer, Mimi Biable/Sr. RPHM and Susan Truitt/RHPM

Sponsor/Applicant Participants - Albert Chau/Statistician, Thomas Thevenet/Manager, Clinical Research, Jack Erion/VP, Research and Development, Victor Paulus/Head, Regulatory Affairs

BACKGROUND

Due to the inability to derive data in the NETTER-1 Clinical Study Report (CSR) based on the submitted datasets as well as the lack of clarity in the applicant's NDA submission regarding datasets and related data derivation issues, the FDA Clinical reviewer requested a brief teleconference with the applicant to discuss some key dataset-related questions/issues.

DISCUSSION

1. The clinical reviewer (Joohee Sul) stated that FDA is unable to confirm the data in the CSR for the demographic tables as there are several key variables missing from the subject-level analysis dataset (ADSL). For example, age is missing for 8 patients; BMI, hepatic impairment, renal impairment and other variables are also missing for some patients.

AAA (Albert Chau) stated that the hepatic and renal impairment information was derived based on laboratory values/parameters; for example, "hepatic impairment" may be derived from several liver function tests. Therefore, these variables may not be recorded if some of the laboratory values used to determine these were missing. AAA also indicated that perhaps some values were missing because patients in the PK population may have data collected after the database cut off. FDA clarified that the missing data were for the patients randomized to the clinical efficacy/safety population, and not for the PK population. FDA stated that information regarding BMI, baseline liver and renal function was required for patient enrollment; therefore, these data should be available.

FDA also requested clarification for the following discrepancies between the datasets submitted and the information in the NETTER-1 CSR:

- Explain how the patient disposition populations in the NETTER-1 CSR were derived and why they differed from the populations described in the DM dataset provided by AAA. For example, the DM dataset describes thirty-three (33) patients as “screen failures;” however, the CSR describes eighty-seven (87) patients as “screen failures.”
- In the “IE” dataset, there are thirty-three (33) patients with inclusion/exclusion criteria not met, but eighty-seven (87) screen failures are described in the CSR. The reasons for all screen failures are required for FDA to assess whether patients were not included in the study for reasons that may potential bias the results.
- Certain terms are not defined in the “define files.” For example, “DVSEQ” and “No PV” are not described in the “define file” for the “protocol deviation” (DV) dataset. AAA indicated that DVSEQ is a unique number associated with each patient and “No PV” = no protocol violation. FDA explained that the define files should include all definitions for the variables in order to be able to analyze the data.

FDA stated that these variables are required to recreate tables in the CSR and in order to confirm the information in the CSR. FDA also stated that it is unclear why it is so challenging to derive the tables in the CSR based on the data in the datasets submitted.

2. AAA stated the data submitted to FDA differed from the data that was analyzed for the CSR. FDA asked how the tables in the CSR were generated, and AAA stated these were created by the CRO and generally based on raw data (non-CDISC compliant) from the database. For submission to FDA, AAA mapped the raw and derived datasets into ADaM/STDM datasets and presented these datasets to FDA. FDA stated that it is highly unusual for the data used to derive tables and information in the CSR to differ from the data submitted to FDA. FDA will further discuss this issue internally, and in the meantime will move forward with working with AAA to analyze the data in the available formats. FDA further stated that the discussion thus far was related to the NETTER-1 CSR, but that AAA should review the ERAMSUS CSR and datasets and resolve any issues with missing data or discrepancies as well.
3. The FDA clinical pharmacology reviewer also requested clarification on the timing of PK data collection, and AAA confirmed that the database was locked in September 2015, but that for some patients data collection continued beyond the database lock date. AAA further clarified that the patients included in Amendment #4 are not part of efficacy population.

SUMMARY AND ACTION ITEMS

Summary:

The key issue appears to be that the tables in the CSR were derived by the CRO using raw data (not CDISC compliant) and these data were not easily convertible to CDISC compliant data. In order to submit CDISC compliant datasets to FDA, AAA converted these data into SDTM &

ADaM. It is not clear how the data were converted, and what programs AAA used to convert the raw data to CDISC compliant data.

For now, FDA will move forward with IRs to resolve issues with missing data in the datasets, and will continue with the review.

Action Items

- AAA will submit their response to the most recent FDA statistics/clinical IR (due July 1, 2016 by 5:00 p.m.) and FDA will review before sending additional requests for clarifications/missing data in the ADSL dataset and other key datasets.
- AAA will review the programming used to derive the datasets submitted to FDA and check for missing data (e.g., age, BMI).

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/s/

SUSAN B TRUITT
07/06/2016



NDA 208700

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Advanced Accelerator Applications, USA
Attention: Victor Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received April 28, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Lutathera ($^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$) injection for intravenous infusion, 370 MBq/mL single-use vial.

We also refer to your amendments dated May 3, 17, 18, 20, and June 7, 8, 10, and 15, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 28, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2016.

In addition, the planned date for our internal mid-cycle review meeting is July 27, 2016. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information.

Clinical Pharmacology

We request that you submit all of the following information by **COB Monday, June 30, 2016.**

1. Electronic datasets from the Erasmus MC dosimetry and PK study containing all patient characteristics (e.g. creatinine clearance, body weight, age, etc.) at baseline and throughout the study; measurements of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (e.g. % IA (GBq), dose (Gy), concentration (ng/mL)) in blood and urine samples; and generated PK parameters including AUC, Cmax, volume of distribution, clearance, etc. for individual patients.
2. Electronic datasets with matching administered amino acid solution, unique patient identification number, creatinine clearance, exposure as a %IA and ng/mL, and dose (Gy) to the kidneys from both the Erasmus MC and NETTER-1 studies.
3. List of abbreviations with corresponding designations used in NETTER-1 and Erasmus MC dosimetry and PK studies.
4. Side-by-side individual urine concentration measurements utilizing well-type gamma-counting system and HPLC methods in NETTER-1.
5. Description of the well-type gamma-counting systems used at each clinical site including the make, model, and limit of quantitation.
6. Your plan to assess the need for dose adjustment in patients with renal or hepatic impairment.

Statistics

As previously communicated in our electronic mail (email) of June 10, 2016, submit the following information by **COB Monday, July 11, 2016.**

7. For the NETTER-1 study, please provide results from subgroup analyses by:
 - a. Age (<65 years vs. ≥ 65 and < 75 versus ≥ 75);
 - b. Sex;
 - c. Race and ethnicity;
 - d. Baseline body mass index (BMI) groups (<=21, 21 to <=27, >27, missing);
 - e. Mean Octreoscan tumor uptake (among target lesions);
 - f. Extent of overall tumor burden at inclusion;

- g. Somatostatin receptor scintigraphy (OctreoScan) tumor uptake score (grade 2, 3, 4);
- h. Length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤ 6 and > 6 months), Previous anticancer treatment (chemotherapy, external beam radiation, surgery);
- i. Karnofsky Performance Status;
- j. Region (US vs ex-US), overall tumor burden (limited, moderate, extensive).

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions.

Highlights of General Format

8. The length of HL must be one-half page or less; the HL Boxed Warning does not count against the one-half page requirement. The current length of your HL is more than one-half page. If, during our review and labeling discussions, the HL remains more than one-half page, you could submit a request for a waiver of this requirement.
9. A horizontal line must separate:
 - HL from the Table of Contents (TOC); **and**
 - TOC from the Full Prescribing Information (FPI).

A horizontal line does not separate the items above; please revise.

10. “Recent Major Changes (RMC) does not need to be included as this is an original label. Please remove this section instead of listing it with “Not applicable.”

11. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

A bullet is not needed since there is only one dosage form. Please remove the bullet.

12. For drug products other than vaccines, the verbatim **bolded** statement must be present: **“To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”**

A toll-free number is not listed for the U.S. manufacturer (current labeling lists (b) (4)); please revise to include a toll-free number.

13. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

The subsections are not in title case: for example, “Patient Preparation,” etc. Please revise.

Full Prescribing Information (FPI)

14. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

The subsections are not in title case; for example, should read “Patient Preparation,” etc. Please revise.

15. When adverse reaction data are included from clinical trials (typically in the “Clinical Trials Experience” subsection), the following **verbatim** statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

The verbatim statement above does not precede the presentation of adverse reactions from clinical trials; please revise the labeling to include this statement.

We have also identified several additional issues in our preliminary review of your PI. These issues are described using the track changes “comment” function within the text of your PI, and are included as an attachment to this letter. Please review all issues identified and revise your PI accordingly. Please also do not anonymize your comments when you provide the revised labeling in track changes, so that we will be able to easily distinguish FDA vs. AAA comments.

Note that we will schedule a teleconference with you to answer any questions you may have and provide clarification on our comments.

We request that you resubmit labeling (in Microsoft Word, both clean and red-lined track changes shown versions) that addresses these issues by **COB July 11, 2016**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Susan Truitt, Regulatory Project Manager, at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Steve Lemery, M.D., M.H.S.
Associate Director (acting)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

STEVEN J LEMERY
06/23/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

FROM: Steven Lemery, M.D., M.H.S.
Associate Director (Acting)
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research

SUBJECT: Review Designation Memo for NDA 208700 (^{177}Lu -DOTA⁰-Tyr³-Octreotate);
Advanced Accelerator Applications, USA, Inc.

TO: NDA 208700

The review status of this file submitted as an original NDA is designated to be:

Priority (PDUFA V - 8 Months)

In the original NDA submission, Advanced Accelerator Applications, USA, Inc. (AAA) requested priority review designation for the following proposed indication: treatment of (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut tumors.

Qualifying Criteria for Priority Review Designation

1. Serious Condition:

A serious condition is defined in the expanded access regulations in 21 CFR 312.300(b)(1) as follows: a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

I agree with the applicant that inoperable, progressive, well-differentiated GEP-NETs constitute a group of serious and life-threatening malignancies. In the application, AAA stated that as many as 80% of patients die within 5 years of diagnosis of metastatic disease. This statement is consistent with the 5 year survival rate described by NCI (<http://www.cancer.gov/types/pancreatic/hp/pnet-treatment-pdq>, accessed June 16, 2016) of approximately 15%.

2. Demonstrating the Potential to Be a Significant Improvement in Safety or Effectiveness:

In the NDA, AAA submitted data from NETTER-1, an international, multicenter, randomized trial that compared $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ to a long acting release formulation of octreotide in patients with progressive, somatostatin-receptor-positive (based on Octreoscan) locally advanced, inoperable (for curative intent) or metastatic midgut carcinoid tumors.

AAA also submitted retrospectively verified data from an Erasmus University Medical Center study which enrolled patients with GEP-NETs (since 2000). AAA is submitting this data in order to seek expanded claims in the broader GEP-NET population (compared to the patient population enrolled in the NETTER-1 study). Although the Erasmus study was listed as a phase 1/2 study and assessed certain endpoints (e.g., ORR and safety), it was, in essence, a large access protocol that enrolled patients from the Netherlands and those who traveled to Erasmus from outside of the Netherlands. Because data collection was limited for many non-Dutch patients, in the pre-NDA meeting, FDA agreed to primarily review data from the Dutch population. A total of 810 Dutch patients were enrolled although 317 did not have tumor measurements recorded at baseline. A total of 404 non-Dutch patients were also enrolled.

Although, AAA is seeking claims in the broader GEP-NET population, for this memorandum, I will focus on the unmet medical needs of the population of patients with midgut carcinoid tumors (which was the population of patients enrolled in the NETTER-1 trial). To be eligible for NETTER-1, patients had to be receiving a fixed dose of octreotide LAR at a dose of 20 or 30 mg every 3-4 weeks for at least 12 weeks. Patients in the control arm received high dose octreotide LAR. Although yet to be confirmed, the application stated that PFS was improved when $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was compared to high dose octreotide LAR [HR 0.21 (95% CI: 0.13 to 0.33)]; the median PFS for the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm had not yet been reached (versus 8.4 months in the control arm). The overall survival analysis also favored $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ [HR 0.40 (95% CI: 0.21 to 0.77)]; however, the nominal p value of 0.0043 was not statistically significant based on the design of the protocol (i.e., the analysis of OS was an interim analysis). Based on the results of NETTER-1 (if confirmed and determined to have a favorable risk-benefit ratio), $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ has the potential to be an improvement in safety or effectiveness over octreotide LAR (in patients who already progressed on a lower dose of octreotide LAR).

FDA approved sunitinib for the treatment of progressive, unresectable, locally advanced, or metastatic well-differentiated pancreatic neuroendocrine tumors on May 20, 2011.

The sunitinib trial (n =171) that supported approval enrolled a different patient population than the NETTER-1 trial (although AAA is also requesting approval for patients with pancreatic somatostatin-receptor-positive neuroendocrine tumors). Patients in the NETTER-1 trial had somatostatin-receptor-positive midgut carcinoid tumors whereas patients in the sunitinib study that supported approval had pancreatic neuroendocrine tumors. Approximately 50% of patients across both arms in the sunitinib study had non-functioning tumors and only 35% had previously received somatostatin receptor analogues. Median PFS in the sunitinib study was 10.2 months in the sunitinib arm versus 5.4 months in the placebo arm [HR 0.43 (0.27, 0.67)]. Ultimately, if the clinical review confirms benefit for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, it would provide treatment for a patient population (i.e., somatostatin-receptor-positive midgut carcinoid tumors) not covered by the sunitinib labeling.

Everolimus is approved for adults with progressive unresectable, locally advanced, or metastatic neuroendocrine tumors of pancreatic origin (PNET) and adults with progressive, well-differentiated, *non-functional* neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin. Everolimus is *not* indicated for the treatment of patients with functional carcinoid tumors. A study of everolimus in 429 patients with carcinoid tumors was conducted and did not meet its primary efficacy endpoint of an improvement in PFS (and the final analysis of OS favored placebo plus depot octreotide). As such, because $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ would provide for treatment of somatostatin receptor-positive (and functional) midgut carcinoid tumors, it has the potential to be an improvement in safety or effectiveness.

Lanreotide is approved for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The approval was based on the results of a multicenter, randomized, double-blind, placebo-controlled trial of 204 patients with unresectable, well or moderately differentiated, metastatic or locally advanced, gastroenteropancreatic neuroendocrine tumors. Patients in the (lanreotide) trial were required to have non-functioning tumors without hormone-related symptoms. Patients received lanreotide 120 mg or placebo every four weeks until disease progression. Four percent of patients in the lanreotide trial had progressive disease in the six months prior to enrollment (14% received prior chemotherapy) whereas all patients in NETTER-1 were required to have progressive disease while receiving an uninterrupted fixed dose of octreotide LAR. Approval of lanreotide was based on the demonstration of a significant prolongation of PFS [HR 0.47 (95% CI: 0.30 to 0.73)]; median PFS was 16.6 months in the placebo group and had not yet been reached in the lanreotide group. Although the lanreotide trial limited enrollment to patients with nonfunctioning neuroendocrine tumors, the indication for lanreotide was extrapolated to include both functional and non-functional tumors.

Although lanreotide has a broad indication, $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ would provide a treatment for patients with inoperable, progressive, well-differentiated, somatostatin-receptor-positive gastroenteropancreatic neuroendocrine tumors. Because long acting octreotide formulations (including lanreotide) are generally considered first-line therapy

(e.g., in NCCN Guidelines Version 2.2016), ^{177}Lu -DOTA⁰-Tyr³-Octreotate could provide for a treatment for patients who progress on long-acting octreotide (in the lanreotide study described above, the efficacy of lanreotide was not assessed in patients who previously received long-acting octreotide therapy).

Limited effective treatment options exist for patients with somatostatin-receptor-positive midgut carcinoid tumors following treatment with a long-acting release formulation of octreotide. Various cytotoxic chemotherapy drugs or interferons are administered; however, evidence to support use of any specific agent is generally limited to uncontrolled studies.

As stated in FDA Guidance [Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014)] and CDER MAPP 6020.3 (priority review policy), an application for a drug will receive priority review designation if it is for a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. As stated in this memorandum, I believe that this application meets the criteria for priority review. Although ^{177}Lu -DOTA⁰-Tyr³-octreotate was not tested head-to-head against sunitinib or everolimus, ^{177}Lu -DOTA⁰-Tyr³-octreotate has the potential (if substantiated by the FDA review) to be an effective treatment for certain patients with GET-NETs (i.e., functional mid-gut carcinoid tumors) for which sunitinib and everolimus are not labeled. Furthermore, ^{177}Lu -DOTA⁰-Tyr³-octreotate has the potential to be an effective treatment for patients after progression on a long acting octreotide formulation (including lanreotide).

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/s/

STEVEN J LEMERY
06/23/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Statistics and Clinical Information Request: Response Required
Date: Tuesday, June 21, 2016 12:02:00 PM

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Statistics and Clinical information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Friday, July 1, 2016**, or sooner if possible, followed by a formal submission to your NDA.

1. In your 6/10/2016 submission (SD 12, SN 0012), you have provided programs and datasets for the information found in section 11.4 (Efficacy results) of the CSR version 1.0. Please provide similar information for Sections 11.1, 11.2 and 11.3.
2. FDA cannot locate multiple variables reported in the tables in Section 11 (Efficacy evaluation) in the submitted datasets. For example, in Table 11-2 Demographic summary by treatment group (all populations), Hispanic is not included in the race variable in the submitted ADSL data. There is no stage variable in the submitted ADSL data. The definitions of the categories in the Tumor uptake score in the CSR, Table 11-12 and in the ADSL data (variable OCTUP) seems not consistent. Please provide the datasets following CDISC format (raw and derived in xpt file), the define files, and the related programs for the variables used to generate tables in Section 11. In particular, please include the following variables in addition to the ones that have been included in the datasets:
 - Country
 - Race/ethnicity
 - treatment duration (standard date format)
 - Treatment start and end date (standard date format)
 - exposure duration
 - last visit date
 - time since diagnosis
 - date of last adequate CT/MRI
 - time that patients have been on the most recent constant dose of Octreotide prior to randomization (≤ 6 and > 6 months)
 - Baseline hepatic tumor load
 - baseline CgA
 - Ki67
 - total number of injections
 - status at end of study
 - withdrawal flag, date of withdrawal, withdrawal reason
 - date of death, days since last dose of drug to death, primary reason for death
 - dose delay due to AE flag

- dose interrupted due to AE flag
 - exclusion reason from per protocol population
 - exclusion reason from ITT population
3. Please provide a clear pathway for generating the data for PFS, OS and ORR analyses so that the FDA reviewer can conduct the related analyses using the derived data and also the raw data.

For example, the dataset “(b) (4)_data_final” used for the PFS analysis data generated cannot be found in the submission. The data issues have been conveyed to AAA orally in the “walk through” meeting held on 6/7/2016. AAA confirmed that some of the datasets were not included in the NDA submission and sensitivity analyses for PFS cannot be conducted using the information included in the NDA submission, and would like to provide information based on FDA’s request.

4. Please indicate how many cases required adjudication between the IRC and site.
5. Please provide the protocol for the following study: A multicenter study comparing treatment of patients with neuroendocrine Gastro-Entero-Pancreatic (GEP) tumors with 177Lu-octreotate versus combined 177Lu-octreotate and capecitabine (Xeloda); Netherlands Trial Register (NTR) Number 91. Also, please provide a dataset that flags patients who were enrolled on this protocol and were included in the Erasmus study datasets.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
06/21/2016

From: Biable, Missiratch (Mimi)
To: ["mark.ibrahim@adacap.com"](mailto:mark.ibrahim@adacap.com); [Victor Paulus](#)
Cc: [Truitt, Susan](#)
Subject: NDA 208700 - Statistical Information Request: Response Required
Date: Friday, June 10, 2016 4:24:00 PM
Importance: High

Dear Mark and Victor,

I am sending this email on behalf of Susan Truitt who is currently out of the office at the moment. She will return to the office on Monday, June 13, 2016.

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Statistical information request via **email** to Susan Truitt (Susan.Truitt@fda.hhs.gov) by **COB on Monday, July 10, 2016**, or sooner if possible, followed by a formal submission to your NDA.

For the NETTER-1 study, please provide results from subgroup analyses by:

1. Age (<65 years vs. >=65)
2. Gender
3. Ethnicity
4. Baseline body mass index (BMI) groups (<=21, 21 to <=27, >27, missing)
5. Mean Octreoscan tumor uptake (among target lesions)
6. Extent of overall tumor burden at inclusion
7. Somatostatin receptor scintigraphy (OctreoScan®) tumour uptake score (grade 2, 3, 4)
8. Length of time that a patient has been on the most recent constant dose of Octreotide prior to randomization (≤6 and > 6 months), Previous anticancer treatment (chemotherapy, external beam radiation, surgery)
9. Karnofsky Performance Status
10. Region (US vs ex-US), Ki67 (<= 2%, >2-5%, > 5-10%, unknown), overall tumor burden (limited, moderate, extensive).

Please contact Susan Truitt if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
06/10/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Clinical Information Request: Response Required
Date: Thursday, June 09, 2016 12:50:00 PM

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Clinical information request via **email** to me (Susan.Truitt@fda.hhs.gov) by **COB on Wednesday, June 15, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Filing issues:

1. Regarding the financial disclosure information:
 - a. Please submit the financial disclosure form FDA 3454 or form 3455 that includes an authorized signature per 21 CFR 54.4(a)(1) and (3), as required for the NDA submission.
 - b. In addition to the scanned PDF files of signed financial disclosure, provide a summary of the financial disclosure information or indicate where this may be found in the NDA.
 - c. Please provide a rationale for why there are 2 forms included for Dr. Ansquer at study site FR01.
 - d. Please provide a rationale for why Dr. Schlumberger at site FR02 has a signed form without statements.
 - e. Please provide a rationale for why Dr. Strosbery at US13 has a blank disclosure form.
 - f. Please provide the details of the types of financial interests that Dr. Van Cutsem from site BE01 has declared.
 - g. Please provide the statement of financial interests for Dr. DJ Kwekeboom.

Additional requests:

2. In appendix 14.1.1, Table 14.1.1.2 *Number of patients screened and treated by center (study site)*. It appears that all patients screened at each site were also randomized, and there were no screen failures. Please confirm that there were no screen failures identified for the NETTER-1 study, or provide a rationale for why the information in Table 14.1.1.2 does not include screen failures.
3. Please provide a dataset with the protocol deviations for NETTER-1, or indicate where this may be found in the submission.
4. The CSR states that a final review of the progressive cases has been performed (b) (4), to confirm that all steps in the collection, quality control and assessment process were conducted according to the study protocol and the Imaging Charter. Please provide a report of the findings from this review, or indicate where this may be found in the submission.

Please contact me if you have any questions and kindly respond to confirm receipt of this

communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
06/09/2016

From: Truitt, Susan
To: "[Victor Paulus](#)"
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: RE: NDA208700-Sequence 0011- FOLLOW UP: Statistics Information Request: Response Required
Date: Thursday, June 09, 2016 12:17:00 PM

Dear Victor,

Please respond to the Statistics follow up information request (IR) below, regarding your June 8 response to the Statistics IR, via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. today, June 9, 2016**, or sooner if possible, followed by a formal submission to your NDA if the information requested below is not currently in your NDA submission.

We cannot locate the SAS programs you mentioned in the programs guidance attached in your 6/8/2016 email. Please provide the exact locations of the programs if they are included in the NDA submission.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Truitt, Susan
Sent: Wednesday, June 08, 2016 1:41 PM
To: 'Victor Paulus'
Cc: Biable, Missiratch (Mimi)
Subject: RE: NDA208700-Sequence 0011- Statistics Information Request: Response Required

Victor,

I confirm receipt and have forwarded your response to the review team.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Wednesday, June 08, 2016 1:31 PM
To: Truitt, Susan

Cc: Biable, Missiratch (Mimi)

Subject: NDA208700-Sequence 0011- Statistics Information Request: Response Required

Dear Susan,

I hope this on make it though the firewall. Everything is contained in the zipped folder.

All the best,

Victor

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/s/

SUSAN B TRUITT
06/09/2016

FILING MEETING MINUTES
June 8, 2016

NDA 208700 - 505 (b)(1) New Molecular Entity

Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial

Proposed Proprietary Name: Lutathera
Established Name: Lutetium Lu 177 dotatate

Submission Date: April 28, 2016
Received Date: April 28, 2016 (Final 3rd part of 3-Part Rolling Submission)

Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)

Proposed Indication: Treatment of patients with [REDACTED] (b) (4)
[REDACTED] somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors [REDACTED] (b) (4)]

The complete application can be accessed via DARRTS (SDN 1-3 and eCTD 0001 – 0003).

Current Review Team/Collaborators for NDA 208700

Patricia Keegan, M.D., Director, DOP2 - ATTENDED
Steven Lemery, M.D., M.H.S., Acting Associate Director, DOP2 - ATTENDED
Suzanne Demko, PA-C., Clinical Team Leader (CDTL), DOP2 - ATTENDED
Joohee Sul, M.D., Medical Officer (DOP 2), Clinical Reviewer, DOP2 - ATTENDED
Melanie Pierce, CPMS, DOP2 - ATTENDED
Susan Truitt, R.N., M.S., Regulatory Health Project Manager, DOP2 - ATTENDED
Mimi Biable, M.S., Senior Regulatory Health Project Manager, DOP2
Kun He, Ph.D., Statistics Team Leader - ATTENDED
Lan Huang, Ph.D., Statistics Reviewer - ATTENDED
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader - ATTENDED
Brian Furmanski, Pharm, D., Clinical Pharmacology Reviewer - ATTENDED
Whitney Helms, Ph.D., Nonclinical Team Leader - ATTENDED
Anwar Goheer, Ph.D., Nonclinical Reviewer - ATTENDED
Jennie Chang, Pharm. D. Associate Director for Labeling - ATTENDED
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead (ATL) - ATTENDED
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA
Erica Pfeiler, Ph.D., Microbiology (TL), ONDQA
Peggy Kriger, Ph.D., Microbiology, ONDQA

Krishnakali Ghosh, Ph.D., Facilities - ATTENDED
Steven Kinsley, Ph.D., ONDQA, Regulatory Business Process Manager - ATTENDED
Okpo Eradiri, Biopharmaceutics Team Leader
Banu Zolnik, Biopharmaceutics Reviewer - ATTENDED
Lauren Iacono-Connor, OSI Reviewer - ATTENDED
Devi Kozeli, IRT/QT Regulatory Project Manager - ATTENDED
Carole Broadnax, OPDP Reviewer - ATTENDED
Steve Bird, DEPI Team Leader
Carolyn McCloskey, DEPI Reviewer
Naomi Redd, DRISK Team Leader
Mei-Yean Chen, DRISK reviewer - ATTENDED
Chi-Ming (Alice) Tu, DMEPA Team Leader
Janine Stewart, DMEPA Reviewer - ATTENDED
Afrouz Nayernama, DPV Team Leader
Peter Waldron, DPV Medical Officer/Reviewer - ATTENDED
Latonia Ford, OSE, Safety Regulatory Project Manager - ATTENDED
Tamara Johnson, DPMH Team Leader - ATTENDED
Christos Mastroyannis, DPMH Reviewer/Maternal Health MO - ATTENDED
Denise Johnson-Lyles, DPMH Regulatory Project Manager - ATTENDED
Cynthia Welsh, DMIP Medical Officer/Reviewer – ATTENDED

Additional Attendees at Filing Meeting:

Amy McKee, OHOP Acting Deputy Office Director
Lorraine Pelosof, DOP2 Medical Officer

Agenda Items

*Reminder - All team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

1. Review Status:
 - a. **Priority Review** requested (PDUFA V – 8-month review) – **Steve Lemery to confirm and upload a review designation memo before Day 60/June 27 at the very latest.**
 - b. User Fee – Exempt due to orphan drug designation status
 - c. Exclusivity Request and Patent: No exclusivity requested. Patent form FDA 3542a requested via IR sent by RPM on Tues. 5/17/16.
 - d. Categorical Exclusion from environmental assessment requested
 - e. Requested full waiver of pediatric studies - exempt due to orphan status
 - f. Proprietary Name Review - Conditional acceptance granted April 8, 2016 (Lutathera) under IND 077219. Team confirmed on May 17, 2016, that the name is acceptable. **Proprietary name was granted May 27, 2016.**
 - g. The established name requested is “lutetium Lu 177 dotatate.”
 - h. The clinical development of Lutathera was conducted under IND 077219.

2. Milestone Dates: 8-Month Priority Review Clock

The new review template will be used for this NDA; reviewers will enter a note in DARRTS regarding review completion and where it can be located (SharePoint).

Note: Amy McKee stated on June 6 that the OTS team sent her a link for the SharePoint review site to review late last week, so the SharePoint site should be up and running within a week or so. Refer to “Other Issues/Concerns.”

Milestone	8-Month Priority Review Goal
Acknowledgment Letter	May 12, 2016 [within 14 days] <i>Issued May 2, 2016</i> (Acknowledge Presubmission issued April 18, 2016)
Applicant Orientation Meeting (AOM) , with Application “Walk Through” meeting prior to AOM **NOTE: <i>Team members please attend AOM meeting on 6/17 in WO 22, room 2205 at 1:00 pm.</i>	Scheduled Fri., June 17, 2016 – 1:00 OHOP Rounds; Application “ Walk Through ” with sponsor 6/17/16, 11:30-12:30 , WO 22 rm. 1311
Filing Action Letter – Day 60 (Inform applicant of review designation, filing determination) • <i>Do we have any filing issues that we should discuss today?</i> • <i>Do we need to have teleconference with the Applicant before the filing meeting?</i>	June 27, 2016 <u>Filing Meeting June 8, 2016</u>
Filing Issues Identified (Day 74 Letter) --- if not sent in Day 60 letter	July 11, 2016
Mid-Cycle Internal Meeting	July 27, 2016 [Month 3 = by July 28, 2016]
Mid-Cycle Sponsor Communication (TC)	August 2, 2016 [Month 3.5 = by August 11, 2016]
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 = by September 28, 2016
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	[Month 5.25 = by October 5, 2016]
Late Cycle Internal Meeting	September 30, 2016 [Month 5.25 = by October 5, 2016]
Late Cycle Sponsor Meeting (no Advisory Committee)	October 18, 2016 [Month 6 if <u>no</u> AC (current plan) = by October 28, 2016]
Advisory Committee	N/A
Review Target Due Dates: Primary Review Due <i>Secondary Review Due</i> <i>CDTL Review Due (4 weeks before action)</i> <i>Division Director Review Due (3 weeks before action)</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 = September 28, 2016 Month 5.1 = ~ September 30, 2016 Month 7 = November 30, 2016 3 weeks prior = December 7, 2016 December 28, 2016
Wrap-Up Meeting w/ Safety discussion	November 18, 2016 [5 weeks pre-action = November 23, 2016]

Compile and circulate Action Letter and Action Package	[3 weeks pre-action = December 7, 2016]
FINAL Action Letter Due	December 28, 2016

3. Consults/Collaborative Reviewers:

OPDP	Carole Broadnax; <i>Consult submitted 5/2/16</i>
OSE	Latonia Ford - OSE RPM Sarah Harris, Acting OSE PM TL <u>DMEPA</u> - Janine Stewart Chi Ming (Alice) Tu (TL) <u>DRISK</u> - Mei-Yean Chen, DRISK reviewer Naomi Redd, DRISK (TL) <u>DPV</u> Peter Waldron, MO Afrouz Nayernama (TL) <u>DEPI</u> Carolyn McCloskey, DEPI reviewer Steve Bird, TL <i>Proprietary Name Review</i> – Confirmed there are not any objections to the sponsor’s request.
Maternal Health	Is consult needed? Yes; <i>Maternal consult uploaded 5/18/16.</i> Tamara Johnson, DPMH Team Leader Christos Mastroyannis, DPMH Reviewer/MO Denise Johnson-Lyles, DPMH RPM
OSI	Lauren Iacono-Connor assigned; 6 initial sites confirmed. <i>OSI consult uploaded 5/26/16.</i>
Facility/OMPQ	Krishnakali Ghosh
Microbiology	Peggy Kriger
IRT/QT	<i>Consult uploaded 5/3/16</i> – Devi Kozeli, RPM
DMIP	<i>Consult uploaded 6/1/16</i> ; Confirmed reviewer is Cynthia Welsh, MO.
Pediatric Page/PeRC	EXEMPT due to orphan status
SEALD	Not needed.
SGEs or Patient Representatives	<i>SGEs are needed</i> per Planning meeting, Steve and Joohee each identified one. <i>Steve requested that Joohee obtain at least 2 more.</i> See #8 below for updates.

Are there any additional consults needed? Yes; Clinical **DMIP** – Joohee will follow up with Cynthia Welsh to confirm specific needs.

Discussion:

4. **Filing Issues**

--**Please bring a copy of your filing review** and any interim deliverables needed. Please note your filing review will need to be uploaded and signed off on in DARRTs prior to day 60 (= prior to June 27, 2016 at the very latest).

--Send all TL-approved comments to both Susan Truitt and Mimi Biabile by **June 10, 2016** latest.

--**Please be prepared to discuss any significant filing issues for inclusion in the day 74 letter.**

Discussion:

- a. **Clinical: Key issues:** *Financial disclosure incomplete (filing issue);* screen failures vs. randomized; no information on protocol deviations for NETTER-1 (will be an IR); other issues. **Ok to file**, but will send IRs, particularly to resolve financial disclosure missing information. It is likely that many IRs will be sent.
- b. **Statistics: Ok to file.** IRs being sent. Plan is to include information in the filing letter.
- c. **Clinical Pharmacology: Ok to file.** Initial IR sent and response received; no analytical validation or reports for blood/PK urine analyses. Missing electronic dataset for ERASMUS data (only summary reports provided). Plan is to include information in the filing letter.
- d. **Nonclinical: Ok to file.** No issues.
- e. **CMC: Ok to file.** Might have issues for filing letter. Steve Kinsley may follow up with another IR; will confirm.
- f. **Biopharmaceutics: Ok to file.** No issues.
- g. **Microbiology: Ok to file.** No issues.
- h. **Regulatory: Note** - AAA did not submit Form 3474, Form 3542a (Patent), a complete list of CRO/CRO tasks, *clear* list of sites, and the correct financial disclosure forms FDA 3454 and/or 3455 as part of their NDA submission. AAA has currently provided these upon request via

FDA IRs, except for the correct financial disclosure forms – IR to be sent for these financial disclosure forms (part of Clinical’s IR list).

5. **Inspections:**

- **Clinical Site Inspections: Ok to file.** 4 clinical U.S. sites; 2 CROs in Europe ((b) (4) and (b) (4) for imaging). All assignments have been issued. Lauren Iacono-Connor may send another IR.
- **Manufacturing Site Inspections:** 6 sites – 2 already acceptable (no preapproval inspections). Of 4 sites, 3 are international – will conduct those inspections at the end of August. EIRs will be available at the end of September. Facility reviews will be done in October. Inspection timings/dates are already established.

6. **Upcoming Internal Meetings:**

- a. **Applicant Orientation Meeting:** June 17, 2016, 1:00 p.m., rm. 2205;
and
Applicant “Walk Through” Meeting: June 17, 2016, **11:30-12:30** p.m.,
rm. 1311

Discussion:

- RPM received list of sponsor attendees; 11 total. Sponsor’s slides are due June 10, 2016 at the latest. Reminder - Please attend AOM on 6/17/16.
 - Invite Donna Griebel to AOM - regarding use of amino acid solution as part of the use of this product, and company’s future plans to develop a new amino acid solution to be used specifically for this product.
- b. **Mid-Cycle Internal Meeting: July 27, 2016**
- c. **Mid-Cycle Sponsor Communication (TC): August 2, 2016** – Pat to cover for Steve.
- d. **Labeling Meetings** (suggested section groupings): Per the current procedure, the plan is to hold 8 labeling meetings with the labeling sections below. Begin labeling meetings month 3.5 – 4.5 (per 21st Century Review)
**New OHOP Procedure: send draft labeling at time of first labeling meeting to Press Office (if applicable)

Labeling Meeting Organization and Scheduling: NME/NDA 208700

Meeting Date	Discipline Attendance Required	Label Section(s) to be discussed	Length of Meeting	Meeting Date/Time/Room (Check Invites)
1 st meeting	CMC, DMEPA, Clinical	3, 11, 16 and carton and container labeling	1 hour	Mon., 8/29/16; 1-2, rm. 3201
2 nd meeting	Clinical, Statistics	1, 14	1 hour	Tues., 8/30/16; 11-12, rm. 2376
3 rd meeting	Clinical Pharmacology, DMEPA, Clinical	2, 7, 8.5, 8.6, 8.7, 12.2, 12.3 and 6.2 (Immunogenicity)	1.5 hours	Thurs., 9/1/16, 2-3:30, rm. 4201
4 th meeting	Non-clinical, Maternal Health Team (MHT), Clinical	12, 13, 8.1-8.4, 5 (if warning for embryo-fetal toxicity)	1.5 hours	Tues., 9/6/16, 12-1:30, rm. 2327
5 th meeting	Clinical	6	1 hour	Thurs., 9/8/16; 1:30-2:30, rm. 2376
6 th meeting	Clinical	4, 5, 2, 17	1.5 hours	Mon., 9/12/16; 1:30-3, rm. 4201
7 th meeting	Initially include all review disciplines (to hold time)	Any items not covered during originally scheduled time	1 hour	Mon., 9/19/16; 12-1, rm. 3201
When PI is substantially complete, send label to applicant, OPDP & Patient Labeling Team.				
8 th Meeting (Schedule 2-3 weeks after labeling sent to applicant-by 9/28)	Review revised labeling from applicant, include all review disciplines and OPDP and PLT		1.5 hours	Fri., 10/14/16; 11-12:30, rm. 3201

Discussion: Important for Cynthia Welsh and Stanley Stern to be present for section 2 (current meeting #3). Also include Rich Fejka in meeting 3 invite. May need to add an extra meeting, or additional time.

e. **Monthly Team Meetings**

Date/Time/Room	Notes/Comments
#1: Tues., 8/23/16, 2:30-3:30, rm. 3201	<i>Mimi Bioble covering for Susan Truitt (OOO). Other team meetings were held in June, July; Wrap Up is in Nov.</i>
#2: Thurs., 9/22/16, 2:30-3:30, rm. 3201	
#3: Fri., 10/28/16, 11-12, rm. 3201	

f. **Internal Late Cycle Meeting: September 30, 2016**

g. **Wrap-Up Meeting: November 18, 2016**

7. **ODAC**: Not Required, per Planning Meeting

Discussion: Per Planning meeting, an AC meeting is unlikely, mainly due to the study design being acceptable; other reasons TBD as applicable.

Discussion: Confirmed that AC meeting is not currently required.

[If needed Target AC date: By October 28, 2016 (Month 6)]

If not needed, for an original NME include the reason in the RPM filing review memo. For example:

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

[If needed, and if we plan on going to Advisory Committee- we will need a planning meeting and _____practice sessions]

8. **SGEs**: Required

Proposed SGEs: In process. On May 1, Steve Lemery identified a potential SGE: (b) (4) She is not currently on the SGE list so she will have to be cleared (general and application specific). She said she would be interested in participating. She is not senior faculty so she would likely clear as a general SGE.

Proposed Patient Representative: TBD; Deb Miller to be contacted.

Discussion/Update(s):

- Steve to follow up with other potential SGEs.
- Joohee to contact another potential SGE or two.
- Steve and/or Joohee to keep RPM informed.

9. **Other Issues/Concerns**

- Study presented again at ASCO.
- Amy McKee – Tamy Kim is the owner of review SharePoint site; ask for access permission if needed. There will be one master document in which reviewers work. Common document is based on the CDER clinical review template and will be in a Lutathera folder. Instructions will be at the top regarding disciplines. CDTL is the only person with complete

access to sections. Suggestion: Reviewers should save a hard copy of review on their own drive. CDTL is responsible for final review. Each reviewer is to upload a memo in DARRTS noting to refer to the multidisciplinary review and confirm that the review is completed.

- Jennie Chang: Labeling should be ready by Friday, June 10.

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/s/

SUSAN B TRUITT
06/10/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable_Missiratch \(Mimi\)](#)
Subject: NDA 208700 Clinical Pharmacology Information Request: Response Required
Date: Monday, June 06, 2016 11:29:00 AM

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Clinical Pharmacology information request via email to me (Susan.Truitt@fda.hhs.gov) by **noon on Wednesday, June 8, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Indicate the location of the following items within the NDA application or submit the requested information.

Clinical Pharmacology

1. Summary of bioanalytical reports with functional hyperlinks.
2. Bioanalytical reports for Erasmus and NETTER-1 distribution studies for both blood and urine analysis. Reports should contain methods and data captured for individual patients. Also include sample collection times and time elapsed from collection to analysis for 177Lu-DOTA0-Tyr3-Octreotate urine and plasma analyses.
3. Method validation reports for Erasmus and NETTER-1 distribution studies for both blood and urine analyses. Reports should contain applicable metrics used to ensure assay validity.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>
4. Electronic data set (SDTM) for Erasmus MC blood and urine concentrations.
5. Side-by-side comparisons between amino acid solutions used in Erasmus and amino acid solutions used in NETTER-1 studies. Ensure consistent unit values in the comparison.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
06/06/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 Clinical/OSI Information Request: Response Required
Date: Friday, June 03, 2016 10:16:00 AM

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Clinical/OSI information request via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. ET on Wednesday, June 8, 2016**, or sooner if possible, followed by a formal submission to your NDA.

1. Provide all documentation associated with the (b) (4) CRO's role in the Erasmus study. This would include the contract, charters, or other forms of agreements with AAA (b) (4). In addition, provide a copy of the final report(s) on the collection of data points and verification process. If this information already exists somewhere within the application, please provide the exact location.
2. Please confirm that the (b) (4) site (b) (4) will have all documentation and knowledgeable available personnel on site to support a full FDA inspection. Note that the FDA needs everything in one location for an inspection; e.g., not only EU records. Documentation should be available that clearly validates all of the Phase 3 study obligations.

Contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
06/03/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 Statistics Information Request: Response Required
Date: Wednesday, June 01, 2016 8:59:00 AM

Dear Victor,

Please refer to your NDA 208700 for Lutathera.

Please respond to the following Statistics information request via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. on Tuesday, June 7, 2016**, or sooner if possible, followed by a formal submission to your NDA.

For the NETTER-1 phase 3 study, provide the SAS programs for generating the results in Section 11 (efficacy evaluation) in the clinical study report. For example, PFS_analysis_FAS_summary_m2.sas was used to generate Table 14.2.1.1; please provide this SAS program. If you have included all the programs in the NDA submission, please clarify the location of the programs.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
06/01/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208700

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue
Suite 6902
New York, NY 10118

ATTENTION: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received April 28, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for ^{177}Lu -DOTA⁰-Tyr³-Otreotate Solution for Infusion, 370 MBq/mL.

We also refer to your correspondence, dated and received April 28, 2016, requesting a review of your proposed proprietary name, Lutathera.

We have completed our review of the proposed proprietary name, Lutathera and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 28, 2016 submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Susan Truitt, Regulatory Project Manager, in the Office of New Drugs at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
05/27/2016

From: Truitt, Susan
To: "[Victor Paulus](#)"
Cc: [Biable, Missiratch \(Mimi\)](#); [mark Ibrahim](#)
Subject: RE: NDA 208700 OSI Information Request Clarification: Response Required
Date: Tuesday, May 24, 2016 5:10:00 PM

Dear Victor,

Thank you for your email. Please note the following.

1. OSI requests a detailed list of any CRO(s) involved with *exact responsibilities* and *all contact information* (company name, contact person with *phone, email and fax*), preferably in a table format for clarity. This detailed list needs to be submitted to NDA 208700. As part of the list/table, please remember to include the email and fax for the CRO contact you specified below, Roberta Piadena.
2. You mention in your email that safety and regulatory functions are a "shared responsibility with the sponsor." Please clarify in your list *exactly* what safety and regulatory functions, if any, have been transferred.

As a reminder, per 21 CFR 312.52 (a) [*italics emphasis mine*]:

"A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization. Any such transfer shall be described in writing. *If not all obligations are transferred*, the writing is required to describe *each* of the obligations being assumed by the contract research organization. *If all obligations are transferred*, a general statement that all obligations have been transferred is acceptable. Any obligation not covered by the written description shall be deemed not to have been transferred."

We request that you respond via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. on May 25, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Please contact me should you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Monday, May 23, 2016 8:31 PM
To: Truitt, Susan

Cc: Biable, Missiratch (Mimi); mark Ibrahim

Subject: Re: NDA 208700 OSI Information Request: Response Required

Importance: High

Dear Susan,

The obligations transferred to the CRO have been listed in all of the Form FDA 1571 submitted to the IND: Monitoring, Regulatory (e.g. submission of applications to competent authority and ethic committee, investigator recruitment, interactive voice response system-treatment randomization, data management, e-data capture, quality assurance auditing, statistical analysis, medical writing, signature of agreement with public institutions participating in the clinical trial.

Trial related functions: project management; clinical trial monitoring and site management; medical monitoring, review and oversight; biometrics, including statistics and data management; medical writing, and trial master file. With a shared responsibility with the sponsor – safety and regulatory functions.

The contact information for the CRO:



Please let me know if you have additional questions.

Mark will submit via the ESG tomorrow.

All the best,

Victor

Victor G. Paulus, PhD

Head, Global Regulatory Affairs
Advanced Accelerator Applications

www.adacap.com

The Empire State Building
350 Fifth Avenue, Suite 6902
69th Floor
New York, NY 10118

tel. 212.235.2391

Bridging Science with Life

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From: "Truitt, Susan" <Susan.Truitt@fda.hhs.gov>
Date: Monday, May 23, 2016 at 4:48 PM
To: victor paulus <victor.paulus@adacap.com>
Cc: "Biabie, Missiratch (Mimi)" <Missiratch.Biabie@fda.hhs.gov>
Subject: NDA 208700 OSI Information Request: Response Required

Dear Victor,

Please respond to the following Office of Scientific Investigations (OSI) information request via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. on May 24, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Provide a list of the name, address, and point of contact information, including phone/email/fax, for all Contract Research Organizations (CROs) used in the conduct of the clinical trials and a brief statement of trial-related functions. This list should clearly identify all regulatory responsibilities Advanced Accelerator Applications (AAA) transferred to any CRO(s) in a written agreement as per 21 CFR 312.52. As part of the list, confirm the location of the TMF with the associated regulatory contact information.

Also note that since FDA will likely conduct an inspection of the sponsor and possibly a CRO, AAA should ensure that knowledgeable personnel are on site to support such an inspection.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656

Fax: 301-796-9849

Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
05/24/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 OSI Information Request: Response Required
Date: Monday, May 23, 2016 4:48:00 PM

Dear Victor,

Please respond to the following Office of Scientific Investigations (OSI) information request via email to me (Susan.Truitt@fda.hhs.gov) by **5:00 p.m. on May 24, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Provide a list of the name, address, and point of contact information, including phone/email/fax, for all Contract Research Organizations (CROs) used in the conduct of the clinical trials and a brief statement of trial-related functions. This list should clearly identify all regulatory responsibilities Advanced Accelerator Applications (AAA) transferred to any CRO(s) in a written agreement as per 21 CFR 312.52. As part of the list, confirm the location of the TMF with the associated regulatory contact information.

Also note that since FDA will likely conduct an inspection of the sponsor and possibly a CRO, AAA should ensure that knowledgeable personnel are on site to support such an inspection.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
05/23/2016



FACSIMILE TRANSMITTAL SHEET

DATE: May 18, 2016

To: Dr. Victor Paulus

From: Steven Kinsley
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

Company: Advanced Accelerator
Applications USA, Inc.

Fax number: 212 235 2381

Fax number: 301-595-5093

Phone number: 917 972 0449

Phone number: 240-402-2773

Subject: Update on facilities

Total # of pages including cover: 2

Comments: Please verify receipt of this fax via phone at 240-402-2773.

Original document to be mailed:

Yes

No

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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Dear Victor,

Please make sure that these sites are registered on the Drug Establishments Current Registration Site. Our internal data gives the FEI numbers for these sites below; verify if they are correct. Also, verify that these sites follow Current Good Manufacturing Principles (CGMP) and provide updates on all facilities on a new 356h form and in the Module 3 of the submissions.

Advanced Accelerator Applications
Via Ribes 5
101000 Colletterto Giacosa (TO,) Italy
FEI: 3010175147
DUNS: 338664304

Advanced Accelerator Applications
Via Piero Maroncelli 40
47014, Meldola (FC) Italy
FEI: 3010469290
DUNS: 428469971

IDB Radiopharmacy B.V.
Weverstraat 17
5111 PV Baarle-Nassau
The Netherlands
FEI: 3010293768
DUNS: 489201088

Thank you, very much, it's been a pleasure working with you.

Kind Regards,
Steve

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/s/

STEVEN A KINSLEY

05/19/2016

This document was faxed to the sponsor on May 18, 2016

From: Truitt, Susan
To: "[Victor Paulus](#)"
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 Document Information Request: Response Required
Date: Tuesday, May 17, 2016 10:34:00 AM

Dear Victor,

Please respond to the following information request via email to me (Susan.Truitt@fda.hhs.gov) by **noon on Friday, May 20, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Submit the patent declaration Form FDA 3542a via email to me and to your NDA. This form is required to be submitted to the FDA with an NDA application, as per 21 CFR 314.53.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
05/17/2016

PLANNING MEETING MINUTES
May 17, 2016

NDA 208700 - 505 (b)(1) New Molecular Entity

Product: Lutathera (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial

Proposed Proprietary Name: Lutathera
Established Name: lutetium Lu 177 dotatate

Submission Date: April 28, 2016
Received Date: April 28, 2016 (Final 3rd part of 3-Part Rolling Submission)

Sponsor: Advanced Accelerator Applications USA, Inc. (AAA)

Proposed Indication: Treatment of patients with [REDACTED] (b)(4) [REDACTED] somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut [neuroendocrine tumors [REDACTED] (b)(4)]

The complete application can be accessed via DARRTS (SDN 1-3 and eCTD 0001 – 0003).

Current Review Team for NDA 208700

Patricia Keegan, M.D., Director, DOP2 - ATTENDED
Steven Lemery, M.D., M.H.S., Acting Associate Director, DOP2 - ATTENDED
Suzanne Demko, PA-C., Clinical Team Leader (CDTL)
Joohee Sul, M.D., Medical Officer (DOP 2), Clinical Reviewer - ATTENDED
Melanie Pierce, CPMS, DOP2 - ATTENDED
Susan Truitt, R.N., M.S., *Regulatory Health Project Manager* - ATTENDED
Mimi Biable, M.S., *Senior Regulatory Health Project Manager* - ATTENDED
Kun He, Ph.D., Statistics Team Leader - ATTENDED
Lan Huang, Ph.D., Statistics Reviewer - ATTENDED
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader - ATTENDED
Brian Furmanski, Pharm, D., Clinical Pharmacology Reviewer - ATTENDED
Whitney Helms, Ph.D., Nonclinical Team Leader - ATTENDED
Anwar Goheer, Ph.D., Nonclinical Reviewer - ATTENDED
Jennie Chang, Pharm. D. Associate Director for Labeling - ATTENDED
Eldon Leutzinger, Ph.D., ONDQA Application Team Lead (ATL) - ATTENDED
John Amartey, Ph.D., Drug Product/Process, Product Quality, ONDQA - ATTENDED
Erica Pfeiler, Ph.D., Microbiology (TL), ONDQA - ATTENDED

Peggy Kriger, Ph.D., Microbiology, ONDQA - ATTENDED
Krishnakali Ghosh, Ph.D., Facilities - ATTENDED
Steven Kinsley, Ph.D., ONDQA, *Regulatory Business Process Manager (RBPM)* - ATTENDED
Okpo Eradiri, Biopharmaceutics Team Leader
Banu Zolnik, Biopharmaceutics Reviewer - ATTENDED
Lauren Iacono-Connor, OSI Reviewer - ATTENDED
Latonia Ford, OSE, *Safety Regulatory Project Manager (RPM)*
IRT/QT Reviewer - *Devi Kozeli, IRT/QT RPM*
Carole Broadnax, OPDP Reviewer - ATTENDED
Steve Bird, DEPI Team Leader
Naomi Redd, DRISK Team Leader
Chi-Ming (Alice) Tu, DMEPA Team Leader
Janine Stewart, DMEPA - ATTENDED
Afrouz Nayernama, DPV Team Leader
Peter Waldron, DPV Medical Officer

Agenda Items

***Reminder** - All team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

1. **Review Status:**
 - a. Priority Review requested (PDUFA V – 8-month review) – This will likely be a priority review; Steve Lemery to confirm with Clinical and upload a review designation memo.
 - b. User Fee – Exempt due to orphan drug designation status
 - c. Exclusivity Request and Patent: No exclusivity requested. Patent form FDA 3542a requested via IR sent by RPM on Tues. 5/17/16.
 - d. Categorical Exclusion from environmental assessment requested
 - e. Requested full waiver of pediatric studies - exempt due to orphan status
 - f. Proprietary Name Review - Conditional acceptance granted April 8, 2016 (Lutathera) under IND 077219. Review currently ongoing; due July 27, 2016. Team confirmed that the name is acceptable. OPDP also confirmed in a May 17, 2016, in response to a Clinical request, that the “thera” component does not have a misleading promotional implication.
 - g. The established name requested is “lutetium Lu 177 dotatate.”
 - h. The clinical development of Lutathera was conducted under IND 077219.
2. **Milestone Dates: 8-Month Priority Review Clock**

Discussion: Note that these dates will change if priority review is not granted. The new review template will be used for this NDA; reviewers will enter a note in DARRTS regarding review completion and where it can be located (SharePoint).

Milestone	8-Month Priority Review Goal
Acknowledgment Letter	May 12, 2016 <i>Issued May 2, 2016 (Acknowledge Presubmission issued April 18, 2016)</i>
Filing Action Letter – Day 60 (Inform applicant of review designation, filing determination) <ul style="list-style-type: none"> •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? 	June 27, 2016
Filing Issues Identified (Day 74 Letter) --- if not sent in Day 60 letter	July 11, 2016
Mid-Cycle Internal Meeting	Month 3 = by July 28, 2016
Mid-Cycle Sponsor Communication (TC)	Month 3.5 = by August 11, 2016
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	Month 5 = by September 28, 2016
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Month 5.25 = by October 5, 2016
Late Cycle Internal Meeting	Month 5.25 = by October 5, 2016
Late Cycle Sponsor Meeting (no Advisory Committee)	Month 6 if <u>no</u> AC (current plan) = by October 28, 2016
Advisory Committee	N/A
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due (4 weeks before action)</i> <i>Division Director Review Due (3 weeks before action)</i> <i>Office Director Review Due/Sign-Off</i>	Month 5 = September 28, 2016 Month 5.1 = ~ September 30, 2016 Month 7 = November 30, 2016 3 weeks prior = December 7, 2016 December 28, 2016
Wrap-Up Meeting w/ Safety discussion	5 weeks pre-action = November 23, 2016
Compile and circulate Action Letter and Action Package	3 weeks pre-action = December 7, 2016
FINAL Action Letter Due	<u>December 28, 2016</u>

3. **Potential Consults/Collaborative Reviewers Needed:**

OPDP	Carole Broadnax; <i>Consult submitted 5/2/16</i>
OSE	Latonia Ford - OSE RPM Sarah Harris, Acting OSE PM TL <u>DMEPA</u> - Janine Stewart Chi Ming (Alice) Tu (TL) <u>DRISK</u> - Naomi Redd, DRISK (TL) <u>DPV</u> Peter Waldron, MO Afrouz Nayernama (TL) <u>DEPI</u> Steve Bird, TL <i>Proprietary Name Review – Confirmed there are not any objections to the sponsor’s request.</i>
Maternal Health	Is consult needed? Yes; <i>Maternal consult to be sent.</i>
OSI	Lauren Iacono-Connor assigned; 6 initial sites confirmed. <i>OSI consult to be submitted with list of sites/addresses from Joohee Sul.</i>
Facility/OMPQ	Krishnakali Ghosh
Microbiology	Peggy Kriger
IRT/QT	<i>Consult submitted 5/3/16 – Devi Kozeli, RPM</i>
Pediatric Page/PeRC	EXEMPT due to orphan status
SEALD	Not needed.
SGEs or Patient Representatives	<i>Are SGEs needed? Yes; Steve and Joohee each identified one. Steve requested that Joohee obtain at least 2 more. Steve and/or Joohee to confirm.</i>

Are there any additional consults needed? **Yes**; Clinical **DMIP** – *Joohee will follow up with Cynthia and confirm needs with RPM.*

4. **Applicant Orientation Meeting: Friday, June 17, 2016, 1:00 p.m.**

Discussion: Per Division Director’s suggestion, RPM will set up a team meeting with the sponsor either before or after the Applicant Orientation Meeting if possible for a “walk through” of the application. RPM will also ensure complete team is invited for Applicant Orientation Meeting and request Stats/Programmer, Clinical, ClinPharm, etc. personnel for sponsor attendees. RPM confirmed that a

list of sponsor attendees is due June 3, 2016 and the sponsor's slides are due June 10, 2016 at the latest.

5. **Upcoming/TBD Internal Team Meetings:**

a. **Filing Meeting:** Wednesday, June 8, 2016, 3:00 p.m., WO 22, Rm. 4270

- Bring Filing review (TL signature) and Interim Deliverables
- Please be prepared to identify and discuss significant filing issues for either a day 60 or a day 74 letter. The template is available on the 21st Century website.
<http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm>

Discussion: Send all TL-approved comments to Susan Truitt and Mimi Biabile by **June 10, 2016 latest**.

b. **Mid-Cycle Internal Meeting:** TBD; by July 28, 2016

c. **Mid-Cycle Sponsor Communication (TC):** TBD; by August 11, 2016

d. **Labeling Meetings (suggested section groupings):** Per the current procedure, the plan is to hold 7 labeling meetings with the labeling sections below – does the team agree? When should we begin labeling meetings?

****New OHOP Procedure:** send draft labeling at time of first labeling meeting to Press Office (if applicable)

Labeling Meeting #1 (Sections 3, 11, 16, & container labeling)
Labeling Meeting #2 (Sections 1 & 14)
Labeling Meeting #3 (Sections 2, 7, 8.5, 8.6, 8.7, 12.2, & 12.3)
Labeling Meeting #4 (Sections 12, 13, 8.1-8.4, & 5)
Labeling Meeting #5 (Section 6)
Labeling Meeting #6 (Sections 4, 5, 2, & 17)
Labeling Meeting #7 (Any items not previously addressed)

Discussion: A determination regarding when labeling meetings should begin will be made after a decision has been made regarding priority review.

- Steve Lemery will be out the first 2 weeks of August; Pat Keegan will cover for Steve.
- Team currently agrees to hold 7 labeling meetings according to the labeling sections above; dates TBD.

e. **Team Meetings and/or PMR/PMC Working Meetings:**

- Do we want to schedule monthly team meetings?

Discussion: Yes, monthly internal meetings will be scheduled.

- Do we want to schedule any separate PMC/PMR meetings?

Discussion: No; not at this time.

f. **Internal Late Cycle Meeting** - TBD [Month 5.25 = by October 5, 2016]

g. **Wrap-Up Meeting:** TBD [5 weeks pre-action = by Nov. 23, 2016]

6. ODAC Needed/Not Needed:

Discussion: An AC meeting is unlikely, mainly due to the study design being acceptable; other reasons TBD as applicable.

[If needed Target AC date: By October 28, 2016 (Month 6)]

If not needed, for an original NME include the reason in the RPM filing review memo. For example:

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

[If needed, and if we plan on going to Advisory Committee- we will need a planning meeting and _____practice sessions]

7. Miscellaneous Items or Issues:

- Status of OSI inspections - When does clinical/stats team need to pick the sites that will be inspected?

Discussion: Initial Site Selection Meeting was held on May 16, 2016 with the Clinical team and OSI. On May 16 Clinical sent OSI representative an initial list of 6 sites for review. Sites selected to be confirmed by May 20, 2016. Awaiting IR information from sponsor (due COB 5/20/16) regarding submission of OSI information requested in prior meeting minutes. Both studies will be included in inspections. *Clinical reviewer will follow up and provide the site names/addresses information to the RPM for entering into the OSI consult form.*

- Do we need any preclinical study site audits?

Discussion: No, preclinical study site audits are not required.

- Status of facility review inspections (CMC/Krishna Gosh)

Discussion: Requesting preapproval inspections of 4 of 6 sites; 3 are international sites; 2 in Italy, 1 in the Netherlands. Confirmed that inspections are scheduled for the end of August, with the inspection reports due in September. Also need to confirm GMP manufacturing. *The CMC RBPM will follow up on GMP status and verify records re FEI numbers with the sponsor.*

- Is Press Release or Burst planned? Both?

Discussion: Both are planned.

8. Other Issues/Concerns

- **Any other IRs/Advice to Sponsor?** Yes; will likely be many IRs. It is optimal to batch IRs if possible. Any outstanding IRs will be included in the Filing Letter. The Clinical reviewer stated that no major implementation issues have been identified at this time.

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/s/

SUSAN B TRUITT
05/18/2016

From: Truitt, Susan
To: ["Victor Paulus"](#)
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: NDA 208700 - Information Request: Response Required
Date: Monday, May 16, 2016 4:56:00 PM

Dear Victor,

We refer to the pre-NDA meeting between representatives of your firm and the FDA on March 14, 2016 under IND 77219 and the Meeting Minutes dated March 17, 2016, specifically the section entitled "Office of Scientific Investigation (OSI) Requests."

Upon preliminary review of your NDA submission, we were unable to locate the OSI requested information. Please provide the information in your NDA submission requested by OSI in the Minutes for items I. and II. at a minimum, with item III being optional, or direct us to where the information requested is located.

Submit the requested information via email to me by **COB Friday, May 20, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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/s/

SUSAN B TRUITT
05/16/2016



NDA 208700

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Advanced Accelerator Applications USA, Inc.
350 Fifth Avenue
Suite 6902
New York, NY 10118

ATTENTION: Victor G. Paulus, Ph.D.,
Head of Regulatory Affairs

Dear Dr. Paulus:

Please refer to your New Drug Application (NDA) dated and received April 28, 2016, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lutetium Lu 177 Dotatate Injection 370 MBq/mL.

We acknowledge receipt of your correspondence, dated and received April 28, 2016, requesting a review of your proposed proprietary name, Lutathera.

The user fee goal date is July 27, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Latonia Ford, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4901. For any other information regarding this application, contact Susan Truitt, Regulatory Project Manager, in the Office of New Drugs at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Latonia Ford, MBA, BSN, RN
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LATONIA M FORD
05/13/2016

From: Truitt, Susan
To: "[Victor Paulus](#)"
Cc: [Biable, Missiratch \(Mimi\)](#)
Subject: RE: NDA 208700 - Request to Complete Table & Dataset Request
Date: Friday, May 06, 2016 11:35:00 AM

Hi Victor,

Our review team has the following additional information request. Please submit an SDTM EG domain raw dataset (eg, xpt), including all ECGs of 18 subjects for study AAA-III-01.

Submit both the completed table as per my May 5, 2016, email and your response to this dataset request via email to me by **COB May 16, 2016**, or sooner if possible, followed by a formal submission to your NDA.

Please contact me if you have any questions and kindly respond to confirm receipt of this communication.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Truitt, Susan
Sent: Thursday, May 05, 2016 2:45 PM
To: 'Victor Paulus'
Cc: Biable, Missiratch (Mimi)
Subject: RE: NDA 208700 - Request to Complete Table

Hi Victor,

Thank you for your prompt response. Although the deadline is COB May 16, 2016, at the latest, please email the completed table to me as soon as possible before then.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP2
Phone: 240-402-3656
Email: susan.truitt@fda.hhs.gov

From: Victor Paulus [<mailto:victor.paulus@adacap.com>]
Sent: Thursday, May 05, 2016 2:31 PM
To: Truitt, Susan
Cc: Biable, Missiratch (Mimi)

Subject: Re: NDA 208700 - Request to Complete Table

Hi Susan,

I have forwarded the request to the rest of my team.

Thanks,

Victor

Sent from my iPhone

On May 5, 2016, at 8:21 PM, Truitt, Susan <Susan.Truitt@fda.hhs.gov> wrote:

Dear Victor,

Please complete the attached "Highlights of Clinical Pharmacology and Cardiac Safety" table for NDA 208700 and email the completed table to me by **COB Monday, May 16, 2016**.

Let me know if you have any questions.

Regards,

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Office of New Drugs
Center for Drug Evaluation and Research
Phone: 240-402-3656
Fax: 301-796-9849
Email: susan.truitt@fda.hhs.gov

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This email was Virus checked by Advanced Accelerator Applications security gateway.

<Highlights_ClinPharm_and_Cardiac_Safety.doc>

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/s/

SUSAN B TRUITT
05/06/2016



NDA 208700

NDA ACKNOWLEDGMENT

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial

Date of Submission: April 27, 2016

Date of Receipt: April 28, 2016

Our Reference Number: NDA 208700

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 27, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/ct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 208700** submitted on April 28, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

SUSAN B TRUITT
05/02/2016



NDA 208700

ACKNOWLEDGE PRESUBMISSION

Advanced Accelerator Applications USA, Inc.
Attention: Victor G. Paulus, Ph.D.
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of a marketing application under 506 of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: LUTATHERA (^{177}Lu -DOTA⁰-Tyr³-Octreotate), Injection for Intravenous Infusion; 370 MBq/mL single-use vial

Date of Submission: March 31, 2016

Date of Receipt: March 31, 2016

Our Reference Number: NDA 208700

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the application number listed above at the top of the first page of any communications concerning this supplemental application.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

SUSAN B TRUITT
04/18/2016



IND 77219

MEETING MINUTES

Advanced Accelerator Applications USA, Inc. (AAA USA, Inc.)
Attention: Dr. Victor Paulus
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.”

We also refer to the meeting between representatives of your firm and the FDA on March 14, 2016. The purpose of the meeting was to discuss the content and format of planned NDA for ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 14, 2016, 2:00PM
Meeting Location: White Oak 22, Room 1419

Application Number: 77219
Product Name: ^{177}Lu -DOTA⁰-Tyr³-Octreotate
Indication: Treatment of (b) (4)
somatostatin receptor positive
gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in
adults

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA USA, Inc.)

Meeting Chair: Steven Lemery
Meeting Recorder: Ruth Maduro

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Division Director
Steven Lemery, M.D., M.H.S, Associate Director (Acting)
Suzanne Demko, P.A.-C., Clinical Team Leader
Joohee Sul, M.D., Clinical Reviewer
Denise Casey, M.D.
Ruth Maduro, Regulatory Project Manager

Division of Biostatistics (DB-V)

Kun He, Ph.D., Statistical Team Leader
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer

Division of Hematology Oncology Toxicology (DHOT)

Whitney Helms, Ph.D., Supervisor
Anwar Goheer, Ph.D., Nonclinical Reviewer

Office of New Drug Products (ONDP)

Danae Christodoulou, Ph.D., Drug Quality Team Lead
Eldon Leutzinger, Ph.D., Drug Quality Reviewer
John Amartey, Ph.D., Drug Quality Reviewer

Office of Process and Facilities (OPF)
Peggy Kriger, Ph.D. Microbiology Reviewer

Office of Clinical Pharmacology (OCP)
Hong Zhao, Ph.D., Clinical Pharmacology Team Lead
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Stefano Buono, CEO
Gerard Ber, COO
Jack Erion, Ph.D., Vice President R&D USA
Claude Hariton, Ph.D., DSc, Global Head Research and Development
Maurizio Mariani, M.D., Ph.D., DAPT, Head, Pre-Clinical Development
Victor Paulus, Ph.D., Head, Regulatory Affairs
Paola Santoro, Ph.D., Senior Clinical Project Manager
Maribel Lopera Sierra, M.D., Chief Medical Officer
Eric Paul Krenning
Dirk Kwekkeboom

1.0 BACKGROUND

Advanced Accelerator Applications, USA, Inc. (AAA) requested a Type B meeting with FDA to discuss the format and contents of a proposed NDA submission to support the use of ^{177}Lu -DOTA⁰-Tyr³-Octreotate (Lutathera) for the treatment of patients with [REDACTED] (b) (4) somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Regulatory History:

On June 14, 2007, BioSynthema Inc. met with FDA (under this IND) via teleconference during a pre-IND meeting to discuss the development program for ^{177}Lu -DOTA⁰-Tyr³-Octreotate as an investigational treatment for patients with somatostatin receptor positive neuroendocrine tumors (NETs).

In January 2009, ^{177}Lu -DOTA⁰-Tyr³-Octreotate was designated as an orphan drug for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

In December 2010, BioSynthema requested parallel scientific advice from FDA and the European Medicines Agency (EMA) to discuss the design of a proposed clinical trial (NETTER- 1) to provide the primary safety and efficacy data intended to support a marketing approval of ^{177}Lu -DOTA⁰-Tyr³-Octreotate for the treatment of patients with [REDACTED] (b) (4) somatostatin receptor positive GEP-NETs.

On March 8, 2011, the pre-IND/parallel scientific advice meeting was held to discuss the acceptability of the proposed randomized, active-controlled trial comparing the overall response rate observed in patients with inoperable midgut carcinoid tumors who experienced progressive

disease while being treated with octreotide LAR randomized to $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with those randomized to Sandostatin LAR Depot. FDA stated that while the subpopulation of midgut carcinoid tumors was an acceptable population for study, given the biological and clinical heterogeneity of GEP-NETs, it would be unlikely that an indication for the treatment of (b) (4) (b) (4) somatostatin receptor positive GEP-NETs would be granted based upon data derived from the proposed trial.

On April 23, 2012, the IND-enabling study (NETTER-1) was submitted by AAA to IND 77219. The IND was allowed to proceed on September 6, 2012.

In April 2015, AAA was granted Fast Track Designation for the investigation of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the treatment of patients with inoperable, progressive, well-differentiated, octreoscan positive, carcinoid tumors of the mid-gut.

On August 27, 2015, AAA met with FDA to provide background information on the development program for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the proposed indication of the treatment of adult patients with (b) (4) somatostatin receptor positive GEP-NETs and to obtain general advice on the contents of an NDA seeking approval based on the results of the NETTER-1 study, supported by safety data from the Erasmus medical center (EMC) trial. AAA provided the top-line results of the analysis of PFS from NETTER-1, which demonstrated a significant improvement in PFS [HR 0.21 (95% CI 0.13, 0.34); $p < 0.001$]; at the time of this final analysis, median PFS was 8.4 months in the control (Sandostatin LAR Depot 60 mg) arm and had not been reached in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm. The following key issues were discussed at this meeting:

- Integrity testing (b) (4) would not be required.
- AAA needs to fully support their proposal (b) (4) at the receiving clinical site is needed to ensure patient safety. FDA stated that the adequacy of the data provided in the NDA to support this approach will be determined during the review of the NDA. AAA will provide shipping validation studies and stability studies in the NDA.
- FDA agreed with the definitions of drug substance and drug product provided by AAA.
- AAA's proposal to perform (b) (4) testing (b) (4) was acceptable.
- FDA stated that although its general policy is to require 12 months of real-time stability data for a new molecular entity, it would be acceptable to file the planned NDA with 6 months real-time stability data, which is consistent with the stability dating for the product administered to patients in clinical trials. Expiry dating at approval could be limited to (b) (4) months. Therefore, FDA encouraged AAA to include supportive data for establishing the expiry dating period of octreotate.
- AAA's proposal to submit separate, study-specific, efficacy and safety datasets and to include separate analyses in the CSE, ISE, CSS, and ISS for the Erasmus and the NETTER-1 studies was acceptable. In addition, in the ISE, FDA stated that it would be acceptable to submit the results of an exploratory, pooled analysis which includes all

patients enrolled in the NETTER-1 study and the subgroup of all patients with inoperable, locally advanced or metastatic, octreoscan positive, midgut carcinoid tumors who progressed during prior treatment with a somatostatin analog (SSA) in the Erasmus study. The data for patients with pancreatic NETs and bronchial NETs should be analyzed separately. Additionally, subgroup analyses should be performed based on the stratification factors employed in the NETTER-1 study and the functional status of the tumor, as well as by age, gender, and race.

- For the ISS, it would be acceptable to perform a pooled analysis of all patients in both studies who received at least one dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study.
- A potential broader indication for patients with GEP-NET would require demonstration of a clinically meaningful antitumor effect in an adequate number of patients with progressive and inoperable GEP-NETs treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study in one or more adequate and well-controlled trials. FDA cannot determine the adequacy of the data from the Erasmus study to support the broader indication until the data is reviewed at the time of the NDA submission. All concerns raised by FDA in prior meetings regarding these data should be addressed in a justification for seeking claims based on data from retrospectively identified subgroups from the Erasmus trial.
- Summary data from at least ten patients enrolled in the substudy along with supportive data from the EMC study and justification and supporting data for measurement of PK by radioactivity rather than HPLC would be provided in the pre-NDA meeting package.
- The non-clinical pharmacology/toxicology program appeared sufficient to support filing of the planned NDA.
- The contents of the clinical pharmacology program required to support filing of the NDA were summarized, as was the need for adequate dosimetry data.
- Possible approaches to developing an expanded access program were discussed.

On September 30, 2015, AAA submitted a request for a pre-NDA, which was granted and scheduled for November 24, 2015. The pre-meeting package did not include completed analyses of safety data from NETTER-1; therefore, it was determined that there was insufficient information to reach agreement on the contents of an NDA under the PDUFA V program. The following key issues were discussed during the meeting:

- FDA reiterated that a potential indication for patients with GEP-NET will require demonstration of a clinically meaningful ORR by RECIST as determined by independent review that is of sufficient magnitude and duration in an adequate number of patients with progressive and inoperable bronchial NET or pancreatic NET treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study. FDA further stated that the meeting package did not include data on the ORR and DOR per RECIST v 1.1 in the intent-to-treat population for patients in the Erasmus Study with midgut carcinoid or in the broader GEP-NET subgroup; therefore, a determination of the adequacy of the EMC study data to support the broader GEP-NET indication was not possible. FDA requested the following additional information in a future pre-NDA meeting package:

- ORR results based on RECIST v1.1, limited to complete and partial responses and the median duration of response (DOR) per RECIST v.1.1 observed in all patients who received any part of a dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with GEP-NET enrolled in the Erasmus study (i.e., the intent to treat GEP-NET population consisting of FAS and patients with GEP-NET who received treatment with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and did not have a post baseline tumor assessment). Patients without a post-baseline tumor assessment should be identified as non-responders.
 - The ORR and the median DOR per RECIST v.1.1 observed in the retrospectively identified subgroup of patients with midgut carcinoid tumors enrolled and who received any part of any dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and who would otherwise have met the NETTER-1 criteria.
 - The ORR and the median DOR per RECIST v.1.1 observed in the pooled population of patients with midgut carcinoid tumors treated in the Erasmus and NETTER-1 studies (i.e., the planned efficacy population for the ISE).
 - Additional efficacy analyses identified in section III. B. 2 of the background document in the pre-NDA meeting package should be conducted in all patients who received any part of any dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.
 - A tabular listing of adverse events occurring in > 10% of patients (per-patient incidence, rather than per-dose incidence) in each treatment arm in the NETTER-1 study, organized by system organ class (SOC), preferred terms (PTs), and by severity grade, with separate columns for the incidence of all AE (NCS CTCAE Grades 1-5) and grade 3-5 AEs, regardless of physician attribution of relationship to study drug.
 - A tabular listing of the per-patient incidence of laboratory abnormalities in each treatment arm for the NETTER-1 study, including columns for all grades and grade 3-4 toxicities.
 - A table displaying the per-patient incidence of laboratory abnormalities that occurred in the Erasmus study.
 - A tabular listing of safety information collected in the Erasmus study. If this level of detail is not available from the Erasmus study, provide justification for the adequacy of the safety database from the Erasmus study to provide supportive information.
 - A table that summarizes the per-patient incidence rates of AEs of special interest based on the mechanism of action of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the Erasmus and NETTER-1 studies.
- FDA stated that the proposed analyses of time to progression (TTP), progression-free survival (PFS) and overall survival (OS) are uninterpretable in the single arm Erasmus trial [REDACTED] ^{(b) (4)} The exploratory efficacy analyses performed in the pooled dataset (NETTER-1 and Erasmus) should be limited to ORR and DOR.
 - FDA did not object to AAA's proposal to open an expanded access trial at NETTER-1 study sites and to allow patients in the NETTER-1 study who progress during treatment with Sandostatin LAR 60 mg to receive $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.
 - FDA discouraged AAA from submitting the interim analysis of OS as the final analysis in the NDA and encouraged AAA to conduct additional analyses at later time points

when a greater number of events have occurred. FDA emphasized that in order for the OS results to be included in the label, an effect on OS must meet the criteria for substantial evidence of efficacy.

- There is insufficient safety data provided in the meeting package to make a determination on whether a risk evaluation and mitigation strategy (REMS) would be required for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. If it is determined that a REMS is not required, a risk evaluation and mitigation plan is still expected as part of the NDA.
- Insufficient information on the validation for the HPLC analysis of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in urine was provided in the meeting package, and FDA identified several deficiencies in the report.
- FDA requested that AAA include in the pre-NDA meeting materials, a description of the process by which investigator-assessed disease status determined by SWOG criteria for the Erasmus trial will be re-assessed using RECIST 1.1.

Background

On December 18, 2015, AAA submitted a second pre-NDA request to discuss the contents and format of their planned NDA for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. In the current meeting package, AAA submitted the following data in response to FDA's request during the November 24, 2015, meeting:

- Results for ORR and the median DOR per RECIST observed in all patients who received any part of a dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with GEP-NET enrolled in the Erasmus study,
- ORR and the median DOR results per RECIST observed in a retrospectively identified subgroup of patients with midgut carcinoid tumors enrolled in Erasmus and who received any part of any dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and who would have otherwise have met the NETTER-1 criteria. Those patients with midgut carcinoid tumors who were treated but did not have a post baseline tumor assessment are considered non-responders,
- ORR and the median DOR results per RECIST v.1.1 observed in the pooled population of patients with midgut carcinoid tumors treated in the Erasmus and NETTER-1 studies (the planned efficacy population for the ISE),
- Tabular listing of the per-patient incidence of laboratory abnormalities in each treatment arm for the NETTER-1 study including columns for all grades and grade 3-4 toxicities,
- Tabular listing displaying the per-patient incidence of laboratory abnormalities that occurred in the Erasmus study,
- Tabular listing of serious adverse events (SAEs) and laboratory toxicities collected in the Erasmus study,
- Tabular summary of the per-patient incidence rates of AEs of special interest based on the mechanism of action of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the Erasmus and NETTER-1 studies.

Also included in the meeting package are a table comparing the similarities and differences between the NETTER-1 and the Erasmus studies, a proposed table of contents for the NDA, list

of SDTM datasets, a draft product label, the analytic plans for the Erasmus study and the ISS/ISE, and the Drug Master File for the Lu-177 Chloride Radiopharmaceutical Precursor.

Erasmus Medical Center Clinical Study (MEC 127.545/1993/84-01)

An investigator sponsored single arm clinical study $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was conducted at EMC in Rotterdam, The Netherlands, between January 2000 and March 2007. The study enrolled patients with various inoperable, somatostatin receptor positive NETs including bronchial carcinoid tumors. The primary objective of the study was to assess the clinical effects of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ given as four intravenous (IV) administrations of 7.4 GBq at 6-13 week intervals. AAA performed a retrospective, independent verification of the source data of this trial in 2012 and updated the analysis in 2015. The 2015 updated analysis, not available for the November 2015 Type C meeting but discussed in the current meeting package, included follow-up data for the 615 patients analyzed in 2012 and an additional 599 patients who were enrolled between March 2007 and December 2012 (total of 1,214 patients).

The original protocol utilized modified SWOG criteria for response assessment. AAA conducted a series of retrospective response analyses in the subgroup of 118 patients with midgut carcinoid tumors who had progressive disease within 12 months of study entry (the target population of the NETTER-1 study). These patients were part of the Full Analysis Set (FAS) defined as all patients who received $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and had a baseline tumor assessment available. FDA requested an additional analysis that included patients in the FAS plus those patients who did not have a post-baseline tumor assessment in which patients with missing response assessments were counted as non-responders. AAA additionally conducted subgroup analyses of safety and efficacy in Dutch patients and international (non-Dutch) patients to address the potential negative bias caused by loss of follow-up and missing data in the international group.

According to AAA's analysis of the Erasmus data, the best overall response observed in the subgroup of 118 patients with midgut carcinoid tumors who had a baseline tumor assessment was 33% [95% confidence interval (CI): 25, 42]. Including those patients who did not have a baseline tumor assessment, the ORR for 234 patients with midgut carcinoid tumor who received $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was 17% (95% CI: 12, 21). Table 2 in the meeting package provides a summary of the updated 2015 ORR and DOR data for the midgut carcinoid tumor subgroup in the Erasmus MC study.

Table 2. Overall response, objective response rate and duration of response in the Phase I/II Erasmus MC study in the subgroup of patients with progressive midgut neuroendocrine tumor

Tumor type	Analysis set	Population	N	CR		PR		SD		PD		ORR*		DOR (months)				
				n	%	n	%	n	%	n	%	n	%	95%CI	Median	95%CI		
Progressive Midgut NET	FAS**	All	118	2	2%	37	31%	70	59%	3	3%	39	33%	25%	42%	9.9	3.6	16.3
		Nationals	98	2	2%	31	32%	56	57%	3	3%	33	34%	24%	43%	11.3	4.3	17.6
	Sens***	All	234	2	1%	37	16%	70	30%	3	1%	39	17%	12%	21%			
		Nationals	153	2	1%	31	20%	56	37%	3	2%	33	22%	15%	28%			

*All patients with no post baseline tumor assessment are counted as non-responders
 **FAS: Full analysis set include all patients treated who have a baseline tumor assessment available
 ***Sens: in addition to the FAS, sensitivity analysis set also includes patients with missing baseline tumor assessment. Those patients are counted as non-responders; DORs are not reported for this analysis set since not impacted by adding non-responder patients in the analysis

NETTER-1

NETTER-1 was a multicenter, stratified, open label, randomized, active controlled trial comparing PFS in 230 patients randomized 1:1 to receive ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate or octreotide LAR. Enrollment was completed in February 2015. Study eligibility was limited to patients with inoperable, somatostatin receptor positive midgut carcinoid tumors having documented disease progression after treatment with fixed doses of octreotide LAR. Patients with functional or nonfunctional tumors were eligible. Patients were stratified by OctreoScan® tumor uptake score (Grade 2, 3 and 4) and the length of time that patients were on the most recent constant dose of octreotide prior to randomization (≤ to 6 months and > 6 months).

Patients in the ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate arm received a total cumulative administered radioactivity of 29.6 GBq with the dosing equally divided among 4 administrations of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate (7.4 GBq) at 8 week intervals, extendible up to 16 weeks to accommodate resolving acute toxicity. These patients continued to receive supportive care with cold octreotide 30 mg (Sandostatin® LAR Depot), preferably administered the day after each administration of the ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate, and no earlier than four hours after completion of the ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate infusion. Patients in the comparator arm received 60 mg Sandostatin® LAR Depot (Octreotide Acetate) intramuscular injections every 4 weeks. Octreotide rescue injections were allowed in both arms for the treatment of clinical symptoms (e.g., diarrhea and flushing) associated with carcinoid tumors.

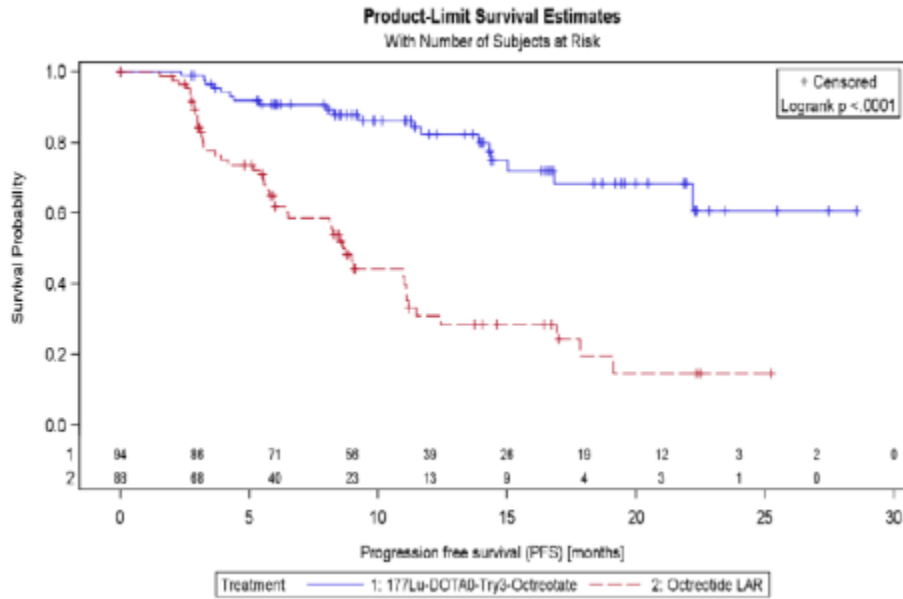
The ORR and DOR data for the NETTER-1 study is provided in Table 3 of the meeting package (copied from submission):

Table 3. Overall response, objective response rate and duration of response in the Phase III NETTER-1 (centrally assessed)

	Lutathera										Octreotide LAR										p												
	N	CR		PR		SD		PD		ORR		DOR (months)		N	CR		PR		SD			PD		ORR		DOR (months)							
		n	%	n	%	n	%	n	%	n	%	95%CI	Med.		95%CI	n	%	n	%	n		%	n	%	n	%	95%CI	Med.	95%CI				
FAS	116	1	1%	17	15%	77	66%	6	5%	18	18%	10%	25%	5.6	2.5	7.2	113	0	0%	3	3%	70	62%	27	24%	3	3%	0%	6%	1.9	0.0	2.8	0.0008
Sens*										18	16%	9%	22%																			0.0009	
PP	94	1	1%	15	16%	68	72%	4	4%	16	18%	10%	26%	5.4	2.5	7.2	88	0	0%	3	3%	61	69%	18	21%	3	4%	0%	8%	1.9	0.0	2.8	0.0029
Sens*										16	17%	9%	25%																			0.0030	

*Sens: ORR sensitivity analysis; patients with no tumor response available are classified as non-responders instead of missing
 Abbreviations: Med., Median; CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progression; ORR, Objective Response Rate; DOR, Duration of Response

The primary endpoint of PFS was performed when the pre-specified threshold of 74 evaluable events was reached. The median PFS for the control arm was 8.4 months while the median PFS for the ^{177}Lu -DOTA⁰-Tyr³-Octreotate arm had not been reached [hazard ratio: 0.21 (95% CI: 0.13-0.34)]. Figure 2 from the briefing document copied below shows the Kaplan-Meier analysis for PFS in the NETTER-1 study.



Safety data describing adverse events occurring in $\geq 10\%$ of patients in each treatment arm in the NETTER-1 study are provided in the table below (copied from submission):

Table 11. Adverse events reported in the Phase III NETTER-1 study in at least 10% of patients who received Lutathera

SOC	PT	Lutathera (N = 111)				Octreotide LAR (N = 110)			
		All grades		Grade 3 to 5		All grades		Grade 3 to 5	
		n _{pat}	%	n _{pat}	%	n _{pat}	%	n _{pat}	%
All SOCs	All PTs	105	95%	46	41%	92	84%	36	32%
Gastrointestinal disorders	Nausea	65	59%	4	4%	13	12%	2	2%
	Vomiting	52	47%	8	7%	11	10%	1	1%
	Diarrhoea	32	29%	3	3%	21	19%	2	2%
	Abdominal pain ¹	29	26%	3	3%	29	26%	6	5%
	Abdominal distension	14	13%	0	0%	15	14%	0	0%
General disorders and administration site conditions	Fatigue ²	44	40%	2	2%	28	25%	2	2%
	Oedema peripheral	16	14%	0	0%	8	7%	0	0%
Musculoskeletal and connective tissue disorders	Musculoskeletal pain ³	32	29%	2	2%	22	20%	1	1%
Blood and lymphatic system disorders	Thrombocytopenia ⁴	28	25%	2	2%	1	1%	0	0%
	Lymphopenia ⁵	20	18%	10	9%	2	2%	0	0%
	Anaemia ⁶	16	14%	0	0%	6	5%	0	0%
	Leukopenia ⁷	11	10%	1	1%	1	1%	0	0%
Metabolism and nutrition disorders	Decreased appetite	20	18%	0	0%	9	8%	3	3%
Nervous system disorders	Headache	18	16%	0	0%	5	5%	0	0%
	Dizziness	12	11%	0	0%	6	5%	0	0%
Vascular disorders	Flushing	14	13%	1	1%	10	9%	0	0%
Skin and subcutaneous tissue disorders	Alopecia	12	11%	0	0%	2	2%	0	0%
Respiratory, thoracic and mediastinal disorders	Cough	12	11%	0	0%	6	5%	0	0%

MedDRA V18.0; Safety Set, Treatment emergent adverse events (ICHE9)

SOC: System Organ Class; PT: Preferred term; n_{pat}: patient count

¹ Includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper and Gastrointestinal pain

² Includes Asthenia and Fatigue

³ Includes Arthralgia, Back pain, Bone pain, Flank pain, Groin pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity, Spinal pain

⁴ Includes Thrombocytopenia and Platelet count decreased

⁵ Includes Lymphopenia and Lymphocyte count decreased

⁶ Includes Anaemia, Haemoglobin decreased, Normochromic normocytic anaemia

⁷ Includes Leukopenia and White blood cell count decreased

2.0 DISCUSSION

1. Erasmus study and NETTER-1 study safety and efficacy results have been completed with the main summary tables provided in the background document. As requested by the Agency, AAA has also specifically provided the following in the background document:
 - results for objective response rate (ORR), the median duration of response (DOR) per RECIST observed in all patients who received any part of dose of ^{177}Lu -DOTA⁰-Tyr³-Octreotate with GEP-NET enrolled in the Erasmus Phase I-II study,
 - ORR and the median DOR results, per RECIST v.1.1 observed in the retrospectively identified subgroup of patients with midgut carcinoid tumors enrolled and who received any part of any dose of ^{177}Lu -DOTA⁰-Tyr³-Octreotate who would otherwise have met the NETTER-1 criteria. Those patients with midgut carcinoid tumors who were treated but did not have a post baseline tumor assessment are considered non-responders,
 - ORR and the median DOR results per RECIST v.1.1 observed in the pooled population of patients with midgut carcinoid tumors treated in the Erasmus and NETTER-1 studies (the planned efficacy population for the ISE),
 - tabular listing of the per-patient incidence of laboratory abnormalities in each treatment arm for NETTER-1 study, which include columns for all grades and grade 3-4 toxicities,
 - tabular listing displaying the per-patient incidence of laboratory abnormalities that occurred in the Erasmus study,
 - tabular listing of safety information (serious adverse events and laboratory toxicities) collected in the Erasmus study,
 - tabular summary of the per-patient incidence rates of AEs of special interest based on the mechanism of action of ^{177}Lu -DOTA⁰-Tyr³-Octreotate in the Erasmus and NETTER-1 studies.

Does the Agency find these additional results and the way they are presented appropriate and comprehensive enough to serve as a basis for assessing the efficacy and safety of Lutathera in the claimed indication?

FDA Response: The presentation of the data from the NETTER-1 and EMC studies in the meeting package appears to be adequate for submission of an NDA; however, FDA continues to have significant concerns regarding the utility of the data presented from the Erasmus trial. FDA reiterates that a potential indication for patients with GEP-NET would require demonstration of a clinically meaningful ORR and DOR by RECIST as determined by independent review in one or more trials that are well designed, well executed and internally consistent. Whether the results of the Erasmus trial are able to support the proposed indication of GEP-NETs will be determined at the time of the NDA review. All concerns raised by FDA regarding these data should be addressed in the NDA submission (see additional comments for further details).

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

2. AAA has provided, in Annex 4, a table (Table 2-1) presenting the similarities and differences between the NETTER-1 and the Erasmus studies. Does the Agency find this table informative enough for conducting an appropriate assessment of the NDA dossier? If so, is it necessary to include the diagram in the NDA?

FDA Response: The table describing similarities and differences between the Erasmus study and the NETTER-1 study may be included in the NDA submission; however, please modify the table to include a column describing the rationale for why the differences in study design and conduct do not impact the interpretation of trial results. Alternatively, include the rationale as text in the Clinical Study Report (CSR) for the trial with an active hyperlink to the table.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

3. Clinical Pharmacology points raised in previous meetings have been addressed in the background document and will also be addressed in the NDA. For each of the points listed below, the rationale for the adopted approach is described or a justification is given if the analysis is not performed:
 1. Conduct a formal organ impairment study to determine alterations in systemic exposures,
 2. Conduct population pharmacokinetic analyses to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics,
 3. Explore the exposure-response relationships for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and its active metabolites, if any, for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers.
 4. Validation the analytical methods used to determine the concentrations of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and its active metabolites.

Does the Agency agree that the presented approaches are adequate to support the NDA?

FDA Response: The justifications for not conducting the recommended clinical pharmacology studies appear reasonable. Include these justifications with supporting data in the NDA submission and its adequacy will be determined upon the NDA review. In the NDA submission, include the following from both Erasmus and NETTER-1 trials, when applicable:

- a. Biodistribution
 - i. Dosimetry study results and analyses
 - ii. Concomitant administration of amino acid solution study results
- b. PK characterization
 - i. Plasma and urine pharmacokinetic (PK) results with estimated PK parameters for ^{177}Lu -DOTA0-Tyr3-Octreotate (e.g. C_{max}, AUC, V_d, etc.) based on radioactivity and HPLC with gamma detection
 - ii. Metabolite characterization by HPLC of ^{177}Lu -DOTA0-Tyr3-Octreotate in urine
 - iii. In vitro metabolic stability data (e.g. serum, hepatocyte, liver microsomes)
- c. Analytical Methodology
 - i. Sample collection analysis times for ^{177}Lu -DOTA0-Tyr3-Octreotate urine and plasma analyses
 - ii. Bioanalytical methods and validation reports used to generate PK characterization data
 - iii. The specific activity of ^{177}Lu -DOTA0-Tyr3-Octreotate
 - iv. Conversion of the 200 mCi dose to mg or mg/kg
- d. Relevant data to justify not conducting organ dysfunction studies and a proposed recommendation on how to dose patients with established liver cirrhosis. Also provide justification with supporting data for excluding patients with creatinine clearance < 50 mL/min from treatment.
- e. Submit the following items for QTc study/assessment
 - i. Copy of the QT/QTc study protocol and report
 - ii. Copy of the Investigator's Brochure
 - iii. Annotated CRF
 - iv. Define file which describes the contents of the electronic data sets
 - v. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
 - vi. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

4. During the meeting with the Agency in August 2015, AAA stated that in order to reduce confusion and review time, information on critical precursor materials would be provided directly rather than relying entirely on references to drug master files. To address questions such as the level of [REDACTED] (b) (4) section 3.2.S for the radiopharmaceutical precursor is provided as Annex 7. Does the Agency feel that the level of detail provided in this Annex is sufficient to facilitate NDA review?

FDA Response: The information provided in Annex 7 of the meeting briefing package may be included in 3.2.S of the NDA. However, in order to consider this section of the NDA to be complete, in addition to this information, please also provide the following:

- Indicate the minimum acceptance [REDACTED] (b) (4) level [REDACTED] (b) (4)
- Describe the [REDACTED] (b) (4) preparation in detail, including the [REDACTED] (b) (4) process
- A certificate of analysis (CoAs) for materials used in the preparation (such as [REDACTED] (b) (4) etc.)
- Information [REDACTED] (b) (4)
- [REDACTED] (b) (4) description details
- Executed batch records

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: The draft section 3.2.S is all that we will be able to provide. The details being requested will be found in a DMF that will be referenced in the NDA.

Discussion During the meeting: FDA stated that this approach is acceptable.

5. To facilitate the review of the data, the following SDTM domains will be provided (data will be presented based on SDTM IG 3.1.3 structure) for the pooled studies database used in the ISS/ISE:
- AE (Adverse Events)
 - CM (Concomitant Meds)
 - DM (Demographics)
 - DS (Disposition)
 - EX (Exposure)
 - LB (Laboratory Data)
 - MH (Medical History)
 - RS (Disease Response)
 - SV (Subject Visits)
 - TA (Trial Arms)
 - TR (Tumor Results)
 - TS (Trial Summary)
 - TU (Tumor Identifiers)
 - VS (Vital Signs)

Where appropriate, the corresponding SUPPQUAL domains will also be provided. The proposed SDTM domains and variables to be provided in the submission package can be found in Annex 6.

The following ADaM datasets will be provided – all the variables required to allow traceability of the tables and figures in the ISS/ISE will be included in these datasets:

- ADSL (Subject-Level Analysis Dataset)
- ADAE (Adverse Events Analysis Dataset)
- ADOR (Response Rates Analysis Dataset)
- ADTTE (Time-to-event Analysis Dataset) – this would include duration of response (for responders only), progression-free survival and overall survival)
- ADLB (Laboratory Data Analysis Dataset)

AAA is seeking for advice on the following:

In the meeting minutes from the Type C meeting on November 24, 2015, FDA specifies 5 new variables for the SDTM domain TA (namely ANCHDTC, MAXPRD, MINPRD, STOFFSET and TGTPRD). TA is the Trial Arm domain and does not contain subject-specific data. However, these variables appear to be subject-specific data. Would the FDA clarify on the definition of these variables?

FDA Response: Based upon discrepancies between “DOP2 Additional CDISC Guidance” and current CDISC technical standards, FDA no longer requires that sponsors address the requests made in “DOP2 Additional CDISC Guidance” appended to previous meeting minutes.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

6. Does the FDA agree with the proposed list of SDTM domains and variables is adequate, and the principle that only variables used in the generation of tables and figures will be included in the ADaM datasets?

FDA Response: FDA agrees with the proposed list of SDTM domains; however, please revise the proposed list of variables for the ADaM datasets as follows:

- a. Revise the following domains to include additional variables:
 - AE: Date of last visit, date since most recent treatment, study duration, AE outcome, AE lower level term, AE high level term, AE start relative day, AE ongoing flag, AE duration, AE leading to withdrawal flag, concomitant/additional treatment, treatment emergent flag
 - CM: dose per administration, dosing frequency per interval, route of administration, prior medication flag, post medication flag

- EX: analysis date, analysis visit, planned volume administered, relative day since last dose, delayed drug administration flag, interrupted drug administration flag
 - LB: baseline value, change from baseline, percent change from baseline
- b. Include the Inclusion/Exclusion Analysis Dataset
- c. Include the following variables for all domains:
- Treatment arm
 - Basic demographic information such as age and sex
 - Basic tumor characteristics such as diagnosis
 - ITT flag
 - Per protocol (PP) flag

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA response is being formulated and will be presented, verbally, as discussion points during the meeting.

Discussion During the meeting: AAA asked for clarification regarding the additional variables FDA requested for the datasets. For Erasmus, AAA stated they did not have HLTs or LLTs coded for adverse events, but verbatim terms and PTs are available. FDA stated that coding is typically derived from verbatim terms to lowest level terms (LLT), and all other terms including PT, HLT, HLTG and SOCs are thereafter automatically mapped in the MedDRA coding dictionary. FDA prefers to see adverse events at all levels of the MedDRA hierarchy in safety analyses, and asked whether coding of adverse events for the NETTER-1 study was also incomplete. AAA clarified that for NETTER-1, terms at all levels of the MedDRA hierarchy are available since the coding was completed by a different entity.

AAA agreed to check the adverse event coding protocol for the Erasmus trial and to provide a description of this process to FDA for further consideration.

In regards to item (b), AAA stated that the inclusion/exclusion dataset is available for NETTER-1 but not for the Erasmus study. FDA stated that there were subsets of patients from the Erasmus study that were selected to match the population of patients in the NETTER-1 study based on eligibility criteria, and requested clarification on how these patients were identified. AAA stated that these subgroups of patients were selected by identifying certain key eligibility criteria and then flagged in the dataset; however, a specific dataset with the matching criteria used to select patients is not available. AAA agreed to provide a detailed description of the process used to identify patients from the Erasmus study that were selected to match the population of patients in NETTER-1, including a description of the specific eligibility criteria that were used.

7. The SDTM domains will be based on SDTM IG 3.1.3 structure, and ADaM datasets will be based on ADaM IG 1.0 structure. All the datasets will be presented in SAS XPORT (Transport files, .xpt) format. Define.xml files will accompany the datasets. In addition, blankcrf.pdf will be provided to accompany the SDTM datasets. Does the FDA agree with this?

FDA Response: Yes, this approach appears acceptable.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

8. Only the proposed SDTM and ADaM datasets for the ISS/ISE will be submitted – the STUDYID will be the identifier for the two different studies to be submitted. These datasets will not be repeated/copied into the individual studies folders. Does FDA agree with this approach?

FDA Response: No. FDA requests that AAA submit the SDTM and ADaM datasets for the NETTER-1 and EMC studies separately in the appropriate individual study folders.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA response is being formulated and will be presented, verbally, as discussion points during the meeting.

Discussion During the meeting: FDA confirmed AAA's understanding that submission of datasets in three separate folders (study folder for NETTER-1, study folder for Erasmus, and the ISS/ISE) is acceptable.

9. Given that rolling submissions are possible under Fast-Track, would the Agency consider a submission plan that includes all parts of the NDA except for the ISS and ISE which would be submitted thirty days after the bulk of the submission?

FDA Response: In general, FDA only accepts complete sections of an NDA, such as the entire CMC section, toxicology section, or clinical section. A section of an NDA should be submitted for review in a form adequate to have been included in a complete NDA submission. Drafts should not be included in a submission and AAA should confirm that all subsections are final reports.

A request to submit portions of an application ordinarily should be included in the information package for the pre-NDA meeting. If AAA seeks to submit portions of an application to the IND after the pre-NDA meeting, AAA should make such a request and provide a proposed schedule for submission of portions of the application as an amendment to the IND as soon as possible. Clearly identify the submission as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold,

uppercase letters. FDA will respond to AAA's requests for submission of portions of an application by letter.

Finally, the review clock for the NDA will not begin until AAA informs FDA that a complete NDA has been submitted, which will include the ISS and ISE.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: Based on discussions which have occurred after receipt of the Preliminary Comments we will submit a request to submit Modules 3 and 4 to be followed by Modules 2 and 5. That request will come next week.

Discussion During the meeting: Please see "DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION" below.

3.0 ADDITIONAL COMMENTS

Clinical

10. In the NDA, address the following significant concerns regarding data from the NETTER-1 and Erasmus trials.
 - a. It is unclear whether the EMC study analyses of ORR and DOR requested by FDA at the November 24, 2015, meeting are complete. FDA requested the results of ORR and median DOR based on RECIST v 1.1 observed in the intent to treat (ITT) population defined as all patients who received any part of a dose of ^{177}Lu -DOTA⁰-Tyr³-Octreotate with GEP-NET including those patients who did not have a post-baseline tumor assessment. The tables provided by AAA include the ORR for the "FAS" population defined as patients treated who have a baseline tumor assessment available. Please confirm that the "FAS" population described in Tables 1-5 includes patients who did not have a post-baseline assessment, and that these patients were counted as non-responders.
 - b. The purpose of the "SENS" analysis in Tables 1-5 is unclear. For Tables 1, 2 and 4, the "SENS" population is defined as patients in the "FAS" and also patients with missing baseline tumor assessments. For Table 3, the "SENS" population is described as patients with no tumor response available. Please provide a rationale for including analyses of these patient populations.
 - c. In the November 24, 2015, meeting package, AAA presented a retrospective analysis of ORR for a subgroup of 51 patients enrolled in the Erasmus study with midgut carcinoid tumors and progressive disease that matched the target population of the NETTER-1 study. The ORR at that time was reported to be (b)(4)% (0/51). The updated results from the 2015 retrospective analysis (included in the current meeting package) described an ORR of (b)(4)% (0/118). The ORR in the analysis of an additional 67 patients from the 2015 review (b)(4) than for the 51 patients identified during the 2012 review (0/67)%. ORR

and DOR results for the NETTER-1 study and the Erasmus study (2012 and 2015 analyses) are summarized below (reviewer table):

STUDY	N	ORR		DOR (95% CI)
		n	%	
EMC (2012)	51	(b) (4)		
EMC (2015)	118			
NETTER-1	116			

The additional analysis of 67 patients resulted (b) (4) in the ORR and calls into question the reliability of the results and internal validity of the EMC study. In the NDA, provide a discussion of the validity, reliability and internal consistency of these results.

- d. The EMC 2015 results for ORR (b) (4) and median DOR (b) (4) per RECIST reported for the retrospectively identified subgroup of patients with midgut carcinoid tumors differ significantly when compared with the ORR and DOR results for patients on the NETTER-1 trial. This inconsistency calls in to question whether the data from the Erasmus study can be used to support the efficacy of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate in patients with midgut carcinoid tumors, and ultimately extrapolated to support efficacy of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate in all patients with GEP-NETs. Differences in patient characteristics, methods of evaluating response and patient management over time in the Erasmus trial may have contributed to the differing ORR results in this study compared with NETTER-1.
- e. Clarify whether the 118 patients in the retrospectively identified subgroup of patients with midgut carcinoid tumors in the Erasmus study were selected based on fulfillment of all eligibility criteria for NETTER-1 (e.g. progressive disease based on RECIST, not SWOG criteria, while receiving a fixed dose of octreotide, somatostatin receptors present on all target lesions based on OctreoScan imaging within 24 weeks prior to randomization, etc.).
- f. Following is the description of the assessments of response in the Erasmus study:

(b) (4)

(b) (4)

(b) (4)

- g. At the September 30, 2015, meeting, FDA requested that AAA include in the pre-NDA meeting materials a description of the process by which investigator-assessed disease status determined by SWOG criteria for the Erasmus trial will be re-assessed using RECIST 1.1. It remains unclear how the images from the Erasmus trial were re-assessed using RECIST; therefore, provide a detailed and specific protocol for how tumor assessments were made by the independent reviewer.
- h. The analysis of SAEs of special interest collected retrospectively indicates that the majority of the data was collected from the Dutch national population of patients. For example, the reported incidence of myelodysplastic syndrome (MDS) is 1.2% (15/1214) in all patients; however, almost all these patients are from the Dutch national population (14/15). Similar results are seen for multiple other SAEs including hematologic SAEs. These findings raise the concern that there was inadequate follow-up of non-Dutch patients on the Erasmus study; therefore, safety data from this population of patients are not adequate to include in a pooled analysis of safety. Safety data from the Dutch national population may be included in the pooled analysis of safety to be submitted in a future NDA.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA's response is being formulated and will be presented, verbally, as discussion points during the meeting.

Discussion During the meeting: AAA prefaced the discussion by stating that irregularities in the data provided from the Erasmus study were likely due to inconsistent follow-up of patients who were Dutch nationals versus patients from other countries. AAA stated that about 95% of Dutch national patients had follow-up visits; therefore, the data from these patients are the most relevant to include in an analysis of the safety and activity of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. FDA acknowledged that incomplete follow-up data from the non-national patients in the Erasmus study is problematic; however, AAA should provide justification in the NDA for which datasets are considered to be most reliable.

Regarding the tables with data for ORR, DOR and PFS, AAA acknowledged there are discrepancies in how the FAS and SENS analysis populations are defined for the different patient populations in Erasmus and NETTER-1 and committed to refining these definitions to be consistent across subgroups and studies in the NDA.

AAA stated that discrepancies in ORR between the first and second analyses of the Erasmus study may be related to less favorable disease and patient characteristics for patients enrolled at the start of the study several decades ago, compared with patients enrolled more recently. AAA also stated that there may have been differences regarding the timing of response follow-up between NETTER-1 and Erasmus that may have contributed to the differences in ORR between studies. AAA agreed to provide their rationale with any supporting data for the disparate ORR results from the Erasmus study and the NETTER-1 study in the NDA.

AAA also clarified that the original imaging measurements from the Erasmus study that were captured using SWOG criteria were re-evaluated by an independent reviewer; however, the images themselves were not re-assessed to be consistent with RECIST. AAA confirmed that although non-target lesions were not captured at baseline, they were considered in the assessment of disease progression on subsequent evaluations. AAA committed to providing a detailed description of how the imaging data were evaluated to determine disease status and response in the NDA.

11. For all future submissions, provide a table of definitions for the study populations analyzed (e.g., ITT, FAS, Sensitivity analyses, PP, etc.). Ensure that these definitions are consistent across all documents submitted (e.g. ISS/ISE, protocol and SAP) or provide a description of where these definitions vary.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA response is being formulated and will be presented, verbally, as discussion points during the meeting.

Discussion During the meeting: No discussion occurred during the meeting.

12. The Erasmus study CSR submitted in the meeting package is inadequately organized to permit timely and efficient review of an NDA. Please ensure that the structure and content of any CSRs submitted to the NDA are consistent with the guidelines as outlined in the “Guideline for Industry, Structure and Content of Clinical Study Reports, ICH E3” found at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf>.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

13. The draft label included in the meeting package does not adhere to the regulations governing the content and format of prescribing information for drug and biological products (i.e. the “Physician Labeling Rule”). Please note the following examples:
- a. The Highlights of Prescribing Information (Highlights) is intended to include selected information taken from the Full Prescribing Information (FPI); therefore, information found in the Highlights should be consistent with the FPI.
 - b. The information under the **Warnings and Precautions** in the Highlights should describe individual risks presented in a bulleted format. Ambiguous and uninformative information such as “adjust dose as appropriate” and terminology that describes a contraindication should be avoided.
 - c. The statement that a batch release certificate will be provided to each center receiving the product (Section 5.1 General warnings and precautions) is not appropriate to include under Section 5 **Warnings and Precautions**.

Please refer to the “Guidance for Industry, Labeling for Human Prescription Drug and Biological Products-Implementing the PLR Content and Format Requirements” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf>. For additional guidance on labeling, please refer to <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm> and to the section below titled “Prescribing Information.”

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: The draft label is being revised based on the comments provided.

Discussion During the meeting: AAA stated they are working on revising the label based on the comments received from FDA. FDA stated that there were additional areas of concern in the proposed label, aside from the few examples provided, and specified that AAA should pay particular attention to consistency among the different sections of the label, use of direct language, and editing of unnecessary or redundant information. FDA strongly recommended that AAA refer to FDA labeling guidance documents as they revise the proposed label.

(b) (4)

14. Include datasets for prior treatments for the indication (i.e., systemic therapy, radiation, surgery), protocol deviations, and patient survival data in the NDA.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

15. There is insufficient safety data provided in the meeting package to make a determination on whether a risk evaluation and mitigation strategy (REMS) would be required for this product. Given the expectation that this product is likely to be administered by qualified hospital-based staff at centers with experience in handling and administering a radiopharmaceutical product, labelling that adequately addresses potential safety concerns may be sufficient to ensure safe use and that the product's benefits outweigh its risks. If it is determined that a REMS is not required, a risk evaluation and mitigation plan for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is still expected as part of the NDA.

Advanced Accelerator Applications USA, Inc. March 11, 2016, Response: AAA acknowledges and accepts the response to the Preliminary Comments. No discussion of this point during the conduct of the meeting is necessary.

Discussion During the meeting: No discussion occurred during the meeting.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

AAA stated they are planning to submit a request for a rolling NDA next week and the details of the request will be included in the request. AAA will then submit complete Modules 3 and 4 along with or followed by a separate submission with Modules 2 and 5 without the ISS and ISE components. The ISS and ISE will be submitted as the last part of the NDA. FDA stated that this is acceptable.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS is not needed in the initial application in order for the NDA to be filed.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. AAA stated that AAA intends to submit a complete application and therefore, there are no agreements for late submission of application components (i.e., following the final component of the rolling NDA submission designating the application as complete).

POST MEETING ADDENDUM:

For additional information on product quality microbiology data that should be included in the NDA submission, please refer to the following Guidance documents:

- 1994 Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf>).
- 2004 Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf>).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation that was granted on January 12, 2009, this drug is exempt from these requirements for the proposed indication of the treatment of gastro-entero-pancreatic neuroendocrine tumors. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human

- drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
 - Regulations and related guidance documents
 - A sample tool illustrating the format for Highlights and Contents, and
 - The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
 - FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA and Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

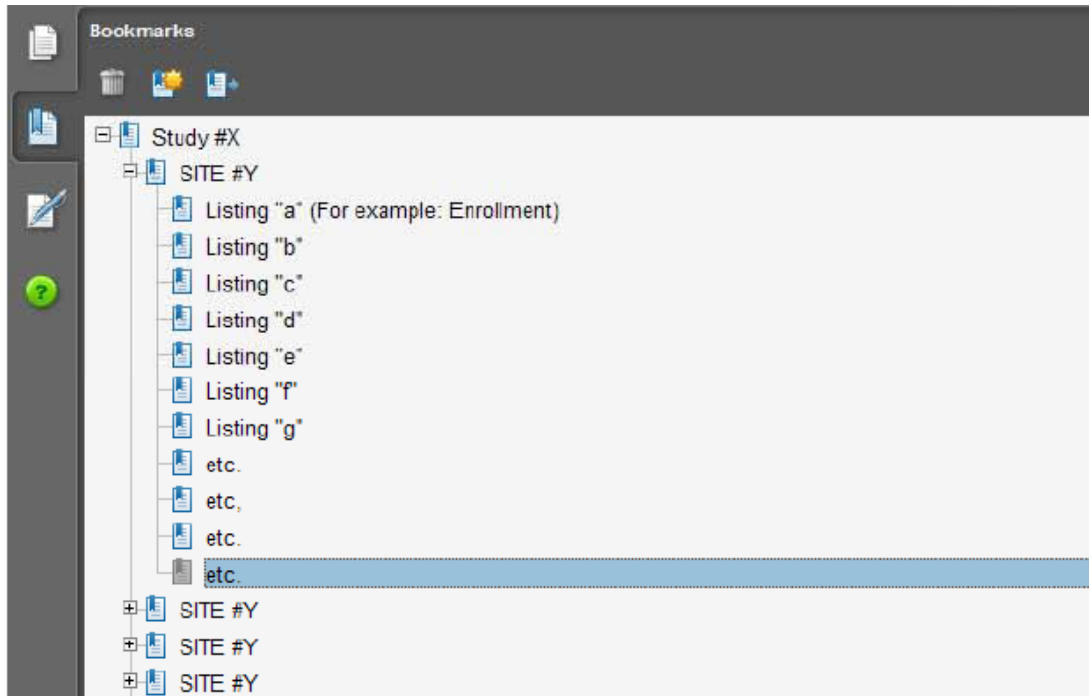
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUTH L MADURO
03/17/2016



IND 77219

MEETING MINUTES

Advanced Accelerator Applications USA, Inc. (AAA USA, Inc.)
Attention: Dr. Victor Paulus
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.”

We also refer to the meeting between representatives of your firm and the FDA on November 24, 2015. The purpose of the meeting was to discuss the timing, product labeling, and expanded access for proposed NDA submission for ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
DOP2 CDISC Guidance



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: General Advice

Meeting Date and Time: November 24, 2015, 3:00 PM
Meeting Location: White Oak 22, Room 1309

Application Number: 77219
Product Name: ^{177}Lu -DOTA⁰-Tyr³-Octreotate
Indication: Treatment of [REDACTED] (b) (4)
[REDACTED] somatostatin receptor positive
gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in
adults

Sponsor/Applicant Name: Advanced Accelerator Applications USA, Inc. (AAA USA, Inc.)

Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Ruth Maduro

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director
Suzanne Demko, Clinical Team Leader
Denise Casey, M.D., Clinical Reviewer
Ruth Maduro, Regulatory Project Manager

Division of Biostatistics (DB-V)

Kun He, Ph.D., Statistical Team Leader
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer

Division of Hematology Oncology Toxicology (DHOT)

Whitney Helms, Ph.D., Supervisor
Anwar Goheer, Ph.D., Nonclinical Reviewer

Office of New Drug Products (ONDP)

Danae Christodoulou, Ph.D., Drug Quality Team Lead
Eldon Leutzinger, Ph.D., Drug Quality Reviewer

Office of Clinical Pharmacology (OCP)

Hong Zhao, Ph.D., Clinical Pharmacology Team Lead

Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Stefano Buono, CEO

Jack Erion, Ph.D., Deputy CEO and Vice President

Claude Hariton, Ph.D., DSc, Head, Clinical Development

Maurizio Mariani, M.D., Ph.D., DAPT, Head, Non-Clinical R&D

Victor Paulus, Ph.D., Head, Regulatory Affairs

Paola Santoro, Ph.D., Senior Clinical Project Manager

Maribel Lopera Sierra, M.D., Chief Medical Officer

1.0 BACKGROUND

On June 14, 2007, BioSynthema Inc. met with FDA via teleconference for a pre-IND meeting to discuss the development program for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ investigating its use for treatment of somatostatin receptor positive neuroendocrine tumors.

In January 2009, $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was designated as an orphan drug for the treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

In December 2010, BioSynthema requested parallel scientific advice from FDA and the European Medicines Agency (EMA) to discuss the design of a proposed clinical trial (NETTER-1) to provide the primary safety and efficacy data intended to support for marketing approval of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the treatment of patients with $^{(b)(4)}$ somatostatin receptor positive GEP-NETs. On March 8, 2011, the pre-IND/parallel scientific advice meeting was held to discuss the acceptability of the proposed randomized, active- controlled trial comparing the overall response rate observed in patients with inoperable midgut carcinoid tumors who experienced progressive disease while being treated with octreotide LAR randomized to $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with those randomized to Sandostatin LAR Depot. FDA stated that while the subpopulation of midgut carcinoid tumors was an acceptable population for study, given the biological and clinical heterogeneity of GEPNETs, it would be unlikely that an indication for the treatment of $^{(b)(4)}$ somatostatin receptor positive, GEPNETs would be granted based upon data derived from the proposed trial.

On April 23, 2012, the IND-enabling study (NETTER-1) was submitted to IND 77219. The IND was allowed to proceed on September 6, 2012.

On September 3, 2014, FDA acknowledged change in the sponsorship of IND 77219 from Biosynthema to Advanced Accelerator Applications (AAA).

In April 2015, AAA was granted Fast Track Designation for the investigation of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the treatment of patients with inoperable, progressive, well-differentiated, octreoscan-positive, carcinoid tumors of the mid-gut.

On August 27, 2015, AAA met with FDA to provide background information to the Agency on the development program for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the proposed indication of the treatment of adult patients with (b)(4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and to obtain general advice on the content of an NDA seeking accelerated approval based on the results of the NETTER-1 study, supported by safety data from the Erasmus trial. The following key issues were discussed at this meeting:

- Integrity testing (b)(4) would not be required.
- AAA needs to fully support their proposal (b)(4) at the receiving clinical site is needed to ensure patient safety. FDA stated that the adequacy of the data provided in the NDA to support this approach will be determined during the review. AAA will provide shipping validation studies and stability studies in the NDA.
- FDA agreed with the definitions of drug substance and drug product provided by AAA.
- AAA's proposal to perform sterility testing (b)(4) was acceptable.
- FDA stated that although its general policy is to require 12 months of real-time stability data for a new molecular entity, it would be acceptable to file the planned NDA with 6 months real-time stability data, which is consistent with the stability dating for the product administered to patients in clinical trials. Expiry dating at approval could be limited to (b)(4) months. Therefore, FDA encouraged AAA to include supportive data for establishing the expiry dating period of octreotate.
- AAA's proposal to submit separate, study-specific, efficacy and safety datasets and to include separate analyses in the CSE, ISE, CSS, and ISS for the Erasmus and the NETTER-1 studies were acceptable. In addition, in the Integrated Summary of Efficacy, it would be acceptable to submit the results of an exploratory, pooled analysis which includes all patients enrolled in the NETTER-1 study and the subgroup of all patients with inoperable, locally advanced or metastatic, octreoscan positive, midgut carcinoid tumors that progressed during prior treatment a somatostatin analog (SSA) in the Erasmus study. The data for patients with pancreatic neuroendocrine tumors (NETs) and bronchial NET should be analyzed separately. Additionally, subgroup analyses should be performed based on the stratification factors employed in the NETTER-1 study and the functional status of the tumor, as well as by age, gender, and race. In the NDA submission, please place appropriate flags in the datasets to identify tumors as functional or nonfunctional.
- For the Integrated Summary of Safety, it would be acceptable to perform a pooled analysis of all patients in both studies who received at least one dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study.
- A potential indication for patients with GEP-NET would require demonstration of a clinically meaningful antitumor effect in an adequate number of patients with progressive and inoperable GEP-NET treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study in one or more adequate and well-controlled trials. FDA cannot determine the adequacy of the data from the Erasmus MC study to support the broader indication until the data is reviewed at the time of the NDA submission. All concerns raised by FDA in prior meetings regarding these data should be addressed in a

justification for seeking claims based on data from retrospectively identified subgroups of Erasmus.

- Summary data for at least ten patients enrolled in the substudy along with the supportive data from the Erasmus MC study and justification and supporting data for measurement of PK by radioactivity rather than HPLC would be provided in the pre-NDA meeting package.
- The non-clinical pharmacology/toxicology program appeared sufficient to support filing of the planned NDA.
- The content of the clinical pharmacology program required to support filing of the NDA were summarized, including the need for adequate dosimetry data.
- Possible approaches to developing an expanded access program

During the August 2015 meeting, AAA provided the top-line results of the analysis of PFS from NETTER-1, which demonstrated a significant improvement in PFS [HR 0.21 (95% CI 0.13, 0.34); $p < 0.001$]; at the time of this final analysis, the median PFS was 8.4 months in the control (Sandostatin LAR Depot 60 mg) arm and had not been reached in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm.

On September 30, 2015, AAA submitted a request for a pre-NDA, which was granted and scheduled for November 24, 2015. Based on the premeeting package, which states that the analysis of safety from the NETTER-1 study has not been completed, there is insufficient information to reach agreement on the content of an NDA under the PDUFA V program.

Clinical

Disease:

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare, clinically diverse group of malignancies that originate from the gastrointestinal tract and pancreas (GEP-NETs). GEPNETs are classified by site of origin, stage and tumor differentiation, and are characterized as functional or non-functional depending on whether or not they secrete peptide hormones that result in clinical symptoms. The clinical symptoms associated with functional tumors frequently lead to their diagnosis at an earlier stage compared with nonfunctional tumors that often present with symptoms related to mass effect or metastatic disease. Initial treatment of GEP-NET consists of surgical resection if feasible and treatment of hormone-related symptoms. For asymptomatic patients with more indolent disease, observation with routine surveillance imaging is an option, while somatostatin analogs are used for patients with hormone-related symptoms. For patients with inoperable GEP-NETs, lanreotide is available for the treatment of patients with unresectable, locally advanced or metastatic GEP-NETs, and targeted therapies (i.e., everolimus, sunitinib) are available for the subset of patients with GEP-NETs who have inoperable pancreatic neuroendocrine tumors. There are currently no peptide receptor radionuclide therapy (PRRT) products approved for the treatment of neuroendocrine tumors including GEP-NET; however, according to AAA, a compassionate use program has been initiated in nine countries in the European Union, and $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ has been administered in 47 clinical centers participating in the program.

Erasmus Medical Center (MC) Clinical Study (MEC 127.545/1993/84-01)

An investigator sponsored single arm clinical study $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was conducted at Erasmus MC in Rotterdam, The Netherlands, between January 2000 and March 2007. The study enrolled patients with various inoperable, somatostatin receptor positive GEP-NETs including bronchial carcinoid tumors. The primary objective of the study was to assess the safety and efficacy of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ given as four intravenous (IV) administrations of 7.4 GBq at 6-13 week intervals. AAA performed a retrospective, independent verification of the source data of this trial in 2012 and updated the analysis in 2015. According to the briefing document, the updated clinical study report (CSR) based on the most recent independent assessment is not yet available.

Efficacy in the Erasmus study was assessed by measuring the individual best responses according to the modified SWOG v 1.1 criteria as follows: complete response (CR), partial response (PR), minor response (MR) and also assessed the “best overall response rate”, defined as the a complete, partial or minor response. Efficacy endpoints were assessed in the full analysis set (FAS) population consisting of 404 of the 615 patients exposed to $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the time of the analysis. Patients who did not have GEP-NET (84 patients had other somatostatin receptor positive tumors such as melanoma, thyroid tumors and non-small cell lung carcinomas) or who did not have a post baseline tumor assessment (n=184) were excluded from the FAS. According to AAA’s independent analysis of the data, the best overall response observed in 404 patients with GEP-NET with any post-baseline tumor assessment was 59% [95% confidence interval (CI): 54, 64]. The estimated median PFS was 30 months (95% CI: 27, 33) in the FAS.

Analyses of response rates, duration of response, and PFS according to RECIST v1.1, based on the intent-to-treat (ITT) GEP-NET population were not performed.

A series of retrospective response analyses in a convenience sample [75% (38/51)] of the subgroup of 51 patients enrolled in the Erasmus study with midgut carcinoid tumors who had progressive disease within 12 months of study entry, which is the target population of the NETTER-1 study, are summarized below. These retrospective analyses are summarized in the table below:

Table 5. Individual best responses and objective tumor response as scored by investigator and independent reviewer - Erasmus MC Phase I/II study

		95% CI	
	N (%)	Lower	Upper
Modified SWOG by investigator			
Objective tumor response (CR+PR+MR)	18 (35.3)	22.43	49.93
Modified SWOG by independent reviewer			
Objective tumor response (CR+PR+MR)	15 (29.4)	17.49	43.83
Modified SWOG by computer[±]			
Objective tumor response (CR+PR+MR)	17 (33.3)	20.76	47.92
RECIST by independent reviewer			
Objective tumor response (CR+PR)	5 (9.8)	3.26	21.41
RECIST by computer[±]			
Objective tumor response (CR+PR)	7 (13.7)	5.70	26.26

According to the Clinical Overview document, adverse drug reactions were evaluated in 504 patients with GEP-NET enrolled in the Erasmus trial. Adverse events (AE) occurring within 24 hours of the administration of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate were nausea (25%), vomiting (10%), and abdominal discomfort or pain (10%). Grade 3 or 4 hematological toxicity detected 4–8 weeks after administration of study drug occurred in 4% of patients, Grade 3 or 4 renal toxicity was reported in two patients, and Grade 3-4 liver toxicity in three patients (0.6%), two of whom died from hepatic failure two to three months after starting the drug. Five patients (1%) developed myelodysplastic syndrome. Detailed narratives of these patients were not included in the meeting materials.

Based on a retrospective chart review, data on serious adverse events (SAE) were identified in all 615 patients exposed to at least one dose of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate. Among the 615 patients, 11% of patients experienced one or more SAEs considered by investigators as possibly or probably study-drug related. The most common SAEs that were considered possibly or probably related to study drug were pancytopenia (6%), anemia (2%) and thrombocytopenia (2%). Myelodysplastic syndrome (MDS) was reported in five patients and acute leukemia occurred in 3 patients. Four of the five patients who developed MDS had no prior chemotherapy or radiation before treatment with ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate. According to AAA, the incidence of MDS and leukemia in patients treated in the Erasmus study are within the reported ranges of current chemotherapy practice in oncology and hematology and use of radioiodine for treatment of thyroid cancer.

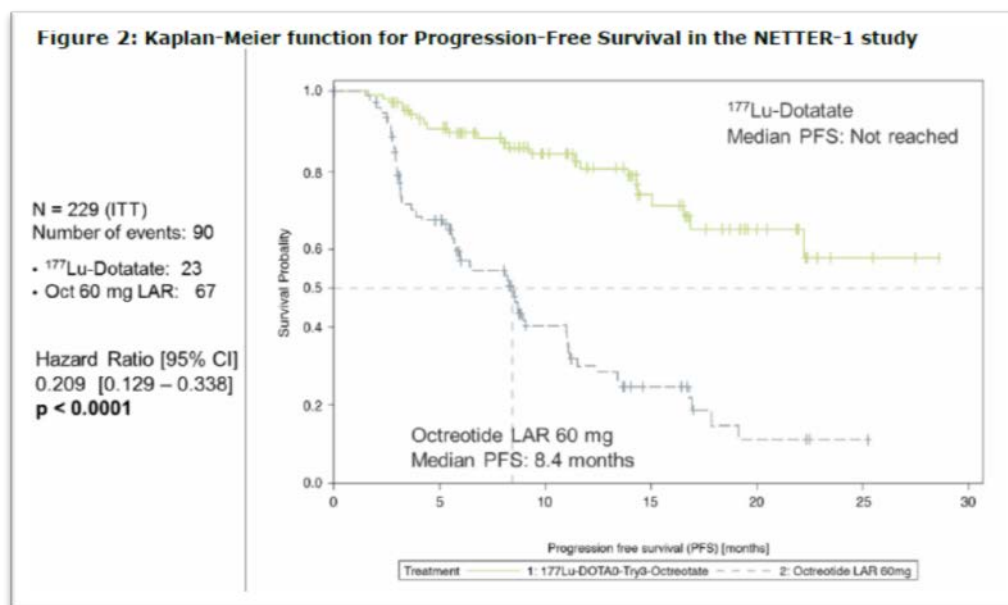
NETTER-1 Study

The NETTER-I study is a multicenter, stratified, open label, randomized, active controlled study comparing progression-free survival in 230 patients randomized 1:1 to treatment with ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate to patients randomized to octreotide LAR. The NETTER-1 study completed enrollment in February 2015. Study eligibility was limited to patients with

inoperable, somatostatin receptor positive midgut carcinoid tumors that have documented disease progression after treatment with fixed doses of octreotide LAR. Patients with functional or nonfunctional tumors were eligible. Patients were stratified by OctreoScan® tumor uptake score (Grade 2, 3 and 4) and the length of time that patients have been on the most recent constant dose of octreotide prior to randomization (less than or equal to 6 months and greater than 6 months).

Patients in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm receive a total cumulative administered radioactivity of 29.6 GBq with the dosing equally divided among 4 administrations of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (7.4 GBq) at eight week intervals, extendible up to 16 weeks to accommodate resolving acute toxicity. Concomitant amino acids are given with each administration for kidney protection. These patients continue to receive supportive care with cold octreotide, 30 mg (Sandostatin® LAR Depot), preferably administered the day after each administration of the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, and no earlier than four hours after completion of the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ infusion. Patients in the comparator arm receive 60 mg Sandostatin® LAR Depot (Octreotide Acetate) intramuscular injections every four weeks. Octreotide rescue injections are allowed in both arms for the treatment of clinical symptoms (e.g., diarrhea and flushing) associated with carcinoid tumors.

The primary endpoint PFS analysis for NETTER-1 was performed when the number of events had reached the pre-specified threshold of 74 evaluable events. The median PFS for the control arm was 8.4 months while the median PFS for the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm had not been reached [Hazard ratio: 0.21 (95% CI: 0.13-0.34)]. Figure 2 from the briefing document copied below shows the Kaplan-Meier analysis for PFS in the NETTER-1 study.



The briefing document included a general overview of the incidence of AEs and the severity of the AEs per event by treatment arm in Tables 7 and 8 copied below.

Table 7: Number of patients experiencing adverse events (safety dataset includes patients who received at least one administration of studied products)

	¹⁷⁷ Lu-DOTA ⁰ -Tyr ³ - Octreotate (n=111)	Octreotide LAR 60mg (n=110)
Any adverse event	106 (96%)	95 (86%)
Related to treatment	95 (86%)	34 (31%)
Serious adverse events	29 (26%)	26 (24%)
Related to treatment	10 (9%)	1 (1%)
Withdrawals due to adverse events	7 (6%)	10 (9%)
Related to treatment	5 (5%)	0 (0%)

Table 8: Number and grading of adverse event episodes in patients experiencing adverse events and who received at least one administration of the product

Maximal severity (number of episodes)	¹⁷⁷ Lu-DOTA ⁰ -Tyr ³ - Octreotate (n = 1435 episodes)	Octreotide LAR 60mg (n = 744 episodes)
Grade 1 (mild)	938 (65.4%)	494 (66.4%)
Grade 2 (moderate)	370 (25.8%)	178 (23.9%)
Grade 3 (severe)	98 (6.8%)	56 (7.5%)
Grade 4 (threatening / disabling)	5 (0.3%)	6 (0.8%)
Grade 5 (fatal)	5 (0.3%)	8 (1.1%)
Missing	19 (1.3%)	2 (0.3%)

AAA expects to complete a full analysis of the safety profile based on the NETTER-1 study at or within a few weeks of the November 24, 2015 meeting scheduled with FDA.

Clinical Pharmacology

A dosimetry, pharmacokinetics and ECG sub-study is being conducted in a subset of 20 patients enrolled in the NETTER-1 study at selected sites to provide a more complete assessment of the safety aspects of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate. The Preliminary Dosimetry Study Report providing data on 12 patients is found in Annex 10 with HPLC analysis of urine samples presented in Annex 11, the Clinical Background Information, and the Summary of ¹⁷⁷Lu-DOTATATE Urine Metabolites HPLC Study.

2.0 DISCUSSION

FDA GENERAL COMMENTS

Although this meeting request was granted as a pre-BLA meeting, based upon review of the information submitted in the meeting package, it will be held as a Type C/Guidance meeting as the data summary provided is insufficient to reach agreement on the content of a planned NDA under the PDUFA V program. FDA requires specific clarifications regarding the data collection methods for safety the Erasmus study and efficacy and safety analyses from both the Erasmus and NETTER-1 studies performed in accordance with standard oncology practice in the US.

Provide the following information in a future pre-NDA meeting package:

- The results for objective response rate (ORR) based on RECIST v1.1, limited to complete and partial responses, the median duration of response (DOR) per RECIST v.1.1 observed in all patients who received any part of dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with GEP-NET enrolled in the Erasmus study, i.e., the intent to treat GEP-NET population consisting of FAS and patients with GEP-NET who received treatment with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and did not have a post baseline tumor assessment). Patients without a post-baseline tumor assessment should be identified as non-responders.
- The ORR and the median DOR per RECIST v.1.1 observed in the retrospectively identified subgroup of patients with midgut carcinoid tumors enrolled and who received any part of any dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ who would otherwise have met the NETTER-1 criteria. Those patients with midgut carcinoid tumors who were treated but did not have a post baseline tumor assessment should be considered non-responders.
- The ORR and the median DOR per RECIST v.1.1 observed in the pooled population of patients with midgut carcinoid tumors treated in the Erasmus and NETTER-1 studies (i.e., the planned efficacy population for the ISE).
- Additional efficacy analyses identified in section III. B. 2 of the background document in the pre-NDA meeting package should be conducted in all patients who received any part of any dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.
- A tabular listing of adverse events occurring in $\geq 10\%$ of patients (per-patient incidence, rather than per-dose incidence) in each treatment arm in the NETTER-1 study, organized by system organ class (SOC), preferred terms (PTs), and by severity grade, with separate columns for the incidence of all AE (NCS CTCAE Grades 1-5) and grade 3-5 AEs, regardless of physician attribution of relationship to study drug. See the following table copied from the SutentTM label for an example of an acceptable presentation of the AE data.

Table 5. Adverse Reactions Reported in the Phase 3 pNET Study in at Least 10% of Patients who Received SUTENT and More Commonly Than in Patients Given Placebo*

Adverse Reaction, n (%)	pNET			
	SUTENT (n=83)		Placebo (n=82)	
	All Grades	Grade 3/4 ^a	All Grades	Grade 3/4
Any	82 (99)	45 (54)	78 (95)	41 (50)
Constitutional				
Asthenia	28 (34)	4 (5)	22 (27)	3 (4)
Fatigue	27 (33)	4 (5)	22 (27)	7 (9)
Weight decreased	13 (16)	1(1)	9 (11)	0 (0)
Gastrointestinal				
Diarrhea	49 (59)	4 (5)	32 (39)	2 (2)
Stomatitis/oral syndromes ^b	40 (48)	5 (6)	15 (18)	0 (0)
Nausea	37 (45)	1 (1)	24 (29)	1 (1)
Abdominal pain ^c	32 (39)	4 (5)	28 (34)	8 (10)
Vomiting	28 (34)	0 (0)	25 (31)	2 (2)
Dyspepsia	12 (15)	0 (0)	5 (6)	0 (0)
Cardiac				
Hypertension	22 (27)	8 (10)	4 (5)	1 (1)
Dermatology				
Hair color changes	24 (29)	1 (1)	1 (1)	0 (0)
Hand-foot syndrome	19 (23)	5 (6)	2 (2)	0 (0)
Rash	15 (18)	0 (0)	4 (5)	0 (0)
Dry skin	12 (15)	0 (0)	9 (11)	0 (0)
Neurology				
Dysgeusia	17 (21)	0 (0)	4 (5)	0 (0)
Headache	15 (18)	0 (0)	11 (13)	1 (1)
Musculoskeletal				
Arthralgia	12 (15)	0 (0)	5 (6)	0 (0)
Psychiatric				
Insomnia	15 (18)	0 (0)	10 (12)	0 (0)
Hemorrhage/Bleeding				
Bleeding events ^d	18 (22)	0 (0)	8 (10)	3 (4)
Epistaxis	17 (21)	1 (1)	4 (5)	0 (0)

* Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0

^a Grade 4 ARs in patients on SUTENT included fatigue (1%).

^b Includes aphthous stomatitis, gingival pain, gingivitis, glossitis, glossodynia, mouth ulceration, oral discomfort, oral pain, tongue ulceration, mucosal dryness, mucosal inflammation, and dry mouth.

^c Includes abdominal discomfort, abdominal pain, and abdominal pain upper.

^d Includes hematemesis, hematochezia, hematoma, hemoptysis, hemorrhage, melena, and metrorrhagia.

- A tabular listing of the per-patient incidence of laboratory abnormalities in each treatment arm for NETTER-1 study, which include columns for all grades and grade 3-4 toxicities. Provide a similar table displaying the per-patient incidence of laboratory abnormalities that occurred in the Erasmus study.
- A tabular listing of safety information collected in the Erasmus study. If this level of detail is not available for the Erasmus study, provide justification for the adequacy of the safety database from the Erasmus study to provide supportive information.
- A table that summarizes the per-patient incidence rates of AEs of special interest based on the mechanism of action of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate in the Erasmus and NETTER-1 studies.

Please also include a complete table of contents (TOC) for the planned NDA submission based on the eCTD modular format.

FDA strongly encourages AAA to submit the requested information and analyses and to refer to the guidances and websites referenced in this document in order to ensure that the future pre-NDA meeting can be productive and informative regarding the planned NDA submission.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency consider that information provided in section 3.2.S [REDACTED] (b) (4) [REDACTED] sufficient to assess the quality of the precursor and the manufacturing process?

FDA Response: The information to be provided as described in section 1.1, pages 1-25, of the meeting briefing package appears sufficient to initiate the assessment of the precursor quality when the application is submitted; nonetheless other issues may arise during the review process. In that case, information requests would be communicated to the applicant. Confirm that the following information will be included in the NDA to ensure that the CMC information is complete

- a. Level [REDACTED] (b) (4) in the production of Lu-177.
- b. Metal impurity profile [REDACTED] (b) (4)
- c. Identification test by HPLC, comparing the retention time [REDACTED] (b) (4) [REDACTED] with the retention time of the standard. Include a quantitative acceptance criterion, such as a relative retention time (RRT).

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

2. The Applicant intends to request the following indication: treatment of [REDACTED] (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults.

Does the Agency find the more complete data package more supportive of the planned indication than when a similar question was presented in August 2015?

FDA Response: AAA has not provided information on the ORR and duration of responses per RECIST v 1.1 in the intent-to-treat population for patients in the Erasmus Study with midgut carcinoid or in the broader GEP-NET subgroup, therefore, FDA cannot make any determination as to the adequacy of the Erasmus MC study data to support the broader GEP-NET indication.

FDA reiterates that a potential indication for patients with GEP-NET will require demonstration of a clinically meaningful ORR by RECIST as determined by independent review that is of sufficient magnitude and duration to be likely to predict clinical benefit

and demonstrate an advance over available therapy in an adequate number of patients with progressive and inoperable bronchial NET or pancreatic NET treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study. As stated in the minutes from the August 27, 2015 Type C meeting, a robust justification for seeking claims based on data from retrospectively identified subgroups should be submitted with the NDA.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA confirmed that tumor-based efficacy analyses, per RECIST v 1.1, for the intent-to-treat patient population in the Erasmus study will be provided in the pre-NDA meeting package. AAA agreed to provide a side-by-side comparison of the Erasmus and NETTER-1 studies to allow FDA to identify where differences exist in the data, their collection and analyses and how these differences might impact pooling, how data were verified in each study (e.g., IRC, chart reviews), and the planned analyses for safety and efficacy and the planned populations for evaluation in each study.

3. Would the Agency suggest additional analyses of the Phase I/II study based on the draft SAP provided?

FDA Response: The analyses of ORR, using descriptive statistics, as outlined in the updated draft Statistical Analysis Plan (SAP) provided in Annex 7.4 of the briefing materials appear acceptable provided that the efficacy analyses based on the intent to treat (ITT) population (i.e., all patients with a diagnosis of GEP-NET who received at least one dose of study drug) as well as the FAS population and that duration of response is also characterized. The proposed analyses of time to progression, progression-free survival and overall survival are uninterpretable in a single arm trial (b) (4)

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA proposed that the time-to-event results could be used to demonstrate $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ performance in different subgroups of neuroendocrine tumors. AAA believes these analyses could demonstrate that there are no significant differences in efficacy across different patient subsets in the Erasmus and NETTER-1 study populations. FDA agreed that the time to event results can be provided as descriptive statistics, but stated that comparative analyses could not be performed using the data from the single-arm trial because the results are not interpretable.

FDA additionally noted that there are concerns with regard to the completeness of the Erasmus datasets (e.g., missing data) that could introduce bias into the study results and have a significant impact on the reliability of the results. AAA explained that the Erasmus study was initially designed as an access protocol and there is not extended follow-up on patients who came to the Netherlands center for treatment and left after completion of treatment. AAA stated that of the 1268 enrolled patients, there are 567 patients who are Dutch nationals with more comprehensive assessments and follow-up. FDA agreed that AAA could propose subset analyses of the populations (e.g., Dutch nationals and non-Dutch patients) provided that there are prospective, clear-cut criteria set out for the analyses and adequate detail and justification regarding selection of the subsets. In addition, AA should include a robust explanation of how the selection criteria eliminate bias from the analyses in the proposal.

4. Does the Agency agree with the proposed location of the ISE and ISS in the NDA?

FDA Response: Yes, FDA agrees with AAA's proposal to split the ISE and ISS such that the narrative discussions of the integrated analyses be included in the *Summary of Clinical Efficacy* (Module 2.7.3) and *Summary of Clinical Safety* (Module 2.7.4) and the integrated datasets, tables, appendices and figures be submitted as part of *Reports of Analyses of Data from More than One Study* (Module 5.3.5.3).

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

5. On the basis of discussion during the Type C Meeting conducted on August 27, 2015, the Company is providing the statistical analysis plan for the ISE and ISS (Annex 8). Does the Agency concur with this plan?

FDA Response: No. The exploratory efficacy analyses performed in the pooled dataset (NETTER-1 and Erasmus) should be limited to ORR and response duration. Please note that integrated analyses of the pooled dataset cannot be interpreted for the endpoints of PFS, TTP, and OS. Subgroup analyses for PFS, TTP, and OS must be limited to the NETTER-1 Study.

Section 3.1 of Annex 8 states: "The integrated efficacy analysis population will be the pooled full analysis set, which will include all patients enrolled in the NETTER-1 study and the subgroup of all patients with inoperable, progressive, locally advanced or metastatic, somatostatin receptor positive, midgut carcinoid tumors in the Erasmus MC Phase I/II (Erasmus) study." Patients from the Erasmus study who are included in the integrated efficacy population for analyses of ORR and response duration should meet all of the criterion for enrollment in NETTER-1, including documentation of disease progression per RECIST v1.1 during prior treatment with a somatostatin analog as outlined in the briefing document.

With regard to the planned analyses for the ISS, in addition to the proposed analyses of SAE data, please perform an analysis of adverse events of special interest in the pooled safety population. See General Comments.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: Please refer to the discussion under question 2 for additional information on the appropriate analysis plan.

6. The recent analysis of the Phase III study data has presented dramatic results and an ethical dilemma (also submitted separately to the IND). Given the statistically significantly prolonged progression-free survival, the impact on overall survival and the previous recommendation of the DSMB, the Applicant believes that it will be impossible to maintain patients in the Octreotide LAR arm after progression. Support and guidance from the Agency is sought on a one-way crossover of all patients to Lutathera after progression on Sandostatin LAR 60 mg. Does the Agency support crossing over the patients to Lutathera arm after progression? Because of the urgency of this question it was also presented in Serial 0027 submitted October 22, 2015.

The Applicant will propose an Expanded Access Program (treatment protocol). A draft protocol is included as Annex 9.

FDA Response: FDA does not object to AAA's proposal to allow patients in the NETTER-1 study who progress during treatment with Sandostatin LAR 60 mg to crossover to receive $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. Submit a protocol amendment and a revised informed consent document to IND 077219 detailing the modified study design and rationale for the protocol changes.

With regard to the "Request for Advice" submission received on October 23, 2015, and the draft expanded access protocol provided in Annex 9 of the briefing materials, please clarify AAA's proposal for expanded access by addressing the following:

- a. Does AAA plan to open an expanded access protocol at NETTER-1 study sites only or additional centers with adequate resources to enroll patients and administer $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA clarified that an expanded access protocol will be opened only at NETTER-1 study sites because these are centers with expertise in administration of peptide receptor radionuclide therapy (PRRT). Rather than submitting a protocol amendment to allow for patients randomized to

the control arm to receive the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the time of disease progression in NETTER-1, AAA plans to enroll these patients into the expanded access trial. AAA states that this would be more efficient and would still allow for follow-up of these patients for safety and survival.

With regard to the impact on overall survival of post-progression $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ administration to patients in the control arm of NETTER-1 study, FDA stated that assessment of the impact could be evaluated by performing various sensitivity analyses.

FDA discouraged AAA from submitting the interim analysis of OS as the final analysis in the NDA and encouraged AAA to conduct additional analyses at later time points when a greater number of events have occurred. FDA emphasized that in order for the OS results to be included in the label, an effect on OS must meet the criteria for substantial evidence of efficacy.

- b. Provide rationale for the proposal to have each clinical site submit a separate IND rather than have one expanded access protocol submitted to IND 077219.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA stated that the intent is to provide both the drug and a protocol template for investigators to use at their respective institutions for the purpose of opening an IND. AAA noted that such an approach is more efficient from an administrative perspective. FDA had no objections to this proposal.

- c. Provide an estimate of the number of patients with progressive midgut carcinoid tumors AAA anticipates would likely be treated in the proposed expanded access program. Depending on this estimate, FDA may recommend submitting either an intermediate-size patient population expanded access protocol or a treatment protocol.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA clarified that they will submit an intermediate expanded access protocol.

- d. As discussed at the August 27, 2015 Type C meeting, for patients with GEP-NETs other than midgut carcinoid tumors, does AAA plan to make $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ available to investigators under single patient INDs?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA confirmed that their plan is to make $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ available to investigators under single patient INDs for patients with GEP-NETs other than midgut carcinoid tumors. A letter of cross-reference will be provided and investigators will be given a copy of the expanded access protocol as a treatment guide.

7. In accordance with "Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics and light of the Fast-Track designation for Lutathera, would the Agency agree to a plan to submit module 4 (also 2.4 and 2.6) as the first section followed by Module 3, then pieces of Modules 1 and 5? What level of granularity does FDA consider appropriate for clinical sections? Would stand alone reports, for example, be sufficient?

FDA Response: In general, FDA accepts for submission complete sections of a NDA during a rolling review; AAA's proposal to submit sections 2.4 and 2.6 with a complete Module 4 followed by a complete Module 3 is acceptable. There is insufficient information provided in the briefing document regarding the proposal to subsequently submit "pieces" of Modules 1 and 5. Either submit complete sections for Modules 1 and 5 or provide a detailed proposal of the information to be submitted and adequate justification for submission of subsections of these modules.

For Module 5 of the NDA, include a tabular listing of all clinical study reports in Section 5.2 of the NDA submission. FDA expects complete study reports for the Erasmus MC study, the NETTER-1 study, all human pharmacokinetic and pharmacodynamics studies, and the dosimetry study. Reports should be formatted according to eCTD standards with functional hyperlinks in the table of contents and throughout the case report forms (CSRs) to referenced sections of the report, other documents, case report forms, patient narratives and source data. Patient narratives and individual CRFs for all patients enrolled in clinical studies of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ who died, experienced a serious adverse event or an adverse event of special interest due to the nature of the product (e.g., hematologic toxicity, nephrotoxicity, secondary malignancy etc.) or discontinued study drug due to an adverse event should be included in Section 5.3 with the respective CSR.

For the clinical summary sections in Module 2, provide a brief but thorough overview of the efficacy and safety results supporting the proposed indication in sections 2.5.4 and 2.5.5. As discussed in FDA response #4, narrative discussions of the integrated analyses of efficacy and safety may be included in sections 2.7.3 and 2.7.4.

For planning the format of the NDA submission, please also refer to the following website and guidances found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

ICH Harmonized Tripartite Guideline E3: *Structure and Content of Clinical Study Reports*, found at

http://www.ichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guidance.pdf

Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf>

Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document, found at

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm136174.pdf>

Guideline For The Format and Content of The Clinical And Statistical Sections of an Application, found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071665.pdf>

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

8. A risk evaluation and mitigation strategy included in the design of the NETTER-1 study because of the nature of the product, does FDA agree that this is appropriate for a marketed product?

FDA Response: There is insufficient safety data provided in the meeting package to make a determination on whether a risk evaluation and mitigation strategy (REMS) would be required for this product. Given the expectation that this product is likely to be administered by qualified hospital-based staff at centers with experience in handling and administering a radiopharmaceutical product, labelling that adequately addresses potential safety concerns may be enough to ensure safe use and that the product's benefits outweigh its risks. If it is determined that a REMS is not required, a risk evaluation and mitigation plan for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is still expected as part of the NDA.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

9. During the Type C Meeting conducted on August 27, 2015, AAA agreed to provide summary data for at least ten patients enrolled in the dosimetry substudy. The Preliminary Dosimetry Study Report providing data on 12 patients is found in Annex 10 with HPLC analysis of urine samples presented in Annex 11 and below (B. Clinical Background Information, 2. Summary of ^{177}Lu -DOTATATE Urine Metabolites HPLC Study. Does the Agency agree that the commitment made during the Type C Meeting has been fulfilled?

FDA Response: Insufficient information on the validation for the HPLC analysis of ^{177}Lu -DOTA⁰-Tyr³-Octreotate in urine is provided in the Preliminary Dosimetry Study Report to allow FDA to fully address this question. In addition, from the available information, following deficiencies were identified in the report of urine data:

- a. Lack of "cold" standard of Lu-DOTA⁰-Tyr³-Octreotate confirming retention time by UV analysis and overall performance throughout the assay.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

- b. High and unacceptable inter-patient variability in the retention time (range (b) (4) to (b) (4) mins) of ^{177}Lu -DOTA⁰-Tyr³-Octreotate.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

- c. Lack of information on sample collection to analysis times.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting for items 9a-9c: FDA communicated concerns over multiple deficiencies found in the methodology used in the HPLC analysis of urine samples collected from patients treated with ^{177}Lu -DOTA⁰-Tyr³-Octreotate in a dosimetry study. AAA acknowledged FDA's concerns and agreed to improve the HPLC method by including a cold reference standard of Lu-DOTA⁰-Tyr³-Octreotate and minimizing variability in the chromatographic retention of ^{177}Lu -DOTA⁰-Tyr³-Octreotate. AAA stated that they will use the improved assay

method to analyze the urine samples from the 8 remaining patients and asked FDA if this data will be sufficient to fulfill the commitment made during the Type C meeting on August 27, 2015. FDA stated that this determination will be made after review of the submission of available data from all patients and analytical methods used in the dosimetry study.

Clinical

10. Please provide clarification on the following items:

- a. Did the Excel safety database that was used to capture AE and laboratory data during the Erasmus study contain the causality assessment using specific criteria for attribution of toxicity to study drug?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA clarified that the general adverse event (AE) Excel database for Erasmus did not include data on attribution or severity. There were four expected AEs that were captured as present or absent in the Excel database reflecting collection of information on the case report forms (CRFs). The CRFs for Erasmus were less detailed than those for NETTER-1 and may have had different monitoring schedules. AAA stated that the SAE data for Erasmus was independently collected and categorized using the same criteria and analyses as those used for NETTER-1 and that all source data was verified by data managers and statisticians.

- b. Regarding the independent reassessment of imaging from patients in the Erasmus study, the meeting package suggests that only a portion of the patients had their baseline OctreoScan® scintigraphs and their CT scans independently reviewed. Will efficacy data to be included in the planned updated efficacy analysis have central review of their imaging?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and would like to further discuss.

Discussion during the meeting: AAA clarified that the central reassessment of imaging performed for the subset of patients in the Erasmus study was performed with the objective of providing supportive rationale for the population chosen for the NETTER-1 study. Given the high concordance rate for disease assessments between the investigator and the independent reviewer, AAA does not plan to conduct additional central reassessment of imaging in the planned updated efficacy analyses for Erasmus.

POST MEETING FDA COMMENT: Please include in the pre-NDA meeting materials, a description of the process by which investigator-assessed disease status determined by SWOG criteria for the Erasmus trial will be re-assessed using RECIST 1.1

Clinical Pharmacology

11. Conduct a formal organ impairment study to determine alterations in systemic exposures given that the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is predominantly cleared renally. Refer to the FDA draft Guidances for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf>.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

12. Conduct population pharmacokinetic analyses to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and its active metabolites, if any. Refer to the FDA Guidance for Industry entitled “Population Pharmacokinetics” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

13. Explore the exposure-response relationships for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ and its active metabolites, if any, for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled “Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:

Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

14. Validate the analytical methods used to determine the concentrations of ^{177}Lu -DOTA⁰-Tyr³-Octreotate and its active metabolites, if any. Refer to the draft FDA Guidance for Industry entitled “Bioanalytical Method Validation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

15. In the Summary of Clinical Pharmacology of the NDA submission, address the following questions:
- a. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- b. What are the exposure-safety and exposure-efficacy relationships?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- c. How was the potential for ^{177}Lu -DOTA⁰-Tyr³-Octreotate to prolong the QT/QTc interval assessed? What are the conclusion and proposed labeling description?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA’s response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- d. What are the characteristics of distribution, metabolism and elimination of ^{177}Lu -DOTA⁰-Tyr³-Octreotate?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:
Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- e. What influence do intrinsic factors (such as sex, race, weight, disease, organ impairment) have on $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ exposure, efficacy and safety? What dose modifications are recommended?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:
Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- f. What influence do the extrinsic factors (such as drug interactions, diet) have on $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ exposure, efficacy, and safety? What dose modifications are recommended?

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:
Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

16. In addition, apply the following advice in preparing the clinical pharmacology sections of the NDA submission:

- a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics studies.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:
Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- b. Provide complete datasets for all clinical pharmacology and biopharmaceutics studies. The subject's unique ID in the pharmacokinetic datasets should be consistent with those in datasets submitted for clinical review.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response:
Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- c. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- d. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- e. Submit the following information and data to support the population pharmacokinetic analysis.
 - i. SAS transport files (*.xpt) for all datasets used for model development and validation.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- ii. Description of each data item provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- iii. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

- iv. Model development decision tree or table which gives an overview of modeling steps.

Advanced Accelerator Applications USA, Inc. November 24, 2015, response: Advanced Accelerator Applications USA, Inc. acknowledges FDA's response, and no further discussion is needed.

Discussion during the meeting: No discussion occurred during the meeting.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation that was granted on January 12, 2009, this drug is exempt from these requirements for the proposed indication of the treatment of gastro-entero-pancreatic neuroendocrine tumors. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

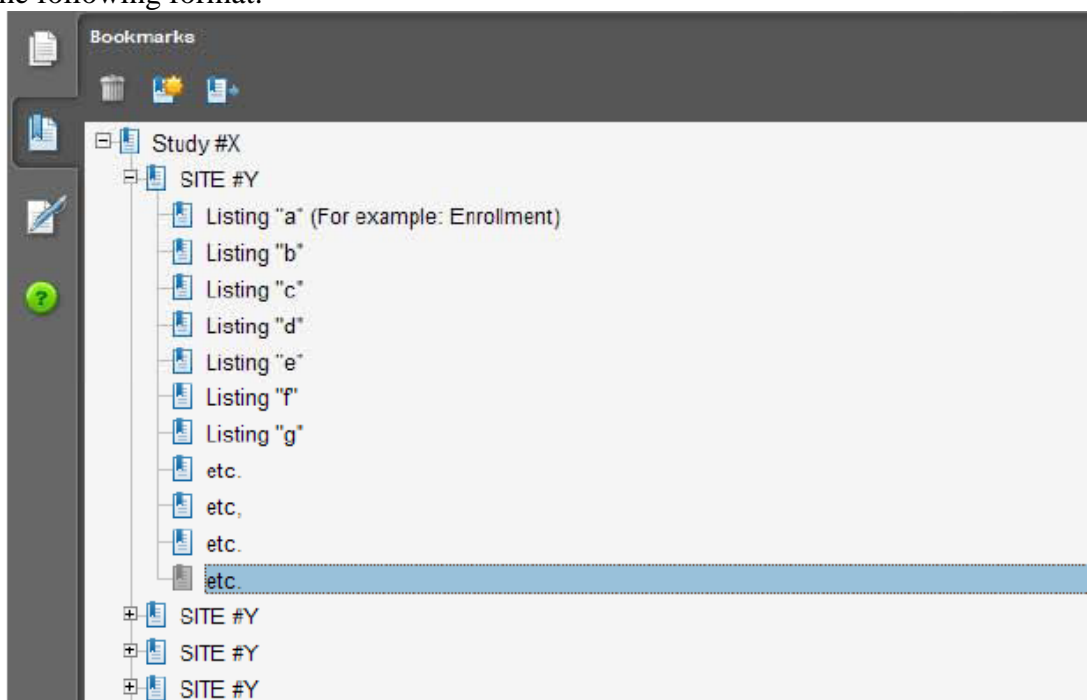
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

- c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
 3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

A. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.gov

APPENDIX I

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--

CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)
CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)

DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601
DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null

RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601
RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601

TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials⁽¹⁾. RECIST (Response Evaluation Criteria in Solid Tumors)⁽²⁾ has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification⁽³⁾ in the assessment lymphomas, or, MacDonald Response⁽⁴⁾ in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:

--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAl to provide an additional level of detail. When multiple assessors play the role identified in TREVAl, values of TREVAlID will attribute a row of data to a particular assessor. For example TREVAl="INDEPENDENT ASSESSOR" and TREVAlID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

- (1) E.A. Eisenhauer,*, P. Therasse, et al. [New response evaluation criteria in solid tumours: Revised RECIST guideline \(version 1.1\)](#) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228–247
- (2) RECIST Criteria - <http://www.eortc.be/recist/>
- (3) Bruce D. Cheson, Beate Pfistner, et al. [Revised Response Criteria for Malignant Lymphoma](#) *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007
- (4) DR Macdonald, TL Cascino, et al. [Response criteria for phase II studies of supratentorial malignant glioma](#) *Journal of Clinical Oncology*, Vol 8, 1277-1280

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. x.x One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<ol style="list-style-type: none"> 1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting. 	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<ol style="list-style-type: none"> 1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY. 	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x x One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.</p>	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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/s/

RUTH L MADURO
12/03/2015



IND 77219

MEETING MINUTES

Advanced Accelerator Applications USA, Inc. (AAA USA, Inc.)
Attention: Dr. Victor Paulus
Head of Regulatory Affairs
350 Fifth Avenue, Suite 6902
New York, NY 10118

Dear Dr. Paulus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.”

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2015. The purpose of the meeting was to seek FDA’s guidance on outstanding regulatory and scientific development issues for ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4232.

Sincerely,

{See appended electronic signature page}

Ruth L. Maduro
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
NETTER-1 Primary Endpoint Outcome presentation from Advanced Accelerator Applications
USA, Inc. (8-27-2015)



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: General Advice

Meeting Date and Time: August 27, 2015 at 3:00pm EST
Meeting Location: WO22, Room 1415

Application Number: 77219
Product Name: ^{177}Lu -DOTA⁰-Tyr³-Octreotate
Proposed Indication: Treatment of [REDACTED] (b) (4)
somatostatin receptor positive gastroenteropancreatic
neuroendocrine tumors (GEP-NRTs) in adults

Sponsor Name: Advanced Accelerator Applications, USA, Inc. (AAA)

Meeting Chair: Patricia Keegan, M.D.
Meeting Recorder: Ruth Maduro

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2)

Patricia Keegan, M.D., Director
Suzanne Demko, P.A.C., Clinical Team Lead
Denise Casey, M.D., Clinical Reviewer
Damiette Smit, M.D., Clinical Reviewer
Ruth Maduro, Regulatory Project Manager

Division of Biostatistics (DB-V)

Kun He, Ph.D., Statistical Team Leader
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer

Division of Hematology Oncology Toxicology (DHOT)

John Leighton, Ph.D., Supervisory Pharmacologist
Anwar Goheer, Ph.D., Nonclinical Reviewer

Office of New Drug Products (ONDP)

Danae Christodoulou, Ph.D., Drug Quality Team Lead
Eldon Leutzinger, Ph.D., Drug Quality Assessment Reviewer

Office of Clinical Pharmacology (OCP)

Hong Zhao, Ph.D., Clinical Pharmacology Team Lead
Lillian Zhang, Ph.D., Clinical Pharmacology Reviewer
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer

Division of Microbiology Assessment (DMA)

Erika Pfeiler, Ph.D., Quality Assessment Lead (Acting)
Peggy Kriger, Ph.D., Review Microbiologist

SPONSOR ATTENDEES

Stefano Buono, Ph.D., CEO
Jack Erion, Ph.D., Vice President and Deputy CEO
Claude Hariton, Ph.D., DSc, Head, Clinical Development
Maurizio Mariani, MD., Ph.D., DABT, Head, Non-Clinical R&D and Business Development
Victor Paulus, MS, Ph.D., Head, Regulatory Affairs

Objective:

Advanced Accelerator Applications USA, Inc. (AAA) seeks to provide background information to the Agency regarding the development program for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for use in their proposed study that would support accelerated approval for the treatment of adult patients with (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

1.0 BACKGROUND

Advanced Accelerator Applications, USA, Inc. (AAA) states their intent to submit a New Drug Application to FDA for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (lutathera) for proposed indication of the treatment of patients with (b) (4) somatostatin receptor-positive, gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

On June 14, 2007, Biosynthema (the IND sponsor at that time) met with FDA in a pre-IND meeting to discuss the adequacy of data from a single arm trial, with emphasis on a subgroup who had progressed following standard treatment, to support a request for accelerated approval. At that time, the development program consisted of a Phase 1 study conducted in six patients with somatostatin receptor-positive tumors and an ongoing single-arm, sequential escalating cohort trial with the objective of defining the maximum tolerated single- and repeat doses and to determine the objective tumor response. At the time of the meeting, Biosynthema indicated that efficacy and safety data were available for 504 patients enrolled in the Erasmus trial from January 2000 to July 2006. Biosynthema stated that the radiographs would be evaluated centrally for determination of overall response rate. FDA noted that study population was heterogeneous, that not all patients treated in the study were OctreoScan positive, that the proposed approach was to conduct retrospective analyses in post-hoc defined subgroups; based on these concerns, FDA advised that additional trials be conducted. As reported by Biosynthema, in a Scientific Advice meeting on January 30, 2009, EMA advised BioSynthema

that a prospective randomized phase 3 study would be required to support an application in Europe.

In January 2009, $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was designated as an orphan drug for the treatment of GEP-NETs.

In December 2010, BioSynthema requested parallel scientific advice from FDA and the European Medicines Agency (EMA) to discuss the design of a proposed clinical trial (NETTER-1) to provide the primary support for marketing approval of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the treatment of patients with (b) (4) somatostatin receptor positive GEP-NETs. On March 8, 2011, this pre-IND/parallel scientific advice meeting was held to discuss the acceptability of the proposed, randomized, active-controlled trial comparing the overall response rate observed in patients with inoperable midgut carcinoid tumors who experienced progressive disease while being treated with octreotide LAR randomized to $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ with those randomized to Sandostatin LAR Depot. FDA advised that the eligibility criteria for the proposed trial be revised to exclude patients who require more than 30 mg Octreotide LAR daily at the time of enrollment to control symptoms due to carcinoid syndrome. Additionally, the protocol stated that somatostatin analogue treatment-naïve patients would receive a standard 20 or 30 mg dose of Octreotide LAR. FDA recommended that BioSynthema revise the protocol so that all patients who were somatostatin analogue (SSA)-naïve receive 30 mg rather than 20 or 30 mg daily. Additionally, FDA recommended that the protocol include well-defined guidelines for modifying the dose of Octreotide LAR in patients who experience toxicity or alteration in disease-related symptoms during the study. With regard to the definition and analysis of PFS, FDA recommended that BioSynthema follow advice provided in FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007), specifically those trial design elements addressing trials using PFS endpoints, that PFS analysis should be a time-to-event analysis that is event-driven, the PFS endpoint will be based upon assessment in "real-time" by a blinded, independent (i.e., external to BioSynthema) review committee (IRC), the overall survival be included as a key secondary endpoint (or preferably, primary endpoint) and that the protocol not offer cross-over to the experimental arm to patients in the control arm in order to allow a clear assessment of effects on survival, if any. FDA urged BioSynthema to standardize the procedures for renal protection to the extent feasible. BioSynthema stated that they planned to conduct dosimetry studies in a subset of patients enrolled in the proposed study using the specific amino acid solutions identified in the protocol to confirm that each amino acid solution provides adequate renal protection. Finally, FDA advised that the definition of progression described in the eligibility criteria should be based solely upon radiographic or objective symptomatic criteria (b) (4). FDA stated that, given the biological and clinical heterogeneity of GEPNETs, it is unlikely that an indication for the treatment of (b) (4) somatostatin receptor positive, GEPNETs would be granted based upon the results of the proposed trial.

The IND-enabling study (NETTER-1) was submitted to IND (b) (4) on April 23, 2012; the IND was initially placed on clinical hold for concerns related to risks to patients. The study design specified that a total of 200 patients would be randomized (1:1); randomization would be stratified by center, Octreoscan uptake score (Grade 2, 3 and 4), and length of time that patients have received a stable dose of octreotide prior to enrollment (≤ 6 months and > 6 months). The

primary endpoint for the proposed clinical trial was progression-free survival. According to Biosynthema, this sample size provided 90% power to detect a statistically significant difference in PFS at a 5% two-sided significance level, assuming a median PFS in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm of 30 months, and median PFS in the Sandostatin LAR arm of 14 months (based on the PROMID study).

The IND was subsequently allowed to proceed on September 6, 2012, following revisions to the protocol submitted on August 3, 2012. Although allowed to proceed, FDA issued an Advice/Information Request letter, dated April 5, 2013, conveying the following comments:

- [REDACTED] (b) (4)
[REDACTED] Given the sample size in the proposed trial, we recommend that you only stop for futility or safety.
- We strongly discourage you from using biased coin randomization. If biased coin randomization is used, then the primary analysis should be a re-randomization test. This would involve reproducing the randomization, accounting for subject stratification factors and time of randomization, a large number of times and conducting a permutation test on this basis.
- Because there are approximately 41 centers and 200 patients, you may consider dropping center as a stratification factor.
- You have proposed [REDACTED] (b) (4)
[REDACTED] Include a method to control the family-wise type I error rate for the two other secondary endpoints.
- Even though the analysis for overall survival (OS) may be underpowered, please provide a statistical analysis plan for OS including the difference to be detected, power, the number of deaths for the final OS analysis, and the estimated number of deaths for an interim OS analysis at the final PFS analysis.
- Since the power calculation of a log-rank test is based on the number of events, please perform the final analysis based on the planned number of events. You propose that [REDACTED] (b) (4)
[REDACTED] which is not acceptable.
- All randomized patients should be included in the primary analysis, regardless of whether they received study medication, and no replacement should be done.
- Specify whether the primary log-rank test is a stratified or un-stratified.

- Regarding the November 29, 2012 submission, the subsection of the case report form (CRF) entitled "Study Drug Administration - $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm," FDA recommends that investigators complete this subsection of the CRF for each of the four doses of test product administered.

On September 3, 2014, FDA acknowledged change in sponsorship of IND 77219 from Biosynthema to AAA.

On April 9, 2015, a teleconference was held with AAA to discuss the Fast Track Designation request. FDA noted that the only proposed investigation designed to demonstrate improvement in progression-free survival and overall survival is the NETTER-1 study, being conducted in patients with patients with midgut carcinoid tumors, with disease progression on octreotide, thus the designation would be limited to this population. In response to a query from AAA, FDA stated that the indication for the Fast Track designation does not necessarily have to be identical to that proposed in the New Drug Application (NDA). FDA advised AAA that if a broader indication is proposed, the NDA should contain appropriate justification and data to support this indication.

In April 2015, AAA was granted Fast Track Designation for the investigation of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for the treatment of patients with inoperable, progressive, well-differentiated, octreoscan-positive, carcinoid tumors of the mid-gut.

On June 12, 2015, AAA submitted a Type C meeting request to seek FDA's guidance on the outstanding regulatory and scientific development of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Clinical

Disease:

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a rare, clinically diverse group of malignancies that originate from the gastrointestinal tract and pancreas (GEP-NETs). GEP-NETs are classified by site of origin, stage and tumor differentiation, and are characterized as functional or non-functional depending on whether or not they secrete peptide hormones that result in clinical symptoms. The clinical symptoms associated with functional tumors frequently lead to their diagnosis at an earlier stage compared with nonfunctional tumors that often present with symptoms related to mass effect or metastatic disease. Initial treatment of GEP-NET consists of surgical resection if feasible and treatment of hormone-related symptoms. For asymptomatic patients with more indolent disease, observation with routine surveillance imaging is an option, while somatostatin analogs are used for patients with hormone-related symptoms. For patients with inoperable GEP-NETs, lanreotide is available for the treatment of patients with unresectable, locally advanced or metastatic GEP-NETs, and targeted therapies (i.e., everolimus, sunitinib) are available for the subset of patients with GEP-NETs who have inoperable pancreatic neuroendocrine tumors. There are currently no peptide receptor radionuclide therapy (PRRT) products approved for the treatment of neuroendocrine tumors including GEP-NET; however, according to AAA, a compassionate use program has been initiated in nine countries in the European Union, and $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ has been administered in 47 clinical centers participating in the program.

Erasmus Medical Center (MC) Clinical Study (MEC 127.545/1993/84-01)

An investigator sponsored single arm clinical study of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was conducted at Erasmus MC in Rotterdam, The Netherlands, between January 2000 and March 2007. The study enrolled patients with various inoperable, somatostatin receptor positive GEP-NETs including bronchial carcinoid tumors. The primary objective of the study was to assess safety and efficacy of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ given as four intravenous (IV) administrations of 7.4 GBq at 6-13 week intervals. AAA performed a retrospective, independent verification of the source data of this trial in 2012. Efficacy was assessed by measuring the individual best responses, complete response (CR), partial response (PR), minor response (MR) and the objective tumor response (CR+PR+MR) according to the modified SWOG Version 1.1 criteria. According to AAA's independent analysis of the data, the best overall response observed in 404 patients with GEP-NET was 59% [95% confidence interval (CI): 54, 64]. The median progression-free survival was 30 months (95% CI: 27, 33). An independent safety analysis demonstrated grade 3/4 hematological toxicity in approximately 10% of patients. Renal toxicity occurred in two patients and liver toxicity occurred in three patients, two of whom died from hepatic failure two to three months after starting the drug. Five patients developed myelodysplastic syndrome. Common toxicities included nausea, diarrhea, vomiting and abdominal pain in approximately 25% of patients.

NETTER-1 Study

The ongoing NETTER-I study is a multicenter, stratified, open label, randomized, active-controlled, study comparing progression-free survival in patients randomized to treatment with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ to patients randomized to octreotide LAR. Study eligibility is limited to patients with inoperable, somatostatin receptor positive midgut carcinoid tumors that have documented disease progression after treatment with Octreotide LAR. The first patient was enrolled in October 2012; enrollment is complete however the number of PFS events for the primary analysis has not been reached. AAA anticipates that the final analysis of PFS will be available in 2015.

Non-Clinical

AAA describes as a somatostatin peptide analog conjugated to DOTA chelated to radioactive lutetium. $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (Lutathera) has been shown *in vitro* to bind somatostatin receptors. AAA summarizes published data characterizing the activity of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ as well as its biodistribution and long term toxicity. AAA has conducted the following nonclinical studies using the non-radioactive molecule ($^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$): *in vitro* metabolism studies, *in vitro* hERG assay, standalone cardiovascular, respiratory, and central nervous system safety pharmacology studies, acute toxicity study in the rat, a maximum tolerated dose study in the dog, 43-day-repeat-dose toxicity studies in the rat and the dog, and *in vitro* genotoxicity assays (Ames test and mouse lymphoma assay). AAA has also conducted an *in vitro* study evaluating human plasma protein binding of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Chemistry, Manufacturing, and Controls (CMC)

("20150723 Lutathera FDA Briefing Document.pdf", p. 1-172)

AAA requested a Type C meeting with FDA, which will be held on 27 August, 2015. The drug

product clinical development program has an orphan and an FDA Fast Track designation. The primary purpose of the meeting is to obtain advice and guidance on the outstanding regulatory and scientific issues related to the development of Lutathera 370 MBq/mL solution for infusion.

The subject drug product, supplied in a single use vial, is a sterile, ready-to-use radiopharmaceutical solution for infusion which will be administered intravenously in nuclear medicine settings (p. 12/172). The drug product expires 72 hours after production and calibration (p. 30/172); the half-life of ¹⁷⁷Lu is 6.7 days (p. 40/172). Dosage is four administrations with an interval between two infusions of 8 weeks (b) (4) (p. 6/172).

The drug product is manufactured at two sites by Advance AAA (b) (4)

Specification testing

Quality control and batch release testing is performed at AAA (p. 43/172), except sterility testing, which is performed at (b) (4) (p. 71, 96/172). The drug product release testing specification is noted in Table 1 below. Stability test methods are stated to be the same as the release methods (p. 110/172); sterility and endotoxins are noted in the stability protocol to be tested at time 0.

Table 1: Product Quality Microbiology – Related Testing included in Drug Product Specification (p. 92/172)

Test	Test Method	Specification
Pre-release		
Bacterial endotoxins	Eur. Ph. N°20614	(b) (4)
(b) (4) test	Eur. Ph. N°50101	(b) (4)
Post-release		
Sterility	Eur. Ph. N°0520 N°20601	Sterile

(b) (4)

Sterility testing (p. 19, 86, 96/172) is performed on 3 (b) (4) samples per batch, (b) (4) vials filled per batch. (b) (4)

(b) (4)
21 CFR
211.165a allows for sterility testing on short-lived radiopharmaceuticals to occur post-release.

For three validation batches at manufactured at the Colletterto Giacosa site and at the Meldola site (six total), batch analyses tables list the (b) (4) test results (b) (4) and the sterility test results as sterile (p. 98, 102/172). For each of the six validation batches, the results passed the specification.

GENERAL COMMENTS

Please note that the responses provided below are general advice on your development program and are intended to facilitate drug development. These comments are **not** considered definitive agreement on the content and format of a future NDA. For general guidance on the preparation of clinical information in clinical study reports submitted in an NDA, refer to “DOP2’s End-of-Phase 2 General Advice for Planned Marketing Applications” (attached).

Agreement on the content and format of the proposed NDA will be reached in the proposed interdisciplinary Type B meeting covering all disciplines and documenting agreements under the PDUFA V Program. Please note that this meeting should occur after you have had a formal pre-NDA meeting on Chemistry, Manufacturing, and Controls (CMC) information with the quality review staff assigned to your IND.

2.0 DISCUSSION

Chemistry, Manufacturing, and Controls (CMC)

1. Does the Agency agree that manufacturer’s integrity testing (b) (4) is sufficient to guarantee the microbiological quality of the finished product (b) (4) ?

FDA Response: The agency agrees that integrity testing (b) (4) is not required.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. agrees with FDA’s response.

Discussion during the meeting: No discussion occurred during the meeting.

2. Considering that:
 - Radionuclidic purity test is already performed by the 177Lu chloride suppliers (the Sponsor uses certificate of analyses to accept the incoming material);
 - The manufacturing process of LUTATHERA (b) (4)
 - The radionuclide purity test of the finished product is performed (b) (4)

Does the Agency agree that the Sponsor does not perform radionuclidic purity test on the finished product?

FDA Response: The Agency agrees that radionuclidic purity testing is not required for the finished drug product; however radiochemical purity testing must be performed (b) (4)

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advance Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: AAA confirmed that radiochemical purity is performed (b) (4)

FDA stated that AAA needs to fully support their proposal (b) (4)

FDA stated that the adequacy of the data provided in the NDA to support this approach will be determined during the review. AAA will provide shipping validation studies and stability studies in the NDA. AAA stated (b) (4)

3. Does the Agency agree with the definition of the Drug Substance and the Drug Product?

FDA Response: FDA agrees with the definition of drug substance and drug product provided by AAA.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

4. Does the Agency agree with the Sponsor's proposal (b) (4)?

FDA Response: The AAA proposal (b) (4) is acceptable.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

5. Does the Agency agree that the LUTATHERA NDA that will be submitted by the Sponsor (including letters of authorization), may refer to the Drug Master Files for ¹⁷⁷Lu chloride of both IDB Radiopharmacy BV and (b) (4)?

FDA Response: FDA agrees that AAA may refer to drug master files for relevant CMC information, however AAA should communicate with the Master File holders to ensure that the letters of authorizing cross reference to the Drug Master Files specify the exact location of all cross referenced information that is essential to review of this product by citing the volume(s) and page number(s), and date(s) of submission of all such information.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advance Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: AAA noted that they are often asked questions about information in the Drug Master File (DMF), which they cannot answer. FDA recognized that there may be challenges in obtaining information from the DMF holder in a timely manner. AAA stated that the DMF holders will provide specific information from the DMF to AAA for inclusion in the NDA.

6. AAA expects to submit (b) (4)

Does the Agency agree with the Sponsor proposal (b) (4)
?

FDA Response: No, FDA does not agree. In order to consider the NDA to be complete at the time of submission, the application must contain a minimum of 12 months of real time stability data at room temperature and a minimum of 6 months of stability data under accelerated conditions.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advance Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: AAA clarified that usual stability conditions are at - 20° C and accelerated stability conditions are at 5° C. FDA stated that although its general policy is to require 12 months of real-time stability data for a new molecular entity, it would be acceptable to file the planned NDA with 6 months real-time stability data, which is consistent with the stability dating for the product administered to patients in clinical trials. Expiry dating at approval could be limited to (b) (4) months. Therefore, FDA encouraged AAA to include supportive data for establishing the expiry dating period of octreotate.

7. Does the Agency agree with the claim of categorical exclusion?

FDA Response: This is a decision made during the review of the NDA; however it would be appropriate to submit a request for categorical exclusion supported by adequate justification.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

Clinical

8. The Agency granted Fast Track Designation for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ within the scope of the indication evaluated in the Phase III study, but explicitly stated in the teleconference held on April 9, 2015 that the Designation would not limit the claimed indication presented in the NDA, provided that appropriate supporting data is submitted. As discussed during the pre-IND meetings, the most relevant clinical experience in terms of number of patients and safety follow up is the Phase I/II trial conducted at the Erasmus MC in patients with various somatostatin receptor positive neuroendocrine tumor types (the majority GEPNETs and pulmonary NETs), treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ from since 2000 (protocol MEC 127.545/1993/84). The results of this study were provided to the FDA at the time of the IND submission (Serial 000). This Phase I/II trial continued after the first independent assessment conducted in 2012, and AAA has resumed the source data verification and the collection of the efficacy/safety data with the objective to include an updated study report in the NDA submission. The safety and efficacy information of the new patients enrolled in the study in the last years and a follow up on the patients included in the report finalized in 2012 will be provided, with a total population of more than 1,000 GEP-NETs patients.

In 2011, the Agency requested that data from the Phase I/II be submitted in a "reviewable" format to be evaluated. The Sponsor will submit all Phase I/II data in support of the proposed indication in a format acceptable for the FDA.

In light of the breadth of data generated in the Phase I/II and the Phase III trials, AAA is seeking guidance on the content and structure of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS). AAA is considering presenting separate efficacy results for the Phase I/II study and for the Phase III study in the NDA. An Integrated Summary of Safety consolidating all safety information (Phase I/II and Phase III trial) at the time of submission will also be provided. Presenting efficacy results in a concise manner would support the proposed indication of the treatment of (b) (4) somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors.

Does the Agency agree with the Sponsor's proposal to present the Phase I/II and Phase III efficacy datasets in Sponsor's NDA?

FDA Response: FDA agrees with AAA's proposal to submit separate, study-specific, efficacy and safety datasets and to include separate analyses in the CSE, ISE, CSS, and ISS for the Erasmus MC (*MEC 127.545/1993/84-01*) and the NETTER-1 studies.

In addition, in the Integrated Summary of Efficacy, it would be acceptable to submit the results of an exploratory, pooled analysis which includes all patients enrolled in the NETTER-1 study and the subgroup of all patients with inoperable, locally advanced or metastatic, octreoscan positive, midgut carcinoid tumors that progressed during prior treatment a somatostatin analog (SSA) in the Erasmus study. In short, the patients treated in the Erasmus study who are selected for the integrated analysis should essentially meet the eligibility criteria of the NETTER-1 study. All patients in the integrated analysis should have been treated at the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ dose and schedule employed in the NETTER-1 study.

The data for patients with pancreatic neuroendocrine tumors (NETs) and bronchial NET should be analyzed separately.

Additionally, subgroup analyses should be performed based on the stratification factors employed in the NETTER-1 study and the functional status of the tumor, as well as by age, gender, and race. In the NDA submission, please place appropriate flags in the datasets to identify tumors as functional or nonfunctional.

For the Integrated Summary of Safety, it would be acceptable to perform a pooled analysis of all patients in both studies who received at least one dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study. The corresponding pooled datasets supporting the ISE and ISS should be submitted in Module 5 of the planned NDA. See additional comments and the attached End-of-Phase 2 standard comments for further information on the appropriate format for data submission.

With regard to the indication being sought in the planned NDA, a potential indication for patients with GEP-NET would require demonstration of a clinically meaningful antitumor effect in an adequate number of patients with progressive and inoperable GEP-NET treated with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ at the dose and schedule employed in the NETTER-1 study in one or more adequate and well-controlled trials. FDA cannot determine the adequacy of the data from the Erasmus MC study to support the broader indication until the data is reviewed at the time of the NDA submission. However, all concerns raised by FDA in prior meetings regarding these data should be addressed in a justification for seeking claims based on data from retrospectively identified subgroups of Erasmus MC.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advance Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: No discussion occurred during the meeting.

9. As part of the Phase III NETTER-1 study, a dosimetry, pharmacokinetics and ECG sub-study is conducted in a subset of 20 patients at selected sites to provide a complete assessment of the safety aspects of ^{177}Lu -DOTA⁰-Tyr³-Octreotate. The primary objective of the sub-study is to calculate whole body and organ radiation dosimetry of ^{177}Lu -DOTA⁰-Tyr³-Octreotate to determine the dose to critical organs (e.g., kidney and bone marrow) and correlate with findings of the Erasmus MC Phase I/II Clinical study.

The secondary objectives of the sub-study are to:

- Define the pharmacokinetic profile (ADME) of ^{177}Lu -DOTA⁰-Tyr³-Octreotate.
- Correlate safety, dosimetry, and pharmacokinetic data obtain in this study with the Erasmus MC phase I/II Clinical study to confirm previous findings.
- Evaluate cardiac safety: determine the acute electrophysiological changes during treatment with ^{177}Lu -DOTA⁰-Tyr³-Octreotate (through 24-hour continuous ECG recording via 12-lead Holter machine).
- Assess the presence of possible radioactive species in urine, as an indication of compound metabolization. The decision of assessing possible metabolites in urine only was based on its very low concentration in plasma (the product being a radioactive tracer) and to its known renal elimination.

AAA has made significant efforts to increase the enrolment of patients into the sub-study. Only 10 patients have completed all the required assessments, which is less than the enrolment target. The reasons indicated by the clinical sites are related to the complexity of the sub-study and the amount of procedures which require long on-site attendance at the hospital both for the patients and the clinical staff. Among the actions taken by the Sponsor, the number of sub-study sites has been increased (from 3 to 12) and the sub-study protocol has been amended (Protocol Version 3.1, September 23rd, 2013) to simplify and enhance the procedures. Despite these efforts, the sub-study failed to meet enrolment expectations. The Sponsor has therefore made additional changes to the sub-study protocol in order to ensure that the FDA requirements are adequately addressed (Protocol Version 4.1, June 5, 2014):

- To facilitate the recruitment, a non-randomized cohort (^{177}Lu -DOTA⁰-Tyr³-Octreotate only) was temporarily activated at all sites participating in the sub-study. According to this Amendment the randomization in the main study is halted at the sub-study sites until 20 patients are enrolled in the sub-study.
- In order to not bias the results obtained from randomized patients in the main study, the data of the patients enrolled in the sub-study according to the Study Protocol version 4.1 (after the activation of the non-randomized ^{177}Lu -DOTA⁰-Tyr³-Octreotate cohort) will only be analyzed descriptively and will not be considered in the primary and secondary analysis of the main study groups.

Patients participating in the sub-study continue to be patients who have been determined to be eligible for the main study and have signed the informed consent specific for the sub-study. Aside from the specific tests conducted in the dosimetry study, the treatment regimen and patient care management remain identical to that implemented in the main study.

[REDACTED] (b) (4)

FDA Response: AAA's proposal [REDACTED] (b) (4)
[REDACTED] is not acceptable. [REDACTED] (b) (4)

A summary of this analysis should be submitted to the IND at least 60 days prior to the planned pre-NDA meeting, so that this question can be addressed at the time of the pre-NDA meeting. Submit all available data including partial results for the NETTER-1 dosimetry, PK and ECG substudy and findings of the Erasmus study to the IND at least 60 days prior to the pre-NDA meeting.

Please note that labeling for a radiochemical product must include a description of the dosimetry of this product under the conditions of intended use per 21 CFR 201.57(c)(3)(J)(iii) which states that "radiation dosimetry information must be stated for both the patient receiving a radioactive drug and the person administering it." in the Dosage and Administration section of the full prescribing information.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advance Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: AAA agreed to provide summary data in the pre-NDA meeting package for at least ten patients enrolled in the substudy along with the supportive data from the Erasmus MC study and justification and supporting data for measurement of PK by radioactivity rather than HPLC.

10. Does the Agency agree that a pediatric waiver is not required?

FDA Response: In the NDA submission, AAA should indicate, under question 15 on the form FDA 356h that this product has received orphan designation for this indication and include the orphan designation number. A pediatric waiver would not be required for marketing if orphan designation has been granted for this product for this indication.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response: Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

11. Does the Agency agree that LUTATHERA is eligible for Priority Review?

FDA Response: AAA may submit a request for priority review in the NDA with a corresponding justification as to how $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ meets the criteria for priority review. A determination on whether FDA will grant priority review will be made after the submission of the NDA. Please refer to the FDA guidance on expedited programs for serious conditions

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

Administrative

12. AAA expects to organize the module 3.2.S Drug Substance of LUTATHERA NDA in 4 parts:

- One module 3.2.S for the Drug Substance Precursor [REDACTED] ^{(b) (4)}
- One module 3.2.S for the Drug Substance Precursor ^{177}Lu Chloride solution supplied by [REDACTED] ^{(b) (4)} containing the ASMF of ^{177}Lu Chloride solution;
- One module 3.2.S for the Drug Substance Precursor ^{177}Lu Chloride solution supplied by IDB Radiopharmacy BV containing general information related to the marketed product ^{177}Lu chloride solution (nomenclature, structure, specifications and certificate of analyses); and
- One module 3.2.S for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, the Drug Substance synthesized by Advanced Accelerator Applications, which is used in the manufacturing process of LUTATHERA.

Does the agency agree with the proposed organization of part 3.2.S?

FDA Response: The proposed organization of 3.2.S appears to be acceptable.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. agrees with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

3.0 ADDITIONAL COMMENTS

In order to have a productive meeting, the meeting package for the Pre-NDA meeting should contain information to address the following comments:

Clinical

13. Summarize the results of the primary PFS endpoint analysis of the NETTER-1 study as well as the response analyses according to RECIST 1.1 conducted in the pool of patients with midgut carcinoid tumors treated in the NETTER-1 study and the Erasmus study.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

14. Provide a description of the study population, including extent of prior treatment, and summary results based on the independent review committee determination of the overall response rate according to RECIST 1.1 and the duration of response from the subgroup of patients with GEP-NET enrolled in the Erasmus study, intended to support a proposed indication for the treatment of patients with (b) (4) GEP-NET. Since these data would support a request under provisions of accelerated approval, provide the justification that the results are better than available therapy or that the data were obtained in patients for whom there is no FDA-approved therapy.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

15. Describe the methods used to conduct the independent efficacy and safety analyses of the data from the Erasmus MC study.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

16. Submit a copy of the imaging charter used to conduct the independent analysis of radiographic response in patients treated in the Erasmus study.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

Non-Clinical

17. The nonclinical data package described in the meeting package appears sufficient

to support the filing of a future NDA. A final determination of the adequacy of the data to from these studies to support the application will be made during their review at the time of NDA submission.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

18. Please clarify whether AAA will rely on the FDA's prior findings of safety and effectiveness for a US approved NDA for octreotate to support any part of the NDA. If so, please identify the information to be relied upon.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. would like to discuss FDA's response during the meeting.

Discussion during the meeting: AAA may reference data in the NDA for gallium DOTA Octreotate, the companion diagnostic product, if the NDA for this test is approved prior to the approval of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. AAA confirmed that they will not reference information for octreotate to which they do not have right of reference.

Chemistry, Manufacturing, and Controls

19. Provide source and specifications for ^{177}Lu radionuclide. Specifications should include chemical form, radionuclidic purity, chemical purity, specific activity and activity concentration.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

20. Provide confirmation that the Quality standards for DTPA, Ascorbic Acid, Sodium Chloride, Sodium Hydroxide and Water for Injection include those of the USP.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

Clinical Pharmacology

21. Complete the sub-study of dosimetry, pharmacokinetics and ECG in 20 patients enrolled in Study NETTER-1 and include the results with proposed corresponding labeling statements in a future NDA submission.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:
Advanced Accelerator Applications, USA, Inc. concurs with FDA's response.

Discussion during the meeting: No discussion occurred during the meeting.

22. Address the clinical pharmacology comments conveyed at the pre-IND meeting occurred on 3/8/2011 (in particular with the items listed below).
- a. Conduct population pharmacokinetic (PK) analyses to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. Refer to the FDA Guidance for Industry entitled "Population Pharmacokinetics" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.

Provide a justification on the absence of the population PK analyses in a future NDA submission if such analyses will not be performed.
 - b. Explore the exposure-response relationships for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for measures of effectiveness, toxicity and pharmacological responses including pharmacodynamic biomarkers. Refer to the FDA Guidance for Industry entitled "Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Provide a justification on the absence of the exposure - response analyses in a future NDA submission if such analyses will not be performed.
 - c. Determine the need to conduct human PK studies for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in patients with renal impairment and in patients with hepatic impairment. Refer to the FDA draft Guidances for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf> and "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

Include justification with relevant data to support this determination in a future NDA submission.
 - d. Conduct a 'thorough QT' study to evaluate $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for its QT prolongation potential. Alternative proposals to the 'thorough QT' study, including ECG collection at baseline, around the anticipated maximal plasma concentrations after single dose and at steady-state with time matched pharmacokinetic sampling in a dedicated study (or a substudy of a clinical trial)

might be appropriate. Refer to the FDA Guidance for Industry entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>.

Include the results of this QT evaluation with proposed corresponding labeling statements in a future NDA submission.

- e. Validate the analytical methods used to determine the concentrations of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. Refer to the draft FDA Guidance for Industry entitled “Bioanalytical Method Validation” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>.

Advanced Accelerator Applications, USA, Inc. August 27, 2015, Response:

Advanced Accelerator Applications, USA, Inc. would like to discuss FDA’s response during the meeting.

Discussion during the meeting: AAA stated that a popPK study is not planned; justification will be provided for not conducting popPK analysis in the NDA. AAA confirmed that ECG data have been collected in the clinical studies and QT assessment will be included in the NDA.

ADDITIONAL DISCUSSION

AAA provided the top-line results of the analysis of PFS, which demonstrated a clinically meaningful improvement [HR 0.21 (95% CI 0.13, 0.34); $p < 0.001$] with a median PFS of 8.4 months in the control (Sandostatin LAR Depot 60 mg) arm and median not yet reached for the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm. These results will be presented at the ESMO meeting on September 29, 2015.

AAA proposed to submit a plan for expanded access in anticipation of the public disclosure of the data. FDA strongly encouraged this approach and suggested that AAA submit a treatment protocol for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ for patients with mid-gut carcinoid tumors (the population studied in the NETTER-1 trial) with limited data collection (primarily serious adverse event reports). For other NET, FDA recommended that AAA make their drug available to investigators under single patient INDs, pending determination of the interest in such access.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, that was granted on January 12, 2009, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

Attachment

DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

If you will be submitting your application in CDISC format, a separate **Study Data Standards Common Issues Document** can be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval:
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in

your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document:

- Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').
- A description of your drug development plan, including each indication that is being or has been studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission:

3) Please submit/address the items below in your SPA request.

- The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
- If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
- If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
- If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
- If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
 - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
 - Applicability of comparator treatment or of disease characteristics to U.S. population
- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot ethically be performed.

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)), which under § 314.510 and 601.41 would usually be underway at the time of accelerated approval in your SPA request and NDA/BLA submission.

- If surrogate endpoint is being used for accelerated approval, you should justify (i.e.,

from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf)).
8) <u>Pediatric Studies:</u> All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric

<p>plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.</p>
<p>9) <u>Quantitative Safety Analysis Plan (QSAP):</u></p> <p>The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:</p> <ul style="list-style-type: none">a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).b) Safety endpoints for Adverse Events of Special Interest (AERI)c) Definition of Treatment Emergent Adverse Event (TEAE)d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter)e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
<p>10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:</p> <ul style="list-style-type: none">a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdfb) Cancer Drug and Biological Products-Clinical Data in Marketing Applications www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf
<p>11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report</p>
<p>12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application</p>
<p>13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.</p>
<p>14) <u>References:</u></p> <p>There should be active links from lists of references to the referenced article.</p>
<p>Studies, Data And Analyses</p>
<p>15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and</p>

<p>title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).</p>
<p>16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:</p> <ul style="list-style-type: none">a) Site numberb) Principle investigatorc) Location: City State, Countryd) Number of subjects screenede) Number of subjects randomizedf) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)g) Number of protocol violations (Major, minor, including definition)
<p>17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf.</p>
<p>18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:</p> <ul style="list-style-type: none">a) subject age and genderb) signs and symptoms related to the adverse event being discussedc) an assessment of the relationship of exposure duration to the development of the adverse eventd) pertinent medical historye) concomitant medications with start dates relative to the adverse eventf) pertinent physical exam findingsg) pertinent test results (for example: lab data, ECG data, biopsy data)h) discussion of the diagnosis as supported by available clinical datai) a list of the differential diagnoses, for events without a definitive diagnosisj) treatment providedk) re-challenge and de-challenge results (if performed)l) outcomes and follow-up informationm) an informed discussion of the case, allowing a better understanding of what the subject experienced.
<p>19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.</p>
<p>20) Provide reports for any autopsies conducted on study.</p>
<p>21) For patients listed as discontinued due to “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the</p>

CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b) Exposure-Response Relationships – important exposure-response assessments.
- c) Less common adverse events (between 0.1% and 1%).
- d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.
- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.

<ul style="list-style-type: none">ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.iv) Drug-demographic interactionsv) Drug-disease interactionsp) Drug-drug interactions<ul style="list-style-type: none">i) Dosing considerations for important drug-drug interactions.ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.
Financial Disclosure Information
25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule
Highlights
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be

<p>contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).</p>
<p>6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).</p>
<p>7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:</p> <p style="padding-left: 40px;">(a) “(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”</p>
<p>8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.</p>
<p>9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).</p>
<p>10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].</p>
<p>11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights</p>
<p>12) The Patient Counseling Information statement must appear in Highlights and must read “See 17 for PATIENT COUNSELING INFORMATION.” [See 21 CFR 201.57(a)(14)]</p>
<p>13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.</p>
<p>14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]</p>
<p style="text-align: center;">Table of Contents</p>
<p>15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]</p>
<p>16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]</p>
<p>17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.</p>
<p>18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.</p>

<p>19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:</p> <ul style="list-style-type: none">8.1 Pregnancy8.3 Nursing Mothers (<i>not 8.2</i>)8.4 Pediatric Use (<i>not 8.3</i>)8.5 Geriatric Use (<i>not 8.4</i>)
<p>20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”</p>
<p>Full Prescribing Information (FPI)</p>
<p>22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).</p>
<p>23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.</p>
<p>24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).</p>
<p>25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm075082.pdf]</p>
<p>26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]</p>
<p>27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]</p>
<p>28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.</p>
<p>29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but</p>

intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

NETTER-1

Primary Endpoint Outcome

Presented at the Type C meeting on 27 August 2015

As this information has only recently become available to us it was not provided in the Background Document, we will submit these pages with our meeting notes as an amendment to IND 77219.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUTH L MADURO
09/02/2015



PIND 77219

MEETING MINUTES

BioSynthema, Incorporated
Attn: Jack L. Erion
President & CEO
4041 Forest Park Avenue
Saint Louis MO 63108

Dear Mr. Erion:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for “Lutate ([REDACTED] (b) (4) Infusion).”

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2011. The purpose of the meeting was to discuss the design of the Phase 3 clinical trial to support of the submission of an IND or NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1273.

Sincerely,

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES TEMPLATE ATTACHED



MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 8, 2011
TIME: 12:00 p.m-1:00 p.m.
LOCATION: White Oak Bldg 22, conference room 1309
SPONSOR: BioSynthema, Inc.
APPLICATION: PIND 77219
DRUG NAME: Lutate (b) (4)
TYPE OF MEETING: Pre-IND/Parallel Scientific Advice
MEETING FORMAT: Face-to-Face
MEETING CHAIR: Steven Lemery
MEETING RECORDER: Melanie Pierce

LIST OF FDA ATTENDEES:

Office of Oncology Drug Products

Division of Biologic Oncology Products

Patricia Keegan Director
Steven Lemery Clinical Reviewer Team Leader
Martha Donoghue Clinical Reviewer
Haw-Jyh Chiu Pharmacology/Toxicology Reviewer
Melanie Pierce Regulatory Project Manager

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment III

Eldon Leutzinger CMC Lead

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Hong Zhao Clinical Pharmacology Team Leader
Gene Williams Clinical Pharmacology Reviewer

Office of Biostatistics

Kun He Statistical Team Leader
Jenny Zhang Statistical Reviewer

Office of Drug Evaluation IV

Division of Medical Imaging Products

Robert Yaes Radio-Imaging Reviewer

Office of Executive Programs

Justina Molzon Senior Program Manager



Office of International Programs

Janice Soreth

Deputy Regional Director

Shena Arellano

International Policy Analyst

Hilde Boone

LIST OF SPONSOR ATTENDEES:

BioSynthema / Advanced Accelerator Applications (AAA)

Maurizio Mariani, M.D., Ph.D.,

Vice President, AAA

Giovanni Tesoriere, Ph.D.,

Qualified Person, AAA

Daniela Chicco, Ph.D.,

Pre-clinical Manager, AAA

Laetitia Schlachter, Ph.D.,

Regulatory Affairs Manager, AAA

Jack Erion, Ph.D.,

President, BioSynthema Inc.

Dik Kwekkeboom, M.D.,

Clinical Development

Larry Kvols, M.D.,

Clinical Development

Jeanine Boesen, Ph.D., MBA,

Director, European Operations

Eric Krenning, M.D., Ph.D.,

Clinical Development

(b) (4)

Regulatory Consultant

(b) (4)

Regulatory Consultant

BACKGROUND:

On December 27, 2010, BioSynthema requested parallel scientific advice from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to discuss the design of a phase 3 clinical trial to support approval of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ (b)(4)

BioSynthema intends to seek marketing approval in Europe (EU) and the United States (US) based on a development program intended to meet the requirements of both regulatory agencies.

$^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, is a lutetium-177 (^{177}Lu) labeled somatostatin analogue peptide conjugated with the metal chelating moiety 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) which binds specifically to malignant cells that overexpress sst2 receptors. A single dose vial contains 7.4 GBq of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was granted orphan drug status in Europe and the US.

FDA recommended in a pre-IND meeting held on June 14, 2007 that BioSynthema conduct two adequate and well-controlled trials to support the proposed indication. In a Scientific Advice meeting on January 30, 2009, EMA advised BioSynthema that a prospective randomized phase 3 study would be required to support an application in Europe.

Nonclinical Investigations:

BioSynthema does not plan to perform additional toxicology studies with radioactive peptide because dosimetry data have been collected in rats and humans. BioSynthema asserts that time course planar imaging (in rats and humans) and SPECT imaging (in humans) provide sufficient pharmacokinetic and pharmacodynamic information to accurately predict toxicity in humans.

To support the marketing application of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, BioSynthema plans to conduct the following nonclinical studies using the non-radioactive molecule ($^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$): *in vitro* metabolism studies, *in vitro* hERG assay, standalone cardiovascular, respiratory, and central nervous system safety pharmacology studies, acute toxicity study in the rat, a maximum tolerated dose study in the dog, 43-day repeat-dose toxicity studies in the rat and the dog, and *in vitro* genotoxicity assays (Ames test and mouse lymphoma assay). BioSynthema also plans to conduct an *in vitro* study evaluating human plasma protein binding of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Completed Clinical Studies:

In a Phase 1 study conducted by Erasmus MC, six patients with inoperable somatostatin receptor positive tumors (by Octreoscan) received a single 50 mCi dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. The distribution pattern of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was comparable to that of Octreoscan (Kwekkeboom *et al.* 2001). Rapid visualization of the kidneys occurred directly post-infusion and visualization of the liver, spleen, and kidneys was evident four hours post-infusion. In some patients, the pituitary, thyroid, and tumors were also visualized four hours post infusion. Dosimetry data obtained during this trial are summarized in the table below (copied from the submission):

Table 1: Patient Organ Dose (cGy/100 mCi) obtained in Phase 1 Study

Patient	Kidneys		Liver		Spleen		Bone Marrow
	-	+	-	+	-	+	
AA	-	+	-	+	-	+	-
1	825	403	90	53	803	503	26
2	533	-	76	-	1010	-	29
3	692	282	112	53	770	407	27
4	359	252	44	40	662	548	27
5	648	366	75	48	740	518	20
Mean	611	326	79	49	797	494	26

*Symbols: AA, amino acid co-infusion; (-), no AA co-infusion; (+) with AA co-infusion

An investigator-sponsored phase 1-2 study of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ was conducted at Erasmus MC between July 2000 and March 2007. In this study, 615 patients with neuroendocrine tumors were enrolled to identify the maximum tolerated dose and explore activity of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. This study included 458 patients with GPNETS, the majority of whom received four doses of Lutate containing 200 mCi ^{177}Lu per dose. Among the 504 patients who were treated according to the protocol, the most common toxicities observed within 24 hours of treatment were nausea, vomiting, and abdominal pain. Six patients were hospitalized within two days of treatment secondary to hormone-related crises. WHO Grade 3 or 4 hematological toxicity occurred 4 to 8 weeks after treatment in 9.5% of patients. Serious delayed toxicities were observed in nine patients: two patients developed renal insufficiency, hepatic toxicity occurred in three patients (one patient with diffuse liver metastases died of hepatic failure five weeks after the first administration), and four patients developed myelodysplastic syndrome (MDS). Among 310 patients with GPNETS described by BioSynthema as evaluable, overall objective tumor response rate was 46%, median PFS was 33 months, and median overall survival (OS) was 46 months (median follow-up 10 months, 101 deaths).

Proposed Clinical Study:

The sponsor proposes to conduct a multicenter, randomized, parallel group study comparing treatment with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ to Sandostatin LAR[®] Depot [Octreotide Long Acting Release (LAR)] in patients with inoperable, progressive somatostatin receptor positive midgut carcinoid tumors. Three hundred patients will be randomized (1:1) to receive either four doses of 7.4 GBq (200 mCi) administered every 7-8 weeks or 30 mg Octreotide LAR on a monthly basis. The interval between $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ administrations may be extended for up to 12 weeks to accommodate treatment logistics, or up to 16 weeks to allow resolution of toxicities. Octreotide LAR injections, which may be increased up to 40 to 60 mg

per dose in patients not responding to standard doses, will continue until the end of the study, development of tumor progression, or patient death. The proposed protocol will allow patients on the Octreotide LAR arm who develop progressive disease to cross-over to the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm.

Tumor assessments will be performed at screening and every 3 to 4 months after the first treatment. Evaluation for toxicity in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ group will occur prior to and four weeks after each treatment administration, and every three to four months thereafter for 12-16 months. Survival and pharmacovigilance in the $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ arm will be recorded up to five years after completion of study therapy.

The protocol submitted in the briefing package stated that the primary endpoint of the proposed trial is "to compare progression-free-survival (PFS) after treatment with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ versus Octreotide LAR in patients with inoperable, progressive somatostatin receptor midgut tumors, as measured by tumor response rate (complete plus partial response rate; RECIST criteria) at 3-4 month intervals." The PFS analysis is scheduled to occur one year after the last treatment of the last patient. Proposed secondary endpoints were safety and Quality of Life (QoL), as measured by the EORTC QLQ-G.I. NET21 questionnaire. The proposed sample size described in the protocol did not describe the number of events expected to have occurred at the time of the final analysis of PFS. Additionally, there was no alpha spending plan described in the protocol for the interim analyses of efficacy or for testing of secondary endpoints. An interim analysis for safety (to characterize the event rate for serious adverse events) and an interim analysis for efficacy (progression free survival) will be performed by an independent board 3-4 months after 50% of the patients have completed $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ therapy. Additionally, the protocol contains a statement that "central statistical evaluation of toxicity and tumor response will be performed at BioSynthema/AAA every six months, starting at 12 months from the beginning of the study."

Sponsor Submitted Questions and FDA Response:

Chemistry, Manufacturing and Controls:

1. **Do the Agencies agree that the proposed ready-to-use, centrally manufactured GMP Drug Product, (b)(4) is suitable for the Phase III study in support of a Marketing Authorization?**

FDA Response: Yes.

Discussion during the meeting: There was no further discussion during the meeting.

2. **Do the Agencies agree that the Sponsor has an adequate development plan to demonstrate product equivalence between the proposed Drug Product and the Erasmus MC Drug?**

FDA Response:

Discussion during the meeting: There was no further discussion during the meeting.

- d. BioSynthema's proposed specifications for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ Injection Solution (Table 11, page 27) includes a limit for gentisic acid concentration, but none for ascorbic acid concentration. Because ascorbic acid is a component [REDACTED] (b) (4) in the formulation, please explain why it is left out of the specifications [REDACTED] (b) (4)

BioSynthema Response: The Company proposes to include a specification for the concentration of ascorbic acid [REDACTED] (b) (4)

Discussion during the meeting: There was no further discussion during the meeting.

- e. Regarding Table 11 (page 27): The chemical purity limit is set at a minimum limit of (b) (4)%. Please clarify the chemical impurities that are measured in the analytical controls.

BioSynthema Response:

- The only significant impurities present in the Drug Product at production are [REDACTED] (b) (4) species.
- The known impurities that have been observed are [REDACTED] (b) (4) species. All can be uniquely identified by common analytical methods.

Discussion during the meeting: There was no further discussion during the meeting.

f. [REDACTED] (b) (4)

BioSynthema Response: The level (b) (4) that occurs in the final product is (b) (4). There is no defined mechanism (b) (4).

- (b) (4)
- Stability studies of the Final Product (b) (4)

Discussion during the meeting: There was no further discussion during the meeting.

- g. Please clarify how (b) (4) will it be used to prepare the Infusion Solution, and how will it be stored during that interval of time before use. In addition, please describe any stability studies that have been performed over this time period.

BioSynthema Response: (b) (4)

- Dispensing of the Final Drug Product Infusion Solution is performed (b) (4)
- Stability tests in validation studies have been performed on the Final Drug product Infusion Solution.

Discussion during the meeting: There was no further discussion during the meeting.

3. **Do the Agencies agree that the (b) (4) of the Drug Product is an acceptable product modification?**

FDA Response: That is a question FDA cannot answer without more detailed information (b) (4)

In the original IND

submission, provide a reasonably detailed impurity profile of the solution in support of the (b) (4)

Discussion during the meeting: There was no further discussion during the meeting.

4. **The ¹⁷⁷Lu-labelled Drug Product (b) (4)
(b) (4) can be administered to patients (b) (4)
and still provide a dose to the patient that is (b) (4) 7.4 GBq dose
specification. Is this approach acceptable to the Agencies?**

FDA Response: Yes (b) (4)

The shipment schedule should be provided in the original IND submission and include details regarding how the product will be shipped (e.g., container closure, type of outer packaging, labeling, conditions of shipment, etc.).

Discussion during the meeting: There was no further discussion during the meeting.

Nonclinical:

5. **Do the Agencies agree that the rat and the dog are suitable rodent and non-rodent species for investigating ¹⁷⁵Lu-DOTA⁰-Tyr³-Octreotate repeat dose toxicity?**

FDA Response: Based on the information provided in the meeting briefing package, the rat and the dog appear to be appropriate species in which to conduct safety testing using ¹⁷⁵Lu-DOTA⁰-Tyr³-Octreotate as a surrogate for the ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate product intended for marketing. In the original IND submission, provide the appropriate scientific justification and all relevant data supporting these species as the most relevant species in which to conduct safety testing of ¹⁷⁵Lu-DOTA⁰-Tyr³-Octreotate.

Discussion during the meeting: There was no further discussion during the meeting.

6. **Does the Agency agree with the treatment schedule of the repeated dose 43-day toxicity study in the rat and in the dog by the intravenous route followed by a 3 month drug withdrawal period?**

FDA Response: The proposed 43-day, repeat-dose toxicity studies in the rat and dog appear to be appropriate to support initial clinical studies of ¹⁷⁷Lu-DOTA⁰-Tyr³-Octreotate. However, provide 3-month, repeat-dose toxicity studies in both the rat and

the dog models to support the NDA of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, as outlined in the ICH S9 Guidance “Nonclinical Evaluation for Anticancer Pharmaceuticals”, posted at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm085389.pdf>.

BioSynthema Response:

- The proposed repeated toxicity studies in the rat and in the dog, consists of a total of 4 i.v. administrations of cold peptide, each separated by a 2-week interval. The 2-week interval between administrations has been chosen to increase the possibility of the occurrence of any toxic effects linked to the treatment of the non-radioactive compound, and also to account for the faster clearance rate in the study animal.
- No additional information would be gained from a 3-month study, which would consist of 4 administrations each spaced by 4 weeks as opposed to 2 weeks.

Discussion during the meeting: There was no further discussion during the meeting.

FDA post-meeting comments:

- a. FDA recommends that based on all available pharmacodynamic and pharmacokinetic information of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$, BioSynthema use a frequency of administration of $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the 3-month, GLP-compliant, repeat-dose toxicity studies in rats and dogs to mimic the proposed clinical treatment schedule of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$. Additionally, the 3-month, GLP-compliant, repeat-dose toxicity studies in rats and dogs should be designed to include an increased number of treatment cycles as compared to the clinical setting for a 3-month duration, followed by a recovery period of an appropriate duration to assess reversibility of toxicities observed during the dosing portion of these studies.
- b. Provide appropriate scientific justifications for the dose levels and dosing frequency selected for any future toxicity studies of $^{175}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the toxicology study reports submitted to FDA.

Clinical:

7. **Do the Agencies agree that Octreotide LAR (Sandostatin LAR® Depot, Long Acting Release) is a suitable comparator to be used in the Phase III clinical trial?**

FDA Response: FDA does not object to the use of octreotide LAR as a comparator.

Discussion during the meeting: There was no further discussion during the meeting.

8. **Do the Agencies agree with the treatment plan for patients in the Octreotide LAR**

treatment arm at enrolment [REDACTED] (b) (4)
[REDACTED] **and for patients in the Lu-**
DOTA -Tyr -Octreotate arm [REDACTED] (b) (4)
[REDACTED] ?

FDA Response: No. Revise the protocol to exclude patients who require more than 30 mg Octreotide LAR at the time of enrollment to control symptoms due to carcinoid syndrome. Additionally, the protocol states [REDACTED] (b) (4)
[REDACTED] FDA recommends that BioSynthema revise the protocol so that all patients will receive 30 mg initially. Additionally, FDA recommends that the protocol include well-defined guidelines for modifying the dose of Octreotide LAR in patients who experience toxicity or alteration in disease-related symptoms during the study.

Discussion during the meeting: There was no further discussion during the meeting.

9. **Do the Agencies agree that the proposed dose modifying toxicity protocol is an acceptable alternative to dosimetry based dosing?**

FDA Response: There is inadequate information to determine whether dosimetry-based dosing will be necessary to minimize patient risk. Please provide comprehensive data from previous dosimetry studies in humans at the time of submission of the protocol to the IND.

If the dose modifying toxicity protocol is deemed acceptable by both agencies after review of the dosimetry data, FDA recommends that criteria for dose modification for hepatotoxicity (including liver enzymes) be included in the protocol.

Discussion during the meeting: There was no further discussion during the meeting.

10. **Do the Agencies agree that the proposed dosing regimen is acceptable for all patients regardless of the patient's weight?**

FDA Response: There is inadequate information to answer this question. In the protocol submitted to the IND, provide justification, including data, showing that patients with lower weight are not at higher risk for severe toxicity. Additionally, submit comprehensive toxicology, dosimetry, and clinical data from previous studies to the IND so that FDA can determine whether this dosing regimen is acceptable.

BioSynthema has not provided adequate data to determine the optimal dosing regimen for patients with GPNETs. FDA recommends that Biosynthema further explore the exposure-response relationship for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the proposed patient population for measures of both effectiveness and toxicity.

BioSynthema Response:

- The Company will provide the requested information.
- We will provide a subanalysis for toxicity and efficacy according to categorized body weight.
- The dose is based on estimates (MIRD) for exposure limits for bone marrow (2Gy) and kidney (23Gy).
- We will provide a subanalysis of the Phase I/II data on toxicity and efficacy in progressive mid-gut carcinoids as requested.

Discussion during the meeting: FDA acknowledges BioSynthema's response. The determination whether the plan is acceptable will be a review issue when the application is submitted. BioSynthema clarified that the MIRD estimates are for cumulative exposure limits.

11. **Do the Agencies agree that the objectives indicated above are adequate endpoints for the Phase III study?**

FDA Response: No. The endpoints, as currently described in the proposed protocol, are not adequate for the following reasons (please see additional comments below regarding the use of PFS for approval in this setting using a radiopharmaceutical drug):

- a. The protocol does not contain an acceptable definition of PFS. The glossary in the information book describes PFS as "survival of patients in study without disease progression or death from studied disease" and the primary endpoint is described as "tumor response rate (CR+PR; RECIST criteria)." FDA recommends that PFS be defined as the time from randomization to disease progression (using RECIST criteria) or death from any cause. PFS rate is not an acceptable primary endpoint. Additionally, the provision to discontinue tumor assessments for patients who discontinue study drugs due to any reason and then to classify these patients as experiencing a progression event is not acceptable.

BioSynthema response:

- The primary endpoint is PFS as measured according to RECIST and death from any cause.
- Regarding discontinuation, the investigators will make every effort to perform tumor evaluation in these patients.

Discussion during meeting: FDA recommends that BioSynthema follows advice provided in FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007), specifically those trial design elements addressing trials using PFS endpoints, found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>.

- b. The protocol indicates that the final PFS analysis will occur one year after the last treatment of the last patient. FDA recommends that the PFS analysis be

performed after the occurrence of a pre-specified number of PFS events, rather than be based upon an arbitrary time period following completion of therapy of the last enrolled patient.

BioSynthema response: Can the Agency comment on what would be an acceptable number of pre-specified PFS events that would trigger the endpoint?

Discussion during meeting: FDA stated that the timing of the analysis is Biosynthema's decision. However, the PFS analysis should be a time-to-event analysis that is event-driven

- c. Please clarify whether PFS will be determined by investigator or blinded central review. Please ensure that the PFS endpoint will be based upon assessment by a blinded, independent (i.e., external to BioSynthema) review committee (IRC). In order to minimize informative censoring, FDA recommends real-time IRC assessments.

BioSynthema response:

- We will employ blinded real-time IRC tumor progression assessment.
- Can the Agency comment on what is an acceptable time frame limit for the real-time assessment.

Discussion during meeting: FDA stated that the optimal approach would be to keep patients on study until the IRC has confirmed disease progression.

- d. In order to ensure that the IRC can adequately measure tumor size, remove the stipulation on page 29 of the draft protocol [REDACTED] (b) (4)
- e. Given the relative indolence of the disease, inherent difficulties associated with interpretation of QoL assessments in an unblinded trial, and potential for late toxicities such as MDS with $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ therapy, FDA does not agree with BioSynthema's plan to allow for patients in the control arm to receive cross-over $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3$ and the protocol's lack of intent to analyze overall survival (OS) as a secondary endpoint. Revise the protocol so that that OS will be included as a key secondary endpoint (or preferably, primary endpoint) in order to provide supportive evidence that $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ is safe and effective for the treatment of patients with midgut carcinoid tumors.
- f. Revise the protocol to define OS as the time from randomization until death due to any cause. [REDACTED] (b) (4)
- g. Quality of Life (QoL) cannot be accurately assessed in an unblinded trial. Therefore, QoL claims based upon this trial will not be considered evidence of

clinical benefit. Please see the FDA guidance entitled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf> for more information. Additionally, a claim cannot be made based on an “improvement in EORTC QLQ-G.I.NET21.”

Discussion during the meeting: There was no further discussion during the meeting.

12. **Do the Agencies agree** [REDACTED] (b) (4)
[REDACTED]
[REDACTED] ?

FDA Response: [REDACTED] (b) (4)
[REDACTED]

Discussion during the meeting: There was no further discussion during the meeting.

13. **Do the Agencies agree** [REDACTED] (b) (4)
[REDACTED]

FDA Response: Please see FDA’s response to Questions 11e and 12.

Discussion during the meeting: There was no further discussion during the meeting.

14. **Do the Agencies agree with using the proposed commercially acid solutions for renal protection during treatment?**

FDA Response: There is inadequate information in the briefing package to answer this question. FDA recommends that Biosynthema identify which commercially available amino acid preparation(s) may be used in the protocol. Please provide dosimetry data derived from patients who receive the specified commercial amino acid solution(s) and proposed dose of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ to demonstrate that there is sufficient reduction in the radiation absorbed dose to the kidneys. If this data has not already been obtained, FDA suggests incorporation of dosimetry measurement in an adequate number of patients to characterize the effectiveness of each solution early in the study.

BioSynthema Response:

- There is sufficient evidence that amino acid solutions do provide renal protection in PRRT (published data, standard practice).
- The company agrees to perform kidney dosimetry in an adequate number of patients early in the study in order to confirm acceptable renal protection.

Discussion during the meeting: FDA acknowledged BioSynthema's response and stated that the Agency may provide additional comments upon receipt of the protocol, if necessary. FDA urged BioSynthema to standardize the procedures for renal protection to the extent feasible. BioSynthema stated that they planned to conduct dosimetry studies in a subset of patients enrolled in the proposed study using the specific amino acid solutions identified in the protocol to confirm that each amino acid solution provides adequate renal protection. In response to FDA's request for individualized dosing, BioSynthema agreed to explore the relationship between body weight and toxicity, as discussed in the response to question 10.

15. **Do the Agencies agree that the proposed number of patients per arm is sufficient to adequately support the evidence of efficacy and safety of the Drug Product?**

FDA Response: There is inadequate information to determine whether the proposed number of patients is sufficient. The sample size should be based on the pre-specified number of events required for the PFS analysis to demonstrate the desired treatment effect. Acceptance of the number of patients in the safety database will depend upon follow-up for OS and late toxicities, whether additional safety signals are identified, and whether BioSynthema obtains comprehensive high quality data from previous clinical trials of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ in the application for marketing approval. Please see addendum for FDA expectations of safety data to be submitted in a marketing application.

Discussion during the meeting: See discussion under 11b.

16. **Do the Agencies agree that the proposed target population, midgut carcinoid tumor patients, is a suitable GEPNET group for study?**

FDA Response: The proposed population is suitable for study. However, the definition of progression described in the eligibility criteria should be based solely upon radiographic or objective symptomatic criteria (b) (4). Given the biological and clinical heterogeneity of GEPNETs, it is unlikely that an indication for the treatment of (b) (4) somatostatin receptor positive, GEPNETs would be granted based upon the results of this proposed trial.

BioSynthema Response:

- (b) (4)

- In a subclass of patients waiting for progression based on RECIST would mean waiting for death.

Discussion during the meeting: FDA recommended that BioSynthema revise the eligibility criteria to ensure that the population enrolled is one in which the risks are acceptable. BioSynthema agreed.

Additional Clinical Comments:

17. FDA recommends that BioSynthema conduct two adequate and well controlled studies to support approval of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3$ for the treatment of (b) (4) somatostatin receptor positive neuroendocrine tumors. For a single trial to support approval, the results of the trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. Please refer to the 1998 FDA guidance entitled “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf> for information regarding the circumstances in which the Agency will consider data from a single adequate and well-controlled study sufficient to support approval.

Discussion during the meeting: There was no further discussion during the meeting.

18. FDA recommends that the primary endpoint of the study be overall survival. FDA may consider PFS as an approval endpoint; however, approval will be based on the magnitude of the treatment effect, safety, and overall risk-benefit profile. Approval may require two trials and be subject to input from the Oncology Drugs Advisory Committee.

Discussion during the meeting: There was no further discussion during the meeting.

19. Please submit comprehensive dosimetry and toxicology data and a formal study report for the Phase 1 and Phase 1/2 study to the IND prior to submission of the Phase 3 study to the IND.

Discussion during the meeting: There was no further discussion during the meeting.

20. Imbalances in tumor-specific prognostic factors may confound study results. Therefore, FDA recommends that BioSynthema stratify randomization based on the most relevant prognostic variables. BioSynthema may consider stratification based upon presence or absence of progression with prior somatostatin therapy, presence or absence of metastatic disease, or extent of hepatic metastases (such as ≤ 5 versus > 5).

BioSynthema Response:

- The Erasmus MC Phase I/II study shows that the OctreoScan tumor uptake score is the most relevant predictor of tumor response.

- Therefore we prefer to limit stratification only to the OctreoScan tumor uptake score.


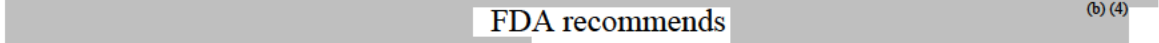
Discussion during the meeting: FDA suggested BioSynthema consider additional factors but acknowledged that it is BioSynthema's decision whether to include these factors or not.

21. In order to minimize imbalances in frequency of assessments that may confound study results, FDA recommends that the timing of baseline and follow-up radiologic assessments be more specifically defined in the protocol. Additionally, the assessments should occur at the same intervals irrespective of study arm.

Discussion during the meeting: There was no further discussion during the meeting.

22. FDA encourages Biosynthema to make every effort to minimize missing data in the proposed trial. Excessive missing data may preclude a valid interpretation of study results.

Discussion during the meeting: There was no further discussion during the meeting.

23. (b) (4)

FDA recommends (b) (4)
 Additionally, if BioSynthema plans to conduct any interim analyses or central assessments of tumor response (page 33), BioSynthema will need to submit a statistical analysis plan that describes the method to control type I error.

Discussion during the meeting: There was no further discussion during the meeting.

24. No primary or sensitivity analyses of PFS are specified. FDA recommends using a log-rank test performed on the intent-to-treat (ITT) population in the primary PFS analysis. FDA also recommends that Biosynthema provide a description of the censoring rules for the proposed trial for FDA review prior to initiation of this study. Refer to the Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics for information about censoring rules and suggested sensitivity analyses of PFS.


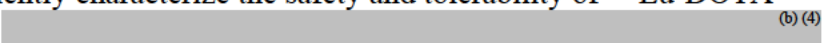
Discussion during the meeting: There was no further discussion during the meeting.

25. FDA recommends that an independent data monitoring committee oversee the safety data of the study rather than the central evaluation of toxicity to be performed by BioSynthema every six months (refer to the following FDA guidance for industry: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>). As discussed in comment 23, FDA recommends against central assessments of tumor response every six months.

Discussion during the meeting: There was no further discussion during the meeting.

26. An NDA submission must establish that the data derived from the proposed clinical trial are applicable to the U.S. patient population (including minority groups) and U.S. medical practice.

Discussion during the meeting: There was no further discussion during the meeting.

27. The protocol for the proposed Phase 3 study indicates that $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ may be administered every ^{(b) (4)}₍₄₎ 8 weeks, ^{(b) (4)}  FDA recommends that the dosing interval be more tightly defined in order to sufficiently characterize the safety and tolerability of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ therapy. ^{(b) (4)} 

Discussion during the meeting: There was no further discussion during the meeting.

28. FDA recommends that monitoring for safety (i.e., laboratory monitoring on page 30) occur at consistent intervals between the two treatment arms. Additionally, in order to comprehensively assess late effects of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ therapy, FDA recommends yearly laboratory assessment of renal, hepatic, and bone marrow function for four years following completion of the 12-16 month follow-up period described on page 26 of the draft protocol.

Discussion during the meeting: There was no further discussion during the meeting.

29. Revise the protocol on page 15 of the draft protocol so that patients who progress prior to completion of four cycles of treatment will no longer be exposed to $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$.

Discussion during the meeting: There was no further discussion during the meeting.

30. FDA cautions BioSynthema ^{(b) (4)} 

Discussion during the meeting: There was no further discussion during the meeting.

31. FDA cautions BioSynthema ^{(b) (4)} 

Discussion during the meeting: There was no further discussion during the meeting.

Additional Nonclinical Comment:

32. Be advised that stand-alone safety pharmacology studies are generally not needed to support clinical studies of anticancer pharmaceuticals in patients with advanced disease and limited therapeutic options if detailed clinical observations and appropriate electrocardiographic measurements in non-rodents are incorporated in toxicology studies and no specific concerns have been identified, as outlined in the ICH S9 Guidance “Nonclinical Evaluation for Anticancer Pharmaceuticals”.

Discussion during the meeting: There was no further discussion during the meeting.

Clinical Pharmacology Comments:

Regarding the planned Phase 3 study:

33. FDA recommends that the protocol include QT assessment (an ECG) at the end of each infusion. A time-matched plasma sample for pharmacokinetics should be collected immediately after the ECG is collected.

The ECG monitoring in the planned study will be insufficient to satisfy the need for clinical evaluation of QT/QTc in the future NDA. As recommended at the 2007 pre-IND meeting (#42 below), a more extensive QT evaluation according to ICH E14 will be needed.

BioSynthema Response:

- No evidence of QT interval prolongation has been observed in the hERG test and in an in vivo safety pharmacology study evaluating potential effects of 177Lu-DOTA0-Tyr3-Octreotate on electrocardiogram in dogs.
- The Company proposes to include an ECG safety evaluation (pre-administration baseline, and after infusion) at the first 177Lu-DOTA0-Tyr3-Octreotate administration in 20 patients early in the study

Discussion during the meeting: FDA continues to recommend QT assessment (an ECG) at the end of each infusion for additional evaluation of safety.

As stated, the ECG monitoring in the planned study appears insufficient to satisfy the need for clinical evaluation of QT/QTc in support of the future NDA submission. FDA recommends that power calculations be performed and a plan developed that will allow for a conclusion that a drug-induced QTc change of 20 msec or more does not occur. FDA further requests that the proposed plan for QT assessment be submitted to FDA for review and comment prior to study initiation.

34. FDA recommends performing pharmacokinetics (sparse sampling is often sufficient to accomplish this) during the proposed clinical trial to allow for exploratory modeling of exposure-response relationships. Response endpoints to be investigated in the modeling should include the clinical efficacy and toxicity outcome measures as well as any biomarker endpoints in the protocol.

BioSynthema Response:

- Plasma and urinary data (as percentage of administered radioactivity) are available from 20 patients in the Phase I/II study are available from Phase I/II in 20 patients. We propose to perform pharmacokinetic evaluation and exploratory modeling based on these data.
- Pharmacokinetic evaluation on the cold compound would be difficult due to analytical assay limitations related to very low plasma concentrations.
- We deem it suitable to use plasma and urinary data obtained from the radioactive compound, knowing that the compound is not substantially metabolized (based on in vitro metabolism data and in vivo data on compound excretion).

Discussion during the meeting: Among the goals of the modeling is to evaluate the effect of covariates including body weight or body surface area, age, gender, race, etc., on drug exposure and to discern a relationship between exposure and clinical response; a Phase 1-2 dataset of 20 patients is unlikely to be sufficient for this purpose. While exposure-response analysis in the proposed study is not a regulatory requirement, it is encouraged. Please refer to the FDA Guidance for Industry: *Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

In the absence of data FDA can not evaluate if: 1) circulating radioactivity closely correlates with circulating parent drug and 2) the presence of active metabolites can be ruled out.

35. FDA expectations for the performance of the analytical methods used for blood drug concentration determination can be found in the May, 2001 Guidance *Bioanalytical Method Validation* located at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

Discussion during the meeting: There was no further discussion during the meeting.

Regarding the overall drug development program:

We reiterate the following Clinical Pharmacology comments conveyed at the 2007 pre-IND meeting:

36. You should develop a validated assay method for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ as well as its major circulating active metabolite(s) in human plasma according the FDA Guidance document on bioanalytical method validation
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

BioSynthema Response:

- No evidence of compound metabolization has been observed in *in vitro* studies in rat, dog and human hepatocytes. As well, from the previous Phase I/II studies, the compound appears to be essentially excreted in the urine as intact compound.
- Based on the above, does the agency still consider it necessary to develop a specific assay and look for metabolites in human plasma?

Discussion during the meeting: If administration of a clinical dose to humans results in all or nearly all of the dose being recovered as parent drug in excreta, additional assay development for determination of metabolites is not needed.

37. You should conduct *in vitro* microsomal studies to determine whether $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ is a substrate of cytochrome P450 (CYP) enzyme(s). The potential of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ to inhibit and/or induce CYP enzymes should be also determined. We refer you to the Guidance for Industry on Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072104.pdf>

Discussion during the meeting: There was no further discussion during the meeting.

38. You should conduct *in vitro* studies to determine whether $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ is a substrate and/or inhibitor of the efflux transporter, P-glycoprotein (P-gp). We refer you to the Guidance for Industry on Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072104.pdf>.

Discussion during the meeting: There was no further discussion during the meeting.

39. We recommend that you conduct formal PK studies for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ in patients with hepatic impairment and in patients with renal impairment.

BioSynthema Response:

- The safety profile in patients with compromised kidney and liver function is such that it is not recommended to perform the suggested study.
- Moreover, the adjusted dose to such patients would be so low that it would not

have anti-tumoral effect.

Discussion during the meeting: Anticipation of a change in safety profile in patients with impaired kidney or liver function does not support that studies are not needed. Rather, it strengthens the conclusion that studies are necessary.

40. You should assess the human plasma protein binding for $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$.

Discussion during the meeting: There was no further discussion during the meeting.

41. The relationship between clearance of $^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-octreotate}$ and creatinine clearance should be established.

Discussion during the meeting: There was no further discussion during the meeting.

42. QT Evaluation:

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

Discussion during the meeting: There was no further discussion during the meeting.

ISSUES REQUIRING FURTHER DISCUSSION

- There are no issues requiring further discussion

ACTION ITEMS

- There are no action items for this meeting

ATTACHMENTS AND HANDOUTS

- BioSynthema's slide presentation emailed 3.08.11

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MELANIE B PIERCE
03/25/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 77219

MEETING MINUTES

BioSynthema, Incorporated
Attn: Jack L. Erion
President & CEO
4041 Forest Park Avenue
Saint Louis MO 63108

Dear Mr. Erion:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Lutate (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on March 8, 2011. The purpose of the meeting was to discuss the design of the Phase 3 clinical, trial to support of the submission of an IND or NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1273.

Sincerely,

Melanie Pierce
Senior Regulatory Health Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES TEMPLATE ATTACHED



MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 8, 2011
TIME: 12:00 p.m-1:00 p.m.
LOCATION: White Oak Bldg 22, conference room 1309
SPONSOR: BioSynthema, Inc.
APPLICATION: PIND 77219
DRUG NAME: Lutate (b) (4)
TYPE OF MEETING: Pre-IND/Parallel Scientific Advice
MEETING FORMAT: Face-to-Face
MEETING CHAIR: Steven Lemery
MEETING RECORDER: Melanie Pierce

LIST OF FDA ATTENDEES:

Office of Oncology Drug Products

Division of Biologic Oncology Products

Patricia Keegan Director
Steven Lemery Clinical Reviewer Team Leader
Martha Donoghue Clinical Reviewer
Haw-Jyh Chiu Pharmacology/Toxicology Reviewer
Melanie Pierce Regulatory Project Manager

Office of New Drug Quality Assessment

Division of New Drug Quality Assessment III

Eldon Leutzinger CMC Lead

Office of Clinical Pharmacology

Division of Clinical Pharmacology V

Hong Zhao Clinical Pharmacology Team Leader
Gene Williams Clinical Pharmacology Reviewer

Office of Biostatistics

Kun He Statistical Team Leader
Jenny Zhang Statistical Reviewer

Office of Drug Evaluation IV

Division of Medical Imaging Products

Robert Yaes Radio-Imaging Reviewer

Office of Executive Programs

Justina Molzon Senior Program Manager



Office of International Programs

Janice Soreth

Deputy Regional Director

Shena Arellano

International Policy Analyst

Hilde Boone

LIST OF SPONSOR ATTENDEES:

BioSynthema / Advanced Accelerator Applications (AAA)

Maurizio Mariani, M.D., Ph.D.,

Vice President, AAA

Giovanni Tesoriere, Ph.D.,

Qualified Person, AAA

Daniela Chicco, Ph.D.,

Pre-clinical Manager, AAA

Laetitia Schlachter, Ph.D.,

Regulatory Affairs Manager, AAA

Jack Erion, Ph.D.,

President, BioSynthema Inc.

Dik Kwekkeboom, M.D.,

Clinical Development

Larry Kvols, M.D.,

Clinical Development

Jeanine Boesen, Ph.D., MBA,

Director, European Operations

Eric Krenning, M.D., Ph.D.,

Clinical Development

(b) (4)

Regulatory Consultant

Regulatory Consultant

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MELANIE B PIERCE
03/25/2011