CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761115Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761115
Priority or Standard	Priority
Submit Date(s)	November 30, 2019
Received Date(s)	December 2, 2019
PDUFA Goal Date	June 2, 2020
Division/Office	Division of Oncology 1/Office of Oncologic Diseases
Review Completion Date	*Electronic Stamp Date*
Established/Proper Name	Sacituzumab govitecan
(Proposed) Trade Name	TRODELVY
Pharmacologic Class	Antibody Drug Conjugate (ADC)
Code name	IMMU-132
Applicant	Immunomedics, Inc.
Dosage form	Intravenous
Applicant proposed Dosing Regimen	10 mg/kg administered once weekly on days 1 and 8 of a 21-day treatment cycle
Applicant Proposed Indication(s)/Population(s)	TRODELVY is (b) (4) for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Triple negative malignant neoplasm of breast
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	TRODELVY is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Triple negative malignant neoplasm of breast
Recommended Dosing Regimen	10 mg/kg administered once weekly on days 1 and 8 of a 21-day treatment cycle

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

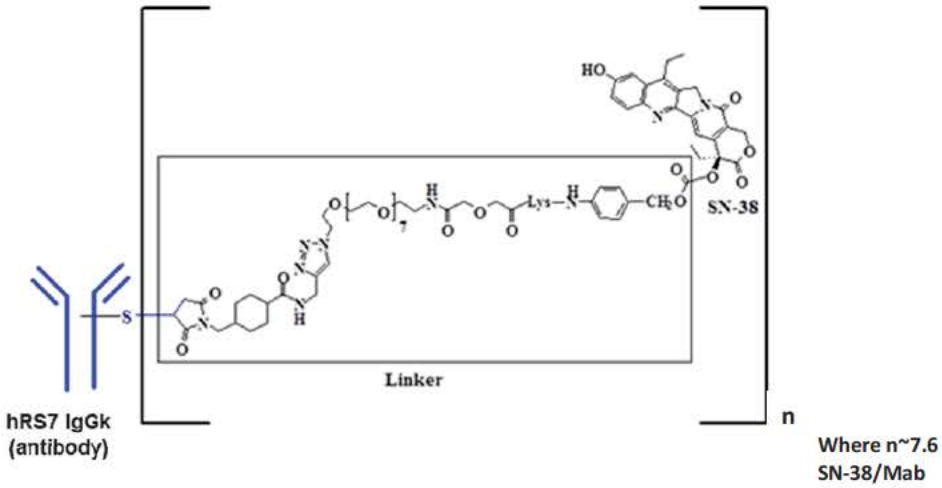
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	Complete Response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation

PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
TNBC	triple negative breast cancer
mTNBC	metastatic triple negative breast cancer

1 Executive Summary

1.1. Product Introduction

Sacituzumab govitecan-hziy (TRODELVY) is an antibody-drug conjugate made up of SN-38, a topoisomerase I inhibitor that is the active metabolite of irinotecan, coupled by a CL2A linker to the humanized monoclonal antibody hRS7 IgGκ which binds to Trop-2 (the trophoblast cell-surface antigen-2). The chemical structure of sacituzumab govitecan-hziy is shown below.



Pharmacology data suggest that sacituzumab govitecan-hziy binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan-hziy decreased tumor growth in mouse xenograft models of triple negative breast cancer.

Sacituzumab govitecan-hziy (TRODELVY) for injection is a sterile, preservative-free, off-white to yellowish lyophilized powder for intravenous use in a 50 mL clear glass single dose vial, with a rubber stopper and crimp-sealed with an aluminum flip-off cap. The proposed dosage for sacituzumab govitecan-hziy is 10 mg/kg administered as an intravenous infusion on days 1 and 8 of a 21-day treatment cycle.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommendation for the accelerated approval of sacituzumab govitecan-hziy, according to 21 Code of Federal Regulations (CFR), Part 601.41, Subpart E of the Biological Licensing

Regulations, is based on efficacy and safety data from Trial IMMU-132-01.

On May 18, 2018, Immunomedics, Inc., (Immunomedics), submitted original Biologics License Application (BLA) 761115 requesting marketing authorization for TRODELVY (sacituzumab govitecan) injection. In the BLA submission, Immunomedics sought accelerated approval for TRODELVY for the following indication:

> SACITUZUMAB GOVITECAN, (b) (4) is indicated for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease.

The applicant submitted the results of Trial IMMU-132-01, a single-arm, multicenter (US only) trial of sacituzumab in patients with advanced solid tumor malignancies to support the BLA. Among the 420 patients who received sacituzumab at various doses, a total of 108 patients who enrolled and received the proposed dose of 10 mg/Kg had mTNBC and had received at least two prior lines of therapy in the metastatic setting; it is this subgroup of patients that comprises the efficacy population for this BLA. Based on a June 30, 2017, data cut-off, among the 108 patients in the efficacy population, the investigator-assessed ORR by RECIST 1.1 was 33.3% (95% CI: 24.6, 43.1). The median duration of response (DOR) among responders was 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment based on a December 1, 2017, data cut-off. The ORR based on Independent central review (ICR) was performed on patients with tumor scans showing complete response, partial response, or at least 20% shrinkage by local site evaluation (n=55). Objective response rate based on this subgroup ICR was 32.4% (95% CI: 23.7, 42.1) with a median DOR among responders of 9.1 months (95% CI: 4.6, 10.7) based on a December 1, 2017, data cut-off. This was supportive of the investigator-assessed response rate; however, results per ICR should be interpreted with caution given that this was based on assessment in a subgroup of patients.

During review of the initial BLA submission, FDA identified several deficiencies in the chemistry, manufacturing, and controls (CMC) data package. FDA issued a complete response (CR) letter on January 17, 2019. On December 2, 2019, Immunomedics submitted a complete response to the CMC deficiencies. The submission also included an updated safety report of Trial IMMU-132-01 with a data cut-off date of March 1, 2019, to support the assessment of any significant changes or findings in the safety profile of sacituzumab.

During review of the complete response submission, FDA learned that the confirmatory trial IMMU-132-05 was fully accrued and that topline results for the primary endpoint of progression free survival (PFS) may be available during the review of the complete response submission. An informal teleconference was held on January 9, 2020, during which Immunomedics stated that topline data would not be available during the BLA review cycle. Consequently, FDA requested Immunomedics to submit ORR and DOR data from both arms in order to support the efficacy observed in trial IMMU-132-01. To maintain data integrity for the ongoing trial, Immunomedics used an independent third-party statistician and put in access

restrictions so that their trial statisticians remained blinded to the results. IMMU-132-05 is a phase 3 trial of sacituzumab vs. treatment of physician's choice (TPC) in patients with mTNBC after ≥2 prior chemotherapies for advanced disease or >1 therapy for pts who progress within 12 months of adjuvant therapy. Patients were randomized 1:1 to receive either IMMU-132 or TPC from one of 4 prespecified single-agent regimens (capecitabine, eribulin, vinorelbine or gemcitabine). The primary endpoint is PFS as assessed by BICR. Secondary endpoints include overall survival (OS), ORR, DOR, safety and quality of life. As of the data cut off date of January 31, 2020, the preliminary results showed that ORR and DOR by BICR were supportive of the efficacy of sacituzumab. Additionally, on April 2, 2020, the data safety monitoring committee (DSMC) recommended that Trial IMM-132-05 be halted due to evidence of "compelling efficacy." FDA requested the topline results from the DSMC without individual-level data. The results further supports the efficacy of sacituzumab.

The safety profile of sacituzumab is acceptable for the intended population. The most common adverse reactions (≥25% in incidence: nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, and respiratory infection, abdominal pain) are manageable with monitoring, dose modifications, and supportive measures. Neutropenia was a common and serious toxicity observed in Trial IMMU-132-01 with one death due to neutropenic typhlitis. Diarrhea was also common and severe. Neutropenia and diarrhea are included in the "Warnings and Precautions" section of the prescribing information and as boxed warnings to provide adequate caution to prescribers regarding these toxicities, particularly in patients known to be homozygous for the UGT1A1*28 allele, who are at increased risk for neutropenia.

Available therapies for patients with mTNBC who have received at least two prior therapies for metastatic disease are eribulin and ixabepilone. Ixabepilone as a single agent was approved with an investigator-assessed ORR of 18.3% (95% CI: 11.9, 26.1) and an ORR by central assessment of 12.4% (95% CI: 6.9, 19.9); median duration of response was 6.0 months (95% CI: 5.0, 7.6) by central assessment. The ORR for patients receiving eribulin was 11% (95% CI: 8.6, 14.3) and median duration of response of 4.2 months (95% CI: 3.8, 5.0). Therefore, the investigator-assessed ORR of 33.3% (95% CI: 24.6, 43.1) supported with a median DOR of 7.7 months (95% CI: 4.9, 10.8) is a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival or progression free survival) and to be better than the available therapies.

Applicant has adequately addressed all the CMC deficiencies outlined in the CR letter. Given the favorable benefit-risk profile, all disciplines were in agreement with accelerated approval of sacituzumab for the following indication:

Sacituzumab govitecan-hziy, (b) (4), is indicated for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

Approximately 20% of breast cancer diagnoses worldwide are deemed to be triple negative breast cancer (TNBC), which describes a subtype of breast cancer that has low expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This subtype of breast cancers is histologically and molecularly heterogenous. The TNBC subtype is more commonly diagnosed in women younger than 40 years compared with hormone-positive breast with a nearly two-fold higher attributable risk of TNBC in women under 40 years compared with women over 50 years (odds ratio [OR] 2.13, 95% CI 1.34-3.39) [Trivers KF, et al; 2009]. In addition, TNBC appears to be more common among black women compared with white women, with a more than two-fold increase in incidence in the former. Other risk factors for the disease include the presence of BRCA mutation, premenopausal status, obesity, and maternal related factors such as parity and age at first pregnancy.

Metastatic triple negative breast cancer (mTNBC) is incurable. It is a disease with a poor prognosis with a median survival of approximately 13.3 months (Kassam, F et al; 2009). Chemotherapy is the mainstay of treatment of TNBC and in general, patients first receive standard chemotherapy regimens that include taxane or anthracycline- containing combinations in the neoadjuvant and adjuvant settings. Because the major cause of disease progression in the metastatic setting is multidrug resistance (either primary or acquired), following progression on these regimens, and in the metastatic setting, patients may receive agents thought to not be cross-resistant (e.g., capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens). For patients whose tumors are PD-L1 positive atezolizumab in combination with nab-paclitaxel is available under accelerated approval. There is no preferred or standard regimen used. In patients who have previously received anthracycline- and/or taxane based treatment, sequential, single agent chemotherapy is typically used, with multi-agent regimens reserved for patients who present with visceral crisis. For the approximately 20% of patients with TNBC who harbor a germline BRCA 1 or 2 mutation, the poly ADP-ribose polymerase (PARP) inhibitors olaparib and talazoparib have been approved for patients who have been previously treated with chemotherapy.

Treatment options are limited for patients who have received two or more regimens in the metastatic setting. FDA-approved therapies that constitute available therapies in this setting are eribulin and ixabepilone. Eribulin was approved in the third-line metastatic setting based on an improvement in OS of less than 3 months (13.1 months versus 10.6 months; HR 0.81; 95% CI: 0.66, 0.99) in a randomized controlled trial of 762 patients who had received at least two prior lines of therapy compared to physician's choice chemotherapy. The observed response rate was 11% with a median DOR of 4.2 months. Ixabepilone was approved based upon a modest response rate (investigator-assessed ORR of 18.3%

[95% CI: 11.9, 26.1]; central, independently-assessed ORR 12.4% [95% CI: 6.9, 19.9]). The median DOR was 6.0 months (95% CI: 5.0, 7.6) by central assessment.

Study IMMU-132-01, a phase 1/2, non-randomized, open-label, multicenter study, provided the data to support the safety and efficacy of sacituzumab. Study IMMU-132-01 evaluated sacituzumab at doses ranging from 8 mg/Kg to 18 mg/Kg, administered as a single agent to patients with advanced solid tumor malignancies. The cohort of patients whose results support the efficacy assessment for BLA 761115 comprise 108 patients with mTNBC who had received at least two prior lines of systemic therapy, and who received sacituzumab 10 mg/kg by intravenous administration on days 1 and 8 of a 21-day cycle until disease progression, loss of clinical benefit, unacceptable toxicity, or death.

Among the 108 patients in the efficacy population, the confirmed investigator-assessed ORR by RECIST 1.1 was 33.3% (95% CI: 24.6, 43.1); the estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8). Independent central review (ICR) was performed on patients with tumor scans showing complete response, partial response, or at least 20% shrinkage by local site evaluation (n=55). Objective response rate based on this subgroup ICR was supportive of the investigator-assessed response rate; however, results per ICR should be interpreted with caution given that this was based on assessment in a subgroup of patients.

The safety assessment was based upon the overall study population in Study IMMU-132-01 who received sacituzumab 8 or 10 mg/Kg (n=408), and in the subset of patients who comprise the efficacy population (n=108). In the efficacy population, the median duration of treatment was 7.2 months (range 0, 51.3). The median number of treatment cycles was 8 (range 1, 73), and the median number of doses administered was 11 (range 1, 146). A third of patients (32.1%) experienced 1 or more dose reductions (1 dose reduction [25.2%]; 2 dose reductions [5.9%]; 3 dose reductions [1%]). Treatment delays occurred in 4.4% of patients and 9.8% of patients discontinued treatment due to AEs.

Among the efficacy population, 100% experienced at least one adverse event (AE). Serious AEs (SAEs) were observed in 33% of patients. The most common (≥2%) SAEs by preferred term were infection (9%), febrile neutropenia (8%), vomiting (6.5%), dyspnea and nausea (3.7% each), and diarrhea (2.8%). Grade 3-4 AEs were observed in 72.2% of patients. The most common (≥5%) Grade 3-4 AEs by preferred term were neutropenia (43%), anemia (12%), diarrhea and hypophosphatemia (9% each), fatigue and febrile neutropenia (8%, each), vomiting (6%), and dehydration (5%). The most common (≥20%) AEs by preferred term were nausea (69%), neutropenia (64%), diarrhea (63%), fatigue (57%), anemia (52%), vomiting (49%), alopecia (38%), constipation (34%), rash (31%), decreased appetite (30%), respiratory infection and abdominal pain (26% each), neuropathy and hyperglycemia (24% each), back pain and headache (23% each), dizziness (22%), dyspnea, urinary tract infection, and hypomagnesemia (21% each) and cough (20%).

Patients with mTNBC who have received two prior therapies for metastatic disease have an advanced condition that is life-threatening and

have an unmet medical need. The results of Study IMMU-132-01 are considered an improvement over available therapy with a near doubling of the response rate with supportive durations of response.

The toxicity profile observed in the overall safety population and in the mTNBC population patients is consistent with the toxicity profile observed in an advanced cancer population receiving treatment with a cytotoxic agent. There was a high incidence of neutropenia and diarrhea, with an increase in the incidence of these toxicities among patients who were homozygous for the UGT1A1*28 allele compared to patients who were heterozygous for this allele. Overall, the most common AEs are manageable with appropriate monitoring, dose interruption/modification, and supportive care.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Breast cancer is the most common cancer in women with more than 260,000 new cases and 40,000 deaths annually. Approximately 10-15% of patients with breast cancer have triple negative breast cancers (TNBC). • Metastatic TNBC has a poor prognosis with an estimated median overall survival (OS) of approximately 13 months.	Metastatic triple negative breast cancer is a serious and life-threatening condition with an estimated median overall survival (OS) of approximately 13 months.
Current Treatment Options	• The goals of treating mTNBC are palliative in nature with the aim of prolonging survival and reducing cancer-related symptoms. Available therapies for the treatment of patients with mTNBC who have had two prior lines of therapy include ixabepilone and eribulin; for patients with a BRCA 1 or 2 mutation, olaparib and talazoparib are available.	There is an unmet medical need to improve the outcomes of patients with mTNBC who have received two or more prior therapies and patients may benefit from an agent with a more favorable response rate and duration of response as compared to available therapy.
Benefit	• The efficacy of sacituzumab was evaluated in trial IMMU-132-01 • In the 108 patients who comprise the efficacy population, the confirmed ORR was 33% (95% CI: 24.6, 43.1) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment.	Study IMMU-132-01 demonstrated an improvement over available therapy based on response rate, an endpoint reasonably likely to predict clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In the efficacy population, 33% of patients experienced SAEs compared to 41% of patients in the pooled safety population. • The serious risks of sacituzumab include diarrhea, neutropenia, nausea, vomiting, and infusion-related reactions. Patients who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia. • One death in the safety population was due to neutropenic typhilitis.	The safety profile of sacituzumab is acceptable when assessed in the context of the life-threatening nature of mTNBC that has progressed following 2 or more therapies. Significant and serious adverse reactions, including neutropenia and diarrhea can be adequately managed with close monitoring, dose modifications, and supportive measures and this risk should be conveyed in labeling Patients with known reduced UGT1A1 activity should be monitored for severe neutropenia.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

X

Christy Osgood, MD
Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Metastatic triple negative breast cancer (mTNBC), defined as breast cancer with low expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is a disease with a poor prognosis. The estimated median survival from the time of diagnosis is approximately 13-18 months. The median age at diagnosis of approximately 50 years (Kassam 2009; Yardley 2018). In male patients with metastatic breast cancer, <1% of patients have mTNBC as most male patients have hormone-receptor positive disease (Giordano 2018).

Unlike hormone receptor positive disease and human epidermal growth factor receptor 2 (HER2) positive disease, there are no approved therapies for TNBC. In the subset of patients who have mTNBC who harbor a germline BRCA mutation (15-20%), there are approved therapies. The primary treatment modality for patients with mTNBC is cytotoxic chemotherapy. In general, cytotoxic chemotherapy is administered as a single agent with multi-agent regimens reserved for patients who present with visceral crisis. In March 2019, the FDA granted accelerated approval to atezolizumab in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1. This was the first FDA approval specifically for mTNBC indication.

There has been extensive work to better understand the molecular subtypes of mTNBC. Though the lack of hormone receptor and HER2 positivity does make this a distinct group, it is clear that mTNBC is heterogenous and includes different molecular subtypes which have differing natural histories and likely different responses to therapy (Prat 2014). Most patients (70-80%) with TNBC have molecular features consistent with the basal-like subtype, however the remaining 20-30% fall into one of the other four intrinsic subtypes based on global gene expression analysis (Prat 2010). Given this, trials evaluating therapies for mTNBC will include a variety of molecular subtypes and may include patients who have different likelihood of response to therapy.

This is a disease that affects younger patients and has an extremely poor prognosis. Therapies for this population are an unmet clinical need.

Current clinical trials are continuing to explore how standard cytotoxic therapies may have differential efficacy in patients with mTNBC, evaluating the role of immunotherapy for this population and subsets of this population, as well as evaluating various targeted therapies.

2.2. Analysis of Current Treatment Options

The management of mTNBC is typically with cytotoxic chemotherapy. For the approximately

15-20% of patients with mTNBC who have a germline BRCA 1 or 2 mutation, there are two approved poly-ADP ribose (PARP) inhibitors: olaparib and talazoparib. For patients with mTNBC whose tumors express PD-L1, atezolizumab in combination with paclitaxel protein-bound is a treatment option.

Most agents are used off-label, and in the absence of visceral crisis, cytotoxic therapies are typically used as single agent, sequential therapy as combination therapies have an improvement in PFS, however they have increased toxicity and a questionable impact on overall survival (Cardoso 2009).

There are multiple chemotherapy agents approved for the treatment of metastatic breast cancer. Data for response and efficacy of currently available therapies includes patients with both hormone receptor positive and hormone receptor negative disease. The objective response rates (ORR) from historical studies in patients who had received two prior systemic therapies varies, though is less than 20% in patients who have been treated with two prior systemic therapies in the metastatic setting. The most relevant comparator is eribulin which is approved for patients with metastatic breast cancer who have received two prior chemotherapeutic regimens in the metastatic setting with an estimated ORR of 11% (95% CI: 8.6, 14.3) and estimated duration of response of 4.2 months (95% CI 3.8, 5.0). The data are somewhat difficult to interpret specifically for patients with mTNBC, however, given the heterogeneity of the cohorts in which these therapies were evaluated.

Table 1: Summary of Treatments Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Approval Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Eribulin	Patients with mBC who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting	2010	1.4 mg/m^2 administered intravenously on days 1 and 8 of a 21-day cycle	OS: 13.1 mos (11.8, 14.3) ORR 11% (8.6, 14.3); DoR 4.2 months (3.8, 5.0)	Neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation
Ixabepilone	Patients with metastatic or locally advanced BC after failure of an anthracycline, a taxane, and capecitabine	2007	40 mg/m^2 infused intravenously every three weeks	ORR: 12.4% (6.9, 19.9) (IRR assessment); 18.3% (11.9, 26.1) (Investigator assessment). DoR: median 6.0 months (5.0-7.6)	Peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, musculoskeletal pain
Atezolizumab + Paclitaxel protein-bound (Accelerated Approval)	Atezolizumab in combination with paclitaxel protein-bound for the treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1	2019	Atezolizumab 840 mg administered intravenously on Days 1 and 15 of every 28-day cycle + Paclitaxel protein-bound 100 mg/m2 administered intravenously on Days 1, 8, and 15 of every 28-day cycle	PFS in the PD-L1-positive population: HR of 0.62 (95% CI: 0.48, 0.77) in favor of Atezo+Paclitaxel compared to placebo+Paclitaxel arm protein-bound arm; PFS difference of 2.6 months (7.5 months vs. 5.0 months)	Peripheral neuropathies, fatigue, nausea, diarrhea, anemia, constipation, cough, headache, neutropenia, vomiting, and decreased appetite

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The original new molecular entity (NME), Biologics License Application (BLA) was submitted to the FDA on May 18, 2018, to support the applicant's request for approval of Sacituzumab govitecan (TRODELVY) for the treatment of patients with metastatic triple negative breast cancer who have (b) (4) received at least two prior therapies for metastatic disease. The original BLA application received a Complete Response (CR) Action from the FDA on January 17, 2019, due to chemistry, manufacturing, and controls (CMC) deficiencies, Per 21 CFR 601.20 (c). The Applicant resubmitted the BLA application to the FDA on December 2, 2019. Sacituzumab is a new molecular entity (NME) and therefore not currently marketed in the United States. Sacituzumab is not approved by any foreign regulatory agency.

3.2. Summary of Presubmission/Submission Regulatory Activity

- June 1, 2012: Original IND submission to evaluate of sacituzumab (IMMU-132, hRS7-SN38) in patients with advanced epithelial malignancies (IND 115621).

- August 29, 2014: Request for Fast Track Designation denied; FDA determined that submission did not include a comprehensive development plan designed to demonstrate clinical benefit.

- December 22, 2014: Fast Track Designation granted for the treatment of patients with triple negative breast cancer (TNBC) who have failed no more than two prior therapies for metastatic disease.

- February 25, 2015: End of Phase 2 meeting to obtain FDA guidance on acceptable trial design for a registration trial of IMMU-132 in the treatment of patients with relapsed/refractory mTNBC. Immunomedics committed to conducting a randomized Phase 3 trial, to seek a Special Protocol Assessment (SPA) for the proposed phase 3 trial, and to submit a Statistical Analysis Plan (SAP) for review. FDA confirmed that progression-free survival (PFS) would be an acceptable primary endpoint for the planned Phase 3 Study.

- June 25, 2015: Written-Response Only meeting to obtain FDA guidance regarding the applicant's approach to the evaluating quality of life. Immunomedics also provided a new SAP based on updated information from IMMU-132-01, revising the analysis of PFS estimates.

- October 8, 2015: FDA issued a Special Protocol Non-Agreement for proposed randomized Phase 3 study.

- November 6, 2015: FDA issued a Special Protocol Non-Agreement FDA did not consider the proposed [redacted] (b) (4) to be clinically meaningful

- November 24, 2015: Special Protocol Agreement granted for "An International, Multi-Center, Open-Label, Randomized, Phase 3 Trial of Sacituzumab versus Treatment of Physician Choice in Patients with Metastatic (Stage IV) Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments."

- February 4, 2016: Breakthrough Therapy Designation granted under IND 122694 for the treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

- May 9, 2016: Type B Multidisciplinary Breakthrough Therapy meeting held to discuss updated safety and efficacy data from Study IMMU-132-01, the regulatory strategy that could potentially support approval of IMMU-132 based on the results of Study IMMU-132-01. FDA determined that the data at the time were not sufficient for a BLA submission. FDA agreed that a single-arm trial demonstrating a durable confirmed objective response rate determined by blinded central review could support accelerated approval for the treatment of patients with relapsed/refractory mTNBC after at least two prior therapies for metastatic disease. FDA stated that it would be important for the confirmatory trial to be underway if not fully accrued, should Immunomedics submit a BLA for accelerated approval.

- November 14, 2016: Type B EOP2 meeting held to discuss the non-clinical and clinical pharmacology development strategies for IMMU-132. FDA confirmed that genotoxicity studies would be required for BLA submission and product labeling, and confirmed that based on genotoxicity studies, embryo-fetal development studies did not appear to be warranted for the proposed indication.

- March 17, 2017: Type C Written Response meeting. FDA concurred that the Phase 3 materials manufactured with a new clone (hRS7-[redacted] (b) (4)) were analytically comparable to the Phase 2 materials manufactured using the hRS-[redacted] (b) (4) clone [redacted] (b) (4) FDA agreed that additional nonclinical safety studies beyond the ongoing 3-month repeat-dose monkey toxicology study were not required for filing. The outlined the requirements for stability data (6 months' stability for both drug substance (DS) and drug product (DP)).

- March 30, 2017: Based upon advice from FDA to identify one IND to be the repository for CMC information for sacituzumab, the applicant submitted an amendment to IND 115621 stating their intent to maintain all CMC information under IND 115621; the submission included a letter of authorization to allow IND 122694 to cross reference IND 115621.

- April 24, 2017 FDA provided feedback on the applicant's amendment to IND 122694, including on the design of the proposed Phase 3 study, and also advised that the applicant

consider modifications and standardization of the Treatment of Physician's Choice Arm. FDA agreed that the proposed study could support a regulatory submission.

- May 3, 2017: Immunomedics submitted amendments to IND 115621, containing clarifications regarding the validation strategy for sacituzumab, in response to FDA's
- March 17, 2017, and requested FDA feedback on some questions. FDA responded to the applicant's submission on June 15, 2017.

- June 15, 2017: FDA provided regulatory advice regarding Immunomedics' manufacturing plans and agreed that to late submission of CMC components. Specifically, the first PPQ lots for DS and DP would be completed prior to BLA filing; however, the second and third PPQ lots may be submitted during the BLA review process. If the Applicant planned to submit a validation data amendment during review of the original BLA, FDA requested that the timeline of the submission be submitted and agreed upon. If the information was submitted to far into the review cycle such a submission would be considered a major amendment. The applicant was reminded that quality standards for expedited approval programs remain consistent with expectations for standard drug development programs and that all manufacturing sites would need to meet full validation requirements for a BLA.

- June 29, 2017: FDA provided written responses which agreed that the package of at least 100 patients with metastatic TNBC who received 10 mg/kg of IMMU-132 after having received at least two prior therapies, with a minimum follow-up of 4 months, appeared to be acceptable to support submitting a BLA. Additionally, it was agreed that the proposal to submit complete efficacy and safety data for the target population of mTNBC patients and safety data for the safety population of patients regardless of tumor type and IMMU-132 was dosing was acceptable but also required the inclusion of ECG and laboratory data. The Agency agreed with the proposed approach to collect and submit tumor scans for ICR in patients with a CR, PR or with at least 20% of reduction in their lesions based on local radiographic assessment as adequate for filing. The anticipated safety database of approximately 300 patients exposed to study drug over all tumor types was agreed to be sufficient for filing.

- September 27, 2017: Type B End-of-Phase 2, CMC meeting was held under IND 115621. The Agency agreed to the proposed validation plan and noted that (b) (4) validation and (b) (4) data to support sterility assurance should be provided at the time of BLA submission. FDA stated that that discipline reviews of the BLA are due approximately 3 months in advance of the PDUFA action date and reiterated that depending on the time when the final drug substance and drug product validation reports are submitted to the BLA, and the extent of the data submitted at that time, it may be considered a major amendment that extends the PDUFA review timeline.

- October 12, 2017: Pre-BLA Meeting where the Applicant and Agency agreed upon the population for the BLA submission, the plan for the data cut-off for the BLA safety update,

the plan to include all SAEs and AEs regardless of attribution, the plans for PK data analysis, and requested the BICR charter for review and expressed concerns for proposed methodology for a single-blinded reviewer. FDA stated that both the initial safety submission as well as the safety update should include information regarding AEs, including SAEs, SAE narratives and death narratives regardless of attribution to the study drug.

- January 3, 2018: Type B pre-BLA CMC meeting. During this meeting the Applicant and Agency made agreement on a late component to the BLA. Specifically, the Agency agreed that given the breakthrough therapy status of the application that the applicant could submit the summary and results (b) (4) by the BLA filing deadline (60 days after the initial BLA submission). Additionally, the applicant agreed (b) (4) The applicant was notified that the proposed overall control strategy (b) (4) will be a review issue and determined based on the totality of information and data submitted to the BLA. The applicant agreed to submit an assay that to ensure (b) (4) is controlled.

- February 5, 2018: In a letter submitted to IND 122694, Immunomedics informed FDA that there had been data integrity issues uncovered (b) (4) Immunomedics stated that an investigation had been conducted and that the integrity issues ended (b) (4)

- March 1, 2018: Immunomedics submitted a second letter to IND 122694, providing an update on the data integrity breach issue reported in the February 5, 2018 letter to FDA. The applicant stated (b) (4) that the issues ended (b) (4) Immunomedics further stated that corrective actions had been initiated to address this issue. Additionally, the Applicant submitted a Health Evaluation Record stating that (b) (4) as a result of issues described in the February 5, 2018 letter.

- May 18, 2018: BLA 761115 Submitted. As the initial BLA submission included a number of responders whose response occurred just prior to the data cut-off, FDA requested that the applicant submit additional efficacy data at the 90-day Safety Update.

- June 22, 2018: Bi-Weekly teleconferences between the Agency and the Applicant commenced with the aim to discuss CMC-related information requests and to clarify any CMC issues as they arose; generally, if no issues required discussion, the teleconference was cancelled.

- August 20, 2018: 90-day Safety and Efficacy Update submitted to BLA 761115.

- September 25, 2018: During the Mid-cycle communication, FDA notified Immunomedics

that the response to the FDA Form 483 (dated August 14, 2018) in which the applicant claimed "attorney client privilege" as the reason for not providing the requested information, was unacceptable. Immunomedics agreed to amend their response within a few days and resubmit them. FDA also stated that additional CMC deficiencies were to be discussed at a future CMC teleconference, and that a follow-up teleconference to discuss in more details, FDA's basis for referring the application to ODAC, would be scheduled.

- October 4, 2018: Teleconference between the applicant and CMC. The Applicant was informed that, while the review of the amended response to the FDA Form 483 was ongoing, there were still deficiencies to be addressed. The FDA stated that the requested information characterizing the applicant's efforts to investigate the full scope of the data integrity breach was necessary to understand the impact of this event, including whether the event was isolated, and to assess the adequacy of Immunomedics' conclusions regarding this issue and the corrective measures that had been implemented to address this issue. During the teleconference, Immunomedics stated that the FDA inspector had refused to receive this information when offered; the FDA inspector in question objected to Immunomedics' characterization of the exchange in question and clarified that at no time during the inspection did was data refused. Rather Immunomedics had refused to provide the data and later provided a summary paper which had been drafted on the day of the inspection. The FDA inspector also noted that, while the document offered did not address the issues at hand, Immunomedics had denied her request to keep the document. FDA again reiterated the need to provide the results of a GMP investigation into the data integrity breach.

- October 10, 2018: teleconference between the applicant and CMC. Immunomedics stated that they were not able to submit the report detailing the GMP investigation due to attorney/client privilege. Immunomedics proposed to share the folders containing this information at a face to face meeting, that would entail FDA review of the documents during the meeting, but would not entail submission of these materials to the FDA or providing FDA with copies of the documents; FDA did not agree with this proposal, stating that any materials or information intended for the purposes of responding to FDA's request for information regarding deficiencies, including information related to data integrity breach, should be submitted in the response to the RAI letter. FDA stated that once the RAI response is received, the review team would decide whether a T-CON or a Face to Face meeting would be appropriate to discuss further. FDA requested detailed information of the investigation and specified that while the interviews can be a component, the applicant should also include the cause, how to prevent, what is the impact, and all the change control.

- November 2, 2018: Type A meeting was held to with the Applicant to discuss ongoing clinical deficiencies, incomplete response to a 483, data integrity and falsification issues at the Morris plains manufacturing facility and the cancellation of ODAC. During the meeting the Applicant agreed to a third-party investigation into the data integrity breach and to 3rd

party oversight of manufacturing. The report detailing the investigation was to be submitted directly to the FDA by December 14, 2018. Immunomedics was informed that a new inspection would need to occur and that depending on the volume of information submitted on December 14, 2018 a major amendment may need to be issued.

- January 17, 2019: FDA issued Complete Response (CR) Action for the original BLA application submission because the manufacturing and controls has determined that the methodologies and processes used for hRS7 antibody intermediate, IMMU-132 DS and DP manufacturing, release testing, and stability testing as submitted in the BLA are not sufficient to assure a consistent, safe, pure and potent product. OPQ identified the following deficiencies:

(b) (4)

- March 25, 2019: Type A with the Applicant to discuss deficiencies and comments in the CR letter regarding safety update, immunogenicity, and labeling. During this meeting Immunomedics and FDA agreed to the proposed content of the safety update to support the assessment of any significant changes or finding in the safety profile with extended follow up in trial IMMU-132-01. FDA agreed that (b) (4)

(b) (4) is available and validated for use.

- May 2, 2019: Type A Meeting held between the applicant and OPQ to obtain FDA concurrence on the required information for the resubmission of the BLA application. During this meeting FDA agreed that the actions taken by Immunomedics (b) (4) appear reasonable, and that the proposed process validation strategy appeared reasonable. Additionally, FDA agreed that the information provided was supportive of the proposed approach to address the concern (b) (4) However, the acceptability of all of these processes will be a review issue.

- September 27, 2019: Type A Meeting held between the applicant and OPQ to further update FDA on Immunomedics progress addressing the required information for the resubmission of the BLA application.

- December 2, 2019: BLA application resubmitted to the FDA.

- February 18, 2020: In response to an information request dated December 18, 1019 and after an informal teleconference held on January 9, 2020, Immunomedics provided Investigator-reviewed and IRC-reviewed ORR summaries and DoR Kaplan-Meier estimates and milestone rates in the primary population of brain metastasis-negative patients, along with basic summary tables to characterize the patient population and treatments including baseline demographics, disease characteristics and drug exposure summaries, according to methods as specified in the SAP

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 1 (DO1) consulted the Office of Scientific Investigations (OSI) to perform an audit of clinical investigator sites, the applicant, and the facility for the independent central radiology review for BLA 761115. DO1, in consultation with the OSI, identified a total of 6 clinical sites for inspection based on high enrollment, a manual assessment of enrollment trends, protocol violations, efficacy findings, and adverse events reporting. Three additional clinical sites were added to the inspection list after information was received by OSI from multiple confidential informants. The confidential informants suggested, in part, that Good Clinical Practice (GCP) compliance violations had occurred during the conduct of the study that may have affected the integrity of the study data submitted to the BLA; an additional concern was that these violations may have negatively impacted patient safety and welfare. Based upon these allegations, 3 additional clinical investigator sites were added to the inspection plan. A summary of the inspection results is shown in Table 2.

Table 2: Office of Scientific Investigations Site for IMMU-132-01

Inspection Site	Site No./ No. of patients	Inspection Date	Interim Classification
Immunomedics, Inc.	Sponsor	Jun 14-Aug 1, 2018	VAI
(b) (4)	CRO	(b) (4)	NAI
Aditya Bardia, MD Massachusetts General Hospital	255/108	Aug 13-17, 2018	VAI
Wells Messersmith, MD University of Colorado	254/56	Sept 12-17, 2018	NAI
Allyson Ocean, MD Cornell-Weill Medical Center	111/70	Aug 6-10, 2018	NAI
Jordan Berlin, MD Vanderbilt University Medical Center	252/36	Aug 16-Sept 10, 2018	NAI
Rebecca Moroose, MD Orlando Health, Inc.	204/19	Jun 26-Jul 2, 2018	NAI
Ebenezer Kio, MD Goshen Center for Advanced Cancer	181/49	Aug 20-23, 2018	NAI
Kevin Kalinsky, MD Columbia University Medical Center	259/12	Sept 4-7, 2018	NAI

NAI= No Action Indicated; VAI= Voluntary Action Indicated

Overall, OSI did not identify significant inspectional findings for clinical investigators Dr. Aditya Bardia, Dr. Jordan David Berlin, Dr. Allyson Ocean, Dr. Rebecca Moroose, Dr. Wells

Messersmith, Dr. Ebenezer Kio, Dr. Kevin Kalinsky, Immunomedics, Inc., or the CRO (b) (4) (b) (4) The data from Study IMMU-132-01 submitted to the Agency in support of BLA 761115, appear reliable.

Inspection of Site 255 (Principal Investigator: Dr. Bardia) revealed that source documentation associated with efficacy assessments for 2 patients was not consistent with datasets submitted to the Agency. Specifically, Patient (b) (6) and Patient (b) (6) were identified as responders in the BLA submission. However, they were noted to have undergone brain imaging (MRI) between scheduled study visits, which revealed that both patients had brain metastases. The findings of brain metastases were not appropriately recorded as an event of disease progression in either patient in the datasets and clinical reports submitted in the BLA. Additionally, it was not clear whether these patients' imaging demonstrating CNS metastases had been referred for central radiology review, given that they were obtained at non-protocol specified times. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations was issued to Dr. Bardia, citing these protocol violations.

Given these inspectional observations, a Clinical Information Request (IR) was issued to the Immunomedics on September 18, 2018, requesting the following:

1. identify patient-level information for all responders that includes all imaging obtained during the course of the study (both scheduled and unscheduled),
2. narrative summaries of each of these imaging assessments (e.g. if not per protocol, why imaging was obtained); and
3. an indication of whether the additional imaging and assessments were submitted for central review.

The Applicant's response was received on September 24, 2018. In response, Immunomedics stated, in part, that they found no additional instances of failure of a clinical site to document and report to the applicant all scheduled and unscheduled MRIs/CT scans and the associated tumor responses based on their re-review of study patients. Immunomedics also indicated that the additional MRI scans for Patients (b) (6) had since been sent to the CRO, (b) (4) for review.

An additional applicant response, dated October 9, 2018, added that they had confirmed that the imaging vendor, (b) (4) had received all images for the TNBC patients as requested above and that an updated database on the scan assessments was included in Serial Number 0053, submitted on October 8, 2018.

Reviewer Comment: While the lack of inclusion of important imaging findings by Dr. Bardia's clinical site represents an important deviation from the protocol (i.e., RECIST 1.1.), the inspectional observations should not have importantly impacted overall study outcomes. Immunomedics confirmed that there were no other instances of missing MRI/CT scans for CRO, (b) (4) for review. The datasets submitted to the BLA have been updated to include the correct efficacy endpoint of Objective Response (OR) for Patients (b) (6)

(b) (6) *and the OR would only have impacted the duration of response, but not the Objective Response Rate (ORR).*

4.2. Product Quality

Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate (ADC) that comprises a humanized (b) (4) IgG1κ monoclonal antibody (hRS7 IgG1) directed against trophoblastic cell-surface antigen (Trop-2) linked to a topoisomerase I inhibitor (SN-38) at heavy and light chain cysteine residues via a maleimide-containing crosslinker (CL2A) and hydrolysable spacer. Binding of IMMU-132 to Trop-2-expressing cancer cells via the antibody portion of the molecule leads to the intracellular and extracellular release of SN-38 upon the cleavage of CL2A linker. The effector portion of the molecule, SN-38, binds to the topoisomerase-1- DNA complex, preventing religation of single stranded breaks and ultimately resulting in double-stranded DNA damage and killing of the cells.

The overall control strategy for hRS7 antibody intermediate, drug-linker, IMMU-132 Drug Substance (DS) and Drug Product (DP) manufacture incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, hRS7 antibody intermediate, drug-linker, DS and DP, and stability of these materials.

During review of the initial BLA submission, FDA identified several deficiencies in the chemistry, manufacturing, and controls (CMC) data package. FDA issued a complete response letter on January 17, 2019, which identified the following deficiencies:

(b) (4)

In response to the complete response letter, Immunomedics implemented extensive improvements to the overall quality management system, manufacturing process and controls, as well as the optimization of analytical methods (including cell binding and cytotoxicity assays). Improvements implemented for the hRS7 antibody intermediate manufacturing process at Immunomedics Inc. (Morris Plains, NJ) were verified on a pre-license inspection held March 2 - 10, 2020. The responses to the deficiencies referenced in the complete response letter were adequately addressed in the BLA resubmission and provide overall assurance of the manufacture of a consistent, safe, pure and potent product.

During review of the complete response submission, eight post marketing commitments were identified in order to provide continued assurance of the manufacture of a consistent, safe, pure and potent product. Please see Section 13 for details.

4.3. Clinical Microbiology

Refer to the OPQ Executive Summary and full review by Maxwell Van Tassell and Thuy Nguyen Thanh in Panorama.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic is included in this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical review was completed and added to the Multi-disciplinary Review and Evaluation for the original BLA submission, which was finalized in DARRTS on January 17, 2019. The nonclinical data submitted to BLA 761115 are adequate to support approval of TRODELVY for the proposed indication.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology review was incorporated in the Multi-disciplinary Review and Evaluation at the time of the Original BLA submission with an approval recommendation. This resubmission included UGT1A1 genotype information for 10 additional patients. However, no additional clinical pharmacology information that would preclude approval or warrant changes to the requested PMRs or the proposed labeling recommendations was included in the current submission. The Office of Clinical Pharmacology recommends the approval of BLA 761115 from a clinical pharmacology perspective.

6.1.1. Clinical Pharmacology Questions

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

UGT1A1*28 genotype and hematological toxicity
Refer to the original review with the following edits based on new information from this cycle. This application with a revised cutoff date of 01 March 2019 included UGT1A1 genotype data on 10 additional patients in Study IMMU-132-01(3 patients heterozygous (*1/*28) and 2 patients homozygous (*28/*28) for the UGT1A1*28 allele, and 5 patients homozygous for the wild-type allele (*1/*1), Table 3).

Table 3. UGT1A1*28 Status by Sacituzumab Govitecan Starting Dose

	Overall Safety Population n = 408		mTNBC n = 108
	8 mg/kg	10 mg/kg	10 mg/kg
Patients, n (%)	81 (100)	327 (100)	108 (100)
UGT1A1 status			
*1/*1	29 (36)	120 (37)	44 (41)

*1/*28	30 (37)	125 (38)	39 (36)
*28/*28	10 (12)	29 (9)	7 (7)
Not done	5 (6)	44 (14)	14 (13)
Missing	7 (9)	9 (3)	4 (4)
Total evaluable	69 (85)	274 (84)	90 (83)

Source: Reviewer Analysis of ADSL.xpt, Data Cutoff Date: 01 March 2019.

Of the 343 patients with available UGT1A1*28 genotype data, 81% were White, 6% were Black or African American, and 4% were Asian. The incidence of Grade 4 neutropenia (based on AE preferred terms) was 26% in patients homozygous for the UGT1A1*28 allele (10/39), 13% in patients heterozygous for the UGT1A1*28 allele (20/155), and 11% in patients homozygous for the wild-type allele (16/149). For additional details refer to section 8.2.5.

Reviewer Comment: *Although there is a higher incidence of AEs in UGT1A1*28 homozygotes, there is insufficient data to inform whether dosing based upon UGT1A1 status is warranted. The reviewer continues to recommend submission of the results of analyses of the relationship between UGT1A1*28 genotype and toxicity in the ongoing confirmatory clinical trial IMMU-132-05 as a PMR.*

Trop-2 expression status

Refer to the original review with the following edits based on new information from this cycle. This application with a revised cutoff date of 01 March 2019 included the result of Trop-2 expression by immunohistochemistry (IHC) for 1 additional patient, whose tumor had a status of “no/weak staining” (IHC 1+) and best response of a PR. This additional data resulted in 58% (63/108) of patients with mTNBC with tumor Trop-2 expression results available and an ORR of 17% (1/6) in the subgroup with no/weak Trop-2 expression, 40% (23/57) in subgroup of patients with moderate/strong expression, and 27% (12/45) in the subgroup of patients without Trop-2 expression results available. (b) (4)

X

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 4. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Trial Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Trial Population	No. of Centers / Countries
		Controlled Studies to Support Efficacy and Safety						
IMMU132-01	01631552	Phase 1/2 (dose escalation [3+3 design], dose expansion [single-arm, multi-cohort])	Dose escalation: doses of 8, 12, 18 mg/kg IV on days 1 and 8 of a 21-day cycle Phase 2: doses 8,10 mg/kg IV on days 1 and 8 of a 21-day cycle mTNBC efficacy cohort: 10 mg/kg IV on days 1 and 8 of a 21-day cycle	ORR by investigator, per RECIST v1.1.	Until PD or lack of tolerability	420 of whom (108 comprised the mTNBC cohort submitted for this BLA)	Patients with advanced epithelial cancers that are relapsed or refractory to ≥ 1 standard therapy for their disease	13 U.S.A.
IMMU132-05	02574455	Multi-center, open-label, randomized phase III trial of sacituzumab versus treatment of physician choice in patients with metastatic triple-negative breast cancer who received at least two prior treatments	Sacituzumab administered intravenously (10 mg/kg on Days 1 and 8 of 21-day cycles) Treatment of physician choice administered per standard of care regimens: Eribulin, Capecitabine, Gemcitabine, Vinorelbine	Primary endpoint: PFS per IRC in BM-ve subpopulation Secondary endpoints: PFS in ITT ,OS in the BM-ve subpopulation and ITT, ORR, DoR, and PRO	Until PD or unacceptable toxicity	488 patients (patients with brain metastasis are capped at 15%)	Patients with locally-advanced or metastatic TNBC who are refractory or relapsing after at least 2 prior standard chemotherapy regimens for unresectable, locally advanced or metastatic breast cancer	Approximately 150 sites (U.S.A and Europe)

Source: Reviewer Table; NCT= PD= disease progression

7.2. Review Strategy

The clinical and statistical review is based on the clinical study report and datasets for Trial IMMU-132-01. The original BLA application was submitted to the FDA on May 18, 2018 and received a Complete Response Action due to CMC deficiencies on January 17, 2019, see Section 3.1 for details. On December 2, 2019, a complete response to the CMC deficiencies was submitted. The submission also included an updated safety report of Trial IMMU-132-01 with a data cut-off date of March 1, 2019 to support the assessment of any significant changes or findings in the safety profile of sacituzumab.

The efficacy results, FDA findings, and review comments presented in Section 8.1 of this review are largely unchanged from the original BLA submission review, except for minor edits throughout the review and the addition of the preliminary ORR/DoR results for IMMU-132-05 Trial in section 8.1.2.

The FDA review of Safety was largely conducted during the review of the original BLA submission. The review of safety in section 8.2 includes the FDA findings and review comments from the review conducted at the time of the original BLA submission, and includes updates from review of the Safety Update Report and related datasets submitted with the BLA resubmission on December 2, 2019.

Data Sources

The first and second cycle reviews included the following:

1. Literature review of metastatic triple negative breast cancer (mTNBC).
2. Research of the FDA database to characterize the regulatory history of the sacituzumab INDs 115621 and 122694 including review of meeting minutes during drug development.
3. Review of the submitted CSR, protocol, protocol amendments, and selected data sets for IMMU-132-01.
4. Review of case report forms for patients in the mTNBC efficacy cohort.
5. Review of patient narratives for serious adverse events and deaths in IMMU-132-01.
6. Review of responses to clinical and biostatistical queries sent to the Applicant.
7. Review of the 90-day Safety and Efficacy Update submitted on August 20, 2018.
8. Review of the Safety Update Report and related datasets submitted on December 2, 2019 with the BLA application resubmission.
9. EDR link for the electronic data sources is: \\CDSESUB1\evsprod\BLA761115\761115.enx
10. The SDTM and ADaM datasets submitted along with software code for data analyses.

Data and Analysis Quality

The data submitted with this application were in ADaM and SDTM formats. The data were of adequate quality with adequate coding of preferred terms and consistency with CRFs. The Applicant's analyses were generally reproducible. Requests for additional information from the Applicant during the review process were addressed in a timely fashion. The Applicant submitted information regarding their data quality assurance plan including their site inspections and provided site audit summaries.

Data were submitted to the Office of Computational Science and Data Fitness assessment found data traceability issues between the SDTM and ADaM datasets that were initially submitted with the BLA submission. Issues were addressed through information requests to the Applicant.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. IMMU-132-01

Trial Design

Trial IMMU-132-01 is an open-label, dose escalation and dose expansion trial of sacituzumab in patients with advanced solid tumors. All trial sites were within the US.

The dose escalation (Phase 1) portion of the trial evaluated patients with epithelial cancer including breast, ovarian, cervical, endometrial, prostate, lung, squamous cell carcinoma of the head and neck, esophageal, colorectal, gastric, pancreas, clear cell renal, papillary thyroid, glioblastoma multiforme (GBM), urothelial, and hepatocellular carcinoma. A 3+ 3 design was employed to evaluate escalating doses of sacituzumab. Dose limiting toxicities (DLTs) were evaluated during the 1st cycle of treatment.

The dose expansion (Phase 2) portion of the trial evaluated four cohorts, including one with patients with metastatic triple negative breast cancer (mTNBC). This cohort was defined by the presence of negative estrogen and progesterone receptors (ER and PR) and negative for human epidermal growth factor receptor 2 (HER2), per ASCO/CAP guidelines (2010) based on testing of patients' most recent tissue biopsy. Patients were to have received at least two prior anticancer therapies for metastatic disease including a prior taxane in any setting. Additionally, prior hormonal or HER2 targeted agents did not count as prior therapies, but all chemotherapy, biological or targeted agents were counted.

Trial oversight was provided by Immunomedics, Inc. After receiving feedback from the Agency, a central review audit of responders was performed by a third-party organization.

Key Eligibility Criteria

Inclusion

- Male or female patients, ≥18 years of age, able to understand and give written informed consent
- Histologically or cytologically confirmed epithelial cancer of one of the following types: gastric adenocarcinoma, esophageal cancer, hepatocellular carcinoma, NSCLC, SCLC, epithelial ovarian cancer, cervical cancer, endometrial cancer, TNBC, non-TNBC, follicular papillary thyroid cancer, GBM, hormone refractory prostate cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma (clear cell), urothelial carcinoma
- Stage IV disease (except for patients with GBM)
- Refractory to or relapsed after at least one prior standard therapeutic regimen

- ECOG performance status ≤1
- Expected survival ≥6 months
- Measurable disease by CT or MRI
- At least 2 weeks since last treatment with chemotherapy, targeted therapy, endocrine therapy, immunotherapy, and/or radiation therapy or major surgery and recovered from all acute toxicities to Grade ≤1
- At least 2 weeks since prior treatment with high dose corticosteroids. Low dose corticosteroids (prednisone equivalent <20 mg) were permitted.
- Adequate hematology parameters that did not require ongoing transfusional support (hemoglobin >9 g/dL, ANC >1500/mm3, platelets >100,000/mm3)
- Adequate renal (creatinine ≤2.0 x ULN) and hepatic (bilirubin ≤1.5 x ULN, ALT and AST ≤3 x ULN or 5 x ULN if known hepatic metastases) function
- All toxicity at trial entry ≤Grade 1 by CTCAE v4.0

Exclusion

- Pregnant or lactating women
- Women of childbearing potential and fertile men unwilling to use effective contraception during the trial and until the conclusion of the 12-week post-treatment evaluation period
- Known Gilbert's disease
- Patients with brain metastases could be enrolled only if treated, non-progressive brain metastases over the past 4 weeks and off of high dose (>20 mg of prednisone or equivalent for at least 4 weeks
- Presence of bulky disease (defined as any single mass >7 cm in greatest dimension). Patients with a mass >7 cm but otherwise eligible could be considered for enrollment after discussion with the medical monitor.
- Patients with active grade ≥2 anorexia, nausea or vomiting, and/or signs of intestinal obstruction
- Patients with non-melanoma skin cancer or carcinoma in situ of the cervix were eligible, however patients with other prior malignancies must have had an at least 3-year disease-free interval
- Known to be HIV, HBV, or HCV positive
- Known history of unstable angina, myocardial infarction, or congestive heart failure present within 6 months or a clinically significant cardiac arrhythmia requiring anti-arrhythmia therapy.
- Known history of clinically significant active chronic obstructive pulmonary disease, or other moderate-to-severe chronic respiratory illness present within 6 months of trial entry
- History of clinically significant GI bleeding, intestinal obstruction, or GI perforation within 6 months of initiation of trial treatment
- Infection requiring IV antibiotic use within 1 week
- Patients with a history of an anaphylactic reaction to irinotecan or grade ≥3 GI toxicity to

prior irinotecan
- Other concurrent medical or psychiatric conditions that, in the investigator's opinion, were likely to confound trial interpretation or prevent completion of trial procedures and follow-up examinations

Reviewer Comments: The eligibility criteria requirement that patients have a life expectancy of >6 months may have led to investigator selection of patients that may be less representative of all patients with mTNBC who have had two prior lines of therapy. It is notable that those with known Gilbert's disease were excluded as this is associated with UGT1A1 deficiency. For most of the trial, patients with known brain metastases, a frequent occurrence in patients with mTNBC, were excluded. Patients with stable brain metastases were allowed to enroll as of Protocol Amendment 9 which was adopted on July 9, 2015. Patients with moderate hepatic dysfunction were excluded as well.

Diagnostic Criteria

With Amendment 10, it was specified that patients were required to have TNBC histology based on most recent local assessment, consistent with ASCO/CAP guidelines (i.e. ER and PR <1% and HER-2 negative).

Assessment of Trop-2 expression was not required, however the applicant requested archived tissue specimen where available for determination of Trop-2 expression.

Reviewer Comments: Amendment 10, in November 2016, clarified that all patients were to have mTNBC as defined as ER and PR expression <1% and HER-2 negative disease based on their most recent biopsy. It is notable that patients who lose HR expression are known to be less responsive to endocrine therapy, however, it is less clear the role that HR expression loss plays in the natural history of disease (Kuukasjarvi 1996).

Trial Treatment

Sacituzumab was administered as an intravenous infusion on days 1 and 8 of a 21-day treatment cycle.

Phase 1 evaluated sacituzumab at a starting dose of 8 mg/kg and at the following additional dose levels: 12 mg/kg and 18 mg/kg. The maximum tolerable dose (MTD) was 12 mg/kg. Due to dose reductions and delays during the treatment beyond the DLT assessment period, additional doses below the MTD (8mg/kg and 10 mg/kg) were further evaluated in the dose expansion portion of the trial.

The Phase 2 portion of the trial enrolled patients in four single-arm cohorts (mTNBC, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and urothelial cancer (UC)). Sacituzumab was administered at doses of 8 mg/kg and 10 mg/kg. Sacituzumab was administered as an

intravenous infusion (IV) on days 1 and 8 of continuous 21-day cycles. The protocol was subsequently amended (Amendment 8; April 23, 2015) to state that all patients should be treated at dose of 10 mg/kg.

In the mTNBC efficacy cohort, all patients received a dose of 10 mg/kg. Treatment was administered until evidence of disease progression or unacceptable AEs.

Trial Procedures and Schedule

Table 5 displays the trial calendar.

Table 5: Trial Calendar for IMMU-132-01

PRETREATMENT		TREATMENT (3-Week Treatment Cycles)						POST TREATMENT	
	Within 4 Wks of Entry	Cycle 1			Cycles 2 - 8			Final[1] Study Eval.	Long-Term Follow-up Every 3 months
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		
Signed Informed Consent	X								
Patient Eligibility	X								
Histology review	X								
Pregnancy Test	X[3]				X[3]			X	
Hepatitis B & C Test	X								
Medical/Surgical History	X								
UGT1A1 genotype	X								
CT (chest, abdomen, pelvis; other if needed)	X	X[4]							
EKG	X				X[10]			X	X[2]
Phys. Exam	X				X			X	X[2]
CBC (with diff, platelets)[5]	X	X	X		X	X		X	X[2]
Serum Chemistries[5]	X	X	X		X	X		X	X[2]
PT/PTT	X				X[11]			X[11]	X[2]
Urinalysis	X				X			X	
Concomitant Medications	X	X	X		X	X		X	X[6]
Serum Biomarkers	X	X[4]							
IMMU-132 infusion		X	X		X	X			
Vital Signs	X	X[7]	X[7]		X[7]	X[7]		X	X[2]
Adverse Event Reporting	X	X	X		X	X		X	X[8]
HAHA	X				X[11]			X[11]	
PK[9]		X							
Biopsy / surgical Tissue	X[12]								
Survival status									X

[1] Performed 14 days after the last treatment or in event of premature study termination.
[2] Otherwise, long-term follow-up required every 3 months for up to 2 years in patients who have not progressed, or only until resolution of any treatment-related abnormalities once patients progress.
[3] Pregnancy test will be performed within 1 week prior to treatment, at every other cycle (2, 4, 6 & 8) and at the end of the study.
[4] CT and biomarkers required 8 weeks after the start of treatment until the first (Physician discretion) or second progression of disease. Additional CT can be performed at the discretion of the physician to assess disease status as medically indicated. Suggested serum biomarkers include CEA levels for colon, rectal, and lung cancers; CEA , CA19-9, AFP and hepatitis panel for hepatobiliary cancer; CA-125, βhCG and LDH for ovarian cancer; CA19-9 for pancreatic cancer; CA15-3 for breast cancer; PSA for prostate cancer.
[5] Serum chemistries include glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO2, magnesium and phosphorus. More frequent laboratories required in event of ≥ Grade-3 toxicity
[6] Only IV or prescription anti-infectives or medications for GI toxicity will be recorded.
[7] VS's obtained prior to infusion, every 15 min for the first hour, then every 30 min until completed, and then 30 and 60 minutes post-infusion.
[8] Ongoing AEs until resolved, new events attributed to test article; otherwise, deaths, hospitalizations, or events requiring IV or prescription anti-infectives or medications related to GI toxicity.
[9] After amendment 6, PK samples will be optional and collected only in selected patients after the first dose, with 6 samples obtained: preinfusion, 30 min and 3-4 hours post infusion, then 1, 2, and 3 days later.
[10] Required after completion of day 1 infusion of every other cycle (2, 4, 6 & 8).
[11] HAHA & PT/PTT at baseline then day 1 of every other cycle (2, 4, 6 & 8) and at the end of the study. Two additional monthly samples for HAHA will be collected if positive result after end of treatment.
[12] For IHC evaluation of tumor Trop-2 expression (by the Sponsor) when tissue is available, but this testing is not required for eligibility
NOTE: Unless otherwise specified, collection windows for study time points are nominally within ± 10% or according to institutional standard procedures.

Source: IMMU-132-01 Trial Protocol, page 14

Dose Modification/Discontinuation

Dose modifications were not permitted during cycle 1 (the 1st 21 days of sacituzumab) of the Phase 1 portion of the trial. Beyond Cycle 1 in the dose escalation portion of the trial, the protocol stated that in the event of severe treatment-related AEs, the IMMU-132 dose was to be reduced by 25% of the assigned dose at the first occurrence and to 50% of the initial

assigned dose for the second occurrence. At the third occurrence, treatment was to be discontinued.

The dose was to be reduced the event of any of the following AEs:

Grade 4 hematological AE ≥7 days or other non-hematological AE grade 4 of any duration;
Grade 3 febrile neutropenia
Treatment related nausea, vomiting, or diarrhea grade ≥3 or other non-hematological AE grade ≥3 persisting for >48 hours despite optimal medical management.
Any AE of grade ≥3 at the time of scheduled treatment whose recovery to grade ≤1 delayed dosing by 2 or more weeks

Management of infusion related reactions was permitted with acetaminophen, diphenhydramine, corticosteroids, H2 antagonists, or other drugs as premedication for prevention of reactions.

In the event of a grade ≥3 infusion reaction, trial treatment was to be permanently discontinued.

In the event of grade 2 infusion reactions, the infusion was paused for at least 15 minutes or until symptoms resolved, whichever was greater. The patient could have a lower infusion rate resumed once the patient was stable.

In the event of a grade 1 infusion reaction, it was recommended to slow the infusion rate.

Permitted Concomitant Medications and Therapies

Therapies permitted for the prophylaxis and management of infusion related reactions are described in subsection: Dose Modification/Discontinuation. Additionally, the protocol stipulated that patients with a cholinergic response such as diarrhea, abdominal cramping, or salivation, could receive anticholinergics such as atropine for subsequent administrations of sacituzumab.

Palliative or supportive medications and procedures were permitted at the investigator's discretion.

All anticancer therapy, including radiation therapy, was to be discontinued at least 2 weeks prior to starting trial therapy.

Hematopoietic growth factors and blood transfusions were permitted at the investigator's discretion after Cycle 1 Day 1.

It was recommended that patients avoid strong CYP3A4 inducers and inhibitors be avoided.

Treatment Compliance

Sacituzumab is an IV infusion administered by trial personnel and treatment compliance was recorded by the trial site and in individual patients' case report forms.

Completion, Discontinuation, or Withdrawal

Patients could withdraw from the trial at any time for any reason.

During the Phase 1 portion of the trial, patients were to be discontinued from trial therapy if they experienced dose-limiting toxicities. Dose limiting toxicities were defined as the following:

- Grade 4 neutropenia ≥5 days or Grade 3 or greater febrile neutropenia of any duration
- Grade 4 thrombocytopenia ≥5 days or Grade 3 or greater thrombocytopenia with significant bleeding
- Grade 4 anemia of any duration
- Grade 4 nausea, vomiting, or diarrhea of any duration or any Grade 3 nausea, vomiting or diarrhea which persists for >48 hours despite optimal medical management
- Any Grade 3 infusion-related reactions (e.g. prolonged reactions not responding to symptomatic treatment) which occurs after pre-medication with antihistamines, H2 blockers, and steroids
- Any other ≥Grade 3 non-hematological toxicity at least possibly due to trial drug

The protocol specified that treatment was to be discontinued for the following reasons:

- Documentation of progressive disease at the investigator's discretion or applicant approval or symptomatic deterioration indicating treatment failure
- Treatment delay of >3 weeks for any reason
- Unacceptable toxicity
- Grade ≥3 infusion-related reaction
- If the patient experienced a third instance of drug-related AEs where the first two events required dose reductions as described above

The initial determination of disease progression did not require treatment discontinuation if, in the opinion of the investigator, the patient was continuing to derive clinical benefit. However, treatment had to be discontinued at subsequent documented disease progression.

Amendment 8 (April 23, 2015) allowed for treatment beyond 8 cycles for patients with PR or SD, patients with objective response that relapsed after treatment discontinuation, and for patients with a first occurrence of PD who wished to continue trial therapy after radiological documentation of PD.

Trial Endpoints

The overall trial endpoints were as follows:

Phase 1: The primary objective is to evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles for up to 8 cycles in previously treated patients with advanced epithelial cancer. The secondary objectives were to obtain initial data concerning pharmacokinetics, immunogenicity, and efficacy with this dosing regimen.

Phase 2: Objective response rate using RECIST version 1.1 per local investigator assessment.

Imaging was obtained every 8 weeks with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response (PR or CR) until permanent treatment discontinuation. Independent central review (ICR) was also obtained for patients whose local scans demonstrated at least 20% decrease.

Reviewer Comment: ICR was prespecified in the SAP but not in protocol. Initially ICR was based on single-read (imaging charter dated August 15, 2016) and double-read was added in the charter amendment (October 30, 2017) after pre-BLA meeting (October 12, 2017) per FDA's recommendation. The applicant initially performed a single-read ICR. In the October 2017 pre-BLA meeting, FDA notified the applicant of concerns regarding using a single blinded reviewer without adjudication for the BICR. Taking FDA's recommendation, the applicant amended their charter to include a double-read ICR with adjudication. The single-read ICR results are not reported in this review.

After treatment discontinuation, patients were followed until resolution or stabilization of any treatment related AEs. Patients treated after Amendment 10 who had not progressed at the end of treatment were followed with CT every three months for up to 2 years or until progression or initiation of other treatment.

The secondary endpoints were defined in the SAP as follows:

- Time to response (TTR), defined as the time from the first dose to the first documentation of response (PR or CR).
- Duration of response (DOR), among responders this was calculated as the date of the first evaluation showing documented PR or CR to the date of the first PD. Patients not progressing were censored.
- Clinical benefit rate (CBR), defined as patients in the Target mTNBC Population with best response as CR or PR or else SD with a duration of at least 6 months. SD for 6 months duration was defined as time from the first dose to the first documentation of PD or to the last adequate response assessment prior to data cutoff date, whichever is earlier
- Progression-free survival (PFS), defined as the interval from the first dose start date to the date of disease progression defined as documented PD or death from any cause, whichever occurs first. Death was considered an end point only while the patient was on

trial and receiving treatment or undergoing response assessments. Patients otherwise without adequate response assessments or without radiologic evidence of progression were censored. Clinical PD was not considered as a PFS event.

- Overall survival (OS), defined as time from the date of the first dose start date to the date of death due to any cause. Patients without documentation of death at the time of the data cutoff for analysis will be censored at the date the patient was last known to be alive or the data cutoff date, whichever is earlier.

Statistical Analysis Plan

There was no formal sample size determination for Trial IMMU-132-01. The Phase II trial planned to enroll up to 150 patients in each of 5 expansion cohorts (TNBC, non-TNBC, NSCLC, SCLC, UC).

Reviewer comment: The CSR submitted for this BLA was based on the mTNBC Target Population consisting of n=108 patients and a database cutoff of June 30, 2017. There was no formal statistical justification for the sample size.

All efficacy analyses were to be conducted in the Target mTNBC population, which included patients with mTNBC who had received at least 2 prior anticancer therapies for metastatic disease and who were treated with an IMMU-132 dose of 10 mg/kg. For the primary analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by investigator, the ORR was summarized by the percentage of responses (CR or PR) with a two-sided exact binomial 95% CI.

The secondary endpoints of DOR, PFS, and OS were analyzed with Kaplan-Meier methods with 95% confidence intervals calculated from the Brookmeyer and Crowley method with log-log transformation. The censoring rules for PFS and DOR are shown in Table 6 and Table 7. Note that DOR is only assessed in responders. Additionally, TTR was summarized descriptively and CBR was presented as a response rate with a two-sided exact binomial 95% CI.

Table 6: Guidelines for Response Assessment and Censoring for Analysis of PFS

Guidelines for Progression Assessment and Censoring for Analysis of PFS		
Case	Outcome	Date of Event/Censoring[1]
No adequate response assessment after start of treatment		
Died prior to second scheduled assessment	PD	Date of death
Did not die prior to second scheduled assessment	Censor	Date of first dose
Continued study until objective PD or death		
At scheduled assessment	PD	Date of objective PD
Between scheduled assessments	PD	Date of objective PD or death
After missing 2 or more scheduled assessments	Censor	Date of last adequate response assessment before missed ones
Continued scheduled response assessments without objective PD or death		
Discontinued for undocumented PD, toxicity, other reasons	Censor	Date of last adequate response assessment
Lost to follow-up	Censor	Date of last adequate response assessment
Initiated other treatment	Censor	Date of last adequate response assessment prior to starting other treatment
No objective PD at final assessment	Censor	Date of last adequate response assessment

Abbreviations: CT = Computed tomography, MRI = Magnetic resonance imaging, PD = Progressive disease, PFS = Progression-free survival.

If the onset of response required evaluations at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date was to be used. For PD based on the sum of target lesion measurements at different times, the last measurement date was to be used. For PD based on new or non-target lesions, if these were equivocal at 1 assessment and later considered unequivocal PD, the earliest date when progression was suspected was to be used.

[1] *Adequate response assessment was defined as a response assessment other than 'not assessed' or 'not evaluable'. As progression was based on the sum of target lesion measurements at different time points, the last measurement date was to be used. For progression based on new or non-target lesions which ware equivocal at 1 assessment but later considered unequivocal PD, the earliest date when progression was suspected was to be used.*

Source: Amended SAP dated March 14, 2018, Table 2

Table 7: Guidelines for Response Assessment and Censoring for Analysis of DOR

Guidelines for Progression Assessment and Censoring for Analysis of Duration of Response			
Condition	Case	Outcome	Date of Progression or Censoring
Objective PD occurred	At or between scheduled assessments or prior to missing 2 scheduled successive assessments	PD	Date of objective PD
	After missing 2 or more scheduled successive assessments	Censor	Date of last adequate response assessment
No objective PD occurred	Initiated other treatment	Censor	Date of last adequate response assessment prior to starting other treatment
	Lost to follow-up	Censor	Date of last adequate response assessment
	Data cutoff	Censor	Date of last adequate response assessment
Abbreviations: CT = Computed tomography, MRI = Magnetic resonance imaging, PD = Progressive disease. *If the onset of response requires evaluations at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on the sum of target lesion measurements at different times (ie, chest CT on 1 day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on new or nontarget lesions, if these are equivocal at 1 assessment and later considered unequivocal progression, the earliest date when progression was suspected should be used. If progression occurred after 2 or more scheduled successive response assessments were missed or inadequate, the outcome will be censored at the last prior adequate assessment. Adequate response assessment is defined as a response assessment other than "not assessed" or "not evaluable" for the determination of duration of response. If objective evidence of progression has not occurred and the patient is either lost to follow-up, died, a new treatment is initiated, or data cutoff occurs, then the outcome will be censored at the last prior adequate assessment.*			

Source: Amended SAP dated March 14, 2018, Table 3

Reviewer Comments: On July 3, 2018, the FDA sent an IR to the applicant asking them to recalculate duration of response with death included. The standard regulatory definition of DOR is defined from the onset of response until PD or death, whichever occurs first. Death after 2+ missing scheduled assessments should be censored at the last assessment prior to the missing ones. The DOR results presented in this review follow the standard regulatory definition.

Additionally, swimmer plots of treatment duration and waterfall plots for percent change from baseline in target lesion measurement were presented. The planned sensitivity analyses included analyses in the 94 patients who received at least 2 lines of prior standard chemotherapy for metastatic disease and the 102 patients in the Per-Protocol (PP) Population, defined as patients of the Target mTNBC Population who received at least one complete cycle of IMMU-132 and had data available from at least one response assessment. The planned subgroup analyses included age, race, ethnicity, ECOG performance status, and Trop-2 status,

as well as number of prior therapies for metastatic disease and number of prior chemotherapies for metastatic disease, given sufficient patient numbers allow for reliable presentation.

The FDA does not use inferential procedures to evaluate results from single-arm trials. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response. Additionally, we note that time-to-event endpoints (PFS and OS) are uninterpretable without a comparator arm.

Protocol and SAP Amendments

A total of 11 protocol amendments prior to the CSR data cutoff date of June 30, 2017. The major changes implemented in each of the amendments are summarized in Table 8.

Table 8: Summary of Amendments to IMMU-132-01

Amendment/ Date	Patients Enrolled	Modifications
1 Jul 26, 2012	0	• Changed the weekly dosing schedule to 2 weekly administrations within a 21-day cycle. • Revised DLT definition to specify that patients receiving therapy for prevention of infusion reactions would not be eligible for evaluation of the MTD. • Removed patients with breast or prostate cancer from list of eligible cancer types. Note: modifications were adopted prior to patient enrollment and prior to the mTNBC cohort of interest.
2 Aug 22, 2012	0	• TNBC and hormone refractory prostate cancer to the list of eligible cancer types. • Clarified the frequency of human anti-human antibody (HAHA) sample collection in patients with a positive HAHA results at the end of treatment.
3 Feb 6, 2013	1	• Allowed for patients with urothelial carcinoma, clear cell renal cell carcinoma, esophageal cancer, and squamous cell carcinoma of the head and neck to be enrolled. • Explained that patients with SCLC and NSCLC would be able to be enrolled as well. • Suggested that serum biomarkers such as PSA or CA-125 for each eligible cancer type were to be assessed.
4 Aug 5, 2013	24	• Modified the trial design to add a Phase 2 portion with up to 15 patients per cancer type being recruited for up to 2 dose levels at or below the maximum acceptable dose. This was to provide additional safety and efficacy data for each of the indications. • Specified that tumor types where ≥15% of patients demonstrated shrinkage of their target lesions, would merit further

Amendment/ Date	Patients Enrolled	Modifications
		investigation. • Specified that patients were allowed to continue treatment beyond 8 treatment cycles at the physician's discretion. • Patients were allowed to continue treatment at the first documentation of PD, however treatment was to be permanently discontinued at the 2nd documentation of PD. • Added collection of samples for UGT1A1 genotyping and the assessment of hematological AEs by UGT1A1 status. • Recommendations for management of infusion related reactions were expanded. • Clarified that in the case of grade ≥3 AEs, treatment was to be temporarily discontinued and patients were to be assessed weekly. If recovery to grade ≤1 delayed the dose by ≤ 1week, no dose reduction was necessary. However, if it delayed the dose by 2-3 weeks, treatment must be resumed at a reduced dose (25% reduction from the original dose at the first event, 50% dose reduction at the second occurrence, and permanent discontinuation at the third occurrence). If recovery required > 3 weeks' delay, treatment had to be permanently discontinued. • Eligibility criteria modified to include patients with an ANC ≥1.5 x 10^9/L and patients with a serum bilirubin ≤1.5 x ULN. • Included preliminary results of the Phase 1 trial to justify the dose for the Phase 2 portion of the trial. Protocol states that a dose of 12 mg/kg had been determined as the MTD and was associated with dose reductions and delays. The next-lower dose of 8 mg/kg had been shown to be safe in Phase 1. An intermediate dose of 10 mg/kg was continuing to be evaluated and was intended to be the second dose level in Phase 2 if found to be safe. It was stated that a lower dose level of 6 mg/kg could be used in certain conditions where patients did not meet the criteria of the maximum acceptable dose at the 8 mg/kg dose level. • Specified that scans were to be obtained 8 weeks after the start of treatment and that scans were to be repeated every 8 weeks as well as when medically indicated. • RECIST 1.1 was specified as the assessment of tumor response. • Efficacy endpoints of PFS, OS and time to treatment failure were removed. • Specified that the efficacy population would be those patients defined as completing 3 full treatment cycles. • Additional PK samples were specified at this time as well.
5 Aug 23, 2013	31	• Specified that the KRAS mutational status had to be determined in patients with colorectal, lung and pancreatic cancer (results not required to determine eligibility).
6	120	• Modified the criterion for patients with bulky lesions to increase

Amendment/ Date	Patients Enrolled	Modifications
May 30, 2014		the maximum size of this lesion from 5 cm to 7 cm. • Extended the required interval between prior therapy from 2 to 4 weeks and patients had to have recovered from AEs from prior therapy to grade ≤1 (excluding alopecia). • Modified the waiting period after high dose systemic steroids to 2 weeks. • Revised eligibility to permit patients with known CNS metastases to enroll if they had received adequate treatment and had no evidence of progression or symptoms for at least 3 months. • Specified that successive groups of 6 patients with a specific tumor type at a particular dose level with the intent to discontinue enrollment if the incidence of severe AEs during the first cycle was ≥33% or if <20% of patients treated at that dose level had at least SD as best response. • The collection of PK samples became optional. • Specified that the dose for IMMU-132 be calculated at the beginning of each cycle or more frequently for patients with a >10% change in body weight. • Revised so that if a patient had neutropenia or a GI AE that was grade ≥2 at the planned start of treatment, treatment should be held until resolution of the AE to grade ≤ 1. If this required a delay of >3 weeks, the patient was to be withdrawn from the trial. • Follow-up of patients every 3 months was added and survival time was added as an efficacy endpoint.
7 Dec 9, 2014	177	• Allowed for patients with cervical cancer or endometrial cancer to enroll and removed restriction to TNBC. • Number of planned patients in each cohort for Phase 2 increased to 50. • Implemented collection of data regarding the treatment response and time to progression for the last treatment prior to trial regimen. • Genotype variants for breast and ovarian cancers (BRCA 1/2); colorectal and pancreatic cancers (KRAS), and lung cancer (ALK, EGFR, and PI3KC) added; however, results were not required to determine patient eligibility. • Tumor biomarkers were specified. • Confirmatory CT/MRI scans were to be obtained in any patient with PR or SD with ≥20% shrinkage of target lesions within 4-6 weeks of this assessment. • Revised trial to allow for use of growth factors as secondary prophylaxis; use prior to trial therapy was not allowed. • Patients who had a first assessment of PD but were determined to derive clinical benefit could continue at the investigator's discretion; treatment was to be discontinued if subsequent

Amendment/ Date	Patients Enrolled	Modifications
		imaging documented PD from that assessment. • PK sample was added at day 7. • Clarification of the laboratory, vital signs, and physical examination assessments. • Deviations in treatment schedule of up to seven days due to holidays, vacations, or personal reasons were allowed.
8 Apr 23, 2015	259	• Revised so that all patients would be treated with IMMU-132 at a dose of 10 mg/kg. • Breast cancer cohort was returned to only TNBC and the bladder cancer cohort was clarified to include urothelial carcinoma. • Planned number of patients for TNBC and NSCLC was increased to 130 patients and 100 patients respectively based on ORR of 26% and 33% respectively. • Clarified that if a confirmatory scan was performed then all subsequent scans had to be scheduled at 8-week intervals from the confirmatory scan. • Frequency of patient follow-up visits for vital status was changed from every 3 months to every month.
9 Jul 9, 2015	279	• Investigators advised to consult the applicant prior to consenting and performing screening procedures in potentially eligible patients to allow applicant planning, particularly with regard to the drug supply. • There was also a temporary suspension of recruitment of TNBC patients to allow the applicant to evaluate efficacy in the TNBC patients included in the trial to date. • Cohorts of patients with GBM, follicular thyroid cancer, and metastatic non-TNBC were added to the list of eligible tumor types. • The colorectal cancer and pancreatic cancer cohorts were removed from the list of eligible tumor types as the respective accrual targets had been reached. • Clarified that patients who had relapsed after or were refractory to at least one standard chemotherapy or hormonal regimen were allowed to participate. • Required wash-out period was shortened from 4 to 2 weeks. • Patients with treated, stable brain metastases who had not received high-dose steroids allowed for inclusion. • Clarified that IMMU-132 dosing was not allowed to be re-escalated after prior dose reductions. • PFS added as an efficacy endpoint.
10 Nov 7, 2016	405	• Modified accrual target for TNBC, NSCLC, SCLC, and UC to 150 assessable patients. • Clarified that patients with mTNBC were clarified to be those patients who had TNBC histology based on the most recently

Amendment/ Date	Patients Enrolled	Modifications
		analyzed biopsy. Furthermore, patients had to have received at least 2 prior therapies for metastatic disease including a taxane in any setting. Chemotherapy, biological or targeted agents were allowed as qualifying prior therapies, but endocrine or HER2 agents were not. • Clarified that patients could continue treatment with IMMU-132 for any number of cycles in the absence of unacceptable AEs or PD requiring termination of further treatment. • Clarified that an initial response of CR or PR was to be confirmed 4-6 weeks after the initial response assessment. For patients with SD who have evidence of tumor shrinkage that was close to PR, the 8-week interval for the next assessment could be shortened at the investigator's discretion. Patients who had not progressed at the end of treatment were to be followed with CT scans every 3 months for up to 2-year or until PD or initiation of another anticancer therapy. • Revised PK sample collection • Reduced the frequency of vital sign assessment in subsequent infusions of IMMU-132.
11 Apr 4, 2017	420	• Updated the vial size and reconstitution guidelines for IMMU-132 after a change in manufacturing.

The original statistical analysis plan (SAP) v1.0 was dated October 24, 2017, and was amended on March 14, 2018 (v2.0) after clinical database lock. Version 2.0 of the SAP served as the final SAP. The major changes in v2.0 included updating the sample size for the efficacy population (mTNBC Population) to 108 based on the enrollment, and, updating/revising various definitions/derivations for secondary/other endpoints, populations, and protocol violation categories.

8.1.2. Trial Results

Compliance with Good Clinical Practices

According to the applicant, IMMU-132-01 was conducted in full conformance with the ethical principles of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) as required by the major regulatory authorities and in conformance with the principles set forth in the Declaration of Helsinki, Directive 2001/20/EC, as well as with applicable laws and regulations. Written informed consent was obtained from each trial participant or their legal representative. The trial protocols and amendments were approved by local Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

Financial Disclosure

According to the BLA submission, all investigators in Trial IMMU-132-01 were assessed for equity interest, other significant payments, and other compensation by the Applicant as well as proprietary interest in this agent. Certification was provided by all 13 investigators listed for Trial IMMU-132-01. No financial arrangements with investigators by the Applicant were reported, and none of the investigators disclosed a proprietary interest in the product or significant equity in the applicant.

Patient Disposition

In the initial submission with a data cut-off date of June 30, 2017, a total of 425 patients had enrolled in Trial IMMU-132-01 (Phase 1, n=25; Phase 2, n=400), of whom a total of 148 had mTNBC. Among the 148 patients who had mTNBC, 131 patients received IMMU-132 10 mg/kg, and 108 of those patients had received 2 or more lines of therapy in the metastatic setting, prior to receiving IMMU-132 (efficacy population). Patient disposition for the cohorts of patients who comprise the efficacy population for this application is summarized in Table 9

Table 9: Patient Disposition for the mTNBC Population of IMMU-132-01

Disposition	mTNBC Efficacy Population N=108
Discontinued therapy	105 (97.2)
Adverse event	5 (4.6)
Withdrawal of Consent	2 (1.9)
Investigator decision	7 (6.5)
Death	1 (0.9)
Progressive disease	90 (86)
Missing	1 (0.9)
Ongoing on treatment	3 (2.8)

Source: Reviewer Table; adsl.xpt dataset data cut off December 1, 2017; Safety Update Report data cut off March 1, 2019; adsl.xpt dataset data cut off March 1, 2019.

Reviewer Comment: At the time of the Safety Update Report with data cut off date of March 1, 2019, 3 patients were continuing therapy. The majority of patients with mTNBC had discontinued treatment due to progression of disease (n=90, 86%).

Protocol Violations/Deviations

In the trial population of IMMU-132-01 where patients regardless of cancer type had received at least one dose of IMMU-132, a total of 11 (10.2%) patients had one or more major protocol violations. Table 10 demonstrates the incidence of major protocol violations by type.

Table 10: Protocol Deviations for Patients Who Received ≥1 dose of IMMU-132

Deviation Category	Total Population n=420 n (%)
Patients with ≥1 major protocol violation	11 (2.6)
Inclusion/exclusion criteria violated	5 (1.2)
• <2 weeks between prior therapy and start of IMMU-132 treatment	5 (1.2)
Prohibited therapy	7 (1.7)
• Anticancer therapy during IMMU-132 treatment	5 (1.2)
• Prophylactic use of growth factors or transfusions prior to Cycle 1	2 (0.5)
• Radiation during treatment with IMMU-132	1 (0.2)

Source: Reviewer analysis using addv.xpt dataset & Table 13 on page 71 of the CSR

In the mTNBC efficacy population from the IMMU-132-01 trial, a total of 3 (2.8%) patients had one or more major protocol violations. Table 11 below demonstrates the incidence of major protocol violations by type.

Table 11: Protocol Deviations for the mTNBC Efficacy Population in IMMU-132-01

Deviation Category	mTNBC Efficacy Population N=108
Patients with ≥1 major protocol violation	3 (2.8)
Inclusion/exclusion criteria violated	1 (0.9)
• <2 weeks between prior therapy and start of IMMU-132 treatment	1 (0.9)
Prohibited therapy	3 (2.8)
• Anticancer therapy during IMMU-132 treatment	2 (1.9)
• Prophylactic use of growth factors or transfusions prior to Cycle 1	2 (1.9)

Source: Reviewer analysis using addv.xpt dataset & Table 13 on page 71 of the CSR

Reviewer Comments: The incidence of protocol violations in the overall trial was similar to that in the mTNBC efficacy population. The review of the CRFs and clinical site inspections revealed additional protocol violations. For example, 2 patients who were identified as responders, were noted to have radiation to new CNS lesions which were not documented as disease progression (b) (6) *; these patients continued to receive IMMU-132 for additional cycles and were not documented as disease progression until a later date. Review of additional information regarding the treatment course of all patients who was identified as responders in the BLA submission (n=36), obtained through several information requests, revealed the following:*

- *Patient* (b) (6) *had an off-protocol brain MRI completed that documented disease progression. The results of this scan were not recorded as disease progression and the brain MRI was not sent for independent central review (ICR) even though this patient had been selected to undergo response assessment by ICR.*

- *Patient (b) (6) underwent multiple thoracenteses until response was achieved.*

The overall impact of these protocol violations is that for the patients who experienced progression in the CNS and received radiation treatment to the CNS lesions, the applicant's report of duration of response did not reflect the progressive events, though there was no impact on the ORR. However, this finding raised concerns about the conduct of the trial and the reporting of trial findings in the BLA submission. For the patient who had multiple thoracenteses while continuing treatment with IMMU-132, went on to no longer require thoracenteses and to have a partial response.

Two patients (b) (6) received other anticancer therapy (navelbine; taxotere, trastuzumab, pertuzumab) while on IMMU-132; however, since these patients were not identified as responders, this deviation did not impact the efficacy findings.

There were 14 patients in the mTNBC population who received a waiver for enrollment. Five of these patients had bulky disease, two patients had a pregnancy test outside of the required window, two patients had extended screening periods, one patient did not meet baseline hematological parameters and had bulky disease, one patient had brain metastases, one patient did not receive a prior taxane, one patient requested that they receive day 8 on day 10, and one patient did not have at least 2 weeks since prior therapy or at least four weeks after surgery.

Table of Demographic Characteristics

Demographic data for the mTNBC efficacy population from IMMU-132-01 are included below in Table 12.

Table 12: Demographic Data for the mTNBC Efficacy Population of IMMU-132-01

Demographic Parameters	mTNBC Efficacy Population N=108 n (%)
Sex	
Male	1 (0.9)
Female	107 (99.1)
Age	
Mean years (SD)	54.2 (10.3)
Median (years)	55
Min, max (years)	31, 80
Age Group	
< 65 years	89 (82.4)
≥ 65 years	19 (17.6)
ECOG	
0	31 (28.7)
1	77 (71.3)

Demographic Parameters	mTNBC Efficacy Population N=108 n (%)
Race	
White	82 (75.9)
Black or African American	8 (7.4)
Asian	3 (2.8)
American Indian or Alaska Native	1 (0.9)
Native Hawaiian or Other Pacific Islander	0
Other	14 (13.0)
Ethnicity	
Hispanic or Latino	7 (6.5)
Not Hispanic or Latino	100 (92.6)
Region (optional)	
United States	108 (100)

Source: Reviewer analysis using adsl.xpt dataset

Reviewer Comments: The patient population generally reflects the patients who would be receiving this therapy after approval. Most patients with mTNBC are younger than 65 and most patients are female. There were small numbers of African-American patients enrolled in this trial, though there is a higher incidence of TNBC among African-American patients (Lund 2009; Carey 2006). Most patients had an ECOG performance status of 1 which reflects that these patients have some debility from their disease and/or prior therapy for their disease.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease characteristics for the patients in the IMMU-132-01 mTNBC efficacy population are included in Table 13.

Table 13: Pretreatment Disease Characteristics of the mTNBC Efficacy Population of IMMU-132-01

Pretreatment Disease Characteristic	mTNBC Efficacy Population N=108 n (%)
Time since initial diagnosis (months) (n=102)	
Mean (Std Dev)	64.0 (58.8)
Median (Q1-Q3)	43.7 (27.9,89.1)
Min, Max	3.6, 413.5
Initial Diagnosis Disease Stage	
Stage 0-II	60 (55.6)
Stage III	32 (29.6)
Stage IV	12 (11.1)
Stage at Trial Entry	
Metastatic	106 (98.1)
Unknown	2 (1.9)

Pretreatment Disease Characteristic	mTNBC Efficacy Population N=108 n (%)
Nature of disease	
Visceral	82 (75.9)
Other	26 (24.1)
Measurable Disease	
Yes	108 (100)
Brain Metastases	2 (1.9)
Creatinine > ULN	4 (3.7)
Hepatic Impairment defined as the presence of at least one of the following criteria: ALT > ULN, AST > ULN, or total bilirubin > ULN	26 (24.1)
Prior (neo)adjuvant chemotherapy (denominator is the 96 patients who did not have initial stage IV diagnosis)	88 (91.7)
Median number of prior therapies in the metastatic setting (range)	3 (2, 10)
Median number of prior cytotoxic chemotherapies in the metastatic setting (range)	2 (1, 8)
Prior chemotherapy in the metastatic setting	
Platinum	74 (68.5)
Gemcitabine	59 (54.6)
Taxane	56 (51.9)
Capecitabine	55 (50.9)
Eribulin	49 (45.4)
Anthracycline (doxorubicin and epirubicin)	28 (25.9)
Alkylating agent (cyclophosphamide or ifosfamide)	21 (19.4)
Vinorelbine	17 (15.7)
Ixabepilone	9 (8.3)
Prior endocrine therapy	25 (23.1)

Source: Reviewer analysis using adsl.xpt & adcm.xpt

Reviewer Comments: Most patients in this trial had received two prior chemotherapies, though there was one patient who had received only one prior chemotherapy but had also received a non-chemotherapy treatment option in the metastatic setting. Few patients had mild hepatic impairment, brain metastases, or a creatinine above the upper limit of normal. Most patients received a platinum (cisplatin or carboplatin) in the metastatic setting, and had received other agents such as taxanes, capecitabine, and gemcitabine that are used in this setting. Most patients (96, 88.9%) were diagnosed in the early stage setting and had received prior adjuvant chemotherapy. While all patients had biopsies consistent with hormone receptor negative disease in the metastatic setting, approximately 23% of patients had received prior endocrine

therapy. All patients had measurable disease as this was an eligibility requirement given that the primary efficacy measurement was ORR by RECIST 1.1. The population overall was generally consistent with the US population that would be eligible for treatment based on the proposed indication.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance of sacituzumab was assessed as this agent was administered as an intravenous infusion by trial personnel at each trial site. For each patient infusion, the start and stop time were documented on the Case Report Form (CRF). Infusion interruptions and discontinuations were also documented.

Concomitant Medications

All patients in the mTNBC efficacy Population were on concomitant therapies at some point during trial participation. Concomitant therapies received by more than 20% of trial participants are described in Table 14.

Table 14: Concomitant Medications Used in >30% of Patients in the mTNBC Efficacy Population

Concomitant therapy	mTNBC Efficacy Population N=108 n (%)
≥ 1 therapy	108 (100)
Antiemetics	105 (97.2)
Ondansetron	78 (72.2)
Prochlorperazine	53 (49.1)
Palonosetron	47 (43.5)
Fosaprepitant	42 (38.9)
Granesitron	26 (24.1)
Corticosteroids	79 (73.1)
Dexamethasone	78 (72.2)
Opioids	71 (65.7)
Oxycodone	38 (35.2)
Drugs for Peptic Ulcer Disease and GERD	70 (64.8)
Famotidine	51 (47.2)
Omeprazole	27 (25.0)
Anxiolytics	70 (64.8)
Lorazepam	54 (50.0)
Vitamin and Mineral Supplements	69 (63.9)
Vitamin D	37 (34.3)
Other analgesics and antipyretics	64 (59.3)

Concomitant therapy	mTNBC Efficacy Population N=108 n (%)
Acetaminophen	39 (36.1)
Antihistamines	62 (57.4)
Diphenhydramine	53 (49.1)
Granulocyte Colony Stimulating Factor (incl. filgrastim & peg-filgrastim)	58 (53.7)
Antidiarrheals	52 (48.1)
Loperamide	45 (41.7)
Non-steroidal anti-inflammatory agents	49 (45.4)
Drugs to relieve constipation	46 (42.6)
Antibiotics	40 (37.0)
Antithrombotic (incl. alteplase for line anticoagulation &heparin flushes)	40 (37.0)
Antidepressants	33 (30.6)

Source: Reviewer analysis using adcm.xpt &Table 23 on page 83 of the CSR.

Reviewer comments: All patients were on one or more concomitant therapies. The most common concomitant therapies were anti-nausea therapies. Corticosteroids were also common and could have been used as antiemetics as well as agents to prevent infusion-related reactions. The most common drug used for peptic ulcer disease/GERD was famotidine, an H2-antagonist that could have also been used to prevent infusion-related reactions. Over one-half of patients received G-CSF agents during their treatment. Approximately one-half of patients received antidiarrheals. This table demonstrates that there were multiple supportive therapies: antiemetics, steroids, antihistamines and H2 blockers, and G-CSF, that patients received in order to tolerate therapy. Additionally, review of the adcm.xpt dataset indicated that eleven patients (10.2%) received atropine to control the cholinergic adverse effects of the therapy which may have included abdominal cramping, diarrhea, diaphoresis, increased salivation, increased lacrimation, and visual changes. These data support the labeling recommendations regarding supportive care for neutropenia, nausea and vomiting, diarrhea, pretreatment medication to and prevent infusion-related reactions that is discussed in section 5 of the USPI. Use of these medications may improve the tolerability of trial therapy and therefore possibly affect treatment efficacy.

Efficacy Results – Primary Endpoint

The analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by investigator was based upon the efficacy population (n=108) and a trial cut of data of June 30, 2017; the results are shown in Table 15. The confirmed ORR was 33.3% (n=36; 95% CI: 24.6%, 43.1%) consisting of 3 complete responses (CRs, 2.8%) and 33 partial responses (PRs, 30.6%).

The median time to response was 2.0 months (range: 1.6, 13.5). During the review of the initial submission, FDA requested that the applicant provide additional data to reflect longer follow-up for patients who were identified as responders in the original BLA submission (i.e., patients

identified as responders based upon a data cut off date of June 30, 2017). The duration of response among these responders based upon a data cut-off date of December 1, 2017 is also shown in Table 15.

Table 15: Primary Analysis of Confirmed ORR by Investigator

	mTNBC Efficacy Population N=108
Responders (CR+PR) n % (95% CI) DCO: June 30, 2017	36 33.3% (24.6, 43.1)
CR, n (%)	3 (2.8)
PR, n (%)	33 (30.6)
Time to Response (months)	
Median (range)	2.0 (1.6, 13.5)
Duration of Response (months) DCO: June 30, 2017	
Median[1] (95% CI[2])	8.4 (4.9, 11.6)
Range	(1.4+, 24.6+)
≥3 months, n (%)	29 (80.6)
≥6 months, n (%)	15 (41.7)
≥9 months, n (%)	11 (30.6)
Duration of Response (months) DCO: December 1, 2017	
Median[1] (95% CI[2])	7.7 (4.9, 10.8)
Range	(1.9+, 30.4+)
≥3 months, n (%)	34 (94.4)
≥6 months, n (%)	20 (55.6)
≥9 months, n (%)	12 (33.3)
≥12 months, n (%)	6 (16.7)

[1] Kaplan-Meier estimate
[2] Brookmeyer and Crowley method with log-log transformation
+ denotes ongoing response
Source: adrs.xpt & adtte.xpt from the original submission dated May 18, 2018 and the final updated datasets submitted October 8, 2018

Reviewer Comment: The BLA submission was based on a DCO of June 30, 2017. Based on the data in the submission, there were 15 patients with response durations censored due to data cutoff, including 7 patients with response durations censored at <3 months. Thus, the FDA requested updated data based on a DCO of 1 December 1, 2017, to get a more mature estimate of duration of response (median of 7.7 months [95% CI: 4.9, 10.8]).

In response to FDA's request for this additional data, the applicant noted that based on the new DCO, 23 of the 36 original responders had no additional efficacy evaluations and no change in efficacy outcome; however, the 13 remaining responders did. The updated data also included changes in dates of PD for three patients (b) (6) *identified by FDA review*

of the CRFs. Patients [redacted] *were part of the 23 patients with no additional efficacy evaluations; both were PD at the June DCO but their PD dates were updated to earlier dates. Patient* [redacted] *was originally censored at the June DCO but FDA review determined it had a PD event. As discussed previously in this review, during clinical site inspections and data review it was determined that patients* [redacted] *had imaging revealing progressive disease in the brain that was not originally considered progressive disease. The PD date for patient* [redacted] *was changed to correspond with what was reported in the CRF.*

Confirmed ORR by RECIST 1.1 per Double-Read ICR

As specified in the SAP, independent central review (ICR) was performed on patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation; a total of 55 patients met these criteria. Results based on the double-read ICR under both DCO dates are shown in Table 16. The confirmed ORR was 32.4% (95% CI: 23.7%, 42.1%) consisting of 6 complete responses (CRs, 5.6%) and 29 partial responses (PRs, 26.9%).

The median time to response was 2.1 months (range: 1.6, 9.2). The Kaplan-Meier estimated median duration of response was 6.7 months (95% CI: 3.8, 11.3) based upon the June 30, 2017 DCO, and 9.1 months (95% CI: 4.6, 10.7) based upon the December 1, 2017 DCO.

Reviewer Comment: To get updated data with a December DCO based on double-read ICR, the applicant noted that they reinitiated the blinded independent central read with the same 2 radiologists and adjudicator. In the updated results, they noted two additional partial responders, updating the new total number of responders to 37. However, the FDA review focused only on the original 35 responders per double-read ICR. Thus, the results shown in Table 16: were adjusted accordingly to present time to response and duration of response for only the original 35 responders.

Table 16: Sensitivity Analysis of Confirmed ORR by Double-Read ICR

	mTNBC Efficacy Population N=108
Responders (CR+PR) n % (95% CI) DCO: June 30, 2017	35 32.4% (23.7, 42.1)
CR, n (%)	6 (5.6)
PR, n (%)	29 (26.9)
Time to Response (months)	
Median (range)	2.1 (1.6, 9.2)
Duration of Response (months) DCO: June 30, 2017	
Median[1] (95% CI[2])	6.7 (3.8, 11.3)
Range	(1.4+, 22.8+)
≥3 months, n (%)	29 (82.9)

	mTNBC Efficacy Population N=108
≥6 months, n (%)	15 (42.9)
≥9 months, n (%)	12 (34.3)
Duration of Response (months) DCO: December 1, 2017	
Median[1] (95% CI[2])	9.1 (4.6, 10.7)
Range	(3.0, 28.6+)
≥3 months, n (%)	35 (100.0)
≥6 months, n (%)	18 (51.4)
≥9 months, n (%)	15 (42.9)
≥12 months, n (%)	5 (14.3)

[1] Kaplan-Meier estimate
[2] Brookmeyer and Crowley method with log-log transformation
+ denotes ongoing response
Source: adrs.xpt & adtte.xpt from the double-read ICR datasets submitted June 29, 2018 & the final updated datasets submitted October 8, 2018

The response concordance between investigator and the double-read ICR is shown in Table 17. There was an overall concordance of 76% if comparing each response category but the concordance of responders vs. non-responders was higher at 92%. Note that of the 36 investigator-assessed responders, 33 were also responders by double-read ICR. The remaining 3 included 2 SD and 1 NA.

Table 17: Concordance between Investigator and Double-Read ICR Assessment of ORR

	Double-Read ICR					
Investigator	**CR**	**PR**	**SD**	**PD**	**NA**	**Total**
CR	2	1	0	0	0	3
PR	4	26	2	0	1	33
SD	0	2	13	2	1	18
PD	0	0	0	1	0	1
Total	6	29	15	3	2	55

Source: adrs.xpt in original submission dated 5/18/18 & double-read ICR datasets submitted 6/29/18

Reviewer Comment: There was good concordance between the investigator and double-read ICR assessment of response. The double-read ICR assessment was based on a subgroup of patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation rather than the entire efficacy population. Given the inherent bias in evaluating response only among patients whom have been identified by investigators as responders or as having 20% tumor shrinkage (i.e. SD), FDA considers the partial review inadequate to determine whether there is consistency in the ORR results across both assessment methods. As such, this reviewer recommends not including this information in product labeling. Instead, the applicant should provide the results of an independent assessment of ORR, that includes the entire efficacy

population, and that is based upon the data cut off date of the original BLA submission (June 30, 2017), and also provide duration of response for these patients, in order to support labeling.

In the applicant's response to the CR, they noted that a blinded independent central review will not be done for the entire efficacy population and agreed to limit the efficacy data presentation in the product label to the investigator-assessed results.

Exploratory Subgroup Analyses

Exploratory subgroup analyses of confirmed ORR by investigator assessment were conducted by age (<65, ≥65), race (Black or African American, White, Other), Trop-2 status (No/Weak Staining, Moderate/Strong Staining, Not Done), visceral disease (yes, no), liver disease (yes, no), and receiving at least 2 prior chemotherapies (yes vs. no). Results are shown in Table 18.

Table 18: Exploratory Subgroup Analyses

	n	# Responders	Confirmed ORR (95% CI)
Age group			
<65	89	29	32.6% (23.0, 43.3)
≥65	19	7	36.8% (16.3, 61.6)
Race			
Black or African American	8	3	37.5% (8.5, 75.5)
White	82	27	32.9% (22.9, 44.2)
Other	18	6	33.3% (13.3, 59.0)
Trop-2 Status			
No/Weak Staining	5	0	0% (0.0, 52.2)
Moderate/Strong Staining	57	23	40.4% (27.6, 54.2)
Not Done	46	13	28.3% (16.0, 43.5)
Visceral Disease			
Yes	82	23	28.0% (18.7, 39.1)
No	26	13	50.0% (29.9, 70.1)
Liver Disease			
Yes	45	11	24.4% (12.9, 39.5)
No	63	25	39.7% (27.6, 52.8)
Receiving at least 2 prior chemotherapies			
Yes	94	31	33.0% (23.6, 43.4)
No	14	5	35.7% (12.8, 64.9)

Source: adrs.xpt & adsl.xpt Data cutoff date June 30, 2017.

Reviewer Comment: Response rates were generally consistent across all subgroups except for Trop-2 Status: No/Weak Staining which only had 5 patients with no responders and a wide confidence interval. Otherwise, no outlier subgroups were observed. All subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference can be drawn. Additionally, in the case of Trop-2, testing was conducted with a test whose

performance characteristics are unknown (see Section 6.3.2 in original BLA review dated January17, 2019).

Data Quality and Integrity

Refer to See section 4.1 regarding the OSI findings. In general, there was evidence of a lack of control, oversight, and management of the conduct of Trial IMMU-132-01. The inspections also revealed some discordance between source data (EMRs, patient clinical charts) and the information in the CRFs and datasets as previously described. Overall, the inspectional findings and this reviewer's review of the case report forms and datasets indicate that the datasets in the BLA were of reasonable quality and consistency. It was generally easy to recreate the results found in the trial CSR.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoints were time to response (TTR), duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS)as assessed by the investigator.

TTR and DOR were described previously as related to the primary endpoint of confirmed ORR.

The investigator-assessed CBR (CR+PR+SD≥6 months) was 44.4% (95% CI: 34.9%, 54.3%), and 45.4% (95% CI: 35.8%, 55.2%), based on data cutoff date of June 30, 2017 and December 1, 2017, respectively.

The investigator assessed PFS showed the following:

- 84 (77.8%) patients had a PFS event with an estimated median PFS time of 5.6 months (95% CI: 4.8, 6.6) based on a data cutoff date of June 30, 2017.
- 94 (87.0%) patients had a PFS event with an estimated median PFS time of 5.5 months (95% CI: 4.1, 6.3) based on a data cutoff date of December 1, 2017.

There were 61 deaths (56.5%) with an estimated median survival time of 13.0 months (95% CI: 11.2, 14.4), and 77 deaths (71.3%) with an estimated median survival time of 13.0 months (95% CI: 11.2, 13.7), based on data cutoff dates of June 30, 2017 and December 1, 2017, respectively.

Reviewer's Comment: Because time to event endpoints such as PFS and OS are not interpretable in a single-arm trial without a control arm, the results of the analyses of these endpoints is considered exploratory/hypothesis generating.

Dose/Dose Response

An analysis of dose and response was not conducted given that the efficacy analysis was based upon the subgroup of patients with mTNBC who had received 2 or more prior therapies for

metastatic disease, and who received sacituzumab 10 mg/kg. Additionally, an analysis of efficacy in patients in the safety population who received doses other than 10 mg/kg was not possible as efficacy data for these patients were not included in the BLA.

Durability of Response

Duration of response is discussed with the assessment of the primary endpoint, ORR. Results of duration of response are shown in Table 15 and Table 16:

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

There were no further analyses completed.

8.1.3 Integrated Review of Effectiveness

Preliminary ORR and DOR from IMMU-132-05

During review of the complete response submission, FDA learned that the confirmatory trial IMMU-132-05 (NCT02574455) was fully accrued and that topline results for the primary endpoint of progression free survival (PFS) may be available before review of the complete response was complete. An informal teleconference was held on January 9, 2020 during which Immunomedics stated that topline data would not be available during the BLA review cycle. Consequently, FDA requested Immunomedics to submit preliminary ORR and DOR data from both arms in order to support the efficacy observed in trial IMMU-132-01. To maintain data integrity for the ongoing trial, the applicant used an independent third-party statistician and put in access restrictions so that Immunomedics remained blinded to the trial results.

IMMU-132-05 is a randomized, open-label, phase 3 trial of sacituzumab (IMMU-132) vs. treatment of physician's choice (TPC) in patients with metastatic triple-negative breast cancer after ≥2 prior chemotherapies for advanced disease or >1 therapy for pts who progress within 12 months of adjuvant therapy . Patients were randomized 1:1 to receive either IMMU-132 or TPC from one of 4 prespecified single-agent regimens (capecitabine, eribulin, vinorelbine or gemcitabine). The primary endpoint is progression-free survival (PFS) as assessed by blinded independent review. Secondary endpoints include overall survival (OS), ORR, DOR, safety and quality of life. The data cut-off for the IRC data was January 31, 2020. The preliminary results of IRC-assessed ORR and DOR were supportive of the efficacy of sacituzumab.

Additionally, during the review of the BLA resubmission, the DSMC for trial IMMU-132-05 recommended that it be halted early due to evidence of "compelling efficacy". The FDA requested the top-line results of IMMU-132-05 trial from the DSMC committee. The results further supports the efficacy of sacituzumab.

Additional Efficacy Considerations

Trial IMMU-132-01 evaluated a relatively small number of patients with mTNBC, most of whom did not have evidence of CNS disease on trial entry. Estimates of the incidence of brain metastases in patients with mTNBC vary with a recent analysis of SEER data estimating that approximately 10-15% of patients with mTNBC have brain metastases at the initial diagnosis of metastatic disease (Martin 2017). It is therefore unclear what the efficacy of sacituzumab may be in a post-market population that is likely to have higher incidence of brain metastases. Another consideration for efficacy the post-market setting is that TNBC is a molecularly heterogenous disease and it is unclear whether particular subpopulations of patients with mTNBC are deriving the differential benefit from treatment with sacituzumab.

Finally, the relationship between tumor Trop-2 expression and response to therapy with sacituzumab is unclear. While data submitted in the BLA suggested that those tumors with Trop-2 expression were experienced higher ORR than those patients whose tumors were deemed to have weak or no expression, the findings were exploratory, as was the Trop-2 test itself.

8.1.4 Integrated Assessment of Effectiveness

The only trial submitted to support the efficacy of sacituzumab in the treatment of metastatic TNBC in patients who have received at least two prior therapies for metastatic disease was IMMU-132-01. No integrated efficacy analysis was performed during this review; however FDA requested preliminary ORR and DOR data from the applicant's planned confirmatory trial IMMU-132-05 which was supportive of the results of IMMU-132-01.

Based on the data submitted from IMMU-132-01, sacituzumab demonstrates evidence of efficacy in patients with mTNBC who have received two prior therapies for metastatic disease. The ORR, along with supportive duration of response, is improved compared to that of available therapies. In the target mTNBC population (n=108), the trial showed a confirmed ORR of 33.3% (95% CI: 24.6, 43.1) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment.

8.2 Review of Safety

8.2.1 Safety Review Approach

This review includes the FDA findings and review comments from the review of safety conducted at the time of the original BLA submission on May 18, 2018, and includes updates from review of the Safety Update Report and related datasets submitted with the BLA resubmission on December 2, 2019.

To support the safety evaluation of sacituzumab for this BLA, the Applicant submitted safety data from Trial IMMU-132-01, a Phase 1/2 trial of IMMU-132 in patients with advanced solid tumors. The safety dataset consists of 420 patients who received at least one dose of trial drug. Adverse events were assessed at baseline, during the trial treatment period, and for at least 30 days after discontinuing trial therapy. Laboratory studies were obtained at baseline, day 1 and 8 of each cycle, at the end of treatment, and during trial follow-up. Hematology labs included a complete blood cell count with differential. Serum chemistries include liver function evaluation, renal function evaluation, and electrolytes. There were no clinical holds for safety during the development of sacituzumab.

Adverse event and therapy exposure datasets were used for these analyses. Where appropriate, narrative summaries and case report forms for serious adverse events were reviewed. Narratives and case report forms for all patient deaths within 30 days of discontinuing trial therapy were reviewed as well.

Specific safety concerns, including infusion-related reactions, diarrhea, and neutropenia were reviewed as well. These events were further assessed by UGT1A1 mutation status given concern that there is increased risk of adverse events in patients who are not UGT1A1 *1 homozygotes.

Given the limited numbers of patients included in the safety database, analyses were conducted for both the overall safety population as well as for the mTNBC efficacy population. The reason for additionally conducting separate analyses in the efficacy population is that, unlike the overall cohort which had received at least one prior line of therapy, patients in the mTNBC efficacy cohort had received at least two prior therapies in the metastatic setting making them more heavily pretreated and potentially at increased risk of adverse events when compared to the overall trial population.

At the time of data cutoff of June 30, 2017, the safety database included 420 patients, including the 108 mTNBC patients who comprised the efficacy population (i.e., patients with mTNBC who received sacituzumab 10 mg/kg). Patients in the safety population received the following doses: 8 mg/kg (n=81), 10 mg/kg (n=327), 12 mg/kg (n=9), and 18 mg/kg (n=3). The 90-Day Safety Update provided cumulative safety information based upon a data cutoff date of December 1, 2017. The Safety Update Report submitted with the BLA resubmission provided cumulative

safety information based upon a data cutoff date of March 1, 2019.

The tumor types that were represented in Trial IMMU-132-01 are shown in Table 19.

Table 19: Tumor Types included in Trial IMMU-132-01

Tumor Type	All Population N=420 n (%)
Metastatic Triple-Negative Breast Cancer	144 (34.3)
Small Cell Lung Cancer	56 (13.3)
Non-Small Cell Lung Cancer	54 (12.9)
Urothelial Carcinoma	45 (10.7)
Colorectal Cancer	31 (7.4)
Metastatic HR positive Breast Cancer	20 (4.8)
Esophageal Cancer	19 (4.5)
Pancreatic Cancer	16 (3.8)
Epithelial Ovarian Cancer	8 (1.9)
Endometrial Cancer	7 (1.7)
Gastric Adenocarcinoma	5 (1.2)
Hormone Refractory Prostate Cancer	4 (1.0)
Glioblastoma Multiforme	3 (0.7)
Squamous Cell Carcinoma of the Head and Neck	3 (0.7)
Hepatocellular Carcinoma	2 (0.5)
Renal Cell Carcinoma	1 (0.2)

Source: *Trial IMMU-132-01, adsl.xpt dataset*

8.2.2 Review of the Safety Database

Overall Exposure

The duration of exposure to sacituzumab in the overall safety population including the mTNBC is summarized in Table 20. As of the DCO of March 1, 2019, a total of 10 patients in the overall safety population, including 3 patients in the mTNBC efficacy analysis population, continued to receive sacituzumab.

Table 20: Drug Exposure Summary in Trial

	mTNBC Population n = 108	Safety Population n = 408
Duration of treatment (months)		
Mean (SD)	7.2 (8.14)	5.7 (7.32)
Median	5.1 (0.0, 51.3)	3.6 (0.0, 55.2)
Duration of treatment (n, %)		
≥6 months	44 (40.7)	122 (29.9)
≥12 months	19 (17.6)	42 (10.3)
≥24 months	6 (5.6)	18 (4.4)
Number of Doses Administered		
Mean (SD)	20.4 (22.33)	16.3 (19.64)
Median	15.5 (1, 146)	11.0 (1, 146)
Number of Cycles		
Mean (SD)	10.4 (11.17)	8.4 (9.85)
Median	8.0 (1, 73)	6.0 (1, 73)

Source: *Trial IMMU-132-01, adsl.xpt, adex.xpt; data cut off March 1, 2019*

Dose Modifications

The analysis of dose modifications (dose delays, dose reductions, dose discontinuation was conducted based upon the overall safety population (n=408) and the mTNBC population (n=108). Adverse reactions leading to dose reduction occurred in 33% of the patients with mTNBC treated with Sacituzumab, with 24% having one dose reduction and 9% with two dose reductions.

Relevant characteristics of the safety population:

Demographic comparisons between the overall safety population and the mTNBC population are captured in Table 21.

Table 21: Demographics of Safety Populations in IMMU-132-01

Demographic Parameter	Safety Population n=408 %	mTNBC Population n=108 %
Sex	100	100
Female	64.7	99.1
Male	35.3	0.9
Age Group	100	100
<65	64.7	82.4
>=65	35.3	17.6
ECOG Performance Status	100	100
Grade 0	27.2	28.7
Grade 1	72.8	71.3
Race	100	100
Black or African American	5.4	7.4
White	82.1	75.9
Other	12.5	16.7
Ethnicity	100	100
Hispanic or Latino	4.2	6.5
Not Hispanic or Latino	92.9	91.7
Other	2.5	0.9
Unknown/other	0.5	0.9

Source: *Trial IMMU-132-01, adsl.xpt dataset*

Adequacy of the safety database:
The safety database of 420 patients treated in IMMU-132-01 is adequate (Table 22). The age and sex of the patients treated in the mTNBC cohort is consistent with what is generally expected for patients with mTNBC. There was one male patient in the mTNBC cohort and there were additional male patients (149, 35.5%) in the overall safety population. Most patients were white (344, 81.9%). There were few African-American (24, 5.7%), Asian (17, 4.0%), or Native American (1, 0.2%) patients included in the overall safety database.

Reviewer Comment: The demographic characteristics of patients in the mTNBC cohort were generally similar to the overall population; age was a notable exception with patients in the mTNBC cohort tending to be slightly younger than those in the overall trial population. Another exception was that patients in the mTNBC cohort were more likely to have hepatic insufficiency and less likely to have a creatinine > ULN than those in the overall trial population. The overall safety database included more male patients than the mTNBC efficacy cohort due to the demographics of disease. The mTNBC cohort was younger than those in the overall safety database, again a reflection of differing disease epidemiology between tumor types. Baseline

ECOG performance status was similar across the overall safety cohort and the mTNBC efficacy cohort. Patients in the overall safety cohort may have been less heavily pretreated as compared to the mTNBC efficacy cohort as patients were permitted to enroll in this trial with at least one prior line of systemic therapy in the metastatic setting while those in the mTNBC cohort had received at least two prior lines of systemic therapy in the metastatic setting. Overall, the populations in the mTNBC cohort and the overall safety cohort are similar. Given the differences, however, analyses were performed and compared for each population.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Case report forms (CRFs) were reviewed and compared to the datasets and patient narratives. The data in the CRFs and AE datasets were generally consistent with any exceptions noted during the course of the review. Overall the data quality for the trial was generally acceptable.

While there were some discrepancies were noted throughout the course of the review, it does not appear that these discrepancies significantly impacted trial results, specifically the ORR.

Notably, the datasets submitted to the BLA were of adequate quality to facilitate FDA's analyses. However, as described in Section 8.2.4, the absence of information regarding the specific adverse events that lead to dose reductions in the submitted datasets, represents a submission quality issue.

Categorization of Adverse Events

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 was employed in IMMU-132-01, to characterize the adverse event (AE) terms and its severity; this was then mapped by the Applicant to corresponding terminology within MedDRA.

Preexisting conditions were defined as AEs that began prior to the first dose of trial drug. Treatment emergent AEs were defined as any AE beginning between the day of the first dose and 30 days after the last dose of trial drug, or any preexisting condition that increased in CTCAE grade between the day of the first dose and 30 days after the last dose of trial drug. A serious adverse event (SAE) was any AE during the trial that resulted in death, initial or prolonged hospitalization, a life-threatening experience, persistent or significant disability, congenital anomaly or birth defect, or was considered significant for any other reason. Events may have been considered SAEs if they required surgical or medical intervention to prevent one of the previously listed outcomes. During the follow-up period, new AEs were documented if determined to be related to trial therapy; otherwise only AEs leading to hospitalization, requiring IV or prescription anti-infectives, medications related to gastrointestinal (GI) events, or AEs leading to death were recorded.

The relationship of the AE to trial treatment was assessed.

Reviewer Comments: *The Applicant used standard definitions for AE and SAE recording and reporting. In FDA's analyses, attribution of the relationship of events to trial therapy was not considered given that this is a single-arm, open-label trial. Given this, the safety review was performed of all TEAEs regardless of investigator assessed attribution.*

Routine Clinical Tests

Routine laboratory testing included complete blood count with differential and blood chemistries including glucose, blood urea nitrogen , creatinine, total bilirubin, total protein, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase (LDH),
calcium, chloride, sodium, potassium, magnesium, phosphorus.

Laboratory studies were obtained on day 1 and 8 of each cycle, at the end of treatment, and during follow-up. Urinalysis, prothrombin time, partial thromboplastin time, and human antihuman antibodies (HAHA) were obtained at baseline, day 1 of even treatment cycles, at the end of treatment and at the end of trial. For patients with positive HAHA testing, 2 additional monthly samples for HAHA were to be collected. Samples were collected for UGT1A1 mutation testing at trial entry.

Vital signs were collected with each infusion. For the first infusion, vital signs were collected every 15 minutes for the first hour, every 30 minutes until the completion of the infusion, at completion, and 30 minutes after the end of the infusion. If no clinically relevant observations during the first infusion, vital signs were collected prior to the infusion, 30 minutes after the start of the infusion, and at infusion completion. Physical examinations were performed on day 1 of cycle 1, day 1 of cycle 2, and then day 1 of every even cycle.

Reviewer Comment: *The frequency of laboratory and clinical assessments was appropriate. Samples collected for UGT1A1 mutation testing were tested retrospectively. This is consistent with clinical practice as there are not currently recommendations to evaluate for this prospectively.*

8.2.4 Safety Results

Deaths

In the IMMU-132-01 trial, at the time of the 90-Day Safety Update (December 1, 2017), there had been 20 deaths within 30 days of discontinuing trial therapy in the overall safety population; 4 of these deaths occurred among patients in the mTNBC efficacy cohort. Narratives of these events were reviewed at the time of the original BLA submission and

reviewer assessments are captured in Table 22 and Table 23. As of the data cut-off date of March 1, 2019, no new fatal AEs were reported in the mTNBC population.

In the Safety Update Report submitted at the time of the BLA resubmission, the applicant provided clarifications regarding the cause of death of 7 of the 20 death events that occurred within 30 days of discontinuing trial therapy in the overall safety population, to be due to progression of disease. This include Patients: (b) (6) For Patients (b) (6) the investigator and applicant's assessments are consistent with the FDA's assessments in Table 22 and Table 23 of PD as the likely cause of death. For Patient (b) (6) the FDA disagrees with the investigator and applicant's assessment, the updated narrative and reviewer assessment are included in Table 22 and Table 23.

Table 22: Death Narratives from IMMU-132-01 for the mTNBC Population

mTNBC Population	
Patient ID	**Narrative**
(b) (6)	*Metastases to spine.* 55-year-old white female with mTNBC with metastases to the liver and a malignant pleural effusion. The first and only dose of IMMU-132 (10 mg/kg) was given on (b) (6) On that date, the was noted to have lower extremity weakness, abdominal pain, and constipation. After receiving the infusion, the patient was sent to the hospital for evaluation. The patient was admitted to the hospital on (b) (6) MRI of the thoracic spine revealed a T11 spinal cord mass suspicious for metastatic disease and an MRI of the brain completed on (b) (6) demonstrated innumerable metastatic lesions to the brain with evidence of hemorrhage and vasogenic edema. The patient died on (b) (6) due to disease progression. No autopsy was performed. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression prior to the infusion which was confirmed during the hospital admission. It is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Hypertension.* 49-year-old white female with mTNBC with metastases to the lungs, hip, and left gluteal muscle. She received her first and only dose of IMMU- 132 (10 mg/kg) on (b) (6) On the day of treatment, her creatinine was 2.13 and she was mildly hypokalemic with a potassium of 3.2 mEq/L. She was given 20 mEq of potassium. She died in her sleep on (b) (6) and the cause of death was recorded as hypertension. Of note, the patient was on multiple concomitant therapies including insulin, amlodipine, methadone, and promethazine. No autopsy

mTNBC Population	
Patient ID	**Narrative**
	was performed. The investigator did not consider the event to be related to trial therapy. *Reviewer Comments: This patient had multiple comorbidities and multiple risk factors for death including the trial therapy. Given that there was no autopsy, it is unclear whether this death may be related to trial therapy as the patient could have had an arrhythmia due to renal failure and electrolyte imbalances, or due to being on multiple QT prolonging agents (methadone and promethazine).*
(b) (6)	*Neutropenia, hyponatremia, death.* 40-year-old white female with mTNBC who received her first dose of IMMU-132 (10 mg/kg) on (b) (6) and received her last dose of IMMU-132 on (b) (6) TEAEs recorded included dyspepsia, fatigue, neuropathy, anemia, neutropenia, edema, difficulty swallowing, and shortness of breath. On (b) (6) the investigator discontinued the patient from trial therapy due to clinical disease progression. On that same date, the patient had an SAE of hyponatremia recorded. The patient died on (b) (6) and the cause of death was attributed to disease progression. *Reviewer Comments: While the patient experienced multiple adverse events prior to discontinuing trial therapy, this reviewer agrees that the cause of death was likely due to progression of the underlying disease as the patient had not received therapy for approximately 3 weeks prior to her death and had been discontinued from trial therapy by the investigator for clinical evidence of disease progression; there was no radiographic confirmation of disease progression.*
(b) (6)	*Progressive Disease.* 64-year-old white female with mTNBC who received her first dose of IMMU-132 (10 mg/kg) on (b) (6) She presented to clinic on (b) (6) (Cycle 1, Day 8) and was ill appearing and oxygen dependent. Two days prior to this, the patient had developed diarrhea which improved with use of loperamide. Laboratory studies demonstrated that she was neutropenic with an ANC of 0.19 X 1000/uL and in acute renal failure with a creatinine of 2.98 mg/dL. Her temperature was 100.9 F, and she was admitted for febrile neutropenia. She was hemodynamically unstable and initiated on pressors. She withdrew consent from the clinical trial on (b) (6) and was discharged to home hospice. She died at her home on (b) (6) (b) (6) While the investigator assessed the septic shock as life threatening and related to trial therapy, her death was attributed to disease progression as she was in hospice care and not receiving disease directed therapy.

mTNBC Population	
Patient ID	**Narrative**
	Reviewer Comments: While the events of febrile neutropenia and septic shock are likely related to trial therapy, the timing of her death is not consistent with this being the primary cause of death as she survived for more than 14 days at home without treatment for septic shock. It is not clear that this patient's death was directly related to trial therapy.
(b) (6)	*Death.* 55-year-old white female with mTNBC who received the first dose of IMMU-132 (10 mg/Kg) on (b) (6) She discontinued trial therapy due to disease progression with documented progression of her liver lesions on repeat scans on (b) (6). She died on (b) (6) due to disease progression. *Reviewer Comments: This reviewer agrees that the cause of this patient's death was disease progression.*

Table 23: Death Narratives from IMMU-132-01 for the Safety Population

Safety Population	
Patient ID	**Narrative**
(b) (6)	*Embolism.* 83-year-old white female with metastatic colon cancer. Past medical history included atrial fibrillation, spinal stenosis, and urosepsis. Initiated therapy with IMMU-132 (dose 8 mg/kg) on (b) (6) Cycle 1 day 8 was held due to neutropenia. She received her last dose of therapy on (b) (6) On the evening of (b) (6) the patient had abdominal pain and was noted to have left arm weakness. She collapsed and died. This event was attributed to a probable thromboembolic event given the patient's atrial fibrillation and cancer, however no imaging or other assessment was performed. This was not thought related to trial therapy. *Reviewer Comment: This reviewer concurs that the clinical description sounds like a possible cerebrovascular accident that was likely related to the patient's history of atrial fibrillation. Additionally, the patient's metastatic malignancy increases her risk of similar events. While a definitive assessment is not possible, it is not likely that this event was related to trial therapy.*
(b) (6)	*Anasarca, systemic inflammatory response syndrome.* 52-year-old white male with metastatic esophageal cancer with metastases to the liver and bone. He was given his first dose of trial therapy (8 mg/kg) on (b) (6) (b) (6) and the last dose was given on (b) (6) On (b) (6), the patient presented to the emergency room with edema, shortness of breath, non-productive cough, and wheezing and was noted to have a SAE

Safety Population	
Patient ID	**Narrative**
	of anasarca. His chest x-ray demonstrated bilateral pleural effusions. He was noted to be neutropenic at the time. Due to progressive dysphagia, a PEG tube was placed. His neutropenia and symptoms resolved and he was discharged on (b) (6) He received his last dose of IMMU-132 (b) (6) (b) (6) On (b) (6) the patient presented to the emergency room with hypotension, a fever of 100.8 F, and confusion. His lung exam revealed crackles and his abdomen was distended with RUQ tenderness. He was neutropenic with an ANC of 0.5 x 1000/uL and his calcium was elevated at 10.4 mg/dL. CT scans demonstrated progression of disease. He was treated with broad spectrum antibiotics, however given the evidence of progressive disease, the patient's family transitioned the patient to hospice care and the patient died on (b) (6) *Reviewer Comment: While the trial therapy may have contributed to this patient's death due to neutropenia and possible infection, the patient was also documented to have disease progression on imaging and had hypercalcemia, likely due to progressive malignancy.*
(b) (6)	*Cardiorespiratory arrest.* 65-year-old female with metastatic small cell lung cancer who received 32 cycles of trial therapy (8 mg/kg). Past medical history was significant for intermittent syncope, urinary retention, and a 30 pack year smoking history On (b) (6) (Cycle 32, Day 6), she reported not feeling well, lost bowel and bladder control, and collapsed. She was unable to be resuscitated by her brother or by EMS using CPR. She was taken to the ED and continued attempts at resuscitation were made including use of CPR and epinephrine. The patient was also given IV bicarbonate. Approximately 30 minutes after arrival to the ED and approximately 1 hour after the initial event, CPR was discontinued. Her last dose of trial therapy had been administered on (b) (6) *Reviewer Comment: It is not clear that trial therapy played a role in this patient's death. The patient had been on therapy for a notable period (>1 year). She had a prior SAE of abdominal pain for which she was hospitalized and the cause of her pain was determined to be constipation as her abdominal pain resolved with laxatives and bowel movements. Prior adverse events included fatigue, nausea, dyspnea, dizziness, dehydration, cough, and tachycardia, but no noted electrolyte abnormalities, seizures, chest pain, or other cardiac events. It is unclear what the actual cause of her cardiopulmonary arrest was, but given her significant smoking history, she could have had cardiovascular disease which may have led to a cardiac arrest or ruptured aortic aneurysm.*

Safety Population	
Patient ID	**Narrative**
(b) (6)	*Failure to thrive, pleural effusion, progressive disease.* This was a 54-year-old white female with metastatic TNBC who received her first dose of IMMU-132 (8 mg/kg) on (b) (6) She discontinued trial therapy on (b) (6) due to documented progressive disease. The patient presented to the hospital with respiratory failure and shortness of breath. The plan was to transfer to hospice are at discharge, however the patient died on (b) (6) prior to discharge. The death was attributed to progressive disease. *Reviewer Comment: This reviewer agrees that this death was due to disease progression and was not due to trial therapy.*
(b) (6)	*Brain Metastasis.* 69-year-old African-American female with metastatic small cell lung cancer. Her past medical history was significant for COPD, hypertension, osteoarthritis, hyperlipidemia, fatigue, neuropathy, dyspnea, anxiety, depression, and hyponatremia. She received her first dose of trial therapy on (b) (6) (10 mg/kg). Her last dose of trial therapy was received on (b) (6) On (b) (6), the patient had an episode of syncope. She was admitted to the hospital and on (b) (6) (b) (6) an MRI of the brain revealed too many brain metastases to count. She was started on dexamethasone and was evaluated for whole brain radiotherapy. During her simulation, she had an episode of respiratory distress and chest x-ray demonstrated bilateral pneumonia. She was transitioned to palliative care. She died on (b) (6) and the cause of death was attributed to disease progression. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. The patient had tolerated therapy for approximately 6 months without significant event and thus trial therapy is unlikely to have contributed to this patient's death.*
(b) (6)	*Pulmonary Embolism.* 65-year-old white male who was diagnosed with stage IV pancreatic adenocarcinoma in (b) (6) Past medical history was significant for GERD, RUE DVT, peripheral neuropathy, partial blindness, ascites, peritoneal carcinomatosis, abdominal pain, loss of appetite, and constipation. He received his first and only dose of trial therapy on (b) (6) (10mg/kg). On Day 7, (b) (6) the patient was admitted with melena and was admitted for a GI bleed. One week prior to the admission, he had undergone paracentesis with removal of 3 L of fluid. Upper endoscopy performed on Day 8 demonstrated severe esophagitis secondary to gastric outlet obstruction. On Day 12, the patient underwent stent placement to relieve the obstruction. On Day13, his course was complicated by the finding of a pulmonary embolism which

Safety Population	
Patient ID	**Narrative**
	was identified after the patient experienced progressive shortness of breath. CT pulmonary angiography demonstrated multiple pulmonary emboli. He had worsening pulmonary status, was trialed on BiPAP, and due to overall deterioration, it was confirmed that the patient was a DNR/DNI and the patient and family elected for comfort measures. The patient died on Day 14. Cause of death was reported as pulmonary embolism. No autopsy was performed. *Reviewer Comment: This reviewer agrees that the cause of death was due to pulmonary embolism, a known risk associated with metastatic pancreatic adenocarcinoma. It is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Acute Respiratory Distress.* 72-year-old white male who was initially diagnosed with stage IV small cell lung cancer with a solitary brain metastasis in (b) (6) The patient's past medical history was significant for diabetes, hypertension, coronary artery disease, dysgeusia, anxiety, anorexia, hyponatremia, dyspnea, pleural effusions, and urinary frequency. The first dose of IMMU-132 (8 mg/kg) was administered on (b) (6) The last dose administered prior to the event was (b) (6) The patient developed worsening ability to swallow and was hospitalized on (b) (6) A PEG tube was placed. On (b) (6) the patient developed delirium due to hospitalization and pain medications. On (b) (6) the patient developed acute respiratory distress. CT pulmonary angiography demonstrated no evidence of a pulmonary embolism, but a new moderate to large pleural effusion and consolidation consistent with pneumonia. His respiratory status continued to decline and he was transitioned to hospice care. The patient died on (b) (6) and the death was attributed to progressive disease/acute respiratory distress. No autopsy was performed. *Reviewer Comment: This reviewer considers this death to be due to pneumonia vs. disease progression. Given the dysphagia preceding the events, it is possible that this patient had an aspiration event. The effusion could have been due to progressive disease as well and the dysphagia possibly due to CNS progression, but there is no report of his CNS being evaluated. Whether due to acute pneumonia or disease progression, this reviewer agrees that it is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Hypoxia, progressive disease.* 74-year-old male with metastatic small cell lung cancer. Additional comorbidities included atrial fibrillation, COPD,

Safety Population	
Patient ID	**Narrative**
	CAD, history of CVA, history of small cell lung cancer, hypomagnesemia, hypokalemia, abdominal aortic aneurysm. The patient initiated therapy with IMMU-132 (10 mg/kg) on (b) (6) Subsequently he developed a lower GI bleed on (b) (6). The dose of IMMU-132 was reduced to 7.5 mg/kg for subsequent doses. The last dose of therapy administered prior to the onset of hypoxia was on (b) (6) On (b) (6) he presented to the emergency department with shortness of breath. CT scan showed stable disease but possible multifocal pneumonia. On clinical exam, inspiratory and expiratory wheezing was noted. On (b) (6) the patient transferred to inpatient hospice. The patient died on (b) (6) and the cause of death was attributed to progressive disease. *Reviewer Comment: The reviewer agrees with the assessment. Given the patient's underlying comorbidities and disease, the patient was at increased risk for pneumonia, including post-obstructive pneumonia. It is not clear that trial therapy played a role in this patient's death.*
(b) (6)	*Progressive disease.* 65-year-old white male who was initially diagnosed with stage IV small cell lung cancer in (b) (6) with metastases to the bone, liver, and mediastinum. Past medical history was significant for anemia, peripheral vascular disease, hyperlipidemia, anxiety, chronic back pain, alcohol abuse, fatigue, weight loss, shortness of breath, kyphosis, and diverticulosis. The patient was treated with 28 doses of IMMU-132 (10 mg/kg) from (b) (6) to (b) (6) The enrolled in Hospice care on (b) (6) and died due to disease progression on (b) (6) No autopsy was performed. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. The reason for trial discontinuation captured in the dataset was "Investigator Decision." The patient had previously tolerated therapy for approximately 10 months without difficulty. It is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Aspiration pneumonia.* 62-year-old white male with stage IV non-small cell lung cancer with a past medical history significant for hyperlipidemia, CAD, esophageal stenosis, hypertension, GERD, pneumonitis, and peripheral neuralgia. The first dose of IMMU-132 (10 mg/Kg) was administered on (b) (6) with the last dose administered on (b) (6) (b) (6) The patient was admitted to the hospital for nausea and dehydration on (b) (6) He had previously taken granisetron and prochlorperazine with limited improvement. He was given IV fluids and

Safety Population	
Patient ID	**Narrative**
	antiemetics and his symptoms improved. He was discharged on (b) (6) (b) (6) with improvement in symptoms, though his nausea was ongoing. The patient presented to the emergency department on (b) (6) with aspiration pneumonia. He was admitted with respiratory distress and chest x-ray demonstrated infiltrates. CT scan of the neck demonstrated persistent right supraclavicular mass and retropharyngeal swelling with new left supraclavicular lymphadenopathy. The patient was treated with broad spectrum antibiotics, but had nausea and clear emesis. On (b) (6) (b) (6) he had a cardiorespiratory arrest with PEA and received 6 rounds of CPR with two pushes of epinephrine and two pushes of naloxone. Multiple attempts at intubation were unsuccessful due to cervical lymphadenopathy and varices. Autopsy was performed and suggested that the underlying cause of death was due to metastatic lung cancer with post obstructive sequalae. The Investigator and Applicant considered the fatal event of aspiration pneumonia to possibly be related to IMMU-132. *Reviewer Comment: This reviewer agrees that the cause of death was aspiration pneumonia, however in the setting of progressive cervical adenopathy, it is not clear that this event was related to trial therapy. Given these findings, it is likely that this event was due to disease progression and not related to trial therapy.*
(b) (6)	*Pneumonia.* 54-year-old female with stage IV non-small cell lung cancer. Past medical history significant for dyspnea with hypoxia, fatigue, chest wall pain, lightheadedness, prolonged QTc, cough, depression, right pleural effusion, insomnia, anemia, and anxiety. Received a single dose of IMMU-132 (10 mg/kg) on (b) (6) Presented for cycle 1, day 8 on (b) (6) but trial therapy withheld due to sinusitis/pneumonia with shortness of breath. Febrile and received a 10-day course of levofloxacin. On (b) (6) admitted for sepsis with respiratory failure and pneumonia. Chest x-ray demonstrated persistent right middle lobe consolidation and collapse and decreased right effusion. Had pulmonary edema and underwent thoracentesis with limited improvement. Permanently discontinued trial therapy on (b) (6) due to disease progression. Transitioned to inpatient Hospice care on (b) (6) and died on (b) (6) The pneumonia was assessed as related to disease progression. No autopsy was performed. The Investigator and Applicant attributed this fatal event to be unrelated to IMMU-132.

Safety Population	
Patient ID	**Narrative**
	Reviewer Comment: This reviewer disagrees and considers this event as possibly related to trial therapy. The cause of death as recorded in the datasets is due to adverse event, though the dataset indicates that the patient was discontinued from trial therapy due to progressive disease. Given the risk of neutropenia associated with this therapy, it is possible that febrile neutropenia contributed to this patient's event. Review of the adlb.xpt dataset demonstrated that the neutrophil count was 1.3 x 109. While there were no additional labs available, it would be difficult to interpret subsequent laboratory results given the patient's sepsis and treatment with broad spectrum antibiotics. While it is not clear that this patient's death is definite due to disease progression, it is possible that it may be given the known risk of neutropenia and infection associated with this therapy.
(b) (6)	*Hypoxia, pleural effusion, progressive disease.* 53-year-old white male with metastatic non-small cell lung cancer. Past medical history was significant for depression, neuropathy, nausea, metastatic disease to the bone, fatigue, OSA, and hypertension. He was treated with his initial dose of IMMU-132 (10 mg/kg) on (b) (6) and received three subsequent doses at a dose reduction to 7.5 mg/kg. He received his last dose of trial therapy on (b) (6) The patient was admitted to the hospital on (b) (6) at which time he was diagnosed with a right pleural effusion that was increasing in size. He additionally had a small left pleural effusion. Ultrasound guided thoracentesis of the left lung was performed and he underwent wire manipulation and declogging of right PleurX catheter. Symptoms improved' received 2 units of packed red blood cells on (b) (6) On (b) (6) admitted due to hypoxia and found to have aspiration pneumonia. He was septic and had evidence of acute kidney injury. Received broad spectrum antibiotics. On (b) (6) experienced clinical deterioration with worsening respiratory failure. Transitioned to comfort measures. Died on (b) (6) due to acute respiratory failure from progressive disease. The investigator and applicant considered the events unrelated to trial therapy. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression with worsening pulmonary effusions. He was not neutropenic with these events as he had received G-CSF and culture data revealed no organism. It is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Neutropenic typhlitis, respiratory failure.* 64-year-old white female with

Safety Population	
Patient ID	**Narrative**
	metastatic small-cell lung cancer with a past medical history significant for R pleural effusion, intermittent right headache, GERD, hypertension, gallstones, kidney stone, 50 pack year smoking history, cholecystitis, and anxiety. She received two doses of IMMU-132 (10 mg/kg) with the first dose on (b) (6) On cycle 1, day 5 (b) (6) the patient developed neutropenic typhlitis. Received broad spectrum antibiotics and antifungals. On (b) (6) symptoms improved, WBC was 9.3 x 1000/uL and ANC was 8.2 x 1000/uL. While the typhlitis resolved, the hypoxemia worsened. CT scan on (b) (6) demonstrated bilateral ground glass opacities and chest x-ray demonstrated a progressive alveolar filling process. Right thoracentesis performed on (b) (6) and it was considered that ARDS was the etiology. Received diuretics without evidence of improvement. Transitioned to comfort care measures and died on (b) (6) with the cause of death indicated as disease progression. No autopsy was performed. The neutropenic typhilitis event was considered severe and related to trial therapy by both the Investigator and the Applicant. The patient's respiratory failure was considered unrelated to trial therapy. *Reviewer Comment: This reviewer disagrees and considers the event of respiratory failure due to ARDS as possibly related to trial therapy. ARDS is known to be a sequela of sepsis or major illness and, in this case, may have been triggered by the patient's neutropenic colitis which both the Investigator and Applicant agree was related to trial therapy.* Updated Narrative submitted in BLA resubmission: The patient was hospitalized with neutropenic colitis 7 days after the 2nd infusion, which resolved with treatment. While hospitalized, she developed acute hypoxic respiratory failure of unclear etiology, although attributed to disease progression by the Investigator (worsened pleural effusions). Her condition worsened despite treatment, including corticosteroids for potential pneumonitis. Due to her poor prognosis, she received supportive care only, and died 20 days after admission, 27 days after the last dose of IMMU-132. The investigator and applicant deem the death to be unrelated to trial drug and due to disease progression. *Reviewer Comment: The reviewer disagrees with the investigator and the Applicant's assessment. The possibility of ARDS being triggered by the concurrent event of neutropenic colitis cannot be excluded, and the event of respiratory failure/death is possibly related to trial drug.*

Safety Population	
Patient ID	**Narrative**
(b) (6)	*Progressive Disease.* 73-year-old white male who was initially diagnosed with stage IV urothelial cancer with metastases to the lymph nodes, lung, liver, adrenal gland, bone and subcutaneous tissue. Past medical history was significant for prostate cancer that was treated with curative intention with radiation therapy and ADT, colon polyps, history of smoking, fatigue, nocturia, depression, arthritis, neuropathy, decreased appetite, nausea, constipation and back pain. Received his first dose of trial therapy on (b) (6) (dose 10 mg/kg) and received 10 total doses with the last dose received on (b) (6) CT scan completed on (b) (6) demonstrated progressive disease. The patient discontinued trial therapy on (b) (6) and was transitioned to Hospice Care. The patient died on (b) (6) due to disease progression. No autopsy was performed. The Investigator and Applicant considered this death due to disease progression. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression on trial imaging, was discontinued from trial therapy, and was transition to Hospice care. It is not likely that trial therapy contributed to this patient's death.*
(b) (6)	*Respiratory failure.* 63-year-old white male with stage IV small cell lung cancer. Past medical history significant for coronary artery disease, GERD, hyperlipidemia, anxiety, inguinal hernia, type 2 diabetes mellitus, hypertension, cough, and headache. Received first dose of trial therapy on (b) (6) and received 27 doses total: 11 doses of 10 mg/kg and 16 doses of 7.5 mg/kg. His last dose of trial therapy was on (b) (6) (b) (6) Progressive disease was confirmed on (b) (6) The patient presented to a local emergency room on (b) (6) with shortness of breath. He was tachycardic and hypoxic with O2 saturations of 82-91% on non-rebreather mask. PE protocol CT demonstrated no PE, but demonstrated evidence of progressive disease with bilateral ground glass opacities in the lungs, an increase in the size of the R lower lobe mass, an increase in the size of the hepatic metastases, and rising total bilirubin (total bilirubin 10.5 mg/dL). He was admitted for symptomatic care and was ultimately transitioned to comfort measures. The patient died on (b) (6) due to progressive disease. No autopsy was performed. Neither the applicant nor the investigator considered this death as related to trial therapy.

Safety Population	
Patient ID	**Narrative**
	Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. It is not likely that trial therapy contributed to this patient's death.
(b) (6)	*Hyperbilirubinemia.* 54-year-old white female with metastatic hormone receptor positive breast cancer with metastases to the lungs, liver and bone. Medical history was significant for GERD, hypercholesterolemia, diverticulosis, seasonal allergic rhinitis, and asthma. Received first dose of trial therapy on (b) (6) (dose 10 mg/kg). On (b) (6) the dose was reduced to 7.5 mg/kg due to neutropenia. Received a total of 15 doses of trial therapy with the last dose received (b) (6) On (b) (6) experienced elevated total bilirubin of 2.0 mg/dL. On (b) (6) (b) (6) the total bilirubin increased to 3.9 mg/dL. Admitted for further evaluation of hyperbilirubinemia in the setting of known hepatic metastases. Abdominal ultrasound performed on (b) (6) demonstrated mild central bile duct dilatation. On (b) (6) serum bilirubin was 7.7 mg/dL with direct bilirubin of 5.9 mg/dL. Assessed as likely related to known hepatic metastases. MRCP performed on (b) (6) (b) (6) and showed innumerable hepatic metastases that were not significantly changed since the prior CT scan on (b) (6) Gastroenterology consultation on (b) (6) indicated that "*given the constellation of progressive symptoms correlating with the initiation of IMMU- 132, cholestatic pattern of LFTs, and the lack of dilatation and metastatic progression on imaging thus far, the most likely etiology of the patient's direct hyperbilirubinemia entail reaction to the patient's clinical trial drug.*" Liver biopsy recommended. Patient requested discharge from the hospital on (b) (6) and the underwent IR-guided biopsy on (b) (6) (b) (6) revealed cholestatic liver with evidence of biliary ductal damage contributing to the elevated bilirubin. The end of treatment was (b) (6) (b) (6) and reason noted was progressive disease as the patient had rising tumor markers. Admitted on (b) (6) with grade 4 weakness and grade 2 confusion. Bilirubin had continued to rise. An autopsy was performed which revealed innumerable hepatic metastases that replaced approximately 80% of the hepatic parenchyma. The cause of death was considered progressive disease. Neither the investigator nor the applicant considered this event related to trial therapy. *Reviewer Comment: This reviewer agrees that the cause of death was due to disease progression. It is not likely that trial therapy contributed to this patient's death.*

Serious Adverse Events

Table 24: Serious Adverse Events in >2% of patients in IMMU-132-01

Adverse Events	Safety Population n=408		mTNBC Population n=108	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
Any serious adverse reaction	167 (41)	127 (31.1)	36 (33)	27 (25)
Infection*	34 (8.3)	30 (7.4)	10 (9.3)	9 (8.3)
Febrile Neutropenia	18 (4.4)	16 (3.9)	9 (8)	7 (6.5)
Respiratory Infection	17 (4.1)	11 (2.7)	3 (2.8)	3 (2.8)
Diarrhea	14 (3.4)	12 (2.9)	3 (2.8)	2 (1.9)
Dyspnea/Dyspnea exertional	11 (2.7)	9 (2.2)	4 (3.7)	2 (1.9)
Vomiting	11 (2.7)	8 (2)	7 (6.5)	6 (5.6)
Neutropenia*	9 (2.2)	9 (2.2)	2 (1.9)	2 (1.9)
Asthenia/Fatigue	6 (1.5)	5 (1.2)	1 (0.9)	1 (0.9)
Nausea	9 (2.2)	8 (2)	4 (3.7)	4 (3.7)
Intestinal Obstruction	2 (0.5)	2 (0.5)	0	0
Respiratory Failure/Hypoxia	7 (1.7)	2 (0.5)	0	0
Pulmonary Embolism/DVT/Embolism*	5 (1.2)	3 (0.7)	0	0
Pleural effusion	6 (1.5)	5 (1.2)	2 (1.9)	2 (1.9)
Sepsis/Septic Shock/Bacteremia	5 (1.2)	5 (1.2)	2 (1.9)	2 (1.9)
Abdominal Pain*	6 (1.5)	5 (1.2)	0	0
Gastrointestinal Bleeding	3 (0.7)	2 (0.5)	0	0
Pain/Musculoskeletal pain*	9 (2.2)	8 (2)	2 (1.9)	1 (0.9)

***Source**: Trial IMMU-132-01- Safety Update Report, adae.xpt dataset; data cut off March 1, 2019.* *=pooled terms

Infection: Abdominal abscess; Atypical pneumonia; Body tinea; Bronchitis; Candida infection; Catheter site infection; Cellulitis; Clostridium difficile colitis; Clostridium difficile infection; Conjunctivitis; Cystitis; Device related infection; Diverticulitis; Escherichia bacteraemia; Escherichia infection; Escherichia urinary tract infection; External ear cellulitis; Eye infection viral; Folliculitis; Fungal infection; Fungal skin infection; Furuncle; Gastroenteritis; Gastroenteritis viral; Gastrointestinal infection; Herpes virus infection; Herpes zoster; Hordeolum; Influenza; Intervertebral discitis; Kidney infection; Liver abscess; Lower respiratory tract infection; Lung infection; Mastitis; Metapneumovirus infection; Mucosal infection; Oesophageal candidiasis; Oral candidiasis; Oral herpes; Peritonitis; Pleural infection; Pneumonia; Pneumonia haemophilus; Rectal abscess; Respiratory syncytial virus infection; Respiratory tract infection; Sepsis; Septic shock; Skin infection; Staphylococcal bacteraemia; Tooth abscess; Tooth infection; Upper respiratory tract infection; Urinary tract infection; Vaginal infection; Viral infection; Viral upper respiratory tract infection; Vulvovaginal mycotic infection; Vulvovaginitis; Wound infection

Neutropenia: Neutrophil count decreased; neutropenia

Abdominal Pain: abdominal pain upper; abdominal pain lower; abdominal distension; abdominal tenderness; abdominal discomfort; abdominal pain

Pain/MSK pain: Back pain; musculoskeletal pain; pain in extremity; musculoskeletal chest pain; bone pain; pain; neck pain; non-cardiac chest pain; arthralgia

Reviewer Comment: The incidence of serious adverse events was similar in the overall safety population and in the mTNBC efficacy cohort. There was increased febrile neutropenia noted in the mTNBC cohort and this may be due to the population being more heavily pretreated than

the overall safety population as at least two prior lines of systemic therapy were required for the mTNBC efficacy cohort. Additionally, there was a numerically greater incidence of nausea and vomiting. The safety update report with data cut off date of March 1, 2019 was reviewed and there were no significant changes.

Dose Reductions:

Adverse reactions leading to dose reduction occurred in 33% of the patients with mTNBC treated with Sacituzumab, with 24% having one dose reduction and 9% with two dose reductions. The most common adverse reaction leading to dose reduction was neutropenia/febrile neutropenia (55%). Other adverse reactions leading to dose reduction included stomatitis (8%), anemia (5%), diarrhea (5%), fatigue (5%), vomiting (5%); and causes for dose-reduction in one patient each (3%) included chest pain, hyperglycemia, hypersensitivity reaction, peripheral sensory neuropathy and septic shock. The Sacituzumab USPI contains dose modifications for severe neutropenia and severe non-neutropenic toxicities.

Reviewer Comment: The ADAE datasets submitted by the applicant did not have a parameter which captured specific adverse events which lead to dose reduction; the datasets only included this information on dose interruptions and dose discontinuations

FDA sent a request for further information, data analysis, and related dataset regarding the AEs leading to dose reductions. In response to FDA's request for information, Immunomedics stated that the dose that patients received during each infusion was captured in the case report forms (CRFs), but information regarding the AE that led to dose reduction was not collected. The Applicant has identified all patients with one or more dose reductions and has performed a manual medical review to examine the patient listings of all adverse events, particularly those with onset dates between the prior dose and the dose reduction. In addition, if narratives had been generated for those patients identified to have a dose reduction, these were reviewed to determine if the site had provided a specific diagnosis that led to dose reduction. Immunomedics provided an Excel file, based upon a manual medical review that examined AEs with onset date between prior dose and dose reduction. The frequency of each adverse event was tallied to estimate specific AEs which occurred prior to the dose reduction in the efficacy population (n=108). An analysis of adverse events led to dose reduction from this spreadsheet was limited by the absence of a dataset including these data, by the method by which the Applicant made a determination of which AE led to dose reductions, and by the absence of this information for the entire safety population.

The data provided is based on applicant's manual medical review of these cases.

Dropouts and/or Discontinuations Due to Adverse Effects

In the IMMU-132-01 safety population, 40/408 (9%) patients discontinued trial therapy due to TEAEs. The most common reason to discontinue trial treatment were fatigue (n=5;1.2%),

pneumonia (n=4; 1.0%), diarrhea (n=3; 0.7%), pruritis (n=3; 0.7%), anemia (n=2; 0.5%), headache (n=2; 0.5%), neutropenia/febrile neutropenia.

In the IMMU-132-01 mTNBC efficacy cohort, 5 patients (4.6%) discontinued trial therapy due to TEAEs. The most common reason specific adverse events that lead to discontinue trial treatment were: hypertension (patient (b) (6)), anaphylaxis (patient (b) (6)), anorexia/fatigue (patient (b) (6)), hyponatremia ((b) (6)), and headache ((b) (6)).

In the BLA resubmission, the Applicant proposed to remove (b) (4) from the Sacituzumab USPI, (b) (4) FDA sent a request for further information to the applicant, to include patient ID, patient narratives, and applicant justification for this action. Upon FDA review of the information provided by applicant particularly the patient narratives provided, the FDA agreed with the investigator and applicant's assessments in regards to hypertension (Patient (b) (6)), and hyponatremia (Patient (b) (6)), as not likely the cause of treatment discontinuation; however, the FDA did not agree with the investigator and applicant's assessment in regards to headache (Patient (b) (6)) as not likely the cause of treatment discontinuation. These changes are reflected in the Sacituzumab USPI.

Significant Adverse Events

The incidence of Grade 3 or 4 adverse events in the overall safety population (n=408) for IMMU-132-01 was 74.8% and for the mTNBC cohort (n=108) was 72.2%. The most common Grade 3 or 4 AEs were neutropenia (38.9% in the overall safety population and 43% in the mTNBC cohort), anemia (11.7% in the overall safety population and 12% in the mTNBC cohort), white blood cell count decreased (8.3% in the overall safety population and 11.1% in the mTNBC), fatigue (11.3% in the overall safety population and 8.3% in the mTNBC cohort), diarrhea (8.8% in the overall safety population and 9% in the mTNBC cohort), hypophosphatemia (4.8% in the overall safety population and 9.3% mTNBC cohort), nausea (4.6% in the overall safety population and 6.5% in the mTNBC cohort), vomiting (3.9% in the overall trial population and 6.5% in the mTNBC cohort).

Reviewer Comment: The Safety Update Report with data cut off of March 1, 2019, are presented here; and there were no significant changes when compared to the original safety submission. Overall, the incidence of the most common Grade 3-4 AEs was similar in the overall safety population and in the mTNBC population. Given the known toxicities associated with treatment with drugs containing irinotecan, and the observed incidence of GI and hematologic (neutropenia) adverse events, safety analyses focused on these toxicities and their complications, were performed. Six percent (6%) of patients in the overall trial population and 9.3% of patients in the mTNBC cohort had at least one episode of febrile neutropenia. Ten patients (2.5%) had neutropenic colitis in the overall safety population and four patients (3.7%) had neutropenic colitis in the mTNBC cohort.

Regardless of neutrophil count, eight patients (1.9%) had c difficile colitis demonstrating that, in addition to diarrhea being due to trial therapy, that there was an increased risk of this particular infectious organism, likely due to antibiotic therapy due to previous infection/neutropenic fever, on this or other anticancer regimens.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) were assessed in the mTNBC efficacy cohort as well as in the overall safety population to characterize safety across a large patient sample. The overall safety population consisted of patients in Trial IMMU-132-01 who received an initial sacituzumab dose of 8 or 10 mg/kg (n=408); patients who received >10 mg/kg as an initial dose in Trial IMMU-132-01 were not included in the analyses of overall safety.

Safety analyses were based on all AEs, irrespective of investigator attribution to trial drug. As this is a single-arm trial and attribution is difficult to assess, adverse event tables included events regardless of investigator attribution to trial therapy. Events in the safety population that received up to 10 mg/kg and in the mTNBC efficacy population are below in Table 25.

Table 25: Most Common (≥10%) Adverse Events in IMMU-132-01

Adverse Events	Safety Population n=408		mTNBC Population n=108	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
Any adverse event	407 (99.8)	305 (74.8)	108 (100)	78 (72.2)
Nausea	281 (68.9)	22 (4.6)	74 (69)	7 (6.5)
Neutropenia*	222 (54.4)	159 (38.9)	69 (64)	46 (43)
Diarrhea	255 (62.5)	36 (8.8)	68 (63)	10 (9)
Fatigue*	241 (59)	46 (11.3)	62 (57)	9 (8)
Vomiting	183 (44.8)	16 (3.9)	53 (49)	7 (6)
Alopecia	179 (43.9)	0	41 (38)	0
Anemia*	172 (42)	48 (11.7)	56 (52)	13 (12)
Constipation	152 (37.2)	3 (0.7)	37 (34)	1 (0.9)
Decreased appetite	147 (36)	5 (1.2)	32 (30)	1(0.9)
Abdominal pain*	116 (28.4)	12 (2.9)	28 (26)	1 (0.9)
Rash*	100 (24.5)	6 (1.5)	33 (31)	3 (0.7)
Dyspnea*	95 (23.3)	19 (4.6)	23 (21)	3 (3)
Cough*	89 (2.8)	0	22 (20.4)	0
Respiratory Infection*	85 (20.8)	16 (3.9)	28 (26)	3 (2.8)
Neuropathy*	79 (19.4)	4 (0.9)	26 (24)	0
Edema*	77 (18.9)	1 (0.2)	21 (19)	0
Hypomagnesemia	69 (16.9)	2 (0.5)	23 (21)	1 (1)

Adverse Events	Safety Population n=408		mTNBC Population n=108	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
Hypokalemia	69 (16.9)	14 (3.4)	21 (19)	2 (2)
Pyrexia	69 (16.9)	0	15 (14)	0
Dehydration	67 (16.4)	8 (1.9)	14 (13)	5 (5)
Dizziness	67 (16.4)	2 (0.5)	24 (22)	0
Back pain	65 (15.9)	3 (0.7)	25 (23)	0
Headache	63 (15.4)	2 (0.5)	25 (23)	1 (1)
Urinary Tract Infection	55 (13.4)	6 (1.5)	23 (21)	3 (3)
Hypophosphatemia	53 (13)	23 (4.8)	17 (16)	10 (9)
Pruritus	50 (12.2)	2 (0.5)	18 (17)	0
Insomnia	48 (11.8)	0	14 (13)	0
Hyperglycemia	46 (11.3)	13 (3.2)	26 (24)	4 (3.7)
Arthralgia	42 (10.3)	0	18 (17)	0
Mucositis*	41 (10)	4 (0.9)	15 (14)	1 (1)
Dry Skin	36 (8.8)	0	16 (15)	0
Pain in extremity	34 (8.3)	1 (0.2)	12 (11)	0
Dysgeusia	34 (8.3)	1 (0.2)	12 (11)	0
Thrombocytopenia*	30 (7.3)	4 (0.9)	14 (12.9)	3
Febrile neutropenia	24 (5.9)	22 (5.4)	10 (9.3)	9 (8.3)

Source: *Trial IMMU-132-01- Safety Update Report, adae.xpt dataset. data cut off March 1, 2019.* *= pooled terms.
Neutropenia: neutropenia and decreased neutrophil counts
Fatigue: fatigue and asthenia
Anemia: anemia and hemoglobin decreased
Rash: rash maculopapular, rash erythematous, rash generalized, dermatitis acneiform, skin disorder, skin irritation, skin exfoliation
Respiratory infection: upper respiratory tract infection, pneumonia, lung infection, influenza, viral upper respiratory infection, lower respiratory tract infection, bronchitis and respiratory syncytial virus infection
Abdominal pain: abdominal pain, abdominal distention, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness
Neuropathy: gait disturbance, hypoesthesia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and muscular weakness
Cough: cough and productive cough
Dyspnea: dyspnea and dyspnea exertional
Edema: edema; localized edema; edema peripheral; lymphoedema; pulmonary edema; generalized edema; testicular edema; periorbital edema; face edema; tongue edema
Mucositis: stomatitis, esophagitis, and mucosal inflammation
Thrombocytopenia: thrombocytopenia and platelet count decreased

Reviewer Comments: *Safety findings were similar in the overall population and the mTNBC population. Cytopenias were increased in the mTNBC cohort, which may reflect that this cohort was required to have received at least 2 prior therapies when the overall safety population had received at least one prior therapy in the metastatic setting. Additionally, the overall safety population has a portion of patients who received 8 mg/kg rather than 10 mg/kg which may*

make the incidence of adverse events slightly lower in the overall group than in the mTNBC cohort. Patients who received doses greater than 10 mg/kg were not included in these analyses as they were not included in package labeling so as not to mislead prescribers that doses of greater than 10 mg/kg are safe. The Safety Update Report with data cut off of March 1, 2019, were reviewed, and there were no significant changes.

Laboratory Findings

Of interest were patients who had a grade 3-4 laboratory abnormality. The incidence of these abnormalities for the safety population is captured in Table 26.

Table 26: Grade 3-4 Laboratory Abnormalities in IMMU-132-01

Laboratory Parameter	Safety Population n=408 Grade 3-4 n (%)	mTNBC Population n=108 Grade 3-4 n (%)
Hematology		
Absolute lymphocyte count decreased	118 (29.3)	31 (29)
Absolute neutrophil count decreased	115 (28.5)	35 (32)
Leukocytes decreased	85 (21.1)	28 (26)
Platelets decreased	28 (6.9)	3 (2.9)
Hemoglobin decreased	28 (6.9)	7 (6.7)
Prolonged APTT	23 (5.6)	13 (12)
Chemistries		
Hyponatremia	34 (8.4)	5 (4.7)
Blood Glucose increased	24 (5.9)	3 (2.9)
Hypokalemia	20 (5.0)	4 (3.7)
Elevated alkaline phosphatase	18 (4.5)	3 (2.9)
Hypernatremia	7 (1.7)	2 (1.9)
Hypophosphatemia	24 (5.8)	5 (4.6)
Hypermagnesemia	11 (3.2)	4 (3.7)
Hyperbilirubinemia	9 (2.3)	2 (1.9)
Elevated AST	9 (2.2)	4 (3.7)
Hypocalcemia	10 (2.5)	3 (2.8)
Hypoalbuminemia	8 (2.0)	1 (1.0)
Hyperkalemia	8 (2.0)	2 (1.9)
Hypomagnesemia	5 (1.3)	3 (2.8)
Elevated ALT	6 (1.5)	2 (1.9)
Blood Glucose decreased	5 (1.2)	2 (1.9)
Creatinine increased	2 (0.5)	1 (1.0)

Source: Trial IMMU-132-01- Safety Update Report, adlb.xpt dataset, data cut off March 1, 2019.

Reviewer Comments: The incidence of grade 3-4 neutropenia in the laboratory dataset is slightly lower than that of the adverse event dataset. Thirty three percent (n=137, 33.6%) of patients in the overall safety population received G-CSF support at some point during trial therapy and 53.7% (n=58) of patients in the mTNBC cohort received g-csf support at some point during the trial. At the time of amendment 7 (December 9, 2014), patients could receive growth factor support at any point in the trial after cycle 1 day 1. This may have led to increased reporting by investigators and lower rates in the actual laboratory datasets. Additionally, it was noted that there was discordance in the lab dataset and the AE dataset regarding reporting dates as there were clinician reported events which did not correspond to laboratory dates. This is likely due to the CRFs having places for laboratory reporting associated with infusion dates while the adverse event reporting was captured on a separate form and permitted capture of events not directly linked to a trial visit. There were no significant changes in laboratory abnormalities in the safety update report with data cut off date of March 1, 2019.

Vital Signs

There were no relevant changes from baseline to the end of treatment for mean vital signs obtained in either the overall safety population or the mTNBC efficacy cohort.

It was noted that 30 minutes post infusion, 37% of patients (n=151) in the overall safety cohort had a decrease in systolic blood pressure from baseline of 20 mmHg or greater. At 60 minutes post infusion, this improved to 22% of patients (n=91) in the overall safety cohort.

Fifty-four patients had a decrease in SBP at the end of trial therapy by ≥20 mmHg (13.2%) and 39 (9.6%) patients had an increase in SBP at the end of trial therapy by ≥20 mmHg.

Bradycardia (defined as HR <60 AND change in HR of ≥20 beats per minute), an adverse event of interest given the cholinergic properties of sacituzumab and other irinotecan derivatives, at 30 minutes post-infusion was identified in 21 (5%) of patients.

Tachycardia (defined as HR >100 and change in HR of ≥20 beats per minute), at 30 minutes post-infusion was identified in 29 (7.1%) of patients.

Reviewer Comments: While there were no significant changes in vital signs overall, there were changes in blood pressure and heart rate associated with infusions. Patients were not uniformly pre-treated with infusion reaction prevention medications in IMMU-132-01; however, as shown in the concomitant medication table, most patients received pretreatment steroids, acetaminophen, and/or H2 blockers. Given the findings from this trial, the applicant proposed in the USPI that all patients should receive pre-infusion medications, that the infusion should be slowed or discontinued for infusion-related reactions and that sacituzumab should be permanently discontinued for severe infusion-related reactions. Additionally, the USPI includes the instructions for post-infusion monitoring for the initial infusion. Using SMQ, 148 patients

(34.8%) had some event that may be considered and infusion related reaction. Of these, most patients were able to proceed with a slower rate of infusion without dose interruption or discontinuation; however 3 patients had a drug interruption and 3 patients discontinued trial therapy due to these events.

Electrocardiograms (ECGs)/QT Single, 12-lead electrocardiograms were obtained at trial screening/baseline, after completion of the infusion on Day 1 of every even numbered treatment cycle, at the end of treatment and at the end of trial. ECGs were interpreted by investigators. Initially, investigators were only required to report abnormal readings.

The analysis of the incidence and severity of the effects sacituzumab are limited by incomplete data. In the initial protocol, investigators were required only to record findings on the ECG if they were abnormal. Therefore, an assessment of the QTc interval was not performed for all patients as and for those patients for whom on-treatment ECG/QTc assessments are recorded in the analysis datasets (adeg.xpt), baseline values are missing for a significant proportion (202/408 (49.5%)). Given the small number of patients with complete information, the interpretation of trial results is limited.

In the overall trial population, 16 (7.2%, missing data on 202 patients) had increases had increases >500ms in the QTc using Bazett's formula while 6 patients (2.7%, missing data on 202 patients) had increases >500 ms in the QTc using Fridericia's formula. In the mTNBC cohort, 7 patients (7.6%, data missing for 26 patients) had increases >500 ms in the QTc using Bazett's formula while 5 patients (6.1%, data missing for 26 patients) had increases >500 ms in the QTc using Fridericia's formula.

Reviewer Comments: In general, a QTc of > 500 milliseconds (ms) or an increase in QTc of > 60 ms over baseline is thought to confer a higher risk of fatal arrhythmias like Torsade de Pointes. In Trial IMMU-132-01, there is some evidence of mild prolongation of the QT interval. There were no ventricular arrhythmia events reported. Fifty-two patients (of 182 with baseline ECG, 28.6%) had a >30 QTc ≤60 milliseconds (ms) and 17 patients (9.3%) had a QTc increase of >60 ms. Whether this is due to trial drug, electrolyte abnormalities or concomitant therapies is unclear. Given the risk of death due to underlying disease, the risk of QT prolongation is minimal. There will be further evaluation of the effect of this therapy on QT interval as part of the ongoing Phase 3 ASCENT trial, IMMU-132-05.

Immunogenicity

There were three patients who developed persistent human anti-human antibodies (HAHA) to trial therapy: (b) (6) Review of the safety database for these patients did not reveal any clear safety issues related to this event.

Reviewer Comment: None of the 3 patients who developed HAHA were responders in the efficacy analysis. Assessment of the relationship between HAHA and therapy efficacy is limited by the small number of patients included.

8.2.5 Analysis of Submission-Specific Safety Issues

Nausea and Vomiting

Nausea and vomiting had a high incidence in this trial population. Given the findings, labeling recommends premedication with antiemetics to reduce this risk. This risk is of concern in the setting of the additional risk of diarrhea all of these events can lead to dehydration, electrolyte abnormalities and decreased oral intake which can create additional risks in an ill population that may have some degree of poor oral intake at baseline.

Diarrhea

Diarrhea was frequent in this trial population and as many as 10% of patients had Grade 3 diarrhea. As noted above, this can lead to dehydration, electrolyte abnormalities and decreased oral intake. Additionally, given the incidence of neutropenia, this can also lead to infection. This is noted as the incidence can be modified through the use of supportive care medications such as loperamide, treatments at the time of infusion such as atropine, and that both patients and providers should be advised of this risk so as to incorporate appropriate supportive care measures. Additionally, given that infections including *c difficile* were noted, appropriate infectious work up and treatment are also recommended.

Infusion-related reactions

Infusion related reactions including shortness of breath, rash, hypotension, and anaphylaxis were reported. Most patients received some type of premedication to prevent infusion reactions including steroids, antihistamines, H2 blockers, and/or acetaminophen. Labeling includes instructions to reduce the infusion rate for grade 1 infusion reactions, to stop the infusion if a grade 2 reaction and consider restarting at a lower infusion rate when clinically stable, and to discontinue trial therapy in the event of a grade 3 infusion related reaction.

Neutropenia

Neutropenia occurred in 63.9% of patients in the mTNBC cohort. The incidence of febrile neutropenia was low, however there were reports of neutropenic colitis and one death in the safety population occurred in the setting of this event. Over half of patients (53.7%) received growth factor support at some point during the trial. Dose modifications for neutropenia are contained within the USPI.

UGT1A1 Mutation Status

The UGT1A1 gene is involved in metabolism of this drug. Of the safety population UGT1A1 status was known for 333/420 (79.3%) patients. Of these, 37/333 (11.1%) were homozygous for the *28 allele (decreased metabolism), 152/333 (45.6%) were heterozygous *1/*28 (possibly decreased metabolism), and 144/333 (43.2%) were homozygous for the *1 allele (normal metabolism). Of those in the mTNBC efficacy population, UGT1A1 status was known for 86/108 (79.6%) patients with 6/86 (7.0%) homozygous for the *28 allele, 37/86 (43.0%) heterozygous, and 43/86 (50.0%) homozygous for the *1 allele. Given the small sample size, there may be additional adverse events associated with UGT1A1 mutations that have not yet been identified. below captures AEs by UGT1A1 mutation status. As indicated in the table, the incidence of neutropenia is increased in those patients who are homozygous for *28/*28 as compared to the other subpopulations. This was consistent in analyses using the adlb.xpt dataset as well where the incidence of grade 4 neutropenia was 27% for patients who are homozygous for the *28 allele, 6% in patients heterozygous for the *28 allele, and 5% for patients with the wild-type allele. Additionally, there was a higher incidence of weight decreased and hypokalemia in those patients who are homozygous for the *28 allele.

At this time, it is not clear that prospective genotyping to dose this therapy based on UGT1A1 status is beneficial. Additional data will be collected in Trial IMMU-132-05 to further characterize the differences in adverse event profiles.

Table 27: Incidence of AEs by UGT1A1 Mutation Status in the Safety Population

	UGT1A1 *1/*1 N=144	UGT1A1 *1/*28 N=152	UGT1A1 *28/*28 N=37
	All Grades n (%)	All Grades n (%)	All Grades n (%)
Any AE	144 (100)	151 (99.3)	37 (100)
Nausea	99 (68.8)	95 (62.5)	27 (73.0)
Neutropenia	74 (51.4)	87 (57.2)	26 (70.3)
Diarrhea	89 (61.8)	91 (59.9)	23 (62.2)
Fatigue/Asthenia	76 (52.8)	86 (56.6)	20 (54.1)
Anemia	63 (43.8)	60 (39.5)	20 (54.1)
Vomiting	70 (48.6)	58 (38.2)	21 (56.8)
Alopecia	61 (42.4)	63 (41.4)	13 (35.1)
Constipation	51 (35.4)	55 (36.2)	13 (35.1)
Decreased appetite	51 (35.4)	48 (31.6)	18 (48.6)
Rash[1]	34 (23.6)	39 (25.7)	7 (18.9)
Abdominal Pain[2]	36 (25.0)	37 (24.3)	12 (32.4)
Hyperglycemia	16 (11.1)	17 (11.2)	3 (8.1)
Cough	30 (20.8)	30 (19.7)	7 (18.9)
White blood cell count decreased	18 (12.5)	28 (18.4)	4 (10.8)
Headache	20 (13.9)	24 (15.8)	5 (13.5)
Hypomagnesemia	29 (20.1)	28 (18.4)	5 (13.5)

	UGT1A1 *1/*1 N=144	UGT1A1 *1/*28 N=152	UGT1A1 *28/*28 N=37
	All Grades n (%)	All Grades n (%)	All Grades n (%)
Dyspnea	31 (21.5)	27 (17.8)	6 (16.2)
Urinary Tract Infection	19 (13.2)	17 (11.2)	4 (10.8)
Dizziness	26 (18.1)	20 (13.2)	5 (13.5)
Respiratory Infection[3]	25 (17.4)	28 (18.4)	7 (18.9)
Edema[4]	20 (13.9)	32 (21.1)	5 (13.5)
Hypokalemia	20 (12.5)	27 (17.8)	12 (32.4)
Pruritis	18 (12.5)	20 (13.2)	6 (16.2)
Hypophosphatemia	23 (16.0)	19 (12.5)	2 (5.4)
Weight decreased	23 (16.0)	25 (16.0)	11 (29.7)
ALT increased	16 (11.1)	14 (9.2)	2 (5.4)
AST increased	16 (11.1)	13 (8.6)	2 (5.4)
Platelet count decreased/thrombocytopenia	10 (6.9)	11 (7.2)	3 (8.1)
Insomnia	14 (9.7)	23 (15.1)	3 (8.1)
Rhinorrhea/Nasal Congestion	16 (11.1)	21 (13.8)	2 (5.4)
Stomatitis/Esophagitis/Mucosal inflammation	11 (7.6)	15 (9.9)	3 (8.1)
Dehydration	21 (14.6)	25 (16.4)	7 (18.9)
Pyrexia	21 (14.6)	20 (13.2)	6 (16.2)
Blood Alkaline Phosphatase Increased	13 (9.0)	16 (10.5)	2 (5.4)

Source: *reviewer analysis using adae.xpt and adug.xpt datasets*

[1] Rash pooled terms: rash maculopapular, rash erythematous, rash generalized, dermatitis acneiform, skin disorder, skin irritation, skin exfoliation.

[2]Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness

[3]Respiratory infection: Viral upper respiratory infection, upper respiratory infection, influenza, pneumonia, pneumonia haemophilus, metapneumovirus, bronchitis

[4]Edema pooled terms: facial edema, generalized edema, peripheral edema.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable. There was no COA data collected or assessed.

8.2.7 Safety Analyses by Demographic Subgroups

In the IMMU-132-01 trial, 144/408 patients (35.3%) were ≥65 years old. In the mTNBC cohort, 19/108 patients (17.6%) were ≥65 years old. The most frequently reported TEAEs (≥10%) in patients ≥65 years are in Table 28.

Table 28: TEAEs ≥10% in Patients ≥65 years

	Safety Population n=144			Efficacy population n=19		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Diarrhea	96 (66.7)	10 (6.9)	-	14 (74)	1 (5)	-
Anemia	59 (41.0)	17 (11.8)	-	13 (68)	3 (16)	-
Fatigue, asthenia, malaise	85 (59.0)	19 (13.2)	-	10 (53)	2 (11)	-
Nausea	91 (63.2)	2 (1.4)	-	10 (53)	-	-
Neutropenia, neutrophil count decreased	79 (54.9)	46 (31.9)	24 (16.7)	13 (68)	7 (37)	3 (16)
Vomiting	49 (34.0)	1 (<1)	-	7 (37)	-	-
Decreased appetite	49 (34.0)	2 (1.4)	-	6 (32)	-	-
Alopecia	56 (38.9)	-	-	6 (32)	-	-
Constipation	48 (33.3)	-	-	9 (47)	-	-
Abdominal Pain[1]	32 (22.3)	4 (2.8)	-	2 (11)	-	-
Dyspnea, dyspnea exertional	30 (20.8)	8 (5.6)	1 (<1)	3 (16)	1 (5)	-
Weight decreased	30 (20.8)	-	-	4 (21)	-	-
Rash[2]	32 (22.2)	1 (<1)	-	5 (26)	-	-
Hypokalemia	26 (18.1)	6	1 (<1)	3 (16)	1 (5)	-
Hypomagnesemia	27 (18.)	1 (0.7)	-	3 (16)	-	-
Edema[3]	28 (19.4)	-	-	3 (16)	-	-
Dizziness/Vertigo	26 (18.1)	1 (0.7)	-	3 (16)	-	-
Dehydration	24 (16.7)	-	-	2 (11)	-	-
Cough/productive cough	24 (16.7)	-	-	2 (11)	-	-
Back and MSK Pain	25 (17.4)	1 (0.7)	-	6 (32)	-	-
Respiratory Infection[4]	25 (17.4)	4	-	2 (11)	-	-
White blood count decreased	20 (13.9)	8 (5.9)	5 (3.5)	4 (21)	2 (11)	1 (5)
Insomnia	20 (13.9)	-	-	3 (16)	-	-
Pyrexia	17 (11.8)	-	-	1 (<1)	-	-
Hypophosphatemia	17 (11.8)	6	-	3 (16)	2 (11)	-
Pruritis/pruritis generalized	16 (11.1)	1 (<1)	-	2 (11)	-	-

Source: *reviewer analysis using adae.xpt dataset*

[1]*Abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower*

[2]*Rash, rash erythematous, rash maculo-papular, rash pruritic*

[3]Facial edema, localized edema, edema, edema peripheral
[4]Influenza, Pneumonia, Atypical pneumonia, bronchitis, lower respiratory tract infection, metapneumovirus infection, pneumonia haemophilus, RSV infection, respiratory tract infection, upper respiratory tract infection, viral upper respiratory tract infection

Reviewer Comments: The incidence of diarrhea (66.7% for the safety population ≥65 compared to 62.0% for the safety population overall and 74% for the mTNBC cohort ≥65 as compared to 62.0% for the mTNBC cohort overall) and neutropenia (54.9% for the safety population ≥65 compared to 54.2% for the safety population overall and 68% for the mTNBC cohort ≥65 as compared to 63.9% for the mTNBC cohort overall) was numerically greater in older patients. The analysis and conclusions are limited by the small numbers of patients in this age range included. The tolerability appears to be generally similar to that of younger patients, though with an increased rate of adverse events. There are inadequate numbers of patients included to further explore safety in other population-based subgroups such as racial/ethnic or gender-based groups.

8.2.8 Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No carcinogenicity or tumor development studies were conducted or warranted to support this BLA, as the proposed indication was for advanced cancer.

Human Reproduction and Pregnancy

No pregnancies were reported in IMMU-132-01. There were no exposures in pregnant or lactating women during this trial.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
No accidental overdoses were reported in Trial IMMU-132-01.

Drug Abused Potential

There are no data available on the potential for abuse or dependence with sacituzumab.

Withdrawal and Rebound
There has been no formal trial of withdrawal and/or rebound after treatment discontinuation of sacituzumab.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Sacituzumab has been studied in a limited number of patients with refractory disease with a variety of solid tumors and a limited number of patients with mTNBC who have received two or more prior therapies.

It is expected that there may be increased adverse events in the postmarketing setting as the indicated population will have received two prior therapies for mTNBC and are likely to have adverse effects from both their persistent disease as well as cumulative toxicities from prior therapies. Additionally, though there is an increased incidence of central nervous system metastases in patients with mTNBC, these patients were initially excluded from participation in this trial. Even with the subsequent amendment to allow patients with stable CNS disease to participate, fewer than 2% of patients in the mTNBC efficacy cohort had evidence of CNS disease at the time of trial entry. Given this, there may be differences in safety and efficacy of this agent when used in this population. Safety is being monitored in the Phase 3 ASCENT IMMU-132-05 trial which serves to further assess clinical benefit and will be evaluating this therapy against other available therapies for patients in a similar disease setting. This trial will also be able to provide additional information regarding subpopulations such as those with alterations in the UGT1A1 gene that affect drug metabolism.

There are limited numbers of patients over the age of 75 in this trial as well. This is somewhat consistent however with the epidemiology of this disease. No overall differences in safety were noted in this population in review of the safety database, though the incidence of neutropenia and diarrhea were numerically greater in older patients. Given this, monitoring of laboratory values and appropriate supportive care as advised in the general USPI for all patients is needed.

8.2.11 Integrated Assessment of Safety

The safety profile of sacituzumab for the treatment of patients with metastatic triple-negative breast cancer that has progressed on two or more prior lines of therapy is acceptable with

adverse reactions managed through dose reductions and modifications, temporary treatment discontinuation, and/or standard medical care. Important safety signals identified in the course of the review of Trial IMMU-132-01 include the increased risk of diarrhea, neutropenia, nausea and vomiting. An additional important risk is that of infusion related reactions. These risks have been conveyed in the USPI along with risk reduction and management strategies. The Safety Update Report and related datasets submitted with the BLA application resubmission were reviewed, and there were no new safety signals with Sacituzumab treatment.

8.3 Statistical Issues

In general, there were no notable statistical issues with the trial design, statistical analysis plan, or efficacy results for the IMMU-132-01 trial. The confirmed ORR was 33.3% (95% CI: 24.6, 43.1) in the target mTNBC population (n=108) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment. Efficacy results based on blinded, independent, central review audit of the subgroup of patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation were consistent with investigator assessment however, results per ICR should be interpreted with caution given that this was based on assessment in a subgroup of patients. We reiterate that no inferential procedures were used to evaluate results from this single arm trial. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although PFS and OS results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm.

8.4 Conclusions and Recommendations

The clinical and statistical review teams viewed the efficacy results of Trial IMMU-132-01 to be an improvement over available therapy for the treatment of patients with mTNBC who have received at least 2 therapies in the metastatic setting and consider the safety profile sacituzumab to be acceptable in the context of an incurable disease in a heavily pre-treated population. The risks described in this review are addressed in the proposed product labelling and are manageable by medical oncologists, with the implementation of monitoring, dose modifications, and supportive measures.

The clinical and statistical reviewers agree with accelerated approval for this BLA for the reasons stated in the FDA assessments above.

X

Joyce Cheng, PhD
Primary Statistical Reviewer

X

Mallorie Fiero, PhD
Statistical Team Leader

X

Sakar Wahby, PharmD
Primary Clinical Reviewer

X

Christy Osgood, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

No advisory committee discussion or consultations external to the FDA were deemed necessary for this BLA application.

10 Pediatrics

FDA is waiving the pediatric trial requirement for this application because the necessary studies are impossible or highly impracticable because triple negative breast cancer is rare in the pediatric population.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The table below summarizes significant changes to the proposed label made by FDA during the review of the original BLA submission. Minor changes were made to the prescribing information and patient labeling during the review of the BLA resubmission based on the Safety Update Report submitted with the resubmission. In this BLA resubmission, Overdosage information (Section 10) of the Trodelvy Prescribing Information (PI) was revised to remove potentially misleading claims (b) (4) The observed increase in severe neutropenia statement was revised and retained in this section for the 18 mg/kg dose of Trodelvy (1.8 times the maximum recommended dose of 10 mg/kg) administered in a clinical trial. In addition, in the BLA resubmission, the applicant proposed to remove (b) (4) from the Sacituzumab USPI, (b) (4) FDA sent a request for further information to the applicant, to include patient ID, patient narratives, and applicant justification for this action. Upon FDA review of the information provided by applicant, the FDA agreed with the investigator and applicant's assessments in regards to hypertension (Patient (b) (6)), and hyponatremia (Patient (b) (6)), as not likely the cause of treatment discontinuation; however, the FDA did not agree with the investigator and applicant's assessment in regards to headache (Patient (b) (6)) as not likely the cause of treatment discontinuation. The Sacituzumab USPI was revised accordingly.

During the Original BLA submission, DO1 consulted with the FDA Office of Regulatory Policy (ORP) and Office of Chief Counsel (OCC) to evaluate the limited data submitted to this BLA by the Applicant related to SN-38 activity and the UGT1A1 metabolic pathway to determine information that may be inferred and used to support the TRODELVY prescribing information. Based on the ORP/OCC advice, DOP1 revised the TRODELVY prescribing information to remove (b) (4) labeling statements. As advised by ORP/OCC, DOP1 focused the TRODELVY labeling information on the data provided in this BLA and the fundamental principles related to SN-38 activity and the UGT1A1 metabolic pathway that were important to fully characterize the safety and efficacy profile of TRODELVY, and to meet the requirements of 21CFR 201.56 and 201.57.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling** *(as of December 17, 2018)*
Highlights		
Boxed Warning	None.	FDA added a Boxed Warning for neutropenia and diarrhea. *See Full Prescribing Information (FPI), Boxed*

		Warning below for more information.
Indications and Usage	…	*See FPI, Indications and Usage.*
Dosage and Administration	…	FDA revised the information under this heading to add the following: • Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or SN-38. (2.1) • Do not administer as an intravenous push or bolus. (2.2) • (recommended dose) …until disease progression or unacceptable toxicity. (2.2) • Premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended. (2.2) • Monitor patients during the infusion and for at least 30 minutes after completion of infusion.
Dosage Forms and Strengths	…	Added "for reconstitution" to the product description.
Contraindications	None.	FDA revised to the following: • Severe hypersensitivity reaction to TRODELVY (4, 5.3).
Warnings and Precautions	Neutropenia: …	FDA moved the Warning and Precaution for Neutropenia into the Boxed Warning in Highlights.
	Hypersensitivity: (b) (4) …	FDA revised the information under this heading as follows: • Deleted (b) (4) • Added "Hypersensitivity reactions including severe anaphylactic reactions have been observed." • Added "Monitor patients for infusion-related reactions."
	Diarrhea: …	FDA moved the Warning and Precaution for Diarrhea into the Boxed Warning.
	None.	FDA added a Warning and Precaution for "Patients with Reduced UGT1A1

		Activity".
	None.	FDA added a Warning and Precaution for "Embryo-Fetal Toxicity" to identify that TRODELVY can cause fetal harm and to advise patients of the risk to a fetus and to use contraception.
Adverse Reactions	…	FDA added "constipation", "rash", and "abdominal pain" to the list of common adverse reactions.
Drug Interactions	…	FDA removed (b) (4) maintained UGT1A1 inhibitors, and added UGT1A1 inducers to the "avoid concomitant use" statement.
Use in Specific Populations	…	• FDA revised this section to move the pregnancy information to the Embryo-Fetal Warnings and Precaution.
Full Prescribing Information		
Boxed Warning	None.	FDA added a Boxed Warning for neutropenia and diarrhea. For neutropenia, advice to hold Trodelvy for ANC < 1500/mm^3 and periodic CBC monitoring, secondary prophylaxis, and anti-infective use for febrile neutropenia were added. For diarrhea, monitoring, fluid and electrolyte repletion, and advice on management of early and late diarrhea were added. This Boxed Warning was added in accordance with 21CFR201.57(c)(1) and the FDA Guidance for the Boxed Warning Sections of Labeling (IV.A) to highlight for prescribers neutropenia and diarrhea associated with TRODELVY "that is essential that it be considered in assessing the risks and benefits of the drug", "that can be prevented or reduced in frequency or severity by appropriate use of the drug", and "to highlight warning

		information that is especially important to the prescriber".
1. Indications and Usage	…	FDA removed (b) (4) since not required and added "adult" to clearly describe the indicated population. To the basis for accelerated approval statement, FDA added "duration for response" to tumor response rate.
2. Dosage and Administration	**2.1 Important Use Information** *(subsection added by FDA)*	FDA added this subsection and the following statement: **"Do NOT substitute TRODELVY for or use with other drugs containing irinotecan."**
	2.2 Recommended Dose and Schedule **…** <u>Premedication</u> …	FDA added "Do not administer as an intravenous push or bolus." … FDA agreed with the premedication regimens proposed with minor revisions to remove passive voice, redundant statements, (b) (4)
	2.3 Dose Modifications for Adverse Reactions **…**	FDA added a subsection for Infusion-related Reactions and information to slow or interrupt the infusion rate of TRODELVY, and to permanently discontinue TRODELVY for life-threatening infusion-related reactions. FDA revised the Dose Modifications Table (Table 1) to require a 25% dose reduction after the first occurrence of Grade 4 neutropenia ≥ 7 days or Grade 3 febrile neutropenia, revised the second dose reduction (b) (6) to 50%, and revised the third dose reduction (b) (6) to discontinuation of treatment. These revisions were to be consistent with how dose modifications were performed in the clinical trial.

	2.4 Preparation for Administration **…**	After reconstitution, FDA added "Use immediately to prepare a diluted TRODELVY infusion solution." At the beginning of the dilution process, FDA added "Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient's body weight. Withdraw this amount from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s)." FDA added the room temperature range and revised the time the diluted solution in the infusion bag can be stored (b) (4) to 4 hours prior to administration based on the data provided by the Applicant. FDA added a statement not to shake and to protect the diluted solution in the infusion bag from light.
4. Contraindications	None.	FDA added "TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions (5.3)]*."
5. Warnings and Precautions		FDA revised the order of the Warnings and Precautions to reflect the relative clinical significance of TRODELVY's adverse reactions (i.e., 5.1 Neutropenia, 5.2 Diarrhea, 5.3 Hypersensitivity, 5.4 Nausea and Vomiting, 5.5 Patients with Reduced UGT1A1 Activity, 5.6 Embryo-Fetal Toxicity). FDA removed (b) (4)

		(b) (4) [redacted]
	5.1 Neutropenia *(FDA moved from 5.2)* **…**	FDA added "TRODELVY can cause severe or life-threatening neutropenia. Dose modifications may be required due to neutropenia *[see Dosage and Administration (2.3)]*." FDA removed (b) (4) [redacted] FDA moved dose modification information for neutropenia to subsection 2.3 (Table 1).
	5.2 Diarrhea *(FDA moved from 5.5)* **…**	FDA added "Neutropenic colitis was observed in (b) (4)% of patients in the mTNBC cohort and 1% of patients (b) (4) [redacted] (b) (4)" and "At the onset of diarrhea evaluate for infectious causes." FDA removed (b) (6) [redacted]

	5.3 Hypersensitivity *(FDA moved from 5.1)* …	FDA added "TRODELVY can cause severe and life-threatening hypersensitivity." and revised (b) (4) reactions to "anaphylaxis" reactions. FDA removed (b) (4) FDA moved (and cross referenced) the infusion-related adverse reaction dose modification information to subsection 2.3. FDA revised the existing monitoring information for the first dose to require monitoring after all infusions as follows: "Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion [*see Dosage and Administration (2.3)*]. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use."
	5.4 Nausea and Vomiting **…**	FDA deleted (b) (4) from the moderately emetogenic statement. FDA removed (b) (4) FDA updated the incidence rates from (b) (4) % (Grade 1-4) and (b) (4) to 4% (Grade 3-4) vomiting based on the updated safety information reviewed.
	5.5 Patients with Reduced UGT1A1 Activity	FDA added the following: • "In (b) (4) % (b) (4) of patients who

	(FDA moved from 5.3) **…**	received TRODELVY (up to 10 mg/kg on days 1 and 8 of a 21-day cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was (b) (4)% in patients homozygous for the UGT1A1*28 allele (b) (4)% in patients heterozygous for the UGT1A1*28 allele (b) (4) and (b) (4) in patients homozygous for the wild-type allele (b) (4) *[see Clinical Pharmacology (12.4)]."* • "The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2.3)]*."
	5.6 Embryo-Fetal Toxicity **…**	FDA removed (b) (4) and (b) (4) FDA added the following: • "Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*." • "Advise females of reproductive potential to use effective

		contraception during treatment with TRODELVY and for 6 months (b) (4) the last dose."
6. Adverse Reactions	**6.1 Clinical Trials Experience** **…**	FDA added a paragraph to describe the safety population used in Warnings and Precautions (n=408 patients) treated with TRODELVY for mTNBC and other malignancies who had received prior systemic therapeutic regimens for advanced disease. As discussed above, only patients who received doses up to 10 mg/kg were included in the safety population (n=408) to be consistent with the approved dosage regimen. *See Section 8.2.4 of this review for more information.* In this section (and throughout the prescribing information), FDA removed (b) (4) FDA removed (b) (4) FDA revised the incidence rate of serious adverse reactions by removing (b) (4) This changed overall SARs (b) (4) to 31%; increased the incidence rates of vomiting (6%) and nausea (3%); and required the addition of colitis (3%) and sepsis (2%) not previously included

		in this section. *See Section 8.2.4 of this review for more information.* FDA removed the statement (b) (4) [redacted] FDA revised the adverse reactions leading to discontinuation (b) (4) [redacted] FDA added a statement to identify that (b) (4)% of patients experienced an adverse reaction leading to treatment interruption (with (b) (4)% due to neutropenia) and a statement that 33% of the patients treated with TRODELVY required dose reductions. FDA revised the Adverse Reactions table (Table 2) to increase the incidence of nearly every Grade 1-4 and Grade 3-4 adverse reaction (b) (6) [redacted] FDA added ARs for mucositis, hypokalemia, peripheral neuropathy, dysgeusia, urinary tract infection, respiratory infection, cough, dyspnea, and insomnia based on the FDA Clinical Safety review findings. FDA required the addition of Table 3 Laboratory Abnormalities to provide the clinically relevant laboratory abnormalities observed for mTNBC patients treated with TRODELVY in the IMMU-132-01 trial. FDA deleted (b) (4) [redacted]

		(b) (4) [redacted]
	6.2 Immunogenicity **…**	FDA added immunogenicity and anti-sacituzumab govitecan antibodies results to this subsection based on FDA review. *See Section 6.3.1 of this review for more information.*
7. Drug Interactions		FDA removed statements (b) (4) [redacted]
	7.1 Effect of Other Drugs on TRODELVY **…**	FDA revised this section to remove statements (b) (4) [redacted] FDA revised the information related to UGT1A1 inhibitors to add a statement that administration of TRODELVY may increase the incidence or severity of adverse reactions due to potential increase in systemic exposure to SN-38. FDA removed (b) (4) [redacted] FDA revised (b) (4) to UGT1A1 inducers (b) (4) [redacted]

		FDA added a statement to avoid administering TRODELVY with UGT1A1 inducers. *See Section 6.3.2 of this review for more information on SN-38 data submitted in this BLA and how known UGT1A1 inhibition or induction activity impacts the safety and efficacy profile of TRODELVY.*
8. Use in Specific Populations	**8.1 Pregnancy** **…**	Risk Summary FDA removed information (b) (4) [redacted] FDA revised can cause (b) (4) [redacted] to "teratogenicity" and "embryo-fetal lethality" when administered to pregnant women. FDA added that there are no available data in pregnant women to inform the drug associated risk. FDA added "TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells" and "females of reproductive potential" to the potential risk to the fetus statement. Data *Animal Data* FDA revised the proposed information to condense and add the following statement: There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

		FDA removed information (b) (4) [redacted] *See Section 5 of this review for more information.*
	8.2 Lactation **…**	Risk Summary FDA agreed to the proposed risk summary with minor revisions. (b) (4) [redacted] *See Section 5 of this review for more information.*
	8.3 Females and Males of Reproductive Potential **…**	FDA agreed with pregnancy testing and contraception information with revisions to the required time to use effective contraception after the final dose for females (i.e., (b) (4) revised to 6 months) and males (i.e., 3 months revised (b) (4)). *See Section 5 of this review for more information.*
	(b) (4) [redacted] **..**	FDA deleted this subsection and statements (b) (4) [redacted]
	8.6 Hepatic Impairment (b) (4) [redacted]	FDA revised this section to the following: "No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin less than or equal to 1.5 ULN and AST/ALT < 3 ULN). The exposure of sacituzumab

		govitecan - hziy in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=45). The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases."
11. Description	**…**	FDA removed (b) (4) [redacted] FDA added the route of administration "for intravenous use" to be consistent with the requirements in 21CFR201.57.
12. Clinical Pharmacology	**12.1 Mechanism of Action** **…**	FDA revised Section 12.1 to limit the information in this section to a concise summary of the established mechanism of action of sacituzumab govitecan-hziy and to avoid speculative and unsupported claims and general information that is educational in nature.
	12.2 Pharmacodynamics *(FDA added this subsection)*	FDA added "Exposure-response relationships and the time course of pharmacodynamics response are unknown sacituzumab govitecan – hziy."
	12.3 Pharmacokinetics **…**	Throughout this subsection, FDA removed information (b) (4) [redacted] *See Section 6.3.1 of*

		this review for more information (b) (4) [redacted] FDA agreed with the Applicant's information related to pharmacokinetics for absorption and distribution of sacituzumab govitecan-hziy with minor revisions, reformatting, and removal of references (b) (4) [redacted] <u>Elimination</u> FDA removed (b) (4) [redacted] <u>Specific Populations</u> FDA added this subsection to provide information on the lack of effect on TRODELVY pharmacokinetics for age or race. FDA added a statement regarding the lack of data for patients with varying degrees of renal impairment. FDA added data from TRODELVY use in patients with mild hepatic impairment and a statement regarding the lack of data for patients with moderate or severe hepatic impairment that may result in an increase in SN-38 concentrations in patients with decreased hepatic function.

		Drug Interaction Studies FDA agreed that no studies of sacituzumab govitecan-hziy have been conducted and added "Inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively." *See Section 6.3.2 of this review for more information.*
	12.4 Pharmacogenomics *(FDA added this subsection)*	FDA added this subsection due to the increased risk of neutropenia and other TRODELVY-related adverse reactions in individuals who are homozygous for the UGT1A1*28 allele. *See Section 6.3.2 of this review for more information.*
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **…**	FDA agreed with the proposed information that sacituzumab govitecan-hziy was clastogenic in nonclinical *in vitro* studies and not mutagenic in *an in vitro* Ames assay with minor revisions. FDA moved the statement related to rapidly dividing cells and potential to cause embryotoxicity and teratogenicity to subsection 8.1. FDA added "In a repeat-dose toxicity trial in cynomolgus monkeys, intravenous administration of sacituzumab govitecan - hziy on Day 1 and Day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the human recommended dose of 10 mg/kg based on body weight)."
		(b) (4)

		(b) (4) [redacted]
14. Clinical Studies	…	FDA accepted the IMMU-0132 trial description with minor revisions. FDA added the following: "Patients with bulky disease, defined as a mass >7 cm, were not eligible. Patients with treated brain metastases not receiving high dose steroids (>20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert's disease were excluded." FDA agreed with the IMMU-0132 demographic and baseline disease information proposed with minor revisions and the added the following clinically relevant information: "(b) (4) [redacted] percent had visceral disease, 42% had hepatic metastases, and 2% had brain metastases. Twelve patients (11%) had Stage IV disease at the time of initial diagnosis." FDA agreed to the prior systemic therapy information in the metastatic setting with the addition of "carboplatin or cisplatin (69%)", "paclitaxel or docetaxel (52%)", and "doxorubicin (24%), vinorelbine (16%), cyclophosphamide (19%), and ixabepilone (8%)" to fully characterize this information. FDA removed (b) (4) [redacted] FDA removed (b) (4) [redacted]

		(b) (4) FDA revised the Efficacy Results table (Table 5) for IMMU-0132 to add complete responses (CRs) (2.8%) and Partial Responses (PRs) (30.6%) and the range and % duration of response at 6 months and 12 months. FDA removed (b) (4) (*see Section 8.1.1, Statistical Analysis Plan, for more information).*
15. References	…	FDA revised outdated references to the current reference for the safe handling of cytotoxic drugs.
16. How Supplied/ Storage and Handling	…	FDA revised this section to include the dosage formulation and identifying characteristics required by 21 CFR 201.58(c)(17). FDA added "(store) in the original carton to protect from light until time of reconstitution". FDA added "TRODELVY is a cytotoxic drug. Follow applicable special handling and disposal procedures[1]."
17. Patient Counseling Information	…	FDA added the following required statement: "*Advise the patient to read the FDA-approved patient labeling (Patient Information)".* FDA reordered this section to reflect

		the new order of the Warnings and Precautions to reflect the relative clinical significance of counseling topics and information provided. FDA revised the Embryo-Fetal Toxicity information and added: "Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*." FDA removed (b) (4)

11.2 Patient Labeling

The following is a summary of major revisions made to the Patient Information during the review of the Original BLA submission, with minor changes made during the review of the BLA resubmission:

- FDA added the "What is the most important information I should know about TRODELVY?" section to be consistent with the Boxed Warning information for severe neutropenia and diarrhea in the prescribing information.
- To the "What is TRODELVY?" section, added:
  - "It is not known if TRODELVY is safe and effective in people with moderate or severe liver problems."
  - "It is not known if TRODELVY is safe and effective in children."
  - "Do not receive TRODELVY if you have had a severe allergic reaction to TRODELVY. Ask your healthcare provider if you are not sure." to be consistent with revisions to the Contraindications in the prescribing information.
- To the "Before receiving TRODELVY, tell your healthcare provider about all of your medical conditions, including if you:" added information regarding UGT1A1 toxicities, liver problems, and revised the information related to pregnancy and contraception to be consistent with revisions to Section 8 of the prescribing information.
- To the "How will I receive TRODELVY?" section, added information related to the risks of infusion-related reactions.
- To the "What are the possible side effects of TRODELVY?" section:
  - Revised to advise patients to contact their healthcare provider if swelling of mouth, tongue, or throat occur.

- o (b) (4)
- o Added side effects for “constipation”, “stomach (abdominal) pain”, and “rash” consistent with the prescribing information and FDA clinical safety review.

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended for Sacituzumab govitecan.

13 Postmarketing Requirements and Commitment

The following Postmarketing requirements and commitments were agreed upon by FDA and the Applicant.

Postmarketing Requirements (PMRs)

PMR 3504-1: Submit the final study report and datasets for progression-free survival and overall survival from trial IMMU-132-05 titled "Phase III Study of Sacituzumab Govitecan (IMMU-132) in Refractory/Relapsed Triple-Negative Breast Cancer", to confirm clinical benefit of sacituzumab that may inform product labeling.

Final Protocol Submission: 08/2019
Trial Completion: 04/2020
Final Report Submission: 10/2020

PMR 3504-2: Submit the clinical study report and related datasets to further characterize the risk of adverse events and UGT1A1 status in the IMMU-132-05 trial to support sacituzumab govitecan dosing recommendation for patients homozygous for UGT1A1*28 allele that may inform labeling. The study should be conducted for sufficient duration with a sufficient number of patients to evaluate safety following multiple dose administration.

Final Protocol Submission: 08/2019
Trial Completion: 04/2020
Final Report Submission: 10/2020

PMR 3504-3: Conduct an open-label, non-randomized, dose-escalation trial to determine an appropriate starting dose of sacituzumab govitecan in patients with moderate hepatic impairment, according to the National Cancer Institute Organ Dysfunction Working Group criteria in the target patient population. Safety and pharmacokinetic information of IMMU-132 and SN-38 will be collected to determine the appropriate starting dose of sacituzumab govitecan for this population. Submit the datasets with the final report.

Draft Protocol Submission: 07/2020
Final Protocol Submission: 10/2020
Trial Completion: 04/2021
Final Report Submission: 09/2021

PMR 3504-4: Submit the final QTc prolongation evaluation report in a sub-study of the ongoing clinical trial IMMU-132-05 titled "Phase III Study of Sacituzumab Govitecan (IMMU-132) in Refractory/Relapsed Triple-Negative Breast Cancer" that may further inform labelling about the QT effect of SN-38 at the recommended dose of sacituzumab govitecan.

Final Protocol Submission: 08/2019
Trial Completion: 04/2020
Final Report Submission: 10/2020

Postmarketing Commitments (PMCs)

3504-5 Perform a real-time drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The study results will be updated annually in the BLA Annual Report. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

Final Report Submission: 12/2022

3504-6: Perform a comparison of results from genetic analysis of Master Cell Bank (MCB) (b) (4) Data to support genetic stability of MCB (b) (4) will be provided in the final report to the BLA.

Final Report Submission: 03/2021

3504-7: Develop an assay (e.g., icIEF) that is capable of providing quantitative control of (b) (4) (b) (4) impurities and to implement this assay in the release and stability programs for sacituzumab govitecan drug substance, drug product and reference standard after sufficient data have been acquired to set appropriate acceptance criteria. The analytical procedure, validation report, proposed acceptance criterion, and data used to set the proposed acceptance criterion will be submitted as a CBE-30.

Final Report Submission: 06/2021

3504-8: Develop and validate a sensitive assay for the detection of binding antibodies to the antibody (hRS7-IgG) and drug-linker (SN-38/CL2A) domains of sacituzumab govitecan for accurate detection of anti-drug antibodies (ADA) against sacituzumab govitecan in the presence of drug levels that are expected to be present in the serum or plasma at the time of patient sampling. The analytical procedures and method validation report will be submitted in the final report to the BLA.

Final Report Submission:11/2020

3504-9: Develop and validate a sensitive assay for the detection of neutralizing antibodies (NAb) to sacituzumab govitecan for accurate detection of NAb to sacituzumab govitecan in the

presence of drug levels that are expected to be present in the serum or plasma at the time of patient sampling. The NAb assay procedures and method validation report will be submitted in the final report to the BLA.sampling. The NAb assay procedures and method validation report will be submitted in the final report to the BLA.

Final Report Submission: 12/2020

3504-10: Perform a study to verify the performance of the compendial visual appearance assay (SOP-0481) used to support lot release and stability testing of hRS7 IgG1 intermediate and hRS7 IgG1 reference standard at Immunomedics, Inc. The final method verification report will be submitted to the BLA.

Final Report Submission: 06/2020

3504-11: Perform a supplemental method validation study to evaluate the (b) (4) at BSP Pharmaceuticals. The study will include the evaluation of samples analyzed by multiple analysts on multiple days at BSP Pharmaceuticals. The final method validation report will be submitted to the BLA.

Final Report Submission:10/2020

3504-12: Establish a two-tiered reference material system for IMMU-132 by qualifying a primary reference standard (PRS) lot against current reference standard batch 1801082. The final qualification reports for the PRS will be submitted to the BLA as a PAS.

Final Report Submission: 06/2020

14 Division Director (DHOT)

X
N/A

15 Division Director (OCP)

X
Nam Atiqur Rahman, PhD

16 Division Director (OB) Comments

X
Shenghui Tang, PhD

17 Division Director (Clinical) Comments

X
Laleh Amiri-Kordestani, MD

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents an approval recommendation for the application under CDER.

X
Richard Pazdur, MD

19 Appendices

19.1 References

1. Barbarino JM, Haidar CE, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for UGT1A1. Pharmacogenet Genomics. 2014 Mar; 24(3):177-83.

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19.2 Financial Disclosure

The FDA review of Financial Disclosure documents was conducted at the time of the orginial BLA submission.

Covered Clinical Trial (Name and/or Number): IMMU132-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the trial where the value could be influenced by the outcome of the trial: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered trial: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3 Additional Clinical Outcome Assessment Analyses

Not applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kimberly Ringgold, PhD	OOD/Division of Hematology Oncology Toxicology	Sections: 5	Select one: _x_ Authored ___ Approved
	Signature: Kimberly Ringgold -S Digitally signed by Kimberly Ringgold -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000347494, cn=Kimberly Ringgold -S Date: 2020.04.21 12:57:05 -04'00'			
Nonclinical Team Leader	Tiffany Ricks, PhD	OOD/Division of Hematology Oncology Toxicology	Sections: 5	Select one: _x_ Authored _x_ Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2020.04.21 12:39:03 -04'00'			
Clinical Pharmacology Reviewer	Salaheldin Hamed, PhD	Office of Clinical Pharmacology/Division of Cancer Pharmacology I	Sections: 6	Select one: × **Authored** ___ Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000952138, cn=Salaheldin S. Hamed -S Date: 2020.04.21 12:48:41 -04'00'			
Genomics Reviewer	Sarah Dorff, PhD	Office of Clinical Pharmacology/Division of Translational and Precision Medicine	Sections: 6	Select one: X Authored ___ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah E. Dorff -S, 0.9.2342.19200300.100.1.1=2001211253 Date: 2020.04.21 12:44:08 -04'00'			
Genomics Team Leader	Rosane Charlab Orbach, PhD	Office of Clinical Pharmacology/Division of Translational and Precision Medicine	Sections: 6	Select one: X Authored X Approved
	Signature: Rosane Charlaborbach -S Digitally signed by Rosane Charlaborbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300436672, cn=Rosane Charlaborbach -S Date: 2020.04.21 12:53:46 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Pengfei Song, PhD	Office of Clinical Pharmacology/Division of Cancer Pharmacology I	Sections: 6	Select one: X Authored X Approved
	Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2020.04.21 14:01:24 -04'00'			
Statistical Reviewer	Joyce Cheng, PhD	OB/DBV	Sections: 7.2, 8.1, 8.3	Select one: x Authored ___ Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2020.04.21 13:02:53 -04'00'			
Statistical Team Leader (Acting)	Mallorie Fiero, PhD	OB/DBV	Sections: 7.2, 8.1, 8.3	Select one: X Authored X Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2020.04.21 14:47:54 -04'00'			
Clinical Reviewer	Sakar Wahby, PharmD	OOD/DO1	Sections: 2, 3, 7, 8, 9, 10, 11, 12, 13, 19.	Select one: X Authored ___ Approved
	Signature: Sakar M. Wahby -S Digitally signed by Sakar M. Wahby -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sakar M. Wahby -S, 0.9.2342.19200300.100.1.1=0013507760 Date: 2020.04.21 14:38:44 -04'00'			
Associate Director for Labeling	William Pierce, Pharm D, MPH	OOD	Sections: Prescribing information, Labeling Recommendations	Select one: X Authored X Approved
	Signature: William F. Pierce -S5 Digitally signed by William F. Pierce -S5 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5 Date: 2020.04.21 14:35:07 -04'00'			
Cross-Disciplinary Team Leader	Christy Osgood, MD	OOD/DO1	Sections:1 2-19	Select one: X Authored X Approved
	Signature: Christy Osgood -S Digitally signed by Christy Osgood -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Christy Osgood -S, 0.9.2342.19200300.100.1.1=2001693552 Date: 2020.04.21 12:32:14 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD		Sections:6, 19	Select one: ___ Authored X Approved
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NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761115
Priority or Standard	Priority
Submit Date(s)	May 18, 2018
Received Date(s)	May 18, 2018
PDUFA Goal Date	January 18, 2019
Division/Office	OND/OHOP/DOP1
Review Completion Date	
Established Name	Sacituzumab govitecan
(Proposed) Trade Name	TRODELVY™
Pharmacologic Class	Antibody Drug Conjugate (ADC)
Code name	IMMU-132
Applicant	Immunomedics, Inc.
Formulation(s)	Lyophilized powder in single use vials containing 180 mg/vial
Dosing Regimen	10 mg/kg administered once weekly on days 1 and 8 of a 21-day treatment cycle
Applicant Proposed Indication(s)/Population(s)	TRODELVY is (b) (4) for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	

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OPQ=Office of Pharmaceutical Quality
OBP=Office of Biological Products
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

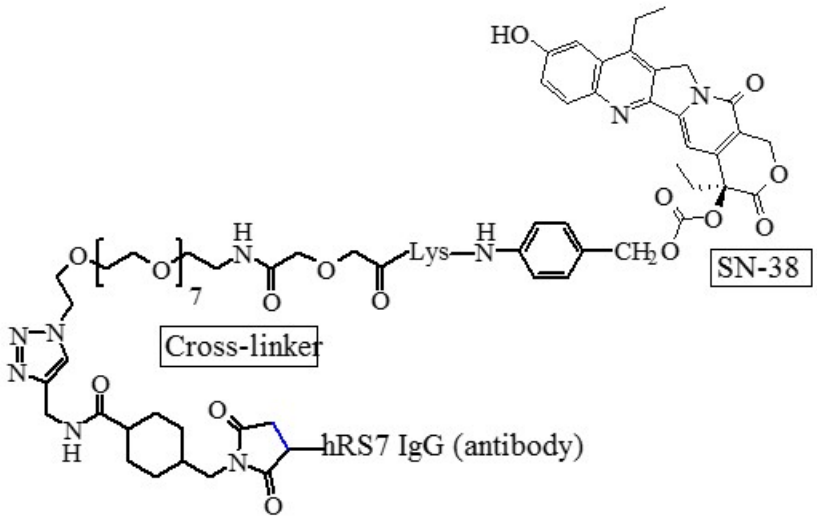
AC	advisory committee
ADCC	antibody-dependent cellular cytotoxicity
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CT	Computed tomography
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
HR	hazard ratio
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	Magnetic resonance imaging
mTNBC	metastatic triple negative breast cancer

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology
OS	overall survival
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
TNBC	triple negative breast cancer

1 Executive Summary

1.1. Product Introduction

Sacituzumab govitecan (TRODELVY) is an antibody drug conjugate made up of SN-38, a topoisomerase I inhibitor that is the active metabolite of irinotecan, coupled by a CL2A linker to the humanized monoclonal antibody hRS7 IgGκ which binds to Trop-2. The chemical structure of sacituzumab govitecan is shown below.



Trop-2 is the trophoblastic cell-surface antigen that is a transmembrane calcium signal transducer glycoprotein of the TACSTD gene family. Trop-2 is expressed on normal tissue including the epithelial barrier/lining of the stratum basale epidermis, breast, cervix, cornea, epithelial secretory tissue of the endocrine and exocrine glands, esophagus, heart, kidneys, larynx, lung, liver, pancreas, prostate, salivary gland, skin, thymus, tonsils, trachea, trophoblast cells, urothelium and uterus.

Trop-2 is overexpressed in many epithelial cancers including metastases. It has been implicated as a potential oncogene and is often found in aggressive tumors. In breast cancer, Trop-2 has been found to be greater in estrogen receptor (ER) negative, human epidermal growth factor receptor 2 (HER2) positive tumors and lower in patients with ER positive, HER2 negative disease suggesting that Trop-2 overexpression may be associated with less favorable phenotypes.

Sacituzumab govitecan (TRODELVY) for injection is a sterile, preservative-free, off-white to yellowish lyophilized powder for intravenous use in a 50 mL clear glass single dose vial, with a rubber stopper and crimp-sealed with an aluminum flip-off cap. The proposed dosage for sacituzumab govitecan is 10 mg/kg administered as an intravenous infusion on days 1 and 8 of a 21-day treatment cycle.

1.2. Conclusions on the Substantial Evidence of Effectiveness

On May 18, 2018, Immunomedics, Inc., (Immunomedics), submitted original Biologics License Application (BLA) 761115, requesting marketing authorization for TRODELVY (sacituzumab govitecan) injection. In the BLA submission, Immunomedics sought accelerated approval for TRODELVY according to 21 CFR Part 601.41, Subpart E, for the following indication:

> SACITUZUMAB GOVITECAN, (b) (4), is indicated for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease.

The applicant submitted the results of a single trial, Study IMMU-132-01, a single-arm, multicenter (US only) study of sacituzumab govitecan in patients with advanced solid tumor malignancies. Among the 420 patients who received sacituzumab govitecan at various doses, a total of 108 patients who enrolled and received the proposed dose of 10 mg/Kg had metastatic triple-negative breast cancer and had received at least two prior lines of therapy in the metastatic setting; it is this subgroup of patients that comprises the efficacy population for this BLA. Among the 108 patients in the efficacy population, the investigator-assessed ORR by RECIST 1.1 was 33.3% (95% CI: 24.6, 43.1). The median duration of response among responders was 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment. The ORR based on Independent central review (ICR) was performed on patients with tumor scans showing complete response, partial response, or at least 20% shrinkage by local site evaluation (n=55). Objective response rate based on this subgroup ICR was supportive of the investigator-assessed response rate; however, results per ICR should be interpreted with caution given that this was based on assessment in a subgroup of patients.

To determine whether the effect of sacituzumab govitecan on the ORR as shown in Study IMMU-131-01 is an improvement over available therapies as required per the provisions of accelerated approval and in accordance with 21 CFR Part 601.41, subpart E, FDA considered therapies to be “available” if the Agency’s previous finding of effectiveness was based upon a study or studies that evaluated patients similar to the study population in the efficacy cohort of Study IMMU-132 01 (i.e., TNBC cohort n=108) in their receipt of prior taxane and anthracycline-based chemotherapy.

Eribulin and ixabepilone, the two agents approved for the treatment of metastatic breast cancer following two or more prior chemotherapy regimens in the metastatic setting, were considered available therapies. Ixabepilone as a single agent was approved based upon investigator-assessed ORR of 18.3% (95% CI: 11.9, 26.1) and an ORR by central assessment of 12.4% (95% CI: 6.9, 19.9); median duration of response was 6.0 months (95% CI: 5.0, 7.6) by central assessment. Approval of eribulin was based on ORR of 11% (95% CI: 8.6, 14.3) and median duration of response of 4.2 months (95% CI: 3.8, 5.0). The ORR of 33.3% and DOR of 7.7

months with sacituzumab govitecan is considered reasonably likely to predict clinical benefit and to be better than the available therapies.

The safety profile of sacituzumab govitecan is acceptable for the intended population. The most common adverse events (≥20% in incidence: nausea, diarrhea, fatigue, vomiting, alopecia, anemia, neutropenia, constipation, decreased appetite, abdominal pain, dyspnea) are manageable with monitoring, dose modifications, and supportive measures. Neutropenia was a common and serious toxicity observed in Study IMMU-132-01 with one death due to neutropenic typhlitis. Diarrhea was also common and severe. Neutropenia and diarrhea should be included in the "Warnings and Precautions" section of the prescribing information and as boxed warnings to provide adequate caution to prescribers regarding these toxicities, particularly in patients known to be homozygous for the UGT1A1*28 allele, who are at increased risk for neutropenia.

Several objectionable conditions were identified during the pre-license inspection of the manufacturing facility for hRS7 antibody intermediate, including data falsification to obtain favorable results. Additionally, the data submitted in the application are not sufficient to support a conclusion that the manufacture of sacituzumab govitecan is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. The main deficiencies included (b) (4)

The clinical data is supportive of an accelerated approval of sacituzumab govitecan for the following indication:

> SACITUZUMAB GOVITECAN, (b) (4) is indicated for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease.

However, the overall benefit-risk assessment of sacituzumab govitecan is unfavorable, based upon the deficiencies identified during the review of the chemistry, manufacturing, and controls (CMC) data package. FDA therefore recommends a complete response for the application.

At the time of action on this application, labeling negotiations had been initiated but final agreement had not been reached. Agreement on postmarketing requirements and post marketing commitments had also not been reached.

1.3. **Benefit-Risk Assessment**

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

Approximately 20% of breast cancer diagnoses worldwide are deemed to be triple negative breast cancer (TNBC), which describes a subtype of breast cancer that has low expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). This subtype of breast cancers is histologically and molecularly heterogenous. The TNBC subtype is more commonly diagnosed in women younger than 40 years compared with hormone-positive breast with a nearly two-fold higher attributable risk of TNBC in women under 40 years compared with women over 50 years (odds ratio [OR] 2.13, 95% CI 1.34-3.39) [Trivers KF, et al; 2009]. In addition, TNBC appears to be more common among black women compared with white women, with a more than two-fold increase in incidence in the former. Other risk factors for the disease include the presence of BRCA mutation, premenopausal status, obesity, and maternal related factors such as parity and age at first pregnancy.

Metastatic triple negative breast cancer (mTNBC) is incurable. It is a disease with a poor prognosis with a median a median survival of approximately 13.3 months (Kassam, F et al; 2009). Unlike hormone receptor (i.e., estrogen receptor [ER]/ progesterone receptor [PR]) positive disease and human epidermal growth hormone receptor 2 (HER2) positive disease, there are no targeted therapies for the treatment of this subset of breast cancers.

Chemotherapy is the mainstay of treatment of TNBC and in general, patients first receive standard chemotherapy regimens that include taxane- or anthracycline- containing combinations in the neoadjuvant and adjuvant settings. Because the major cause of disease progression in the metastatic setting is multidrug resistance (either primary or acquired), following progression on these regimens, and in the metastatic setting, patients may receive agents thought to not be cross-resistant (e.g., capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens). There is no preferred or standard regimen used. In patients who have previously received anthracycline- and/or taxane-based treatment, sequential, single agent chemotherapy is typically used, with multi-agent regimens reserved for patients who present with visceral crisis. For the approximately 20% of patients with TNBC who harbor a germline BRCA 1 or 2 mutation, the poly ADP-ribose polymerase (PARP) inhibitors olaparib and talazoparib have been approved for patients who have been previously treated with chemotherapy.

Treatment options are limited for patients who have received two or more regimens in the metastatic setting. FDA-approved therapies that constitute available therapies in this setting are eribulin and ixabepilone. Eribulin was approved in the third-line metastatic setting based on an improvement in OS of less than 3 months (13.1 months versus 10.6 months; HR 0.81; 95% CI: 0.66, 0.99) in a randomized controlled trial of 762 patients who had received at least two prior lines of therapy compared to physician's choice chemotherapy. The observed response rate was 11% with a median duration of response of 4.2 months. Ixabepilone was approved based upon a modest response rate (investigator-assessed ORR of 18.3% [95% CI: 11.9, 26.1]; central, independently-assessed ORR 12.4% [95% CI: 6.9, 19.9]). The median duration of response was 6.0 months (95% CI: 5.0, 7.6) by central assessment.

Study IMMU-132-01, a phase 1/2, non-randomized, open-label, multicenter study, provided the data to support the safety and efficacy of sacituzumab govitecan. Study IMMU-132-01 evaluated sacituzumab govitecan at doses ranging from 8 mg/Kg to 18 mg/Kg, administered as a single agent to patients with advanced solid tumor malignancies. The cohort of patients whose results support the efficacy assessment for BLA 761115 comprise 108 patients with mTNBC who had received at least two prior lines of systemic therapy, and who received sacituzumab govitecan 10 mg/kg by intravenous administration on days 1 and 8 of a 21-day cycle until disease progression, loss of clinical benefit, unacceptable toxicity, or death.

Among the 108 patients in the efficacy population, the confirmed investigator-assessed ORR by RECIST 1.1 was 33.3% (95% CI: 24.6, 43.1); the estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8). ICR was performed on patients with tumor scans showing complete response, partial response, or at least 20% shrinkage by local site evaluation (n=55). Objective response rate based on this subgroup ICR was supportive of the investigator-assessed response rate; however, results per ICR should be interpreted with caution given that this was based on assessment in a subgroup of patients.

The safety assessment was based upon the overall study population in Study IMMU-132-01 who received sactituzumab govitecan 8 or 10 mg/Kg (n=408), and in the subset of patients who comprise the efficacy population (n=108). In the overall safety population, the median duration of treatment was 3.5 months (range 0, 40.6). The median number of treatment cycles was 6 (range 1, 56), and the median number of doses administered was 11 (range 1, 112). A third of patients (32.1%) experienced 1 or more dose reductions (1 dose reduction [25.2%]; 2 dose reductions [5.9%]; 3 dose reductions [1%]). Treatment delays occurred in 4.4% of patients and 9.8% of patients discontinued treatment due to AEs.

Among the safety population, 99.8% experienced at least one adverse event (AE). Serious AEs (SAEs) were observed in 40.5% of patients. The most common (≥2%) SAEs by preferred term were febrile neutropenia (4.2%), diarrhea (3.4%), pneumonia (2.9%), vomiting (2.7%), dyspnea (2.5%), and nausea (2.2%). Grade 3-4 AEs were observed in 70.3% of patients. The most common (≥5%) Grade 3-4 AEs by preferred term were neutropenia (27.2%), neutrophil count decreased (13.2%), anemia (11.3%), fatigue (9.6%), diarrhea (8.6%), white blood cell count decreased (8.3%), hypophosphatemia (5.6%), febrile neutropenia (5.4%), and nausea (5.4%). AEs leading to death while on treatment were observed in 4.9% of patients; the most common by preferred term were respiratory failure (n=3) death (n=3), hypertension (n=2), hypoxia (n=2).

The most common (≥20%) AEs by preferred term were nausea (67.4%), diarrhea (62%), fatigue (52.5%), vomiting (43.6%), alopecia (42.4%), anemia (40.9%), neutropenia (39.2%), constipation (36.5%), decreased appetite (35.3%), abdominal pain (20.8%), and dyspnea (20.6%).

Among the 333 patients in the safety population (82%) who had retrospective uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) genotype results available, the incidence of Grade 4 neutropenia was 27% in patients homozygous for the UGT1A1*28 allele, 6% in patients heterozygous for the UGT1A1*28 allele, and 5% in patients homozygous for the wild-type allele.

Patients with mTNBC who have received two prior therapies for metastatic disease have an advanced condition that is life-threatening and have an unmet medical need. The results of Study IMMU-132-01 are considered an improvement over available therapy with a near doubling of the response rate.

The adverse event profile observed in the overall safety population and in the mTNBC population patients is consistent with the adverse event profile observed in an advanced cancer population receiving treatment with a cytotoxic agent. There was a high incidence of neutropenia and diarrhea, with an increase in the incidence of these toxicities among patients who were homozygous for the UGT1A1*28 allele compared to patients who were heterozygous for this allele. Overall, the most common AEs are manageable with appropriate monitoring, dose interruption/modification, and supportive care.

Several objectionable conditions were identified during the pre-license inspection of the manufacturing facility for hRS7 antibody intermediate, including data manipulation to obtain favorable results; the resolution of these observations is unsatisfactory. Several deficiencies were identified during the review of the chemistry, manufacturing and controls (CMC) data package in the BLA. The data submitted in the application are not sufficient to support a conclusion that the manufacture of sacituzumab govitecan is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life, as required for approval.

The main deficiencies identified included: (b) (4) While the review team viewed the results of Study IMMU-132-01 favorably, the team concluded that the overall risk-benefit assessment of sacituzumab govitecan did not support approval based upon the deficiencies identified during the pre-license inspection and the review of the CMC data package. FDA therefore recommends a complete response for the applicant's request for marketing authorization.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In 2018, it is estimated that there are over 150,000 patients in the US with metastatic breast cancer. Of these, approximately 25,000 patients have metastatic triple negative breast cancer for whom chemotherapy, including PARP inhibitors for select patients, is the only available therapy. Metastatic TNBC has a poor prognosis with an estimated median overall survival (OS) of approximately 13 months.	Metastatic triple negative breast cancer is a serious and life-threatening condition with an estimated median overall survival (OS) of approximately 13 months.
Current Treatment Options	• The goals of treating mTNBC are palliative in nature with the aim of prolonging survival and reducing cancer-related symptoms. Available therapies of the treatment of patients with mTNBC who have had two prior lines of therapy include ixabepilone and eribulin; for patients with a BRCA 1 or 2 mutation, olaparib and talozaparib are available.	There is an unmet medical need to improve the outcomes of patients with mTNBC who have received two or more prior therapies and patients may benefit from an agent with a more favorable response rate and duration of response as compared to available therapy.
Benefit	• The primary evidence of effectiveness supporting this supplemental BLA is from Study IMMU-132-01. • In the 108 patients who comprise the efficacy population, the confirmed ORR by RECIST 1.1 was 33.3% (95% CI: 24.6, 43.1) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment.	Study IMMU-132-01 demonstrated an improvement over available therapy based on response rate, an endpoint reasonably likely to predict clinical benefit. Confirmation of clinical benefit will be required as stipulated under the accelerated approval provisions.
Risk and Risk Management	• In the efficacy population, 32.4% of patients experienced SAEs compared to 40.5% of patients in the pooled safety population. • The serious risks of sacituzumab govitecan include diarrhea, neutropenia, nausea, vomiting, and infusion-related reactions. Patients who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia. • One death in the safety population was due to neutropenic typhilitis. • Objectional conditions were identified during the prelicense inspection of the manufacturing facility for the hRS7 antibody intermediate and the resolution of these observations was unsatisfactory.	The safety profile of sacituzumab govitecan is acceptable when assessed in the context of the life-threatening nature of mTNBC that has progressed following 2 or more therapies. Significant and serious adverse reactions, including neutropenia and diarrhea can be adequately managed with close monitoring, dose modifications, and supportive measures and this risk should be conveyed in labeling Patients with known reduced UGT1A1 activity should be monitored for severe neutropenia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Several deficiencies were identified during the review of the CMC data package in the BLA and were unresolved, including the following: (b) (4)	There were no significant safety concerns identified during review of this supplemental application that would require a risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use. However, given the death attributable to neutropenic typhlitis and the incidence of neutropenia and diarrhea, a boxed warning for diarrhea and neutropenia are recommended. There were several deficiencies in the manufacturing process that remained unresolved during the review cycle. The CMC package does not support a conclusion that the manufacture of sacituzumab govitecan is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life, as required for approval.

1.4. Patient Experience Data

Patient experience data were not submitted as a part of this application.

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

	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐		

	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____

'Lola Fashoyin-Aje, MD, MPH

Cross-Disciplinary Team Leader

2 Therapeutic Context

- **Analysis of Condition**

Metastatic triple negative breast cancer (mTNBC), defined as breast cancer with low expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), is a disease with a poor prognosis. The estimated median survival from the time of diagnosis is approximately 13-18 months. The median age at diagnosis of approximately 50 years (Kassam 2009; Yardley 2018). In male patients with metastatic breast cancer, <1% of patients have mTNBC as most male patients have hormone-receptor positive disease (Giordano 2018).

Unlike hormone receptor positive disease and human epidermal growth factor receptor 2 (HER2) positive disease, there are no approved therapies for TNBC. In the subset of patients who have mTNBC who harbor a germline BRCA mutation (15-20%), there are approved therapies. The primary treatment modality for patients with mTNBCis cytotoxic chemotherapy. In general, cytotoxic chemotherapy is administered as a single agent with multi-agent regimens reserved for patients who present with visceral crisis.

There has been extensive work to better understand the molecular subtypes of mTNBC. Though the lack of hormone receptor and HER2 positivity does make this a distinct group, it is clear that mTNBC is heterogenous and includes different molecular subtypes which have differing natural histories and likely different responses to therapy (Prat 2014). Most patients (70-80%) with TNBC have molecular features consistent with the basal-like subtype, however the remaining 20-30% fall into one of the other four intrinsic subtypes based on global gene expression analysis (Prat 2010). Given this, trials evaluating therapies for mTNBC will include a variety of molecular subtypes and may include patients who have different likelihood of response to therapy.

This is a disease with an extremely poor prognosis which affects younger patients. Therapies for this population are an unmet clinical need.

Current clinical trials are continuing to explore how standard cytotoxic therapies may have differential efficacy in patients with mTNBC, evaluating the role of immunotherapy for this population and subsets of this population, as well as evaluating various targeted therapies.

2.2. Analysis of Current Treatment Options

To date, there is no agent approved specifically for mTNBC. The management of mTNBC is typically with cytotoxic chemotherapy. For the approximately 15-20% of patients with mTNBC who have a germline BRCA 1 or 2 mutation, there are two approved poly-ADP ribose (PARP) inhibitors: olaparib and talozaparib.

Most agents are used off-label, and in the absence of visceral crisis, cytotoxic therapies are typically used as single agent, sequential therapy as combination therapies have an improvement in PFS, however they have increased toxicity and a questionable impact on overall survival (Cardoso 2009).

To date, there is no therapy specifically indicated for mTNBC, though there are multiple chemotherapy agents approved for the treatment of metastatic breast cancer. Data for response and efficacy of currently available therapies includes patients with both hormone receptor positive and hormone receptor negative disease. The objective response rates (ORR) from historical studies in patients who had received two prior systemic therapies varies, though is less than 20% in patients who have been treated with two prior systemic therapies in the metastatic setting. The most relevant comparator is erlibulin which is approved for patients with metastatic breast cancer who have received two prior chemotherapeutic regimens in the metastatic setting with an estimated ORR of 11% (95% CI: 8.6, 14.3) and estimated duration of response of 4.2 months (95% CI 3.8, 5.0). The data are somewhat difficult to interpret specifically for patients with mTNBC, however, given the heterogeneity of the cohorts in which these therapies were evaluated.

Table 1. Summary of Treatments Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Approval Year	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Eribulin	Patients with mBC who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting	2010	1.4 mg/m^2 administered intravenously on days 1 and 8 of a 21-day cycle	OS: 13.1 mos (11.8, 14.3) ORR 11% (8.6, 14.3); DoR 4.2 months (3.8, 5.0)	Neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation
Ixabepilone	Patients with metastatic or locally advanced BC after failure of an anthracycline, a taxane, and capecitabine	2007	40 mg/m^2 infused intravenously every three weeks	ORR: 12.4% (6.9, 19.9) (IRR assessment); 18.3% (11.9, 26.1) (Investigator assessment). DoR: median 6.0 months (5.0-7.6)	Peripheral sensory neuropathy, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, musculoskeletal pain

3 Regulatory Background

APPEARS THIS WAY ON ORIGINAL

3.1. U.S. Regulatory Actions and Marketing History

This is a Biologics Licensing Application (BLA) supports the applicant's request for approval of Sacituzumab govitecan (TRODELVY) for the treatment of patients with metastatic triple negative breast cancer who have (b) (4) received at least two prior therapies for metastatic disease. Sacituzumab govitecan is a new molecular entity (NME) and therefore not currently marketed in the United States. Sacituzumab govitecan is not approved by any foreign regulatory agency.

3.2. Summary of Presubmission/Submission Regulatory Activity

- June 1, 2012: Original IND submission to evaluate of sacituzumab govitecan (IMMU-132, hRS7-SN38) in patients with advanced epithelial malignancies (IND 115621).

- August 29, 2014: Request for Fast Track Designation denied; FDA determined that submission did not include a comprehensive development plan designed to demonstrate clinical benefit.

- December 22, 2014: Fast Track Designation granted for the treatment of patients with triple negative breast cancer (TNBC) who have failed no more than two prior therapies for metastatic disease.

- February 25, 2015: End of Phase 2 meeting to obtain FDA guidance on acceptable trial design for a registration trial of IMMU-132 in the treatment of patients with relapsed/refractory mTNBC. Immunomedics committed to conducting a randomized Phase 3 trial, to seek a Special Protocol Assessment (SPA) for the proposed phase 3 trial, and to submit a Statistical Analysis Plan (SAP) for review. FDA confirmed that progression-free survival (PFS) would be an acceptable primary endpoint for the planned Phase 3 Study.

- June 25, 2015: Written-Response Only meeting to obtain FDA guidance regarding the sponsor's approach to the evaluating quality of life. Immunomedics also provided a new SAP based on updated information from IMMU-132-01, revising the analysis of PFS estimates.

- October 8, 2015: FDA issued a Special Protocol Non-Agreement for proposed randomized Phase 3 study.

- November 6, 2015: FDA issued a Special Protocol Non-Agreement FDA did not consider the proposed (b) (4) to be clinically meaningful

- November 24, 2015: Special Protocol Agreement granted for "An International, Multi-Center, Open-Label, Randomized, Phase 3 Trial of Sacituzumab Govitecan versus Treatment of Physician Choice in Patients with Metastatic (Stage IV) Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments."

- February 4, 2016: Breakthrough Therapy Designation granted under IND 122694 for the treatment of patients with relapsed/refractory, metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

- May 9, 2016: Type B Multidisciplinary Breakthrough Therapy meeting held to discuss updated safety and efficacy data from Study IMMU-132-01, the regulatory strategy that could potentially support approval of IMMU-132 based on the results of Study IMMU-132-01. FDA determined that the data at the time were not sufficient for a BLA submission. FDA agreed that a single-arm trial demonstrating a durable confirmed

objective response rate determined by blinded central review could support accelerated approval for the treatment of patients with relapsed/refractory mTNBC after at least two prior therapies for metastatic disease. FDA stated that it would be important for the confirmatory trial to be underway if not fully accrued, should Immunomedics submit a BLA for accelerated approval.

- November 14, 2016: Type B EOP2 meeting held to discuss the non-clinical and clinical pharmacology development strategies for IMMU-132. FDA confirmed that genotoxicity studies would be required for BLA submission and product labeling, and confirmed that based on genotoxicity studies, embryo-fetal development studies did not appear to be warranted for the proposed indication.

- March 17, 2017: Type C Written Response meeting. FDA concurred that the Phase 3 materials manufactured with a new clone (hRS7-(b) (4)) were analytically comparable to the Phase 2 materials manufactured using the hRS-(b) (4) clone (b) (4) FDA agreed that additional nonclinical safety studies beyond the ongoing 3-month repeat-dose monkey toxicology study were not required for filing. The outlined the requirements for stability data (6 months' stability for both drug substance (DS) and drug product (DP)).

- March 30, 2017: Based upon advice from FDA to identify one IND to be the repository for CMC information for sacituzumab govitecan, the sponsor submitted an amendment to IND 115621 stating their intent to maintain all CMC information under IND 115621; the submission included a letter of authorization to allow IND 122694 to cross reference IND 115621.

- April 24, 2017 FDA provided feedback on the sponsor's amendment to IND 122694, including on the design of the proposed Phase 3 study, and also advised that the sponsor consider modifications and standardization of the Treatment of Physician's Choice Arm. FDA agreed that the proposed study could support a regulatory submission.

- May 3, 2017: Immunomedics submitted amendments to IND 115621, containing clarifications regarding the validation strategy for sacituzumab govitecan, in response to FDA's
- March 17, 2017, and requested FDA feedback on some questions. FDA responded to the sponsor's submission on June 15, 2017.

- June 15, 2017: FDA provided regulatory advice regarding Immunomedics' manufacturing plans and agreed that to late submission of CMC components. Specifically, the first PPQ lots for DS and DP would be completed prior to BLA filing; however, the second and third PPQ lots may be submitted during the BLA review process. If the Sponsor planned to submit a validation data amendment during review of the original BLA, FDA requested that the timeline of the submission be submitted and agreed upon. If the information was submitted to far into the review cycle such a submission would be considered a major amendment. The sponsor was reminded that

quality standards for expedited approval programs remain consistent with expectations for standard drug development programs and that all manufacturing sites would need to meet full validation requirements for a BLA.

- June 29, 2017: FDA provided written responses which agreed that the package of at least 100 patients with metastatic TNBC who received 10 mg/kg of IMMU-132 after having received at least two prior therapies, with a minimum follow-up of 4 months, appeared to be acceptable to support submitting a BLA. Additionally, it was agreed that the proposal to submit complete efficacy and safety data for the target population of mTNBC patients and safety data for the safety population of patients regardless of tumor type and IMMU-132 was dosing was acceptable but also required the inclusion of ECG and laboratory data. The Agency agreed with the proposed approach to collect and submit tumor scans for ICR in patients with a CR, PR or with at least 20% of reduction in their lesions based on local radiographic assessment as adequate for filing. The anticipated safety database of approximately 300 patients exposed to study drug over all tumor types was agreed to be sufficient for filing.

- September 27, 2017: Type B End-of-Phase 2, CMC meeting was held under IND 115621. The Agency agreed to the proposed validation plan and noted that (b) (4) validation and (b) (4) data to support sterility assurance should be provided at the time of BLA submission. FDA stated that that discipline reviews of the BLA are due approximately 3 months in advance of the PDUFA action date and reiterated that depending on the time when the final drug substance and drug product validation reports are submitted to the BLA, and the extent of the data submitted at that time, it may be considered a major amendment that extends the PDUFA review timeline.

- October 12, 2017: Pre-BLA Meeting where the Sponsor and Agency agreed upon the population for the BLA submission, the plan for the data cut-off for the BLA safety update, the plan to include all SAEs and AEs regardless of attribution, the plans for PK data analysis, and requested the BICR charter for review and expressed concerns for proposed methodology for a single-blinded reviewer. FDA stated that both the initial safety submission as well as the safety update should include information regarding AEs, including SAEs, SAE narratives and death narratives regardless of attribution to the study drug.

- January 3, 2018: Type B pre-BLA CMC meeting. During this meeting the Sponsor and Agency made agreement on a late component to the BLA. Specifically, the Agency agreed that given the breakthrough therapy status of the application that the sponsor could submit the summary and results (b) (4) by the BLA filing deadline (60 days after the initial BLA submission). Additionally, the sponsor agreed (b) (4) The sponsor was notified that the proposed overall control strategy (b) (4) will be a review issue and determined based on the totality of information and data submitted to the BLA. The sponsor agreed to submit an assay

that to ensure [redacted] (b) (4) is controlled.

- February 5, 2018: In a letter submitted to IND 122694, Immunomedics informed FDA that there had been data integrity issues uncovered [redacted] (b) (4) Immunomedics stated that an investigation had been conducted and that the integrity issues ended [redacted] (b) (4)

- March 1, 2018: Immunomedics submitted a second letter to IND 122694, providing an update on the data integrity breach issue reported in the February 5, 2018 letter to FDA. The sponsor stated [redacted] (b) (4) that the issues ended [redacted] (b) (4) Immunomedics further stated that corrective actions had been initiated to address this issue. Additionally, the Sponsor submitted a Health Evaluation Record stating that [redacted] (b) (4) as a result of issues described in the February 5, 2018 letter.

- May 18, 2018: BLA 761115 Submitted. As the initial BLA submission included a number of responders whose response occurred just prior to the data cut-off, FDA requested that the applicant submit additional efficacy data at the 90-day Safety Update.

- June 22, 2018: Bi-Weekly teleconferences between the Agency and the Sponsor commenced with the aim to discuss CMC-related information requests and to clarify any CMC issues as they arose; generally, if no issues required discussion, the teleconference was cancelled.

- August 20, 2018: 90-day Safety and Efficacy Update submitted to BLA 761115.

- September 25, 2018: During the Mid-cycle communication, FDA notified Immunomedics that theresponse to the FDA Form 483 (dated August 14, 2018) in which the applicant claimed "attorney client privilege" as the reason for not providing the requested information, was unacceptable. Immunomedics agreed to amend their response within a few days and resubmit them. FDA also stated that additional CMC deficiencies were to be discussed at a future CMC teleconference, and that a follow-up teleconference to discuss in more details, FDA's basis for referring the application to ODAC, would be scheduled.
- October 4, 2018: Teleconference between the sponsor and CMC. The Sponsor was informed that, while the review of the amended response to the FDA Form 483 was ongoing, there were still deficiencies to be addressed. The FDA stated that the requested information characterizing the applicant's efforts to investigate the full scope of the data integrity breach was necessary to understand the impact of this event, including whether the event was isolated, and to assess the adequacy of Immunomedics' conclusions regarding this issue and the corrective measures that had been implemented to address this issue. During the teleconference, Immunomedics stated that the FDA inspector had

refused to receive this information when offered; the FDA inspector in question objected to Immunomedics' characterization of the exchange in question and clarified that at no time during the inspection did was data refused. Rather Immunomedics had refused to provide the data and later provided a summary paper which had been drafted on the day of the inspection. The FDA inspector also noted that, while the document offered did not address the issues at hand, Immunomedics had denied her request to keep the document. FDA again reiterated the need to provide the results of a GMP investigation into the data integrity breach.

- October 10, 2018: teleconference between the sponsor and CMC. Immunomedics stated that they were not able to submit the report detailing the GMP investigation due to attorney/client privilege. Immunomedics proposed to share the folders containing this information at a face to face meeting, that would entail FDA review of the documents during the meeting, but would not entail submission of these materials to the FDA or providing FDA with copies of the documents; FDA did not agree with this proposal, stating that any materials or information intended for the purposes of responding to FDA's request for information regarding deficiencies, including information related to data integrity breach, should be submitted in the response to the RAI letter. FDA stated that once the RAI response is received, the review team would decide whether a T-CON or a Face to Face meeting would be appropriate to discuss further. FDA requested detailed information of the investigation and specified that while the interviews can be a component, the applicant should also include the cause, how to prevent, what is the impact, and all the change control.

- November 2, 2018: Type A meeting was held to with the Sponsor to discuss ongoing clinical deficiencies, incomplete response to a 483, data integrity and falsification issues at the Morris plains manufacturing facility and the cancellation of ODAC. During the meeting the Sponsor agreed to a third-party investigation into the data integrity breach and to 3rd party oversight of manufacturing. The report detailing the investigation was to be submitted directly to the FDA by December 14, 2018. Immunomedics was informed that a new inspection would need to occur and that depending on the volume of information submitted on December 14, 2018 a major amendment may need to be issued.

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 1 (DOP1) consulted the Office of Scientific Investigations (OSI) to perform an audit of clinical investigator sites, the applicant site, and the facility for the independent central radiology review for BLA 761115. DOP1, in consultation with the OSI identified a total of 6 clinical sites for inspection based on high enrollment, a manual assessment of enrollment trends, protocol violations, efficacy findings, and adverse events reporting. Three additional clinical sites were added to the inspection list after information was received by OSI from multiple confidential informants. The confidential informants suggested, in part, that Good Clinical Practice (GCP) compliance violations had occurred during the conduct of the study that may have affected the integrity of the study data submitted to the BLA; an additional concern was that these violations may have negatively impacted patient safety and welfare. Based upon these allegations, 3 additional clinical investigator sites (254, 181, and 259) were added to the inspection plan. A summary of the inspection results is shown in **Error! Reference source not found.**.

Table 2. Office of Scientific Investigations Inspection Sites for IMMU-132-01

Inspection Site	Site No./ No. of patients	Inspection Date	Interim Classification
Immunomedics, Inc.	Sponsor	Jun 14-Aug 1, 2018	VAI
(b) (4)	CRO	(b) (4)	NAI
Aditya Bardia, MD Massachusetts General Hospital	255/108	Aug 13-17, 2018	VAI
Wells Messersmith, MD University of Colorado	254/56	Sept 12-17, 2018	NAI
Allyson Ocean, MD Cornell-Weill Medical Center	111/70	Aug 6-10, 2018	NAI
Jordan Berlin, MD Vanderbilt University Medical Center	252/36	Aug 16-Sept 10, 2018	NAI
Rebecca Moroose, MD Orlando Health, Inc.	204/19	Jun 26-Jul 2, 2018	NAI
Ebenezer Kio, MD Goshen Center for Advanced Cancer	181/49	Aug 20-23, 2018	NAI
Kevin Kalinsky, MD Columbia University Medical Center	259/12	Sept 4-7, 2018	NAI

NAI= No Action Indicated; VAI= Voluntary Action Indicated

Overall, OSI did not identify significant inspectional findings for clinical investigators Dr. Aditya Bardia, Dr. Jordan David Berlin, Dr. Allyson Ocean, Dr. Rebecca Moroose, Dr. Wells

Messersmith, Dr. Ebenezer Kio, Dr. Kevin Kalinsky, Immunomedics, Inc., or the CRO (b) (4) (b) (4) The data from Study IMMU-132-01 submitted to the Agency in support of BLA 761115, appear reliable.

Inspection of Site 255 (Principal Investigator: Dr. Bardia) revealed that source documentation associated with efficacy assessments for 2 patients was not consistent with datasets submitted to the Agency. Specifically, Patient (b) (6) and Patient (b) (6) were identified as responders in the BLA submission. However, they were noted to have undergone brain imaging (MRI) between scheduled study visits, which revealed that both patients had brain metastases. The findings of brain metastases were not appropriately recorded as an event of disease progression in either patient in the datasets and clinical reports submitted in the BLA. Additionally, it was not clear whether these patients' imaging demonstrating CNS metastases had been referred for central radiology review, given that they were obtained at non-protocol specified times. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations was issued to Dr. Bardia, citing these protocol violations.

Given these inspectional observations, a Clinical Information Request (IR) was issued to the Immunomedics on September 18, 2018, requesting the following:

1. identify patient-level information for all responders that includes all imaging obtained during the course of the study (both scheduled and unscheduled),
2. narrative summaries of each of these imaging assessments (e.g. if not per protocol, why imaging was obtained); and
3. an indication of whether the additional imaging and assessments were submitted for central review.

The Applicant's response was received on September 24, 2018. In response, Immunomedics stated, in part, that they found no additional instances of failure of a clinical site to document and report to the sponsor all scheduled and unscheduled MRIs/CT scans and the associated tumor responses based on their re-review of study patients. Immunomedics also indicated that the additional MRI scans for Patients (b) (6) had since been sent to the CRO, (b) (4) (b) (4), for review.

An additional sponsor response, dated October 9, 2018, added that they had confirmed that the imaging vendor, (b) (4) had received all images for the TNBC patients as requested above and that an updated database on the scan assessments was included in Serial Number 0053, submitted on October 8, 2018.

***Reviewer Comment**: While the lack of inclusion of important imaging findings by Dr. Bardia's clinical site represents an important deviation from the protocol (i.e., RECIST V1.1.), the inspectional observations should not have importantly impacted overall study outcomes. Immunomedics confirmed that there were no other instances of missing MRI/CT scans for CRO, (b) (4) for review. The datasets submitted to the BLA have been updated to include the correct efficacy endpoint of Objective Response (OR) for Patients (b) (6) and the OR would only have impacted the duration of response, but not the Objective Response Rate (ORR).*

Inspection of Immunomedics found notable inspectional observations related to sponsor general oversight and control of the study. Briefly, the sponsor failed to ensure adequate clinical monitoring of the study and to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Per Title 21 CFR 312.50 [General responsibilities of sponsors], *"Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug."*

Immunomedics failed to keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Specifically, Immunomedics did not notify other investigators (b) (4)

Reviewer Comment: *In a written response to the inspectional observations, dated August 20, 2018, Immunomedics stated that* (b) (4)

Immunomedics acknowledged that the finding (b) (4) *should have been communicated to all the participating investigators, outlining what had been observed* (b) (4) *In the written response to the Form FDA 483, dated August 20, 2018, Immunomedics described a corrective action plan, that if implemented, may address these deficiencies moving forward.*

Immunomedics failed to adequately monitor the study in that they did not maintain or have evidence of having reviewed Clinical Site Initiation Visit Reports (SIVs) prior to the initiation of conduct of the study at 5 of 15 clinical sites. SIVs are used by the Sponsor to document that each clinical site had obtained the appropriate training and IRB approvals to conduct the clinical trial. Likewise, two Interim Site Monitoring Visit Reports (IMVRs) for Site 132 were missing from the Trial Master File.

Reviewer Comment: *In a written response to the inspectional observations, Immunomedics stated that gaps in monitoring existed during the conduct of Study IMMU-132-01 and indicated that they are working to improve their clinical monitoring to be in keeping with regulatory and industry standards. Immunomedics further stated that the deficiencies noted were not evidence of intentional neglect or failure to recognize the importance of monitoring. The Applicant's hypothesis is that the monitoring visits did occur and that the monitoring reports were*

misplaced. Nonetheless, the inspectional observations indicate a poorly executed clinical monitoring program that hampered the sponsor's ability to maintain continuous control, oversight, and management of the conduct of Study IMMU-132-01.

Despite the deficiencies in clinical monitoring oversight practices, the 7 clinical site inspections conducted by FDA field investigators found no evidence of under reporting of adverse events. With the exception of the two patients' in Site 255 described above, OSI's assessment and conclusion for the inspectional observations, is that the gaps in clinical monitoring do not appear to have adversely impacted overall reliability of study results or the safety of patients enrolled in Study IMMU-132-01.

For additional details, refer to the Clinical Inspection Summary written by Lauren Iacono-Connors, PhD, Good Clinical Practice Assessment Branch, Division of Good Clinical Practice Compliance, OSI, dated, October 23, 2018.

4.2. Product Quality

Novel excipients: Yes
Any impurity of concern: No

Sacituzumab govitecan is formulated with one novel excipient, 2-(N-morpholino) ethanesulfonic acid monohydrate (MES). The Applicant included (b) (4) in the chronic toxicology GLP study in monkeys. Monkeys received a dose volume up to 5 mL/kg, resulting in a dose of (b) (4) mg/kg MES ((b) (4) mg/m^2 human equivalent dose). At the clinical dose of 10 mg/kg, the levels of MES that patients will receive will be (b) (4) mg/kg or (b) (4) mg/m^2. As (b) (4) the levels are acceptable from the pharmacology/toxicology perspective.

While the manufacturing process is designed to be robust for inactivation and removal of adventitious agents, the general manufacturing practice and overall quality management system at Immunomedics Inc. (Morris Plains, NJ), the sponsor for IMMU-132 and manufacturer for the hRS7 antibody intermediate, were found to be inadequate and presented serious violations of GMPs, leading to lack of appropriate validation of the commercial manufacturing process and poor manufacturing capability, which contribute to the lack of assurance of the manufacture of a consistent, safe, pure and potent product. The main deficiencies are outlined below:

(b) (4)

Overall, the OPQ review of manufacturing and controls has determined that the methodologies and processes used for hRS7 antibody intermediate, IMMU-132 DS and DP manufacturing, release testing, and stability testing as submitted in the BLA are not sufficient to assure a consistent, safe, pure and potent product.

4.3. Clinical Microbiology

Refer to the OPQ Executive Summary and full review by Jessica Hankins, PhD and Reyes Candau Chacon, PhD in Panorama.

4.4. Devices and Companion Diagnostic Issues

No device or companion diagnostic is included in this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sacituzumab govitecan is an antibody-drug conjugate (ADC) that comprises a small molecule drug (SN-38) coupled by a linker (CL2A) to a humanized monoclonal antibody (hRS7) with a drug to antibody ratio of 7 to 8. The antibody hRS7 recognizes trophoblast cell-surface antigen 2 (Trop-2), a transmembrane protein that signals to cells for self-renewal, proliferation, invasion, and survival. Trop-2 has been reported to be overexpressed in the following solid tumors: breast, cervix, colorectal, esophagus, gastric, certain lung cancers, squamous cell carcinoma of the oral cavity, ovary, pancreas, prostate, stomach, thyroid, urinary bladder, and uterus (Shvartsur A et al., 2015).

SN-38 is the small molecule component of the ADC that inhibits topoisomerase 1, which affects cells during DNA replication by relieving the torsional strain in DNA through inducing reversible single-strand breaks. SN-38 binds to the topoisomerase I-DNA complex and prevents re-ligation of these single-strand breaks, which subsequently leads to apoptosis and cell death. The CL2A linkage chemistry is expected to allow SN-38 to be cleaved or released at low pH over time, thereby resulting in its release when the ADC is internalized and catabolized within the cell. The primary mechanism of sacituzumab govitecan involves Trop-2 targeting of the ADC and release of the small molecule payload, SN-38, in the tumor and tumor microenvironment.

Reviewer Comment: *The Applicant submitted data from their own published, peer-reviewed articles and individual study reports of the pharmacodynamic activity, pharmacokinetics, and toxicology of sacituzumab govitecan to support the approval of TRODELVY® for the proposed indication.*

In a surface plasmon resonance (SPR) study, sacituzumab govitecan and the anti-Trop-2 antibody, hRS7, bound to recombinant human Trop-2 with K_D values of 0.26 nM and 0.51 nM, respectively, demonstrating that the addition of SN-38 did not affect antibody binding to human Trop-2. Sacituzumab govitecan and hRS7 also bound to recombinant human FcRn with K_D values of 191.9 nM and 92.4 nM, respectively, by SPR analysis. Treatment of Trop-2-expressing cancer cell lines with sacituzumab govitecan induced pro-apoptotic signaling and double strand DNA breaks (Goldenberg et al., 2015 and Cardillo et al., 2015). In vivo, sacituzumab govitecan reduced tumor growth in mouse xenograft models of Trop-2-expressing triple-negative breast cancer (TNBC). The hRS7 antibody alone or with a cross-linking antibody did not inhibit tumor growth of various cell lines with different levels of Trop-2 expression. These data suggest that the antibody portion of the ADC is insufficient for cytotoxicity alone. The nonclinical pharmacology data in the BLA demonstrate that sacituzumab govitecan binds to Trop-2 expressing cancer cells with the subsequent release of SN-38 via hydrolysis of the linker, resulting in DNA damage, apoptosis, and tumor cell death. The Established Pharmacologic Class (EPC) of “Trop-2-directed antibody-drug conjugate” is applicable to sacituzumab govitecan based on its structure and pharmacologic activity.

In vitro stability studies demonstrated release of SN-38 from sacituzumab govitecan with a half-life of approximately 24 hours in human and monkey serum (Goldenberg et al., 2015). In toxicokinetic analysis, the Applicant measured plasma levels of total antibody, free SN-38, and total SN-38. Exposure (AUC) to these analytes in monkeys increased with increasing dose and was generally dose proportional following two doses of sacituzumab govitecan on day 1 and day 4 but was slightly greater than dose proportional when dosed weekly for 13 weeks across the dose range tested. Exposure for free SN-38 was 2.3% of total SN-38 exposure. These data suggest that the majority of SN-38 was linked to the antibody.

Safety pharmacology endpoints were assessed in the repeat-dose toxicity studies in monkeys. There were no sacituzumab govitecan-related findings on the central nervous, cardiovascular, or respiratory systems.

Sacituzumab govitecan was assessed in Good Laboratory Practice (GLP)-compliant monkey studies. In the acute toxicity study, monkeys were given sacituzumab govitecan at doses of 60 and 120 mg/kg on days 1 and 4 followed by terminal necropsy on day 11 and recovery necropsy on day 32. One mortality occurred at 120 mg/kg on day 7 (3 days after 2nd dose). Target organs of toxicity at ≥ 60 mg/kg included hematopoietic (decreases in RBC, platelets, WBC, neutrophils, lymphocytes, reticulocytes) and lymphoid organs (lymphoid depletion in thymus, spleen, mesenteric and mandibular lymph nodes and bone marrow, mild to moderate decrease in cellularity of the thymus and spleen), gastrointestinal (GI) tract (minimal to moderate hemorrhage, mononuclear and polymorphonuclear infiltration in the lamina propria, degeneration of the mucosa, separation of the glandular epithelium, erosion and ulceration of the duodenum and colon), liver (↓Albumin, ↑ALT, ↑AST) and female reproductive organs (increased numbers of atretic follicles and fewer matured follicles in the ovaries, and mild to moderate hemorrhage and atrophy of the endometrium and atrophy of surface vaginal epithelial cells). GI findings led to reductions in body weights and food consumption. All findings were either partially or fully reversible by recovery day 32.

In a 13-week toxicity study, monkeys were given sacituzumab govitecan at doses of 12.5, 25, and 50 mg/kg once weekly via a 1-hour infusion for 2 weeks of a 3-week cycle for 4 treatment cycles. Target organs of toxicity at ≥ 12.5 mg/kg included hematopoietic (decreases in RBC, platelets, and lymphocytes) and lymphoid organs (decreased cellularity in thymus and mesenteric lymph nodes; erythrophagocytosis in the mandibular lymph nodes). Multi-organ cellular infiltration was observed in the brain, heart, eye, GI tract, kidney, prostate, salivary glands, trachea, and urinary bladder. Injection site toxicity was observed at 50 mg/kg. Milder toxicities in the chronic toxicity study compared to the acute toxicity study were possibly due to decreased exposure. Findings were reversible after the 6-week recovery period. Anti-drug antibodies were detected in all animals at all doses tested in the chronic toxicity study. In general, toxicological findings were consistent with adverse events of GI and hematologic toxicity observed in clinical trials and were expected based on the mechanism of action of sacituzumab govitecan.

SN-38 was negative for mutagenicity in a bacterial reverse mutation (Ames) test but was clastogenic in the in vitro mammalian cell micronucleus test. No embryo-fetal developmental toxicology studies were conducted or warranted to support this BLA submission, based on ICH S9. Because SN-38 is genotoxic and targets rapidly dividing cells, teratogenicity or embryo-fetal

lethality is expected with sacituzumab govitecan. Females of reproductive potential should use effective contraception during treatment with TRODELVY and for 6 months following the last dose. Male patients with female partners of reproductive potential should use effective contraception during treatment with TRODELVY and for 3 months after the last dose. Due to potential adverse reactions in a breastfed child from TRODELVY and SN-38, lactating women should not breastfeed during treatment and for at least 4 weeks after the last dose.

Reviewer Comment: *The current approach in OHOP for recommendations regarding duration of contraception for females of reproductive potential for a genotoxic drug is to recommend the use of contraception for 6 months with an additional 5 half-lives following the last dose of the drug. This period for the use of contraception after cessation of therapy covers the growth and maturation phase of folliculogenesis and is expected to allow elimination of most damaged follicles and oocytes. For males, the approach for a genotoxic drug is 3 months with an additional 5 half-lives after the last dose, which covers the period of spermatogenesis and epididymal maturation to minimize the risk of adverse embryo-fetal effects. For drugs that can cause adverse reactions in a breastfed child, the current approach in OHOP is to recommend that lactating women not breastfeed during treatment and for at least 5 half-lives after the last dose. The duration covers 5 half-lives for sacituzumab govitecan, SN-38, and total antibody. According to the clinical pharmacology review, the terminal half-life of sacituzumab govitecan and SN-38 are 16 and 18 hours, respectively. The total antibody half-life is 6 days.*

The applicant did not conduct fertility studies with sacituzumab govitecan, and these studies are not warranted to support a marketing application in the proposed patient population, according to ICH S9. Based on findings from a repeat-dose toxicology study in monkeys, sacituzumab govitecan may impair fertility in females of reproductive potential. Administration of sacituzumab govitecan to monkeys on day 1 and day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the clinical recommended dose of 10 mg/kg based on body weight). In this study, the applicant measured total antibody, free SN-38, and total SN-38. Exposure to sacituzumab govitecan was not reported, so the animal-to-human ratio in the prescribing information is reported based on body weight.
No carcinogenicity studies were conducted or warranted to support this NDA, as the proposed indication was for advanced cancer.

The submitted nonclinical pharmacology and toxicology data support approval of TRODELVY for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

In binding affinity studies using surface plasmon resonance, sacituzumab govitecan and the anti-Trop-2 antibody, hRS7, bound to recombinant human FcRn with K_D values of 191.9 nM and 92.4 nM, respectively (Study # RR 05-07-12). Further, sacituzumab govitecan and hRS7 bound to recombinant human Trop-2 with K_D values of 0.26 nM and 0.51 nM, respectively (Study # RR 01-17-14). These data suggest that the conjugation of SN-38 to hRS7 did not alter its binding to Trop-2. In an ELISA assay, hRS7 bound to recombinant human Trop-2 with a K_D value of 40 ng/mL but did not bind to murine Trop-2 whereas control polyclonal anti-murine Trop-2 and anti-human Trop-2 antibodies bound to both forms of Trop-2 (Study # STF RR 08-27-13).

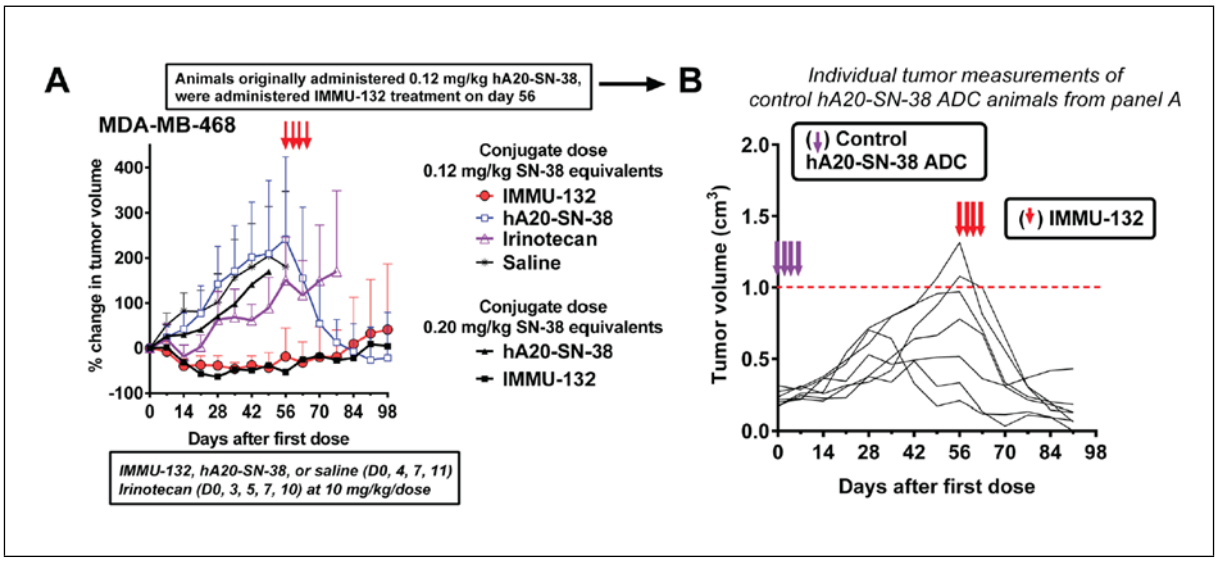
The Applicant tested differences in antibody-dependent cellular cytotoxicity (ADCC)-mediated potency of two clones of hRS7, original clone (b) (4) and new clone (b) (4), as well as the phase 1/2 (IMMU-132-(b) (4)) and phase 3 (IMMU-(b) (4)) lots of sacituzumab govitecan in human triple-negative breast cancer (TNBC) cells from three donors (Study # TR-PD-IMMU-132-17-017). Both clones of hRS7 showed ADCC activity, and there was no significant difference between specific lysis mediated by IMMU-132-(b) (4) (phase 1/2 lots) and IMMU-132-(b) (4) (phase 3 lots).

Complement-directed cytotoxicity (CDC) was compared using hRS7 derived from two clones of hRS7, original clone (b) (4) and new clone (b) (4), as well as the phase 1/2 (IMMU-132-(b) (4)) and phase 3 (IMMU-(b) (4)) lots of sacituzumab govitecan in Trop-2-positive TNBC, prostate adenocarcinoma, and Burkitt lymphoma cell lines (Study # TR-PD-IMMU-132-17-018). None of the clones of hRS7 demonstrated any CDC activity against the two Trop-2-positive cell lines at concentrations up to 33.3 nM.

The Applicant conducted several pharmacology studies and published the resulting data in peer-reviewed journals (Goldenberg et al., 2015 and Cardillo et al., 2015). The results show that Trop-2 was expressed on a variety of human cancer cell lines including gastric, pancreatic, TNBC, colon, and lung with no difference in binding of sacituzumab govitecan and the hRS7 antibody (Goldenberg et al., 2015 and Cardillo et al., 2015). In a microarray containing 31 TNBC specimens, as well as 15 hormone receptor- or HER2-positive breast cancers, Trop-2-positive staining occurred in over 95% of the tumor samples (Goldenberg et al., 2015). Sacituzumab govitecan mediated pro-apoptotic cell signaling and double strand DNA breaks in Trop-2-expressing cancer cell lines. Activation of the apoptotic pathway was demonstrated by an increase in $p21^{WAF1/Cip1}$ expression, phosphorylation of JNK, and pro-caspase 3 and PARP cleavage (Cardillo et al., 2015 and Goldenberg et al., 2015). Induction of double strand DNA breaks was measured by increased levels of phosphorylated histone γ-H2A.X.

The Applicant tested anti-tumor activity of different antibody:drug ratios (DARs) in mice bearing Trop-2-positive human gastric carcinoma (Goldenberg et al., 2015). Based on this information, sacituzumab govitecan is most efficacious with the highest DAR of ~7:1. Six human breast cancer cell lines (4 were TN) were tested for surface expression and for sensitivity to SN-38. Trop-2 surface expression in 5 of the 6 cell lines exceeded 90,000 copies per cell. SN-38 potency ranged from 2 – 6 nM in 5 of the 6 lines. In a mouse xenograft model of Trop-2-expressing MDA-MB-468 TNBC, increased tumor regression was observed with sacituzumab govitecan treatment (0.12 or 0.20 mg/kg SN-38 equivalents) compared to vehicle, 10 mg/kg irinotecan, or a non-specific hA20-SN-38 ADC (Figure 1).

Figure 1 Anti-tumor activity of sacituzumab govitecan (IMMU-132) in a TNBC xenograft model



Source: *Excerpted from Goldenberg et al., 2015*

Secondary Pharmacology

Type of Study	Major Findings
Selectivity	
Study Title: *In Vitro* Growth Inhibition of Anti-CEACAM6 (hMN15) and Anti-Trop-2 (hRS7) Monoclonal Antibodies Against Renal Cell Carcinoma (ACHN, CAL-54, Caki-2, A-704), Colorectal Adenocarcinoma (HT-29), and Breast Adenocarcinoma **Study No.:** RR-06-10-11 In vitro: cytotoxic effects of the unconjugated hRS7 with or without a cross-linking antibody in human solid-tumor cell lines Cell lines: human renal cell carcinoma (RCC), human colorectal and human breast cancer cell lines. Concentrations: 8 µg/mL – 0.0313 µg/mL Test articles: hMN15 IgG (anti-CEACAM6), hRS7 IgG	In the presence or absence of a cross-linking antibody, no signs of growth inhibition were demonstrated by the anti-CEACAM6 antibody (hMN15) or anti-Trop-2 antibody (hRS7)

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Pharmacokinetic Assessment Study of hRS7-(b) (4) hRS7-(b) (4) (b) (4) (IMMU), and hRS7-(b) (4) (b) (4) in New Zealand White Rabbits Following a Single Intravenous Dose Administration
Study No. (b) (4) 1601.24</td><td>Rabbit
PK parameters following a single dose (15 mg/kg) of hRS7 IgG from three sources: hRS7-(b) (4) hRS7-(b) (4) IMMU (Phase 3/(b) (4)) manufactured at Immunomedics, hRS7-(b) (4) manufactured at (b) (4)
(n=3/sex/group)
<table>
<tr><th></th><th>Sex</th><th>hRS7-(b) (4)</th><th>hRS7-(b) (4) (b) (4) IMMU</th><th>hRS7-(b) (4) (b) (4)</th></tr>
<tr><td>$T_{1/2a}$ (h)
$T_{1/2\beta}$ (h)</td><td>M+F</td><td>3.70
178.5</td><td>3.26
177.2</td><td>4.19
253.6</td></tr>
<tr><td>Cmax (µg/mL)</td><td>M+F</td><td>480.2</td><td>439.7</td><td>474.4</td></tr>
<tr><td>$AUC_{(0-\infty)}$ (µg*h/mL)</td><td>M+F</td><td>60006</td><td>57877</td><td>75002</td></tr>
<tr><td>CL (mL/h)</td><td>M+F</td><td>0.77</td><td>0.79</td><td>0.56</td></tr>
</table></td></tr>
<tr><td>A Repeat Dose Toxicity Study of hRS7-SN38 Administered via a 1-hour Infusion in Cynomolgus Monkeys Followed by a 4-week Recovery Period
Study No. (b) (4) 160.03
• Dosed once weekly for 2 weeks of a 21-day cycle over 4 treatment cycles
• Blood samples were collected on Day 1 at 30 minutes, 3, 8, and 24 hours postdose; and pre-dose on Day 4 and at 30 minutes, 3 hours, and 8 hours postdose</td><td>*NC=not calculated
Monkey:
$T_{1/2}$: ~125 h for Total Ab, ~26.5 h Free SN-38, ~13 h for Total SN-
<table>
<tr><th></th><th>Sex</th><th>hRS7</th><th>Free SN-38</th><th>Total SN-38</th></tr>
<tr><td colspan="5">60 mg/kg</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>M+F</td><td>124.82</td><td>25.57</td><td>13.54</td></tr>
<tr><td>Tmax (h)</td><td>M+F</td><td>73.50</td><td>NC*</td><td>NC*</td></tr>
<tr><td>Cmax (µg/mL)</td><td>M+F</td><td>1605.67</td><td>1.27</td><td>41.58</td></tr>
<tr><td>$AUC_{(0-\infty)}$ (µg*h/mL)</td><td>M+F</td><td>243315.32</td><td>80.23‡</td><td>1276.17‡</td></tr>
<tr><td colspan="5">120 mg/kg</td></tr>
<tr><td>$T_{1/2}$ (h)</td><td>M+F</td><td>125.60</td><td>26.96</td><td>13.29</td></tr>
<tr><td>Tmax (h)</td><td>M+F</td><td>76.00</td><td>NC*</td><td>NC*</td></tr>
<tr><td>Cmax (µg/mL)</td><td>M+F</td><td>52904.67</td><td>3.70</td><td>72.92</td></tr>
<tr><td>$AUC_{(0-\infty)}$ (µg*h/mL)</td><td>M+F</td><td>487731.51</td><td>225.17‡</td><td>2493.32‡</td></tr>
</table>
38
Accumulation: not defined, doses were 3 days apart</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Dose proportionality: Yes
NC: not calculated; ‡: AUC for free and total SN-38 is adjusted by WinNonLin program to account for differences in animal weights</td></tr>
<tr><td><u>Monkey: 13-week toxicology study (No. (b) (4) 160-25)</u>
• Dosed once weekly for 2 weeks of a 21-day cycle over 4 treatment cycles
• Blood samples were collected on days 1 & 71 at pre-dose, 30 min, 1, 6, 24, 48, 72, and 120 hours post-dose</td><td><u>Monkey</u>:
Total Ab:
• $T_{1/2}$: 73 – 152 h on day 71
• Accumulation: None for 25 and 50 mg/kg; exposures were higher (2.6-fold) on day 1 for the 12.5 mg/kg dose compared to day 71, suggesting a faster clearance
• Dose proportionality: approximately dose-proportional on day 1 and greater than dose-proportional on day 71

<table>
<tr><th colspan="7">Total Antibody (TAb)</th></tr>
<tr><th>Day</th><th>Dose</th><th>Sex</th><th>$T_{1/2}$</th><th>Tmax (h)</th><th>Cmax (ng/mL)</th><th>$AUC_{(0-168)}$ (µg*h/mL)</th></tr>
<tr><td colspan="7">Day 1</td></tr>
<tr><td rowspan="8">1</td><td rowspan="2">12.5</td><td>M</td><td>NA</td><td>1.6</td><td>406000</td><td>26000</td></tr>
<tr><td>F</td><td>NA</td><td>1.7</td><td>357000</td><td>22700</td></tr>
<tr><td rowspan="2">25
(b) (6) *</td><td>M</td><td>NA</td><td>7.4</td><td>713000</td><td>50100</td></tr>
<tr><td>F</td><td>NA</td><td>1.7</td><td>669000</td><td>47100</td></tr>
<tr><td rowspan="2">25
(b) (6) *</td><td>M</td><td>NA</td><td>1.7</td><td>674000</td><td>50600</td></tr>
<tr><td>F</td><td>NA</td><td>4.9</td><td>681000</td><td>49400</td></tr>
<tr><td rowspan="2">50</td><td>M</td><td>NA</td><td>3.7</td><td>1510000</td><td>124000</td></tr>
<tr><td>F</td><td>NA</td><td>1.8</td><td>1440000</td><td>109000</td></tr>
<tr><td colspan="7">Day 71</td></tr>
<tr><td rowspan="8">71</td><td rowspan="2">12.5</td><td>M</td><td>NA</td><td>1.5</td><td>146000</td><td>17400</td></tr>
<tr><td>F</td><td>NA</td><td>1.5</td><td>137000</td><td>8880</td></tr>
<tr><td rowspan="2">25
(b) (6)</td><td>M</td><td>69.0</td><td>7.4</td><td>952000</td><td>73600</td></tr>
<tr><td>F</td><td>74.3</td><td>2.9</td><td>957000</td><td>77000</td></tr>
<tr><td rowspan="2">25
(b) (6)</td><td>M</td><td>73</td><td>1.6</td><td>779000</td><td>73400</td></tr>
<tr><td>F</td><td>67.3</td><td>1.8</td><td>615000</td><td>36400</td></tr>
<tr><td rowspan="2">50</td><td>M</td><td>152</td><td>3.8</td><td>2160000</td><td>208000</td></tr>
<tr><td>F</td><td>89.7</td><td>1.6</td><td>1850000</td><td>202000</td></tr>
</table>
* (b) (6) – phase 1/2 product, (b) (6) – phase 3 product

Total SN-38:
• $T_{1/2}$: 7 – 31 h
• Accumulation: None for 25 and 50 mg/kg; exposures were higher (2.7-fold) on day 1 for the 12.5 mg/kg dose compared to day 71, suggesting a faster clearance
• Dose proportionality: approximately dose-proportional on day 1 and greater than dose-proportional on day 71
• CL: 1.46 – 7.64 mg/min/kg
• V_{ss}: 1.05 – 2.17 L/kg

<table>
<tr><th colspan="8">Total SN-38</th></tr>
<tr><th>Day</th><th>Dose</th><th>Sex</th><th>$T_{1/2}$</th><th>Tmax h</th><th>Cmax ng/mL</th><th>AUC_{0-168} ng*h/mL</th><th>CL mg/min/kg</th><th>V_{ss} L/kg</th></tr>
</table>
</td></tr>
</table>

Type of Study	Major Findings

Day 1								
1	**12.5**	M	13.9	1.6	6300	122000	1.71	1.72
		F	13.5	1.5	6350	115000	1.84	1.81
	25 (C)	M	19.5	1.5	13300	243000	1.72	1.92
		F	19.0	1.5	13500	255000	1.64	1.84
	25 (A/B)	M	18.2	1.5	12700	240000	1.87	2.03
		F	17.7	1.5	12200	224000	1.76	1.86
	50	M	26.8	1.5	26600	488000	1.57	1.91
		F	24.6	1.5	24900	533000	1.70	2.05
Day 71								
71	**12.5**	M	7.83	1.5	4930	46700	6.46	1.22
		F	16.9	1.5	4430	42200	7.64	10.0
	25 (C)	M	24.6	7.4	13100	254000	1.65	1.05
		F	21.2	2.9	13400	266000	1.58	1.05
	25 (A/B)	M	19.1	1.6	12700	221000	2.23	1.92
		F	16.6	1.8	11300	177000	2.78	2.17
	50	M	31.6	3.8	28000	571000	1.46	1.91
		F	27.8	1.6	25100	495000	1.69	2.11

Free SN-38:

- Accumulation: No
- Dose proportionality: approximately dose-proportional on day 1 and greater than dose-proportional on day 71

Free SN-38						
Day	**Dose**	**Sex**	**$T_{1/2}$**	**Tmax h**	**Cmax ng/mL**	**AUC_{0-168} ng*h/mL**
Day 1						
1	**12.5**	M	15.1	1.5	95	2360
		F	23.6	1.8	103	2910
	25 (C)	M	14.3	1.6	231	5670
		F	15.8	2.0	201	6030
	25 (A/B)	M	16.2	2.9	145	146
		F	16.6	2.0	157	170
	50	M	15.6	1.7	337	8860
		F	17.3	2.0	212	8140
Day 71						
71	**12.5**	M	19.1	2.7	85.2	1260
		F	19.2	2.9	64.6	1300
	25 (C)	M	17.6	3.8	238	5870
		F	12.7	6.0	251	8200
	25 (A/B)	M	16.0	1.7	163	3900
		F	11.7	2.8	190	4280
	50	M	17.4	2.9	341	10000
		F	13.0	1.9	331	8550

Distribution	
Pharmacokinetics and Pharmacodynamics of hRS7-CL2A-SN38 in Mice Bearing Squamous Cell Lung Carcinoma Xenografts ((b) (4)-MES-1)	Single IV injection of 12.5 mg/kg (20 µCi, 250 µg protein dose) ^{111}In-hRS7-CL2A-SN38 (sacituzumab govitecan), ^{111}In-hRS7 IgG (hRS7 IgG) in mice bearing (b) (4)-MES-1 squamous cell lung tumors Clearance: 0.02 ml/h for sacituzumab govitecan compared to 0.01 mL/h for the parental hRS7 IgG

Type of Study	Major Findings
(Study No. 031210-156)	Elimination: 0.006 1/h for sacituzumab govitecan compared to 0.004 1/h for the parental hRS7 IgG 24 h post-injection compared to hRS7 Distribution: widely distributed; highest concentration in liver and spleen, suggesting clearance is mainly through liver
Pharmacokinetics of hRS7-CL2A-SN-38 and Irinotecan in Capan-1 Tumor-Bearing Mice (Study No. 012014-275)	<u>Single IV injection of irinotecan (40 mg/kg) or hRS7-CL2A-SN38 (sacituzumab govitecan, 1 mg/kg) in Capan-1 tumor-bearing mice to measure levels of SN-38, SN-38G, and irinotecan</u> <u>sacituzumab govitecan-treated animals</u> Exposure: AUC of total SN-38, Free SN-38, and Free SN-38G were 148.8, 4.47, 0.18 μg/mL·h, respectively. Total SN-38 was detectable over 72 hr while free SN-38 and SN-38G were detectable through 48 and 6 h, respectively. Biodistribution: Tumor: AUC of 54.25 μg/mL·h for total SN-38, no free SN-38, or SN-38G Liver: AUC of 16.4 μg/mL·h for total SN-38, no free SN-38, or SN-38G Small intestines: Total SN-38 = 232 ± 67.0 ng ; Free SN-38 = 137.8 ± 35.2 ng Irinotecan-treated animals: Exposure: AUC of Total SN-38, SN-38G, and irinotecan were 2.52, 2.84, 21 μg/mL·h, respectively. Conversion rate of 25%. Both Total SN-38 and SN-38G were detected at 5 min with total SN-38 detectable over 6 hr. Biodistribution: Tumor: AUC of Total SN-38, SN-38G, and irinotecan were 48, 0.4, 1.08 μg/mL·h, respectively Liver: AUC of Total SN-38, SN-38G, and irinotecan were 98.7, 8.2, 2.0 μg/mL·h, respectively Small intestine: SN-38 = 1-1.5 μg; SN-38G = 10 μg

5.5. **Toxicology**

5.5.1. General Toxicology

Study title/ number: A Repeat Dose Toxicity Study of hRS7-SN38 Administered via a 1-hour Infusion in Cynomolgus Monkeys Followed by a 4-week Recovery Period ((b) (4).160.03)

Key Study Findings

- One mortality at 120 mg/kg on day 7 (3 days after 2nd dose)
- Target organs of toxicity were the hematopoietic and lymphoid organs, GI tract, liver and female reproductive organs.
- Dose dependent, reversible decrease in RBC, platelets, WBC, neutrophils, lymphocytes, and reticulocytes.
- Mild to moderate decrease in cellularity in thymus, lymph nodes
- GI tract: Hemorrhage, degeneration of mucosa, erosion and ulcerations, and mononuclear and polymorphonuclear infiltration
- ↓Albumin, ↑ALT, ↑AST and ↑creatine kinase (CK), ↑creatinine in one male HD, partially recovered

Conducting laboratory and location: (b) (4)
GLP compliance: **Yes**
Drug/Lot: hRS7-SN38, C1209055 (091096), 97.8%

Methods

Dose and frequency of dosing:	0, 60, & 120 mg/kg; 2 doses three days apart (days 1 and 4)
Route of administration:	IV (1-hr)
Dose volume:	10 mL/kg
Formulation/vehicle:	0.9% Sodium Chloride
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3/sex/group (2/sex/group for recovery)
Age:	Males, 2 - 4 years old; Females, 3 - 5 years old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Observations and Results:

Dose formulation analysis: IMMU-132 was not detected in the control samples. Formulations containing test article were prepared to a nominal concentration of 10 mg/mL. Homogeneity samples were within ±6% of the nominal concentration indicating a homogenous mixture. Stability samples were within ±6% of the nominal concentration.

Parameters	Major findings
Mortality	One male animal was found dead on day 7 (3 days after the last of two doses) with no clinical signs leading to death. Distended cecum and stomach were observed at necropsy. Microscopic findings include: decreased cellularity in lymphatic organs (bone marrow, thymus, lymph nodes [mandibular/mesenteric], and spleen). In the GI tract, there was moderate infiltration of polymorphonuclear cells into the lamina propria and moderate hemorrhage throughout the GI tract. Severe erosion and necrosis of the esophageal mucosa and minimal fibrosis of the lamina propria were also observed. Cause of death was attributed to bone marrow suppression and GI tract complications.
Clinical Signs	60 mg/kg/day: Abnormal color (bilateral forelimb [M]); bruising (bilateral hindlimb [M&F]) 120 mg/kg/day: hunched posture (1/3), loss of fur (2/3), abnormal color (2/3), abnormal feces (1/3)
Body Weights	-11% & -19% for females from control at 60 & 120 mg/kg/day, respectively
Blood pressure & heart rate	Unremarkable
Respiratory Rates	Unremarkable
Rectal Temperature	Unremarkable
Ophthalmology	Unremarkable
Hematology	**RBC**: -10% & -12% for males from control at 60 & 120 mg/kg/day, respectively **PLT**: -25%/-22% (M/F) from controls 120 mg/kg/day **WBC**: -41%/-55% (M/F), -74%/-68% (M/F) from controls at 60 & 120 mg/kg/day, respectively **NEU**: -11%/-54% (M/F), -76%/-82% (M/F) from controls at 60 & 120 mg/kg/day, respectively **LYM**: -49%/-53% (M/F), -72%/-57% (M/F) from controls at 60 & 120 mg/kg/day, respectively **RET**: -83%/-53% (M/F), -92%/-57% (M/F) from controls at 60 & 120 mg/kg/day, respectively Recovery: males only. Recovery females were unremarkable. **RBC**: -17% & -13% from controls at 60 & 120 mg/kg/day, respectively **PLT**: +66% from controls at 120 mg/kg/day **WBC**: +12% & -52% from controls at 60 & 120 mg/kg/day, respectively **NEU**: +44% & -42% from controls at 60 & 120 mg/kg/day, respectively **LYM**: -59% from controls at 120 mg/kg/day
Clinical Chemistry	**ALT**: +76%/+57% (M/F) & +73%/+31% (M/F) from controls at 60 & 120 mg/kg/day, respectively **AST**: +61% & +1.3-fold% (M) from controls at 60 & 120 mg/kg/day, respectively **CK**: +61%/+67% (M/F) & +2.2-fold%/+2.5-fold% (M/F) from controls at 60 & 120 mg/kg/day, respectively **Creatinine**: +29% & +43% (F) from controls at 60 & 120 mg/kg/day, respectively Recovery: **ALT**: +1.3-fold%/+39% (M/F) & +94%/-53% (M/F) from controls at 60 & 120 mg/kg/day, respectively **AST**: +40% & +1.8-fold% (M) from controls at 60 & 120 mg/kg/day, respectively **CK**: +30%/+74% (M/F) & +1.6-fold%/-60 % (M/F) from controls at 60

<table>
<tr><td></td><td>& 120 mg/kg/day, respectively</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td><u>60 mg/kg/day</u>: duodenum discoloration
<u>120 mg/kg/day</u>: cecum distended, colon (contents, discoloration, distention), duodenum discoloration, stomach discoloration</td></tr>
<tr><td>Organ Weights</td><td>Spleen: -45%/-46% (M/F) & -75%/-52% (M/F) from controls at 60 & 120 mg/kg/day, respectively
Thymus: -50%/-75% (M/F) & -80%/-78% (M/F) from controls at 60 & 120 mg/kg/day, respectively
Liver: +24% (M) from controls at 120 mg/kg/day
Epididymides: -39% (M) from controls at 120 mg/kg/day

<u>Recovery</u>:
Spleen: -10%/+22% (M/F) & -38%/+77% (M/F) from controls at 60 & 120 mg/kg/day, respectively
Thymus: -84%/-38% (M/F) & -67%/-34% (M/F) from controls at 60 & 120 mg/kg/day, respectively</td></tr>
<tr><td>Histopathology
Adequate battery: <u>No, did not use adequate number of animals</u>
Signed Pathology Report: <u>Yes</u>
Peer Reviewed: <u>Not stated</u></td><td>
<table>
<tr><td></td><td colspan="3">Male</td><td colspan="3">Female</td></tr>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>60</td><td>120</td><td>0</td><td>60</td><td>120</td></tr>
<tr><td>No. Animals</td><td>2</td><td>2</td><td>1</td><td>2</td><td>2</td><td>2</td></tr>
<tr><td>Bone Marrow, sternum</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Decreased cellularity
-minimal
-mild
-moderate</td><td>
-
-
-</td><td>
1
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-
1
-</td><td>
-
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-</td><td>
1
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-</td><td>
-
1
1</td></tr>
<tr><td>LN, mandibular</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Sinus plasmacytosis, minimal</td><td>-</td><td>-</td><td>1</td><td>-</td><td>1</td><td>2</td></tr>
<tr><td>Hypoplasia, germ center, moderate</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-
2</td><td></td></tr>
<tr><td>LN, mesenteric</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hypoplasia, germ center,
-minimal
-moderate</td><td>
-
-</td><td>
-
-</td><td>
-
1</td><td>
-
-</td><td>
1
-</td><td>
1
1</td></tr>
<tr><td>Hemorrhage</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1</td></tr>
<tr><td>Spleen</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hyperplasia, germinal center
-mild
-moderate</td><td>
-
-</td><td>
1
-</td><td>
-
1</td><td>
-
-</td><td>
1
1</td><td>
-
2</td></tr>
<tr><td>Thymus</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Decreased cellularity
-mild
-moderate</td><td>
-
-</td><td>
2
-</td><td>
-
1</td><td>
-
-</td><td>
1
1</td><td>
1
1</td></tr>
<tr><td>Cecum</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Erosion
-mild</td><td>
-</td><td>
-</td><td>
-</td><td>
-</td><td>
-</td><td>
1</td></tr>
<tr><td>Colon</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hemorrhage, mucosa/lamina
-minimal
-mild</td><td>
-
-</td><td>
-
-</td><td>
-
1</td><td>
-
-</td><td>
-
-</td><td>
1
-</td></tr>
<tr><td>Erosion
-moderate</td><td>
-</td><td>
-</td><td>
1</td><td>
-</td><td>
-</td><td>
-</td></tr>
<tr><td>Fibrosis, mild</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Gland abscess, mild</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Duodenum</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hemorrhage, mucosa/lamina, mild</td><td>-</td><td>1</td><td>1</td><td>-</td><td>-</td><td>2</td></tr>
<tr><td>Gland abscess, minimal</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1</td></tr>
<tr><td>Degeneration, mild</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>2</td></tr>
<tr><td>Fibrosis, mild</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1</td></tr>
<tr><td>Ulceration, mild</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Ileum</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Hemorrhage, mild	-	-	-	-	-	2
Lymphangienctasia, minimal	-	-	-	-	-	1
Gland abscess, minimal	-	-	-	-	-	1
Mixed cell infiltration, mild	-	-	1	-	-	-
Jejunum						
Vacuolation, mucosa, mild	-	-	-	-	-	1
Gland abscess, mild	-	-	-	-	-	1
Mixed cell infiltration, lamina propria, mild	-	-	-	-	-	1
Hemorrhage -minimal -mild	- -	- -	- 1	- -	- -	1 -
Fibrosis -minimal -mild	- -	- -	- 1	- -	- -	1 -
Mononuclear cell infiltration, moderate	-	-	1	-	-	-
Rectum						
Hemorrhage, minimal	-	-	-	-	1	1
Polymorphonuclear cell infiltration lamina propria, mild	-	-	-	-	-	1
Injection site, vein						
Hemorrhage, perivascular -minimal -mild -moderate	- - -	- 1 1	- 1 -	- - -	- - -	1 - -
Necrosis, perivascular, minimal	-	-	-	-	-	1
Mononuclear cell infiltration, vascular wall, minimal	-	-	-	-	-	1
Mixed cell infiltration, subcutis/dermis, mild	-	-	-	-	-	1
Kidney						
Mononuclear cell infiltration interstitium/perivascular -minimal	-	2	-	1	1	2
Glomerulosclerosis, minimal	-	-	-	-	-	1
Hemorrhage, mild	-	-	1	-	-	-
Liver						
Hepatocyte vacuolization -minimal -mold	- -	- -	1 -	- -	- -	- 1
Atrophy, hepatic cord, mild	-	-	-	-	-	1
Adrenals						
Mineralization, minimal	-	-	-	-	1	1
Prostate gland						
Immature	2	2	1	NA	NA	NA
Uterus						
Hemorrhage -mild -moderate	 NA	 NA	 NA	- -	- 2	1 1
Vagina						
Atrophy of surface epithelial cells -mild -moderate	 NA	 NA	 NA	- -	2 -	1 1
Ovaries						
Increased atretic follicles -mild -moderate	 NA	 NA	 NA	- -	1 1	- 2
Mammary gland						
Atrophy, mild	-	-	-	-	-	2

Recovery Necropsy:

	Male			Female		

Dose (mg/kg/day)	0	60	120	0	60	120
No. Animals	1	1	1	1	1	1
Colon						
Brown pigment-laden macrophages, mild	-	-	1	-	-	-
Duodenum						
hemorrhage, minimal	-	1	1	-	-	1
Ileum						
Prominent GALT, minimal	-	-	1	-	-	1
Kidneys						
Mononuclear cell infiltration interstitium/perivascular						
-minimal	1	-	-	-	1	1
-mild	-	-	1	-	-	-
Hemorrhage, mild	-	-	1	-	-	-
Thymus						
Decreased cellularity						
-mild	-	2	-	-	1	1
-moderate	-	-	1	-	1	1
LN, mandibular						
Hemorrhage, minimal	-	1	1	-	-	-
Extramedullary hematopoiesis, minimal	1	-	1	-	1	1
Eosinophil infiltration, minimal	-	-	1	-	-	-
Hyperplasia, germinal center, minimal	-	1	1	-	-	1
Ovaries						
Increased atretic follicles, minimal	NA	NA	NA	-	-	1
Parovarian cyst	NA	NA	NA	-	-	1
Follicular cyst	NA	NA	NA	-	-	1
Liver						
Mononuclear cell infiltration interstitium/perivascular						
-minimal	-	-	-	-	-	1
-mild	-	-	1	-	-	-

-: indicates reduction in parameters compared to control. +: indicates increase in parameters compared to control.

Study title/ number: A Toxicity Study of IMMU-132 in Cynomolgus Monkeys ((b) (4) 160.25)

Key Study Findings

- Target organs of toxicity included hematopoietic (↓ in RBC, platelets, & lymphocytes) and lymphoid organs (↓ cellularity in thymus and mesenteric lymph nodes; erythrophagocytosis in the mandibular lymph nodes).
- Multi-organ cellular infiltration in the brain, heart, eye, GI, kidney, prostate, salivary glands, trachea, and urinary bladder.
- Injection site toxicity observed at 50 mg/kg/day.
- Anti-drug antibodies were detected in all animals at all doses tested in the chronic toxicity study.

Conducting laboratory and location: (b) (4)
GLP compliance: **Yes**
Drug/Lot: The sponsor used 2 IMMU-132 products: phase 1/2, which used hRS7 antibody clone (b) (4) (lot # 1605147) and the phase 3 product, which incorporated hRS7 antibody clone (b) (4) (lot# 1605147)

Methods

Dose and frequency of dosing:	12.5, 25, & 50 mg/kg; once weekly for 2 weeks of a 3-week cycle (Days 1, 8, 22, 29, 43, 50, 64, and 71)
Route of administration:	IV (1-hr)
Dose Volume:	1.25, 2.5, & 5 mL/kg for 12.5, 25, & 50 mg/kg, respectively
Formulation/vehicle:	MES (b) (4) Solution (25 mM MES (b) (4), 25 mM Trehalose, 0.01% v/v Polysorbate 80)
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	5/sex/group (3/sex/group for controls)
Age:	2 – 3 years
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	The Applicant included an arm with the phase 1/2 product at the 25 mg/kg dose to compare with the phase 3 product.

Dose formulation analysis: IMMU-132 was not detected in the control samples. Formulations were within 10% of the expected concentrations**.** The percent relative standard deviation for the top, middle, and bottom strata of IMMU-132 formulations was within 7.7%, indicating a homogenous dispersion.

Observations and Results:

Parameters	Major findings
Mortality	No drug-related mortalities
Clinical Signs	12.5 mg/kg/day: Abnormal color (bilateral forelimb [M]); bruising (bilateral hindlimb [M&F]) 25 mg/kg/day: abnormal color (bilateral forelimb, left hindlimb, chest, lower lip, snout); bruising (right forelimb [F]), 50 mg/kg/day: eyebrow abrasion (M), bruising (chest [F], bilateral hindlimb [M&F]), abnormal color (bilateral hindlimb, knee, eyebrow); eye discharge (F)
Body Weights	50 mg/kg/day: +12% in males
Electrocardiography **Blood pressure**	Unremarkable
Respiratory Rates	Unremarkable
Body Temperature	Unremarkable
Ophthalmology	Unremarkable
Hematology	RBC: -12.7% from control for 50 mg/kg/day (F) PLT: -14%, -37%, & -51% from controls for males at 12.5, 25, & 50 mg/kg/day, respectively LYM: -25%, -51% & -50% from controls for females at 12.5, 25, & 50 mg/kg/day, respectively Recovery: PLT: -37%, -34%, & -31% from controls for males at 12.5, 25 & 50 mg/kg/day, respectively WBC: -26% & -32% from controls for males at 25 & 50 mg/kg/day, respectively BAS: -22% & -39% from controls for males at 25 & 50 mg/kg/day, respectively EOS: -53% & -78% from controls for males at 25 & 50 mg/kg/day, respectively RET: -32% from controls for males at 50 mg/kg/day LYM: -20% & -47% from controls for females at 25 & 50 mg/kg/day, respectively
Clinical Chemistry	ALT: -35%, -44%, & -37% from controls for males at 12.5, 25, & 50 mg/kg/day, respectively AST: -18% & -26% from controls for males at 12.5, 25, & 50 mg/kg/day, respectively Recovery: CREA: -14% (F), -10%/-21% (M/F), -10%/-21% (M/F) from controls for 12.5, 25, & 50 mg/kg/day, respectively GLOB: +15% & +20% from controls for males at 25 & 50 mg/kg/day, respectively K: +14% from controls for males at 50 mg/kg/day TRI: 66% & +67% from controls for females at 25 & 50 mg/kg/day, respectively CHOL: +23% from controls for males at 50 mg/kg/day
Urinalysis	Unremarkable
Gross Pathology	25 mg/kg/day (phase 1/2): skin alopecia 50 mg/kg/day: skin alopecia, injection site discoloration
Organ Weights	Unremarkable

Histopathology
Adequate battery: **Yes**
Signed Pathology Report: **Yes**
Peer Reviewed: **Not stated**

	Male					Female				
Dose (mg/kg/day)	0	12.5	25	25	50	0	12.5	25	25	50
No. Animals	1*	3	3	3	3	2	3	3	3	3
Brain										
Mononuclear infiltration, perivascular, medulla oblongata, minimal	-	-	-	-	-	-	-	-	-	5
Heart										
Infiltration, Mononuclear Cells; myocardial, multifocal, minimal	-	-	-	-	1	-	-	-	1	1
Epididymides										
Immature	1	2	2	3	2	-	-	-	-	-
Testis										
Immature	-	-	1	1	-	-	-	-	-	-
Hypoplasia, mild	-	-	1	1	-	-	-	-	-	-
Prostate										
Infiltration, mononuclear cells, multifocal, minimal	-	1	1	1	2	-	-	-	-	-
Immature	-	2	1	1	2	-	-	-	-	-
Eye										
Mononuclear infiltration, minimal	-	-	-	-	1	-	-	-	-	1
Lymph node, mandibular										
Erythrophagocytosis -minimal -mild	- -	- -	- -	2 -	- 2	1 1	1 1	2 -	2 -	1 1
Lymph node, mesenteric										
germinal centers; follicles; Decreased Cellularity; multifocal, mild	-	-	-	-	1	-	-	-	-	-
Thymus										
Lymphoid, decreased cellularity, multifocal -mild	-	-	-	-	1	-	-	-	-	-
Injection site										
subcutaneous; perivascular; Hemorrhage; diffuse, mild	-	-	-	-	1	-	-	-	-	-
subcutaneous; perivascular; Hemorrhage; focal, mild	-	-	-	-	1	-	-	-	-	-
Infiltration, Mononuclear Cells; venous, focal, minimal	-	-	-	-	-	-	-	-	-	1
perivascular; Edema; subcutaneous, widespread, marked	-	-	-	-	-	-	-	-	-	1
Inflammation, Chronic; subcutaneous, focal, mild	-	-	-	-	-	-	-	-	-	1
Cecum										
- Infiltration, Mononuclear Cells; submucosal, multifocal, mild	-	-	-	-	-	-	-	-	-	1
lumen; Parasite; protozoa, widespread, moderate	-	-	-	-	-	-	-	-	-	1
crypts; mucosa; Abscess; few, mild	-	-	-	-	-	-	-	-	-	1
Colon										
Infiltration, Mononuclear Cells; mucosal, multifocal, mild	-	-	-	-	-	-	-	-	-	1
lumen; Parasite; protozoa, minimal	-	-	-	-	-	-	-	-	-	1
Kidney										
Infiltration, Mononuclear Cells; multifocal	- -	1 -	1 1	- -	2 -	- -	- -	- -	- -	- -

	-minimal -mild										
	medulla; Mineralization; multifocal, minimal	-	-	-	-	1	-	-	-	-	-
	cortex; Degeneration/Regeneration; tubular, multifocal	-	-	-	-	-	-	-	-	-	1
	Lungs										
	interstitium; perivascular; Brown Pigment, Intracellular, minimal	-	1	1	-	2	-	3	3	1	3
	Ovaries										
	Follicles; Mineralization; focal, minimal	NA	NA	NA	NA	NA	-	-	1	1	1
	Follicles; Mineralization; focal -minimal -mild -moderate	NA	NA	NA	NA	NA	- - -	- - -	- - 1	- 1 -	1 - -
	Parathyroid gland										
	Infiltration, mononuclear cells, focal, minimal	-	-	-	1	-	-	-	-	-	1
	Pituitary Gland										
	Pars distalis; cyst, focal, minimal	-	-	-	-	1	-	-	-	-	-
	Pars intermedia; cyst, focal, minimal	-	-	-	-	1	-	-	-	-	-
	Prostate gland										
	Infiltration, mononuclear cells, multifocal, minimal	1	1	1	1	2	-	-	-	-	-
	Tongue										
	Infiltration, Mononuclear Cells; focal, minimal	-	-	-	-	1	-	-	-	-	-
	Trachea										
	Infiltration, Mononuclear Cells; submucosal, focal, minimal	-	1	1	1	1	-	1	-	1	1
	Urinary bladder										
	Infiltration, Mononuclear Cells; submucosal, focal, -minimal -mild	- -	1 -	1 -	- -	- 1	- -	- -	1 -	- -	2 -
	*: one male control animal was removed from the study due to behavioral issues. Recovery: unremarkable										
Anti-drug Antibodies	10/10, 10/10, 10/10, & 10/10 tested positive for ADAs at 12.5, 25, 50 & 25 (b) (6) mg/kg/day, respectively										

-: indicates reduction in parameters compared to control. +: indicates increase in parameters compared to control.

Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Assessment of Genotoxicity of SN-38 Using the Bacterial Reverse Mutation Test (CYP1595_R1a)

Key Study Findings:

- Under the conditions tested, SN-38 was not mutagenic under the conditions tested.

GLP compliance: **Yes**
Test system: *Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA (up to 5000 µg/plate; +/- S9)*
Study validity: **Yes**

In Vitro Assays in Mammalian Cells
Study title/ number: Assessment of Genotoxicity of SN-38 Using the *In Vitro* Mammalian Cell Micronucleus Test (CYP1595_R1b)
Key Study Findings:

- Under the conditions tested, SN-38 was positive for the induction of micronuclei in CHO-K1 cells.

GLP compliance: **Yes**
Test system: Chinese hamster ovary, K1 strain*; up to 60 µg/mL*
Study validity: **Yes**

5.5.3. Carcinogenicity

Not conducted or required to support this BLA of sacituzumab govitecan for patients with advanced cancer.

5.5.4. Reproductive and Developmental Toxicology

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan or required to support this BLA. Sacituzumab govitecan contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells. Based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-fetal lethality.

5.5.5. Other Toxicology Studies

Study title: Cross-Reactivity Study of hRS7 IgG-biotin with Normal Cynomolgus Monkey Tissues (Study No. IM1735)

The Applicant tested the cross-reactivity of hRS7 IgG-biotin with cryosections of normal cynomolgus monkey tissues from 3 independent donors. The concentrations used were 2 µg/mL and 40 µg/mL. A human IgG1-bio Isotype control was used. Cryosections of normal human skin (epithelial cells) was used as a positive control.

Results:
hRS7 IgG-biotin-specific staining was observed in the following tissues.

- Cytoplasm, cytoplasmic granules and/or membrane of various epithelial cells in: breast – mammary gland, eye, gastrointestinal tract – esophagus & stomach, kidney, lung, ovary, fallopian tube (oviduct), pancreas, parathyroid, placenta, prostate, salivary gland, skin, thymus, thyroid, tonsil, ureter, urinary bladder, uterus – endometrium, cervix
- Cytoplasm, cytoplasmic granules of myoepithelium in: breast – mammary gland, salivary gland
- Cytoplasm, cytoplasmic granules and/or membrane of mesothelium in: gastrointestinal tract – esophagus, stomach, kidney, ovary, prostate, ureter
- Cytoplasm and/or membrane of decidual cells in placenta
- Cytoplasmic staining was observed in the nervous plexi of the muscular wall in the digestive tract. Granular cytoplasmic staining of ependymal cells was also observed in the spinal cord.

Study title: Cross-Reactivity Study of hRS7 with Normal Human Tissue (Study No. DMP0411)

The Applicant tested the cross-reactivity of hRS7 IgG-biotin to human tissues in a panel of 32 normal tissues from 5 – 10 different donors. The concentrations used were 0.625 µg/mL and 1.875 µg/mL. Lymphocytes were used as a negative tissue control. Cryosections of tonsil surface [epithelial cells] was used as a positive control tissue.

Results:
Strongest hRS7 IgG-biotin-specific staining was observed in the collecting ducts of the kidney, epithelium of the fallopian tube, bile ducts, centroacinar and columnar ductal cells of the pancreas, acinar epithelial cells of the prostate and the endometrium and endometrium and endocervical epithelium of the uterus. Lower staining was observed in the bronchiolar epithelium (including glands) of the lung, breast epithelium and intermediate lobe remnants in the pituitary gland. Staining was mostly cytoplasmic with some membrane staining.

X X

Kimberly Ringgold, PhD
Primary Reviewer

Tiffany Ricks, PhD
Acting Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Sacituzumab govitecan (IMMU-132) is an antibody-drug conjugate (ADC) consisting of a humanized monoclonal antibody targeting Trop-2 (the trophoblast cell-surface antigen-2). The antibody portion is linked to SN-38, the small molecule portion, via a hydrolysable linker (CL2A). Sacituzumab govitecan induces DNA damage, leading to apoptosis and cell death. The Applicant's proposed indication for sacituzumab govitecan is as follows: the treatment of adult patients with metastatic triple negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

To support the request for the accelerated approval of sacituzumab govitecan, the Applicant submitted the results of a single-arm trial, IMMU-132-01, which evaluated a range of doses across several solid tumor histologies. The BLA relies on the results of a subset of 108 patients with mTNBC who received a starting dose of 10 mg/kg on Days 1 and 8 of every 21-day treatment cycle, to support the Applicant's efficacy claims; the overall response rate (ORR) in patients with mTNBC was 33.3% (95%CI: 24.6 – 43.1). To demonstrate the safety of sacituzumab govitecan, the Applicant included the safety results of patients enrolled in IMMU-132-01, who received doses ranging from 8 mg/kg to 18 mg/kg.

The 10 mg/kg starting dose was found to be acceptable based on an improved safety profile (rate of treatment delays and discontinuations) compared to the maximum tolerated dose of 12 mg/kg and a better efficacy profile across various tumor types compared to 8 mg/kg. PK measurements of components of sacituzumab govitecan (unconjugated SN-38, total SN-38, SN-38 glucuronide [SN-38G], and total antibody) were obtained from a subset of patients with mTNBC (n=57). Population PK and exposure-response analyses were limited by the small sample size.

Patients with mild hepatic impairment had a slightly higher incidence of Grade 3+ adverse events compared to patients with normal hepatic function. However, dose adjustment in this population was not necessary. The effect of moderate hepatic impairment on the safety and PK of sacituzumab govitecan is unknown; a post-marketing requirement (PMR) will be issued to determine an adequate starting dose in this population.

Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is involved in the metabolism of SN-38 to SN-glucuronide (SN-38G) based on information submitted in the BLA, and concomitant administration of drugs that alter UGT1A1 activity may impact the safety or efficacy profile of sacituzumab govetican. Given that the recommended starting dose of 10 mg/kg is close to the MTD of 12 mg/kg and the concentration of unconjugated SN-38 is high, concomitant administration of drugs that inhibit UGT1A1 activity should be avoided to minimize the potential for increased frequency and severity of adverse events. Similarly, drugs that induce the activity of UGT1A1 should be avoided to maintain efficacy. A recommendation for dose adjustment of sacituzumab govitecan based on drug interactions cannot be made because adjusting the dose of the ADC to match the exposure of SN-38 (the small molecule portion) does not account for the contribution of the antibody portion to safety and efficacy.

Samples for UGT1A1 testing were prospectively collected but were retrospectively assayed. UGT1A1*28 genotype information was available for a subset of patients (n=333/420) in Study

IMMU-132-01. Patients homozygous for the UGT1A1*28 allele had higher incidence of Grade 4 neutropenia (10/37) compared to patients heterozygous for the UGT1A1*28 allele (9/152), while patients homozygous for the wild-type allele had the lowest frequency of adverse events (7/144).

The systemic exposure of unconjugated SN-38 is high; the maximum concentration in serum (C_{max}) is approximately 120 ng/mL at the proposed 10 mg/kg sacituzumab govitecan dose. The potential of sacituzumab govitecan to induce QT interval prolongation has not been assessed at such a high concentration.

The Applicant submitted immunogenicity information for 106 patients with mTNBC. Persistent antidrug antibody (ADA) response was detected in serum samples obtained from 3 patients. However, these results may be influenced by assay limitations. Additionally, the employed assay does not have the capability of detecting neutralizing antibodies (nAb).

6.1.1. Recommendations

The Office of Clinical Pharmacology recommends the approval of BLA 761115 from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of sacituzumab govitecan (IMMU-132) was demonstrated in study IMMU-132-01, single-arm trial. An overall response rate of 33.3% (95%CI: 24.6 – 43.1) and a median duration of response of 7.7 months (95%CI: 4.9 – 10.8) was observed in 108 patients with mTNBC who received at least two prior therapies for metastatic disease.
General dosing instructions	The proposed dosing regimen of sacituzumb govitecan is 10 mg/kg administered as an IV infusion on Days 1 and 8 of each 21-day treatment cycle. The 10 mg/kg dose was selected based on an improved safety profile compared to the maximum tolerated dose of 12 mg/kg and a more favorable efficacy profile compared to 8 mg/kg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are proposed based on intrinsic factors. However, an adequate starting dose in patients with moderate hepatic impairment is unknown. A PMR will be requested to determine an appropriate starting dose in this patient population. Patients homozygous for UGT1A1*28 are at an increased risk for adverse reactions, especially neutropenia. The appropriate dose in these patients is not known and should be considered based on individual patient tolerance to treatment. No dose adjustments are proposed based on extrinsic factors. The administration of sacituzumab govitecan should be avoided in patients who are receiving concomitant medications that inhibit or induce UGT1A1 enzyme.

Labeling	Overall, the proposed labeling recommendations are acceptable upon the applicant's agreement to the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in section 11.
Bridge between the to-be-marketed and clinical trial formulations	(b) (4) A subset of patients (n=13) with mTNBC received drug product manufactured (b) (4) PK information obtained from that subset of patients demonstrate PK comparability to the (b) (4) product. Refer to the Office Pharmaceutical Quality review for details regarding the analytical comparability of drug products (b) (4)

6.1.2. Post-Marketing Requirements and Commitments

PMR or PMC	Key Issue to be Addressed	Rationale	Key Consideration for Design Features
PMR	An appropriate starting dose in patients with moderate hepatic impairment	There was a higher incidence, albeit modest, of adverse events in patients with mild hepatic impairment compared to patients with normal hepatic function. There is no safety or PK information in patients with moderate hepatic impairment	The study should be an open-label, non-randomized, dose-escalation study in patients with moderate hepatic impairment (according to NCI ODWG criteria) to determine an adequate starting dose based on safety and PK evaluations.
PMR	QT interval prolongation potential of sacituzumab govitecan	SN-38, the small molecule portion of sacituzumab govitecan, is present at a high concentration and the potential for QT interval prolongation cannot be ruled out	A QT study is currently included as a sub-study of the ongoing confirmatory trial (IMMU-132-05). The applicant will be required to submit the QT evaluation report.
PMR	UGT1A1 genotyping in study IMMU-132-05	Patients homozygous for the UGT1A1*28 allele are at increased risk of Grade 4 neutropenia and other adverse events. Submission of data from the confirmatory trial will inform potential labeling updates related to section 5.5 (Use in patients with reduced UGT1A1 activity).	The confirmatory clinical trial includes an additional exploratory assessment of the relationship between UGT1A1 genotype and toxicity.
(b) (4)			

(b) (4)

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Sacituzumab govitecan contains a humanized monoclonal antibody hRS7 IgG1 which targets Trop-2. The antibody portion is linked to SN-38, the small molecule portion, via a hydrolysable linker. Sacituzumab govitecan induces DNA damage, leading to apoptosis.

Absorption: sacituzumab govitecan is administered as an intravenous (IV) infusion.

Distribution: The mean volume of distribution of sacituzumab govitecan is 0.045 L/kg.

Metabolism: UGT1A1 is involved in the metabolism of SN-38, the small molecule portion of sacituzumab govitecan, to form SN-38 glucuronide (SN-38G).

Elimination: the mean terminal half-life of sacituzumab govitecan is 16 hours and SN-38 is 18 hours.

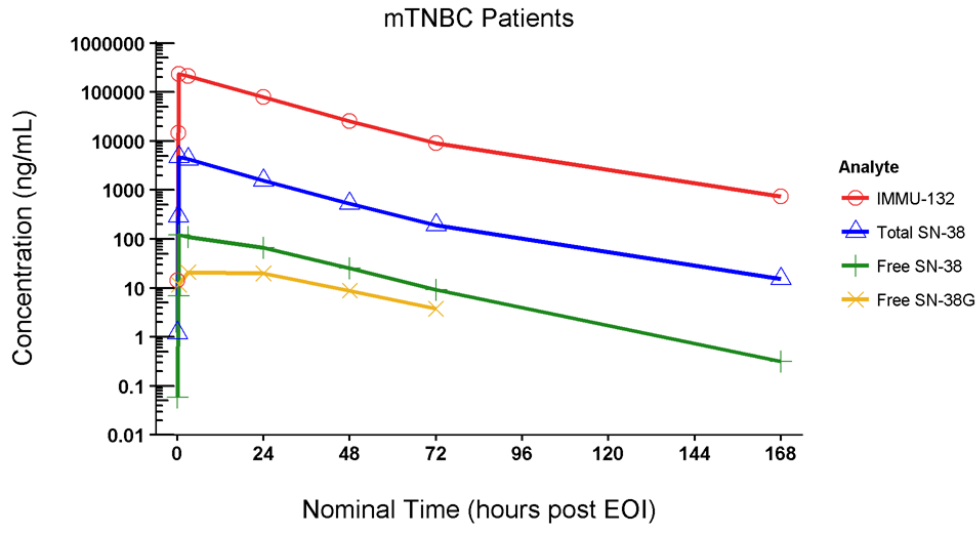


Figure 2: PK profile of sacituzumab govetican and its components.

Table 3: Summary of PK Parameters (Non-Compartmental Analysis) of Sacituzumab Govetican

	IMMU-132	**Unconjugated SN-38**	**Total SN-38**	**SN-38G**	**Total IgG**
Half-life (h)	16	18	15	15	144
$AUC_{0\text{-}168h}$ (h*ng/mL)	5,070,000	3560	173,000	1430	64,200,000
C_{max} (ng/mL)	239,000	117	4,440	24.9	284,000
T_{max} (h)	3.08	3.17 – 4.0		8.0	6.0
Clearance (L/h)	0.132	171		79.1	0.0143
Vd	0.0437 (L/kg)				1.44 (L)

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose of sacituzumab govitecan is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles.

Therapeutic Individualization

No dose adjustments are proposed based on intrinsic or extrinsic factors. Population pharmacokinetic analysis, though of limited value due to small sample size, did not identify an effect of age or race of the PK of sacituzumab govitecan.

No dose adjustment is required for patients with mild hepatic impairment, based on safety and PK information obtained from Study IMMU-132-01. The effect of moderate hepatic impairment on safety and PK of sacituzumab govitecan is unknown.

The administration of sacituzumab govitecan in patients receiving concomitant medications that modulate the activity of UGT1A1 should be avoided.

Outstanding Issues

The effect of moderate hepatic impairment on the safety and PK of sacituzumab govitecan has not been characterized. As such, an adequate starting dose of sacituzumab govetican is to be determined for this population.

The potential of sacituzumab to induce QT interval prolongation has not been assessed. The ongoing confirmatory trial, Study IMMU-132-05 will evaluate the effects of sacituzumab govitecan on QT in a subgroup of patients.

Based on UGT1A1 genotyping results, patients who are homozygous for UGT1A1*28 are at increased risk for neutropenia following initiation of sacituzumab govitecan treatment. The ongoing confirmatory trial, Study IMMU-132-05 includes additional exploratory assessment of

the relationship between UGT1A1 genotype and toxicity to determine whether dose adjustment is needed based on UGT1A1 genotype.

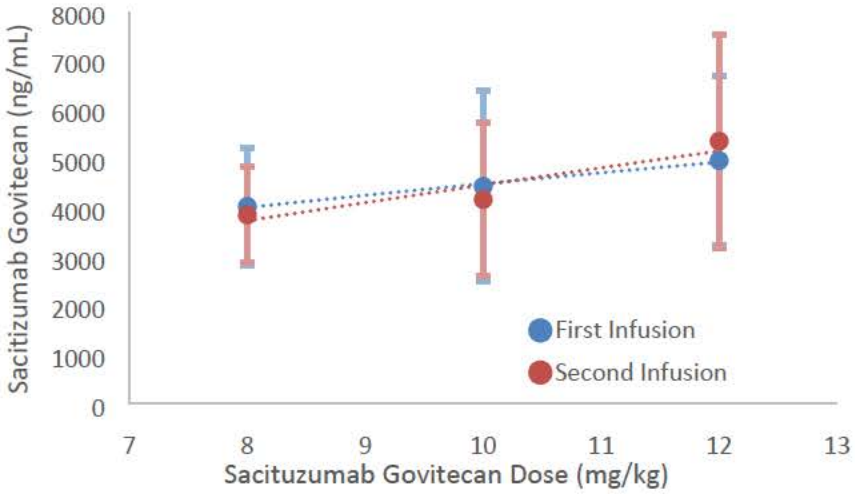
Preliminary data submitted by the Applicant suggest that patients without detectable or with weak Trop-2 expression in their tumor may not benefit from treatment with sacituzumab govitecan. The ongoing confirmatory trial (IMMU-132-05) includes an assessment of the correlation between Trop-2 expression and efficacy.

The characterization of sacituzumab immunogenicity is influenced by assay limitations. The Office of Biotechnology Products (OBP) will issue a (PMC) to develop an assay with improved sensitivity for detecting ADA and nAb.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Structure	Sacituzumab govitecan is an antibody drug conjugate composed of a humanized monoclonal antibody, hRS7 IgG1□, which binds to Trop-2. The antibody is attached via a hydrolysable linker (CL2A) to SN-38.
Mechanism of Action	Sacituzumab govetican binds to Trop-2 expressing cancer cells and is internalized with subsequent release of SN-38 via hydrolysis of the linker CL2A. SN-38 induces DNA damage, which leads to cell cycle arrest and apoptosis.
Proposed Dosing	The recommended dose of sacituzumab govitecan is 10 mg/kg administered on Day 1 and Day 8 of each 21-day treatment cycle.
General Information	
Bioanalysis	Four analytes were measured to characterize the PK of sacituzumab govitecan: total antibody (hRS7 and hRS7-SN38), unconjugated SN-38, SN-38 glucuronide (SN-38G), and total SN-38 (unconjugated SN-38 and hRS7-SN-38). The concentration of sacituzumab was calculated using the concentration of total SN-38, unconjugated SN-38, and a drug-to-antibody-ratio of 8. SN-38 and SN-38G were measured using a high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) assay. Similarly, HPLC-MS/MS assay was used to measure total SN-38 after an acid dissociation step. Total antibody (hRS7-IgG) were measured using an electrochemiluminescence assay.
Dose Proportionality	Sacituzumab govitecan exposure appeared to increase with dose. The IMMU-132 concentration at the end of infusion increased linearly with increasing doses of sacituzumab govetican (8 mg/kg, 10 mg/kg, and 12 mg/kg) as shown below. Power analysis indicated that the exponent was 0.51 (95%CI = 0.41 - 0.61). No formal assessment of time-dependence of PK was conducted. However, there was no difference in ADC trough

	concentrations at later treatment cycles based on the limited PK data collected. 
Accumulation	At the proposed dosing regimen, there is no accumulation of sacituzumab govitecan. The elimination half-life of the ADC is approximately 16 hours (**Table 3**).
Variability	Pharmacokinetic data were obtained from patients with mTNBC in study IMMU-132-01. The coefficient of variation of C_{max} was 19% for sacituzumab govitecan and 47% for SN-38. The coefficient of variation of $AUC_{0\text{-}168h}$ was 24% for sacituzumab govitecan and 47% for SN-38.
Immunogenicity	Immunogenicity of sacituzumab govitecan was assessed in serum samples from 106 patients with mTNBC using an ECL-based immunoassay to test for anti-sacituzumab govetican antibodies (ADA). Detection of the ADA was done using a 3-tier approach: screen, confirm, and titer. Persistent ADA were detected in 3 patients. However, there are limitations associated with drug tolerance of the assay and ability to detect neutralizing antibodies. Refer to Office of Pharmaceutical Quality for details related to immunogenicity assay.
QT Prolongation	In a subset of 184 patients in study IMMU-132-01, 2.7% of patients had QTcF > 500 ms and 4.7% of patients had an increase from baseline of > 60 ms; however, most of these cases were confounded by other risk factors or concomitant medications that are known to prolong QT intervals. There were no time-matched PK samples collected with ECGs to assess concentration-dependent effects or indirect effects of sacituzumab govitecan on QT interval prolongation. A QT study characterizing the relationship between IMMU-132 and QT interval prolongation is currently being conducted as a sub-study of the confirmatory trial IMMU-132-05.
Distribution	
Volume of Distribution	Based on non-compartmental analysis, the mean volume of distribution of sacituzumab govitecan in 0.045 L/kg.

Elimination	
Mean Terminal Half-Life	The clearance of sacituzumab govetican is 0.002 L/h/kg. The mean terminal half-life is 16 hours for sacituzumab govetican, 18 hours for SN-38, and 6 days for the IgG (**Table 3**).
Metabolism	
Primary Metabolic Pathways	The BLA submission did not include any metabolism studies. UGT1A1 is involved in the metabolism of SN-38 and the formation of the SN-38G.
DDI Potential	The BLA submission did not include drug interaction studies (in vivo or in vitro). Drugs that modulate the activity of UGT1A1 enzyme may alter SN-38 exposure.
Excretion	
Primary Excretion Pathway	No studies were conducted for sacituzumab govitecan.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness. The applicant submitted safety and efficacy results from Study IMMU-132-01 to support the accelerated approval of sacituzumab govitecan. IMMU-132-01 was a multicenter, Phase I/II, single-arm study, open-label trial that enrolled patients with multiple tumor types, including 108 patients with mTNBC who received at least two prior treatments for metastatic disease. Major efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

Dose Selection

In Phase I part of Study IMMU-132-01, dose escalation was performed according to a standard 3+3 design. Based on toxicity studies in non-clinical species, dose escalation was started at a dose level of 8 mg/kg on day 1 and day 8 of each 21-day treatment cycle. No dose limiting toxicities were observed at the 8 mg/kg dose level and dose was escalated to 12 mg/kg.

A total of 9 patients received the 12 mg/kg dose because of protocol-required delays in administering the second dose in Cycle 1. Eight patients received a second dose, four of whom received a reduced dose of 9 mg/kg, and the second cycle was delayed by 1 week in three patients. Of note, no DLTs were observed despite the dose delays and dose reductions at 12 mg/kg.

Dose escalation to 18 mg/kg occurred in three patients. The second dose was delayed in all 3 patients and 1 DLT of Grade 4 neutropenia was observed. As such, 12 mg/kg was declared as the MTD. The Applicant, however, explored lower dose levels that would minimize the incidence dose reductions and dose delays. An acceptable dose level was defined as the dose at which ≤ 2 of 6 patients would tolerate a treatment cycle (21 days) without the need for dose delays, dose reductions, or occurrence of any Grade 3+ AE. Five additional patients were treated at the 8

mg/kg dose level with no DLTs and another 5 patients were treated at an intermediate dose of 10 mg/kg with 1 DLT of Grade 4 anemia.

The 8 mg/kg (n=81) and 10 mg/kg (n=97) dose levels were further investigated in the part II of study IMMU-132-01, and comparative analysis was conducted in patients with various tumor types. Patients receiving the 10 mg/kg dose had slightly higher incidence of Grade 3 neutropenia, dose delays, and dose reductions; however, the differences in safety profile of the at the two dose levels were not deemed substantial by the Applicant (**Table 4**).

Table 4: Comparison of Grade 3+ Adverse Events at 8 mg/kg and 10 mg/kg Dose Levels

Grade ≥ 3 AE	**8 mg/kg (N=80)**	**10 mg/kg (N=89)**
Nausea	3%	2%
Diarrhea	4%	10%
Vomiting	3%	3%
Neutropenia	30%	36%
Anemia	13%	12%
Fatigue	9%	9%
Dose Delays	29%	34%
Dose Reductions	19%	28%
Discontinuations	8.6%	10.3%

Analysis of efficacy across tumor types demonstrated a higher ORR at the 10 mg/kg dose compared to 8 mg/kg (**Figure 3**). Thus, 10 mg/kg was chosen for further investigation in study IMMU-132-01. Of note, the applicant submitted efficacy data form patients receiving only the 10 mg/kg dose in this BLA.

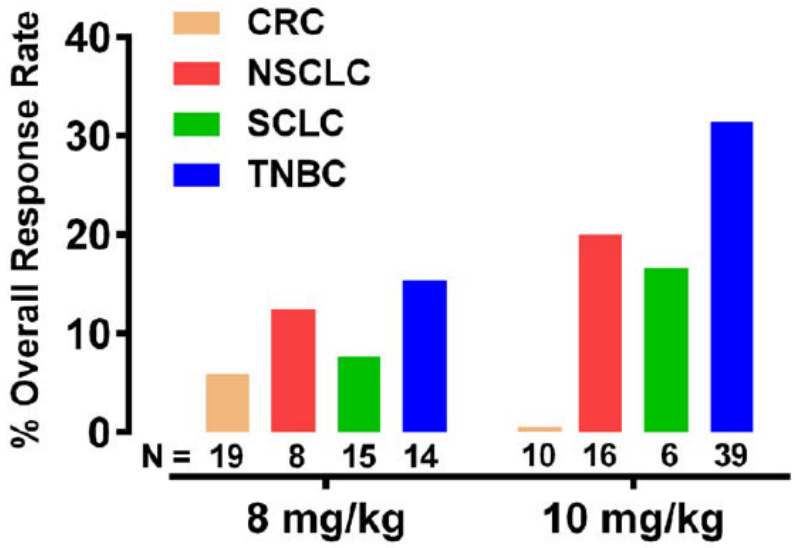


Figure 3: ORR by tumor type and dose level. Numbers below bars represent the number of evaluable patients in each cohort. *Source: Summary of Clinical Efficacy (Applicant's analysis).*

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

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. As detailed above, the 10 mg/kg dose was selected in trial IMMU-132-01, based on a favorable safety and efficacy profile. The overall response rate from study IMMU-132-01 was 33.3% (95%CI: 24.6% – 43.1%) and the median duration of response was 7.7 months (95%CI: 4.9 – 10.8). This observed ORR in study IMMU-132 is a significant improvement compared to ORR reported for the standard of care.

Exposure-Efficacy Analyses

Exposure-response analyses for safety and efficacy were conducted using data collected from 57 patients in trial IMMU-132-01 who received 10 mg/kg. Given that analyses were conducted at single dose and for a small number of patients, the exposure-response information presented herein should be interpreted with caution.

Based on logistic regression analysis, no correlation was found between objective tumor response based on local assessment and AUC of any of the constitutive elements of IMMU-132 (Figure 4). There was no meaningful relationship between exposure (first cycle AUC_{last}) – stratified by quartiles of exposure – and time-to-event endpoints (PFS and OS based on local assessment).

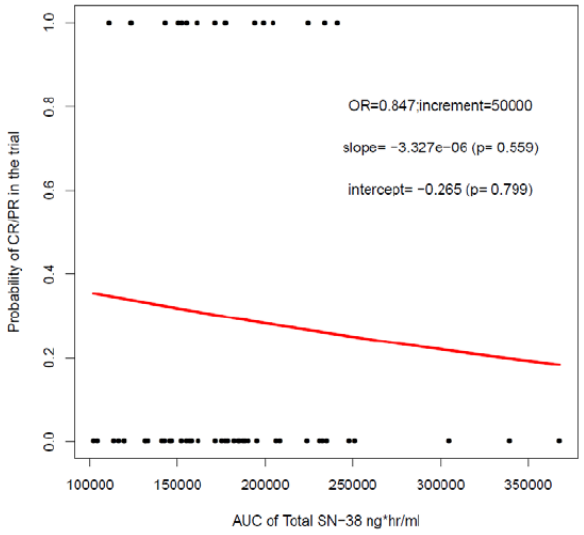


Figure 4: Relationship between ORR and first cycle AUC of total SN-38. *Source: Population Pharmacokinetic Report (Applicant's analysis)*

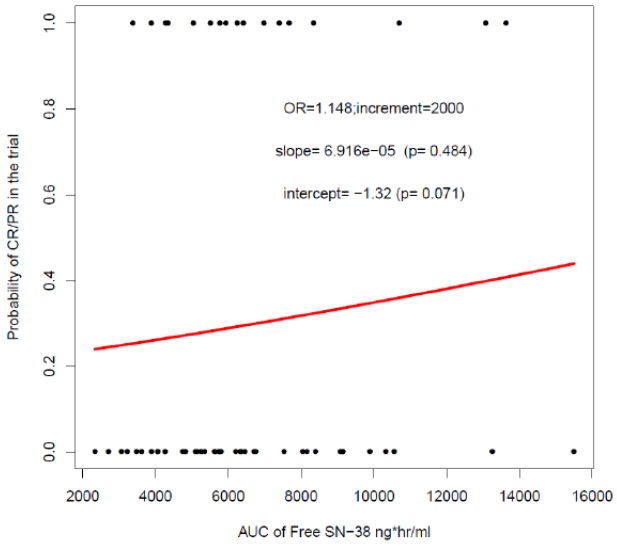


Figure 5: Relationship between ORR and unconjugated SN-38. *Source: Population Pharmacokinetic Report (Applicant's analysis)*

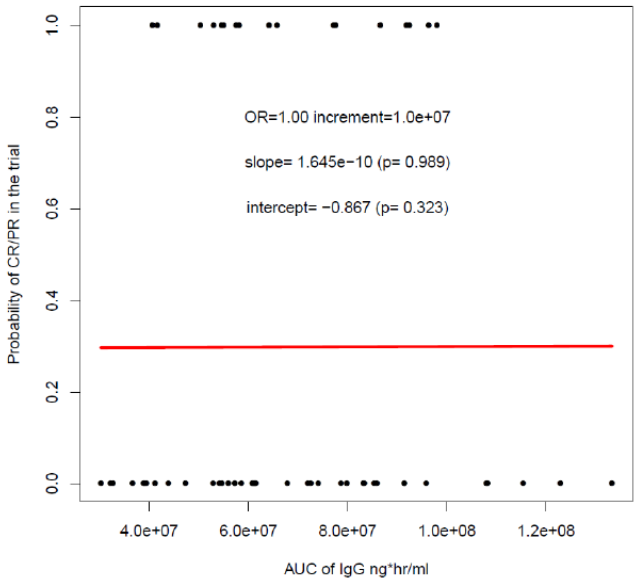


Figure 6: Relationship between ORR and IgG. *Source: Population Pharmacokinetic Report (Applicant's analysis)*

There is no statistically significant relationship between first cycle AUC of any of the components of IMMU-132 and ORR.

Exposure-Safety Analyses

Logistic regression analyses identified a relationship between unconjugated SN-38 AUC (1st cycle) and nausea/vomiting and diarrhea of any grade was correlated with total SN-38 AUC (1st cycle). Additionally, neutropenia of any grade was correlated with total SN-38 Cmax (1st cycle) (Figure 7, 8, and 9).

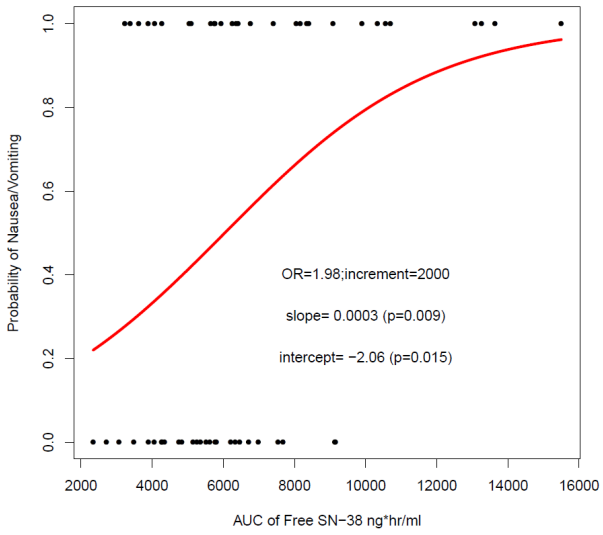


Figure 7: Relationship between SN-38 exposure and nausea/vomiting.
Source: *Population PK Report (Applicant's Analysis).*

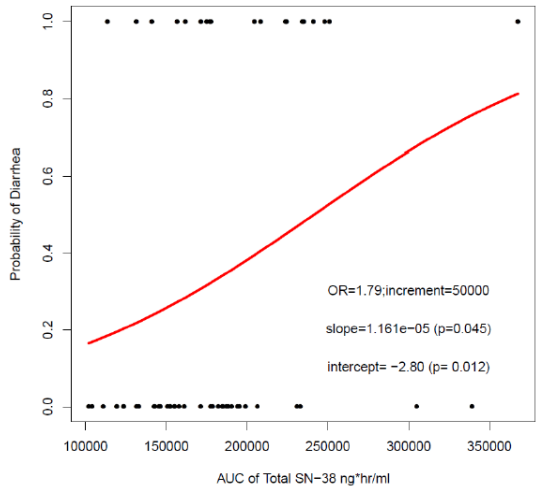


Figure 8: Relationship between SN-38 exposure and Diarrhea.
Source: Population PK Report (Applicant's Analysis).

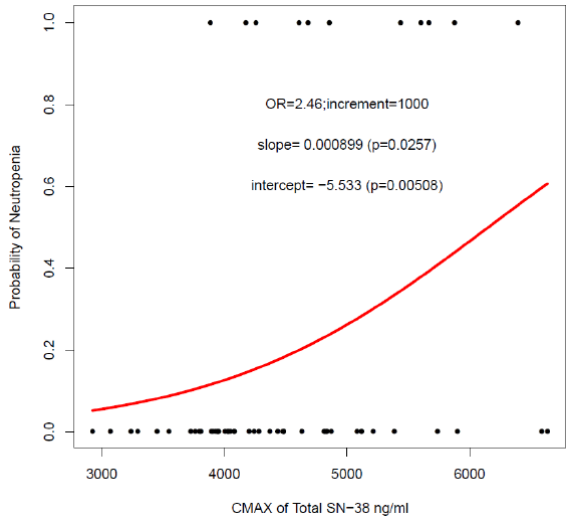


Figure 9: Relationship between SN-38 exposure and neutropenia.
Source: Population PK Report (Applicant's Analysis).

Collectively, safety and efficacy data obtained from study IMMU-132-01 support the proposed 10 mg/kg dose. Given the limitations of the exposure-response analyses, a lower dose cannot be recommended as the concern for loss of efficacy cannot be ruled out.

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

No, an alternative dosing regimen is not required for subpopulations based on intrinsic factors.

Population PK analyses conducted on PK samples collected from 57 patients with mTNBC did not identify an effect of age, race (84% of patients included in the analysis were Caucasian), or hepatic impairment on the pharmacokinetics of IMMU-132. It should be noted, however, that the population PK analysis is of limited value due to the limited number of patients included.

Effect of Bodyweight

Bodyweight was found to be a statistically significant covariate on clearance and volume of distribution of IMMU-132, which supports the bodyweight-based dosing of IMMU-132.

Hepatic Impairment

Study IMMU-132-01 included patients with total bilirubin levels less than 1.5 ULN and AST/ALT levels less than 3 ULN (i.e. only patients with mild hepatic impairment according NCI Organ Dysfunction Working Group). Of the 57 patients with mTNBC from whom PK samples were collected, 12 patients were classified as mild. SN-38 concentrations from patients with mild hepatic impairment were similar to patients with normal hepatic function (Figure 10).

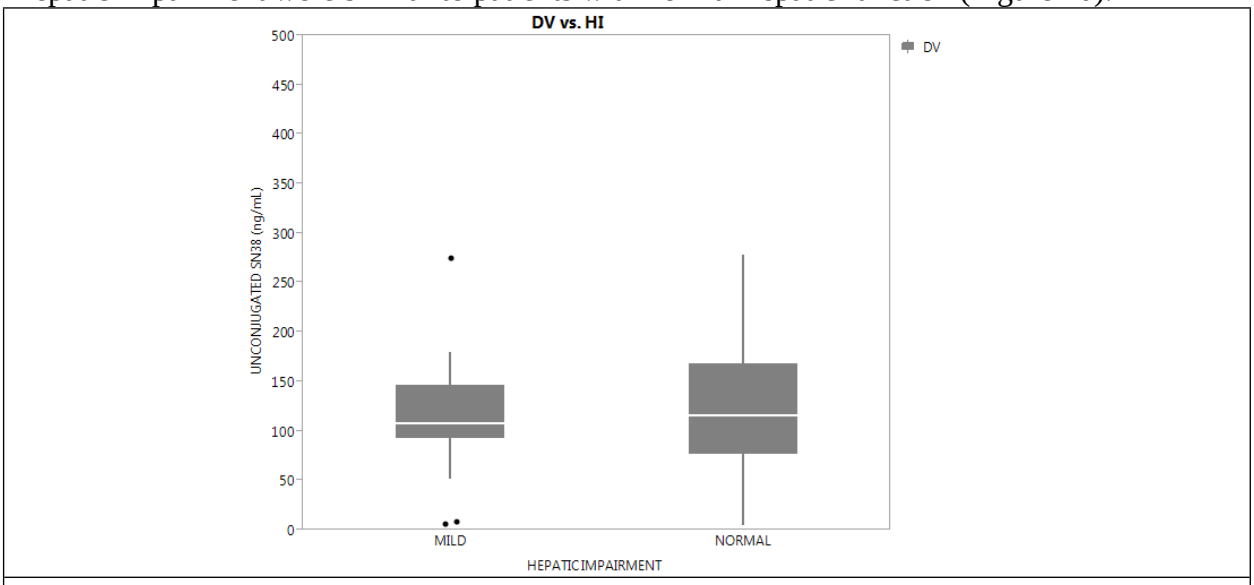


Figure 10: SN-38 exposure at end of infusion in patients with mild hepatic impairment (n=12) and patients with normal hepatic function (n=45).

There was a slightly higher incidence of Grade 3-4 AE is patients with mild hepatic impairment (84%) compared to patients with normal hepatic function (72%) in trial IMMU-132-01. As such, no dose adjustment is needed for patients with mild hepatic impairment.

The effect of moderate hepatic impairment on the pharmacokinetics of IMMU-132 components or the incidence of safety events has not been characterized. The applicant will be requested to conduct a trial in patients with moderate hepatic impairment to determine an adequate starting dose.

UGT1A1*28 genotype and hematological toxicity

SN-38, the cytotoxic moiety of sacituzumab govitecan, is glucuronidated by UGT1A1 to form the inactive SN-38G. UGT1A1 is a polymorphic enzyme with allelic variants that influence enzymatic activity. UGT1A1 alleles that reduce enzyme activity such as UGT1A1*28 are expected to decrease the metabolism of SN-38, thereby increasing SN-38 exposure. UGT1A1*28 allele frequency varies across populations, with the UGT1A1*28 homozygous genotype reported to occur in approximately 20% of the Black of African American population, 10% of the White population, and 2% of the East Asian population (Guillemette C, 2003; Beutler E, 1998; Barbarino JM, 2014. Although UGT1A1*28 is the most commonly studied decreased function allele, other decreased function alleles have been reported to have a significant effect on SN-38 metabolism in certain populations (e.g., UGT1A1*6 in East Asians) (Barbarino JM, 2014).

In Study IMMU-132-01, Amendment 4 introduced the collection of whole blood samples for UGT1A1 genotyping as well as a retrospective assessment of hematological adverse events by UGT1A1 status. Dose adjustments based on UGT1A1 status were not conducted. The applicant indicated in a response to an Information Request (IR) dated June 13, 2019 that UGT1A1 status was determined for the *28 allele. UGT1A1*28 genotype was determined using the EntroGen kit (Immunomedics) or the VAR0106 assay (b) (4) in 82% (333/408) of patients in the Overall Safety Population who received sacituzumab govitecan 8 or 10 mg/kg, including 86/108 patients with mTNBC (efficacy population) (**Table 5**). The distribution of genotypes in the study population were in Hardy-Weinberg equilibrium.

Table 5: UGT1A1*28 Status by Sacizutumab Govitecan Starting Dose

	Overall Safety Population n = 408		**mTNBC n = 108**
	8 mg/kg	**10 mg/kg**	**10 mg/kg**
Patients, n (%)	81 (100.0)	327 (100.0)	108 (100.0)
UGT1A1 status			
*1/*1	29 (35.8)	115 (35.2)	43 (39.8)
*1/*28	30 (37.0)	122 (37.3)	37 (34.3)
*28/*28	10 (12.3)	27 (8.3)	6 (5.6)
Not done	5 (6.2)	54 (16.5)	18 (16.7)
Missing	7 (8.6)	9 (2.8)	4 (3.7)
Total evaluable	69 (85.2)	264 (80.7)	86 (79.6)

Source: Modified from Applicant's tables 1 and 2, Response to IR dated September 5, 2018.
Data Cutoff Date: December 1, 2017.

Of the 333 patients with available UGT1A1*28 genotype data, 82% were White, 6% were Black or African American, and 5% were Asian. The incidence of Grade 4 neutropenia (as measured by laboratory values) was 27% in patients homozygous for the UGT1A1*28 allele (10/37), 6% in patients heterozygous for the UGT1A1*28 allele (9/152), and 5% in patients homozygous for the wild-type allele (7/144).

Reviewer Comment: *The finding that patients homozygous for UGT1A1*28 have a higher incidence of neutropenia compared to patients with the other genotypes is consistent with what is known regarding SN-38-related adverse reactions due to impaired SN-38 metabolism in patients homozygous for UGT1A1*28.*

Based on the Applicant analyses, additional toxicities (any grade) more frequent in patients homozygous for the UGT1A1*28 allele compared to the other genotypes (>10% difference between at least 2 genotype subgroups) included hypokalemia and weight decreased (See Section 8.2.5 for details).

The BLA did not include data to support dosing recommendations based upon UGT1A1 status; in the absence of such information, the dose of sacituzumab govitecan for patients who are homozygous for UGT1A1*28 is not yet established.

Reviewer Comment: *The confirmatory clinical trial IMMU-132-05 includes exploratory analyses of the relationship between UGT1A1*28 genotype and toxicity; this reviewer recommends submission of this data as a PMR.*

Trop-2 expression status

The antibody moiety of sacituzumab govitecan targets Trop-2, a cell-surface protein that is expressed at different levels in a number of normal tissues and is found to be overexpressed by many solid tumors, including TNBC (Shvartsur A, 2015). In study IMMU-132-01, Trop-2 testing was not required to determine patient eligibility. However, available archived tumor tissue was collected at baseline for exploratory evaluation of Trop-2 expression by immunohistochemistry (IHC).

Approximately 57% (62/108) of patients with mTNBC had tumor Trop-2 expression data available as shown in **Table 6**. No responses (CR or PR) were observed in a subgroup of patients whose tumor samples had no detectable or weak Trop-2 staining by IHC (defined as no staining or <10% of tumor cells stained, irrespective of intensity, or weak staining intensity (1+) in ≥ 10% of tumor cells) compared to an ORR of 40% in patients whose tumor samples had moderate or strong Trop-2 staining (defined as moderate (2+) to strong (3+) staining of ≥ 10% of tumor cells). The ORR was 28% in patients without Trop-2 expression results available.

Table 6: Tumor Response Rate by Local Assessment and by Trop-2 Status-Efficacy Population

Best Overall Response	No/Weak Staining n=5 n (%)	Moderate/ Strong Staining n=57 n (%)	Not Done n=46 n (%)
Complete Response (CR)	0 (0)	2 (3.5)	1 (2.2)
Partial Response (PR)	0 (0)	21 (36.8)	12 (26.1)
Stable Disease (SD)	2 (40)	24 (42.1)	15 (32.6)
Progressive Disease (PD)	2 (40)	10 (17.5)	15 (32.6)
Not Assessed	1 (20)	0 (0)	3 (6.5)
ORR (CR or PR)	0 (0)	23 (40.4)	13 (28.3)

Source: *Modified from Applicant's IMMU-132-01 report body, Table 14.2.1.1.5. Data Cutoff Date: June 30, 2017. Trop-2 IHC scoring: Specimens with no staining or <10% of tumor cells stained, irrespective of intensity, were*

given a 0 score. If ≥10% of the cells were positive, staining intensity was given as 1+/weak; 2+/ moderate; or 3+/ strong. CR or PR requires a confirmation scan. ORR: Objective Response Rate

Although this analysis was exploratory in nature and of limited sample size, the results of this analysis coupled with the biological plausibility of lacking the target of the sacituzumab govitecan antibody moiety (Trop-2) suggests a potential for an unfavorable risk/benefit profile in patients receiving sacituzumab govitecan who lack detectable tumor Trop-2 protein expression.

Additional exploration of the relationship between Trop-2 tumor expression and response to sacituzumab govitecan in future clinical studies remains important. The confirmatory clinical trial IMMU-132-05 includes additional exploratory analyses of the relationship between Trop-2 expression and efficacy. (b) (4)

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

Yes, the concomitant administration of sacituzumab govitecan with medications that modulate the activity of UGT1A1 enzyme should be avoided.

The applicant did not submit any in vitro or in vivo drug metabolism studies for the small molecule portion of the ADC (SN-38), nor were there any drug interaction studies in the BLA submission. However, based on data submitted in the BLA, UGT1A1 is involved in the metabolism of SN-38. As discussed earlier, patients with loss of function alleles exhibit decreased UGT1A1 function and higher incidence of neutropenia. UGT1A1 inhibition due to drug interaction could be more drastic and may result in severe safety events.

The recommendation to avoid concomitant medication that alter UGT1A1 function is adequate because the antibody portion as well as the small molecule portion are thought to contribute to the safety and efficacy of the IMMU-132. Dose adjustment of the ADC to match the exposure of only SN-38 will alter the concentration of the antibody portion, which targets tumor tissue. Administering a low dose of ADC with a UGT1A1 inhibitors to match the exposure of SN-38 may lead to loss of efficacy due to decreased targeting. Similarly, increasing the dose of the ADC with a UGT1A1 inducer to match the exposure of SN-38 may increase in the frequency of adverse events due to targeting normal tissues that express Trop-2. Moreover, avoiding concomitant medications that inhibit UGT1A1 function is warranted because IMMU-132 is administered at dose that is very close to the MTD, the concentration of unconjugated SN-38 is high, and Grade 3-4 adverse events are relatively high in frequency.

X X

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Data from one clinical study was submitted to this BLA for review. Data from IMMU-132-01, Phase 1/2 open-label multicenter basket trial with dose-escalation in the Phase 1 part of the study. This trial enrolled patients with advanced epithelial cancers including breast, ovarian, cervical, endometrial, hormone refractory prostate, non-small cell and small cell lung, squamous cell head and neck, esophageal, colorectal, gastric, pancreatic, clear cell renal, follicular papillary thyroid, glioblastoma multiforme (GBM), urothelial, and hepatocellular cancers that were metastatic (except GBM) and relapsed or refractory to at least one standard therapy for their disease. Once a dose was established in the Phase 1 portion, expansion cohorts were established, including an expansion cohort for patients with mTNBC. This study was completed at 13 sites, all in the United States.

Table 7. Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
		Controlled Studies to Support Efficacy and Safety						
IMMU132-01	01631552	Phase 1/2 (dose escalation [3+3 design], dose expansion [single-arm, multi-cohort])	Dose escalation: doses of 8, 12, 18 mg/kg IV on days 1 and 8 of a 21-day cycle Phase 2: doses 8,10 mg/kg IV on days 1 and 8 of a 21-day cycle mTNBC efficacy cohort: 10 mg/kg IV on days 1 and 8 of a 21-day cycle	ORR by investigator, per RECIST v1.1.	Until PD or lack of tolerability	420 of whom (108 comprised the mTNBC cohort submitted for this BLA)	Patients with advanced epithelial cancers that are relapsed or refractory to ≥ 1 standard therapy for their disease	13 U.S.A.

Source: Reviewer Table; NCT= PD= disease progression.

7.2. Review Strategy

The clinical and statistical review is based on the clinical study report and datasets for Study IMMU-132-01. The efficacy and safety reviews were conducted by Dr. Lynn Howie. Statistical review of the BLA was completed by Dr. Joyce Cheng.

Data Sources

The review included the following:

1. Literature review of metastatic triple negative breast cancer (mTNBC).
2. Research of the FDA database to characterize the regulatory history of the sacituzumab govitecan INDs 115621 and 122694 including review of meeting minutes during drug development.
3. Review of the submitted CSR, protocol, protocol amendments, and selected data sets for IMMU-132-01.
4. Review of case report forms for patients in the mTNBC efficacy cohort.
5. Review of patient narratives for serious adverse events and deaths in IMMU-132-01.
6. Review of responses to clinical and biostatistical queries sent to the Applicant.
7. Review of the 90-day Safety and Efficacy Update submitted on August 20, 2018.
8. EDR link for the electronic data sources is: \\CDSESUB1\evsprod\BLA761115\761115.enx
9. SDTM and ADaM datasets were submitted along with software code for data analyses.

Data and Analysis Quality

The data submitted with this application were in ADaM and SDTM formats. The data were of adequate quality with adequate coding of preferred terms and consistency with CRFs. The Applicant's analyses were generally reproducible. Requests for additional information from the Applicant during the review process were addressed in a timely fashion. The Applicant submitted information regarding their data quality assurance plan including their site inspections and provided site audit summaries.

Data were submitted to the Office of Computational Science and Data Fitness assessment found data traceability issues between the SDTM and ADaM datasets that were initially submitted with the BLA submission. Issues were addressed through information requests to the Applicant.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. IMMU-132-01

Trial Design

Study IMMU-132-01 is an open-label, dose escalation and dose expansion study of sacituzumab govitecan in patients with advanced solid tumors. All study sites were within the US.

The dose escalation (Phase 1) portion of the study evaluated patients with epithelial cancer including breast, ovarian, cervical, endometrial, prostate, lung, squamous cell carcinoma of the head and neck, esophageal, colorectal, gastric, pancreas, clear cell renal, papillary thyroid, glioblastoma multiforme (GBM), urothelial, and hepatocellular carcinoma. A 3+ 3 design was employed to evaluate escalating doses of sacituzumab govitecan. Dose limiting toxicities (DLTs) were evaluated during the 1st cycle of treatment.

The dose expansion (Phase 2) portion of the study evaluated four cohorts, including one with patients with metastatic triple negative breast cancer (mTNBC). This cohort was defined by the presence of negative estrogen and progesterone receptors (ER and PR) and negative for human epidermal growth factor receptor 2 (HER2), per ASCO/CAP guidelines (2010) based on testing of patients' most recent tissue biopsy. Patients were to have received at least two prior anticancer therapies for metastatic disease including a prior taxane in any setting. Additionally, prior hormonal or HER2 targeted agents did not count as prior therapies, but all chemotherapy, biological or targeted agents were counted.

Study oversight was provided by Immunomedics, Inc. After receiving feedback from the Agency, a central review audit of responders was performed by a third-party organization.

Key Eligibility Criteria

Inclusion

- Male or female patients, ≥18 years of age, able to understand and give written informed consent
- Histologically or cytologically confirmed epithelial cancer of one of the following types: gastric adenocarcinoma, esophageal cancer, hepatocellular carcinoma, NSCLC, SCLC, epithelial ovarian cancer, cervical cancer, endometrial cancer, TNBC, non-TNBC, follicular papillary thyroid cancer, GBM, hormone refractory prostate cancer, squamous cell carcinoma of the head and neck, renal cell carcinoma (clear cell), urothelial carcinoma
- Stage IV disease (except for patients with GBM)

- Refractory to or relapsed after at least one prior standard therapeutic regimen
- ECOG performance status ≤1
- Expected survival ≥6 months
- Measurable disease by CT or MRI
- At least 2 weeks since last treatment with chemotherapy, targeted therapy, endocrine therapy, immunotherapy, and/or radiation therapy or major surgery and recovered from all acute toxicities to Grade ≤1
- At least 2 weeks since prior treatment with high dose corticosteroids. Low dose corticosteroids (prednisone equivalent <20 mg) were permitted.
- Adequate hematology parameters that did not require ongoing transfusional support (hemoglobin >9 g/dL, ANC >1500/mm^3, platelets >100,000/mm^3)
- Adequate renal (creatinine ≤2.0 x ULN) and hepatic (bilirubin ≤1.5 x ULN, ALT and AST ≤3 x ULN or 5 x ULN if known hepatic metastases) function
- All toxicity at study entry ≤Grade 1 by CTCAE v4.0

Exclusion

- Pregnant or lactating women
- Women of childbearing potential and fertile men unwilling to use effective contraception during the study and until the conclusion of the 12-week post-treatment evaluation period
- Known Gilbert's disease
- Patients with brain metastases could be enrolled only if treated, non-progressive brain metastases over the past 4 weeks and off of high dose (>20 mg of prednisone or equivalent for at least 4 weeks
- Presence of bulky disease (defined as any single mass >7 cm in greatest dimension). Patients with a mass >7 cm but otherwise eligible could be considered for enrollment after discussion with the medical monitor.
- Patients with active grade ≥2 anorexia, nausea or vomiting, and/or signs of intestinal obstruction
- Patients with non-melanoma skin cancer or carcinoma *in situ* of the cervix were eligible, however patients with other prior malignancies must have had an at least 3-year disease-free interval
- Known to be HIV, HBV, or HCV positive
- Known history of unstable angina, myocardial infarction, or congestive heart failure present within 6 months or a clinically significant cardiac arrhythmia requiring anti-arrhythmia therapy.
- Known history of clinically significant active chronic obstructive pulmonary disease, or other moderate-to-severe chronic respiratory illness present within 6 months of study entry
- History of clinically significant GI bleeding, intestinal obstruction, or GI perforation within 6 months of initiation of study treatment
- Infection requiring IV antibiotic use within 1 week
- Patients with a history of an anaphylactic reaction to irinotecan or grade ≥3 GI toxicity to prior irinotecan
- Other concurrent medical or psychiatric conditions that, in the investigator's opinion,

were likely to confound study interpretation or prevent completion of study procedures and follow-up examinations

Reviewer Comments: *The eligibility criteria requirement that patients have an expected life expectancy of >6 months may have led to investigator selection of patients that may be less representative of all patients with mTNBC who have had two prior lines of therapy. It is notable that those with known Gilbert's disease were excluded as this is associated with UGT1A1 deficiency. For most of the study, patients with known brain metastases, a frequent occurrence in patients with mTNBC, were excluded. Patients with stable brain metastases were allowed to enroll as of Protocol Amendment 9 which was adopted on July 9, 2015. Patients with moderate hepatic dysfunction were excluded as well.*

Diagnostic Criteria

With Amendment 10, it was specified that patients were required to have TNBC histology based on most recent local assessment, consistent with ASCO/CAP guidelines (i.e. ER and PR <1% and HER-2 negative).

Assessment of Trop-2 expression was not required, however the sponsor requested archived tissue specimen where available for determination of Trop-2 expression.

Reviewer Comments: *Amendment 10, in November 2016, clarified that all patients were to have mTNBC as defined as ER and PR expression <1% and HER-2 negative disease based on their most recent biopsy. It is notable that patients who lose HR expression are known to be less responsive to endocrine therapy, however, it is less clear the role that HR expression loss plays in the natural history of disease (Kuukasjarvi 1996).*

Study Treatment

Sacituzumab govitecan was administered as an intravenous infusion on days 1 and 8 of a 21-day treatment cycle.

Phase 1 evaluated sacituzumab at a starting dose of 8 mg/kg and at the following additional dose levels: 12 mg/kg and 18 mg/kg. The maximum tolerable dose (MTD) was 12 mg/kg. Due to dose reductions and delays during the treatment beyond the DLT assessment period, additional doses below the MTD (8mg/kg and 10 mg/kg) were further evaluated in the dose expansion portion of the study.

The Phase 2 portion of the study enrolled patients in four single-arm cohorts (mTNBC, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and urothelial cancer (UC)). Sacituzumab govitecan was administered at doses of 8 mg/kg and 10 mg/kg. Sacituzumab govitecan was administered as an intravenous infusion (IV) on days 1 and 8 of continuous 21-day cycles. The protocol was subsequently amended (Amendment 8; April 23, 2015) to state that all patients should be treated at dose of 10 mg/kg.

In the mTNBC efficacy cohort, all patients received a dose of 10 mg/kg. Treatment was

administered until evidence of disease progression or unacceptable AEs.

Study Procedures and Schedule

Figure 11. below is the study calendar.

Figure 11. Study Calendar for IMMU-132-01

PRETREATMENT		TREATMENT (3-Week Treatment Cycles)						POST TREATMENT	
	Within 4 Wks of Entry	Cycle 1			Cycles 2 - 8			Final[1] Study Eval.	Long-Term Follow-up Every 3 months
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		
Signed Informed Consent	X								
Patient Eligibility	X								
Histology review	X								
Pregnancy Test	X[3]				X[3]			X	
Hepatitis B & C Test	X								
Medical/Surgical History	X								
UGT1A1 genotype	X								
CT (chest, abdomen, pelvis; other if needed)	X	X[4]							
EKG	X				X[10]			X	X[2]
Phys. Exam	X				X			X	X[2]
CBC (with diff, platelets)[5]	X	X	X		X	X		X	X[2]
Serum Chemistries[5]	X	X	X		X	X		X	X[2]
PT/PTT	X				X[11]			X[11]	X[2]
Urinalysis	X				X			X	
Concomitant Medications	X	X	X		X	X		X	X[6]
Serum Biomarkers	X	X[4]							
IMMU-132 infusion		X	X		X	X			
Vital Signs	X	X[7]	X[7]		X[7]	X[7]		X	X[2]
Adverse Event Reporting	X	X	X		X	X		X	X[8]
HAHA	X				X[11]			X[11]	
PK[9]		X							
Biopsy / surgical Tissue	X[12]								
Survival status									X

[1] Performed 14 days after the last treatment or in event of premature study termination.
[2] Otherwise, long-term follow-up required every 3 months for up to 2 years in patients who have not progressed, or only until resolution of any treatment-related abnormalities once patients progress.
[3] Pregnancy test will be performed within 1 week prior to treatment, at every other cycle (2, 4, 6 & 8) and at the end of the study.
[4] CT and biomarkers required 8 weeks after the start of treatment until the first (Physician discretion) or second progression of disease. Additional CT can be performed at the discretion of the physician to assess disease status as medically indicated. Suggested serum biomarkers include CEA levels for colon, rectal, and lung cancers; CEA , CA19-9, AFP and hepatitis panel for hepatobiliary cancer; CA-125, βhCG and LDH for ovarian cancer; CA19-9 for pancreatic cancer; CA15-3 for breast cancer; PSA for prostate cancer.
[5] Serum chemistries include glucose, creatinine, BUN, total bilirubin, AST, ALT, LDH, alkaline phosphatase, serum albumin, total protein, Na, K, calcium, Cl, CO2, magnesium and phosphorus. More frequent laboratories required in event of ≥ Grade-3 toxicity
[6] Only IV or prescription anti-infectives or medications for GI toxicity will be recorded.
[7] VS's obtained prior to infusion, every 15 min for the first hour, then every 30 min until completed, and then 30 and 60 minutes post-infusion.
[8] Ongoing AEs until resolved, new events attributed to test article; otherwise, deaths, hospitalizations, or events requiring IV or prescription anti-infectives or medications related to GI toxicity.
[9] After amendment 6, PK samples will be optional and collected only in selected patients after the first dose, with 6 samples obtained: preinfusion, 30 min and 3-4 hours post infusion, then 1, 2, and 3 days later.
[10] Required after completion of day 1 infusion of every other cycle (2, 4, 6 & 8).
[11] HAHA & PT/PTT at baseline then day 1 of every other cycle (2, 4, 6 & 8) and at the end of the study. Two additional monthly samples for HAHA will be collected if positive result after end of treatment.
[12] For IHC evaluation of tumor Trop-2 expression (by the Sponsor) when tissue is available, but this testing is not required for eligibility
NOTE: Unless otherwise specified, collection windows for study time points are nominally within ± 10% or according to institutional standard procedures.

Source: *IMMU-132-01 Study Protocol, page 14*

Dose Modification/Discontinuation

Dose modifications were not permitted during cycle 1 (the 1st 21 days of sacituzumab) of the Phase 1 portion of the study. Beyond Cycle 1 in the dose escalation portion of the study, the protocol stated that in the event of severe treatment-related AEs, the IMMU-132 dose was to be reduced by 25% of the assigned dose at the first occurrence and to 50% of the initial assigned dose for the second occurrence. At the third occurrence, treatment was to be discontinued.

The dose was to be reduced the event of any of the following AEs:

- Grade 4 hematological AE ≥7 days or other non-hematological AE grade 4 of any duration;
- Grade 3 febrile neutropenia
- Treatment related nausea, vomiting, or diarrhea grade ≥3 or other non-hematological AE grade ≥3 persisting for >48 hours despite optimal medical management.
- Any AE of grade ≥3 at the time of scheduled treatment whose recovery to grade ≤1 delayed dosing by 2 or more weeks

Management of infusion related reactions was permitted with acetaminophen, diphenhydramine, corticosteroids, H2 antagonists, or other drugs as premedication for prevention of reactions.

In the event of a grade ≥3 infusion reaction, study treatment was to be permanently discontinued.

In the event of grade 2 infusion reactions, the infusion was paused for at least 15 minutes or until symptoms resolved, whichever was greater. The patient could have a lower infusion rate resumed once the patient was stable.

In the event of a grade 1 infusion reaction, it was recommended to slow the infusion rate.

Permitted Concomitant Medications and Therapies

Therapies permitted for the prophylaxis and management of infusion related reactions are described in subsection: Dose Modification/Discontinuation. Additionally, the protocol stipulated that patients with a cholinergic response such as diarrhea, abdominal cramping, or salivation, could receive anticholinergics such as atropine for subsequent administrations of sacituzumab.

Palliative or supportive medications and procedures were permitted at the investigator's discretion.

All anticancer therapy, including radiation therapy, was to be discontinued at least 2 weeks prior to starting study therapy.

Hematopoietic growth factors and blood transfusions were permitted at the investigator's

discretion after Cycle 1 Day 1.

It was recommended that patients avoid strong CYP3A4 inducers and inhibitors be avoided.

Treatment Compliance

Sacituzumab govitecan is an IV infusion administered by study personnel and treatment compliance was recorded by the study site and in individual patients' case report forms.

Completion, Discontinuation, or Withdrawal

Patients could withdraw from the study at any time for any reason.

During the Phase 1 portion of the study, patients were to be discontinued from study therapy if they experienced dose-limiting toxicities. Dose limiting toxicities were defined as the following:

- Grade 4 neutropenia ≥5 days or Grade 3 or greater febrile neutropenia of any duration
- Grade 4 thrombocytopenia ≥5 days or Grade 3 or greater thrombocytopenia with significant bleeding
- Grade 4 anemia of any duration
- Grade 4 nausea, vomiting, or diarrhea of any duration or any Grade 3 nausea, vomiting or diarrhea which persists for >48 hours despite optimal medical management
- Any Grade 3 infusion-related reactions (e.g. prolonged reactions not responding to symptomatic treatment) which occurs after pre-medication with antihistamines, H2 blockers, and steroids
- Any other ≥Grade 3 non-hematological toxicity at least possibly due to study drug

The protocol specified that treatment was to be discontinued for the following reasons:

- Documentation of progressive disease at the investigator's discretion or sponsor approval or symptomatic deterioration indicating treatment failure
- Treatment delay of >3 weeks for any reason
- Unacceptable toxicity
- Grade ≥3 infusion-related reaction
- If the patient experienced a third instance of drug-related AEs where the first two events required dose reductions as described above

The initial determination of disease progression did not require treatment discontinuation if, in the opinion of the investigator, the patient was continuing to derive clinical benefit. However, treatment had to be discontinued at subsequent documented disease progression.

Amendment 8 (April 23, 2015) allowed for treatment beyond 8 cycles for patients with PR or SD, patients with objective response that relapsed after treatment discontinuation, and for patients with a first occurrence of PD who wished to continue study therapy after radiological documentation of PD.

Study Endpoints

The overall study endpoints were as follows:

Phase 1: The primary objective is to evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles for up to 8 cycles in previously treated patients with advanced epithelial cancer. The secondary objectives were to obtain initial data concerning pharmacokinetics, immunogenicity, and efficacy with this dosing regimen.

Phase 2: Objective response rate using RECIST version 1.1 per local investigator assessment.

Imaging was obtained every 8 weeks with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response (PR or CR) until permanent treatment discontinuation. Independent central review (ICR) was also obtained for patients whose local scans demonstrated at least 20% decrease.

After treatment discontinuation, patients were followed until resolution or stabilization of any treatment related AEs. Patients treated after Amendment 10 who had not progressed at the end of treatment were followed with CT every three months for up to 2 years or until progression or initiation of other treatment.

The secondary endpoints were defined in the SAP as follows:

- Time to response (TTR), defined as the time from the first dose to the first documentation of response (PR or CR).
- Duration of response (DOR), among responders this was calculated as the date of the first evaluation showing documented PR or CR to the date of the first PD. Patients not progressing were censored.
- Clinical benefit rate (CBR), defined as patients in the Target mTNBC Population with best response as CR or PR or else SD with a duration of at least 6 months. SD for 6 months duration was defined as time from the first dose to the first documentation of PD or to the last adequate response assessment prior to data cutoff date, whichever is earlier
- Progression-free survival (PFS), defined as the interval from the first dose start date to the date of disease progression defined as documented PD or death from any cause, whichever occurs first. Death was considered an end point only while the patient was on study and receiving treatment or undergoing response assessments. Patients otherwise without adequate response assessments or without radiologic evidence of progression were censored. Clinical PD was not considered as a PFS event.
- Overall survival (OS), defined as time from the date of the first dose start date to the date of death due to any cause. Patients without documentation of death at the time of the data cutoff for analysis will be censored at the date the patient was last known to be alive or the data cutoff date, whichever is earlier.

Statistical Analysis Plan

There was no formal sample size determination for Study IMMU-132-01. The Phase II study planned to enroll up to 150 patients in each of 5 expansion cohorts (TNBC, non-TNBC, NSCLC,

SCLC, UC).

Reviewer comment: *The CSR submitted for this BLA was based on the mTNBC Target Population consisting of n=108 patients and a database cutoff of 30 June 2017. There was no formal statistical justification for the sample size.*

All efficacy analyses were to be conducted in the Target mTNBC population, which included patients with mTNBC who had received at least 2 prior anticancer therapies for metastatic disease and who were treated with an IMMU-132 dose of 10 mg/kg. For the primary analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by investigator, the ORR was summarized by the percentage of responses (CR or PR) with a two-sided exact binomial 95% CI.

The secondary endpoints of DOR, PFS, and OS were analyzed with Kaplan-Meier methods with 95% confidence intervals calculated from the Brookmeyer and Crowley method with log-log transformation. The censoring rules for PFS and DOR are shown in Table 8 and Table 9. Note that DOR is only assessed in responders. Additionally, TTR was summarized descriptively and CBR was presented as a response rate with a two-sided exact binomial 95% CI.

Table 8: Guidelines for Response Assessment and Censoring for Analysis of PFS

Guidelines for Progression Assessment and Censoring for Analysis of PFS			
Condition	Case	Outcome	Date of Progression or Censoring
After baseline, no adequate objective response assessments	Died prior to 2nd scheduled assessment	PD	Date of death
	Did not die prior to 2nd scheduled assessment	Censor	Date of first IMMU-132 dose
Objective PD or death occurred	At or between scheduled assessments or prior to missing 2 scheduled successive assessments	PD	Date of objective PD or death, whichever came earlier
	After missing 2 or more scheduled successive assessments	Censor	Date of last adequate response assessments.
No objective PD or death occurred	Initiated other treatment	Censor	Date of last adequate response assessment before starting other treatment
	Lost to follow up	Censor	Date of last adequate response assessment
	Data cutoff	Censor	Date of last adequate response assessment
For progression based on the sum of target lesion measurements at different times (i.e., chest CT on one day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on new or nontarget lesions, if these are equivocal at one assessment and later considered unequivocal progression, the earliest date when progression was suspected should be used. If death or progression has occurred, the earlier will be the PD endpoint, unless it occurred after 2 or more scheduled successive response assessments were missed or inadequate, in which case the outcome will be censored at the last prior adequate assessment. Adequate response assessment is defined as a response assessment other than "not assessed" or "not evaluable" for the determination of PFS. If death or objective evidence of progression has not occurred and the patient is either lost to follow-up, a new treatment is initiated, or data cutoff occurs, then the outcome will be censored at the last prior adequate assessment unless no adequate response assessment occurred, in which case the outcome will be censored at the date of the first dose of IMMU-132.			

Table 9: Guidelines for Response Assessment and Censoring for Analysis of DOR

Guidelines for Progression Assessment and Censoring for Analysis of Duration of Response			
Condition	Case	Outcome	Date of Progression or Censoring
Objective PD occurred	At or between scheduled assessments or prior to missing 2 scheduled successive assessments	PD	Date of objective PD
	After missing 2 or more scheduled successive assessments	Censor	Date of last adequate response assessment.
No objective PD occurred	Initiated other treatment	Censor	Date of last adequate response assessment prior to starting other treatment
	Lost to follow up	Censor	Date of last adequate response assessment
	Data cutoff	Censor	Date of last adequate response assessment
If the onset of response requires evaluations at different times (i.e., chest CT on one day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on the sum of target lesion measurements at different times (i.e., chest CT on one day, abdomen and pelvic MRI several days later) the last measurement date should be used. For progression based on new or nontarget lesions, if these are equivocal at one assessment and later considered unequivocal progression, the earliest date when progression was suspected should be used. If progression occurred after 2 or more scheduled successive response assessments were missed or inadequate, the outcome will be censored at the last prior adequate assessment. Adequate response assessment is defined as a response assessment other than "not assessed" or "not evaluable" for the determination of duration of response. If objective evidence of progression has not occurred and the patient is either lost to follow-up, died, a new treatment is initiated, or data cutoff occurs, then the outcome will be censored at the last prior adequate assessment.			

Reviewer Comments: *On 3 July 2018, the FDA sent an IR to the applicant asking them to recalculate duration of response with death included. The standard regulatory definition of DOR is defined from the onset of response until PD or death, whichever occurs first. Death after 2+ missing scheduled assessments should be censored at the last assessment prior to the missing ones. The DOR results presented in this review follow the standard regulatory definition.*

Additionally, swimmer plots of treatment duration and waterfall plots for percent change from baseline in target lesion measurement were presented. The planned sensitivity analyses included analyses in the 94 patients who received at least 2 lines of prior standard chemotherapy for metastatic disease and the 102 patients in the Per-Protocol (PP) Population, defined as patients of the Target mTNBC Population who received at least one complete cycle of IMMU-132 and had data available from at least one response assessment. The planned subgroup analyses included age, race, ethnicity, ECOG performance status, and Trop-2 status, as well as number of prior therapy for metastatic disease and number of prior chemotherapy for metastatic disease, given sufficient patient numbers allow for reliable presentation.

Reviewer Comments: *The FDA does not use inferential procedures to evaluate results from single-arm trials. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response. Additionally, we note that time-to-event endpoints are uninterpretable without a comparator arm.*

Protocol and SAP Amendments

A total of 11 protocol amendments prior to the data cutoff date of December 31, 2016. The major changes implemented in each of the amendments are summarized in Table 10 below.

Table 10. Summary of Amendments to IMMU-132-01

Amendment/ Date	Patients Enrolled	Modifications
1 Jul 26, 2012	0	• Changed the weekly dosing schedule to 2 weekly administrations within a 21-day cycle. • Revised DLT definition to specify that patients receiving therapy for prevention of infusion reactions would not be eligible for evaluation of the MTD. • Removed patients with breast or prostate cancer from list of eligible cancer types. Note: modifications were adopted prior to patient enrollment and prior to the mTNBC cohort of interest.
2 Aug 22, 2012	0	• TNBC and hormone refractory prostate cancer to the list of eligible cancer types. • Clarified the frequency of human anti-human antibody (HAHA) sample collection in patients with a positive HAHA results at the end of treatment.
3 Feb 6, 2013	1	• Allowed for patients with urothelial carcinoma, clear cell renal cell carcinoma, esophageal cancer, and squamous cell carcinoma of the head and neck to be enrolled. • Explained that patients with SCLC and NSCLC would be able to be enrolled as well. • Suggested that serum biomarkers such as PSA or CA-125 for each eligible cancer type were to be assessed.
4 Aug 5, 2013	24	• Modified the study design to add a Phase 2 portion with up to 15 patients per cancer type being recruited for up to 2 dose levels at or below the maximum acceptable dose. This was to provide additional safety and efficacy data for each of the indications. • Specified that tumor types where ≥15% of patients demonstrated shrinkage of their target lesions, would merit further investigation. • Specified that patients were allowed to continue treatment beyond 8 treatment cycles at the physician's discretion. • Patients were allowed to continue treatment at the first documentation of PD, however treatment was to be permanently discontinued at the 2nd documentation of PD. • Added collection of samples for UGT1A1 genotyping and the

		assessment of hematological AEs by UGT1A1 status. • Recommendations for management of infusion related reactions were expanded. • Clarified that in the case of grade ≥3 AEs, treatment was to be temporarily discontinued and patients were to be assessed weekly. If recovery to grade ≤1 delayed the dose by ≤ 1week, no dose reduction was necessary. However, if it delayed the dose by 2-3 weeks, treatment must be resumed at a reduced dose (25% reduction from the original dose at the first event, 50% dose reduction at the second occurrence, and permanent discontinuation at the third occurrence). If recovery required > 3 weeks' delay, treatment had to be permanently discontinued. • Eligibility criteria modified to include patients with an ANC ≥1.5 x 10^9/L and patients with a serum bilirubin ≤1.5 x ULN. • Included preliminary results of the Phase 1 study to justify the dose for the Phase 2 portion of the study. Protocol states that a dose of 12 mg/kg had been determined as the MTD and was associated with dose reductions and delays. The next-lower dose of 8 mg/kg had been shown to be safe in Phase 1. An intermediate dose of 10 mg/kg was continuing to be evaluated and was intended to be the second dose level in Phase 2 if found to be safe. It was stated that a lower dose level of 6 mg/kg could be used in certain conditions where patients did not meet the criteria of the maximum acceptable dose at the 8 mg/kg dose level. • Specified that scans were to be obtained 8 weeks after the start of treatment and that scans were to be repeated every 8 weeks as well as when medically indicated. • RECIST 1.1 was specified as the assessment of tumor response. • Efficacy endpoints of PFS, OS and time to treatment failure were removed. • Specified that the efficacy population would be those patients defined as completing 3 full treatment cycles. • Additional PK samples were specified at this time as well.
5 Aug 23, 2013	31	• Specified that the KRAS mutational status had to be determined in patients with colorectal, lung and pancreatic cancer (results not required to determine eligibility).
6 May 30, 2014	120	• Modified the criterion for patients with bulky lesions to increase the maximum size of this lesion from 5 cm to 7 cm. • Extended the required interval between prior therapy from 2 to 4 weeks and patients had to have recovered from AEs from prior therapy to grade ≤1 (excluding alopecia). • Modified the waiting period after high dose systemic steroids to 2 weeks. • Revised eligibility to permit patients with known CNS metastases to enroll if they had received adequate treatment and had no evidence of progression or symptoms for at least 3 months. • Specified that successive groups of 6 patients with a specific tumor type at a particular dose level with the intent to discontinue enrollment if the incidence of severe AEs during the first cycle

		was ≥33% or if <20% of patients treated at that dose level had at least SD as best response. • The collection of PK samples became optional. • Specified that the dose for IMMU-132 be calculated at the beginning of each cycle or more frequently for patients with a >10% change in body weight. • Revised so that if a patient had neutropenia or a GI AE that was grade ≥2 at the planned start of treatment, treatment should be held until resolution of the AE to grade ≤ 1. If this required a delay of >3 weeks, the patient was to be withdrawn from the study. • Follow-up of patients every 3 months was added and survival time was added as an efficacy endpoint.
7 Dec 9, 2014	177	• Allowed for patients with cervical cancer or endometrial cancer to enroll and removed restriction to TNBC. • Number of planned patients in each cohort for Phase 2 increased to 50. • Implemented collection of data regarding the treatment response and time to progression for the last treatment prior to study regimen. • Genotype variants for breast and ovarian cancers (BRCA 1/2); colorectal and pancreatic cancers (KRAS), and lung cancer (ALK, EGFR, and PI3KC) added; however, results were not required to determine patient eligibility. • Tumor biomarkers were specified. • Confirmatory CT/MRI scans were to be obtained in any patient with PR or SD with ≥20% shrinkage of target lesions within 4-6 weeks of this assessment. • Revised study to allow for use of growth factors as secondary prophylaxis; use prior to study therapy was not allowed. • Patients who had a first assessment of PD but were determined to derive clinical benefit could continue at the investigator's discretion; treatment was to be discontinued if subsequent imaging documented PD from that assessment. • PK sample was added at day 7. • Clarification of the laboratory, vital signs, and physical examination assessments. • Deviations in treatment schedule of up to seven days due to holidays, vacations, or personal reasons were allowed.
8 Apr 23, 2015	259	• Revised so that all patients would be treated with IMMU-132 at a dose of 10 mg/kg. • Breast cancer cohort was returned to only TNBC and the bladder cancer cohort was clarified to include urothelial carcinoma. • Planned number of patients for TNBC and NSCLC was increased to 130 patients and 100 patients respectively based on ORR of 26% and 33% respectively. • Clarified that if a confirmatory scan was performed then all subsequent scans had to be scheduled at 8-week intervals from the confirmatory scan.

		• Frequency of patient follow-up visits for vital status was changed from every 3 months to every month.
9 Jul 9, 2015	279	• Investigators advised to consult the sponsor prior to consenting and performing screening procedures in potentially eligible patients to allow sponsor planning, particularly with regard to the drug supply. • There was also a temporary suspension of recruitment of TNBC patients to allow the sponsor to evaluate efficacy in the TNBC patients included in the study to date. • Cohorts of patients with GBM, follicular thyroid cancer, and metastatic non-TNBC were added to the list of eligible tumor types. • The colorectal cancer and pancreatic cancer cohorts were removed from the list of eligible tumor types as the respective accrual targets had been reached. • Clarified that patients who had relapsed after or were refractory to at least one standard chemotherapy or hormonal regimen were allowed to participate. • Required wash-out period was shortened from 4 to 2 weeks. • Patients with treated, stable brain metastases who had not received high-dose steroids allowed for inclusion. • Clarified that IMMU-132 dosing was not allowed to be re-escalated after prior dose reductions. • PFS added as an efficacy endpoint.
10 Nov 7, 2016	405	• Modified accrual target for TNBC, NSCLC, SCLC, and UC to 150 assessable patients. • Clarified that patients with mTNBC were clarified to be those patients who had TNBC histology based on the most recently analyzed biopsy. Furthermore, patients had to have received at least 2 prior therapies for metastatic disease including a taxane in any setting. Chemotherapy, biological or targeted agents were allowed as qualifying prior therapies, but endocrine or HER2 agents were not. • Clarified that patients could continue treatment with IMMU-132 for any number of cycles in the absence of unacceptable AEs or PD requiring termination of further treatment. • Clarified that an initial response of CR or PR was to be confirmed 4-6 weeks after the initial response assessment. For patients with SD who have evidence of tumor shrinkage that was close to PR, the 8-week interval for the next assessment could be shortened at the investigator's discretion. Patients who had not progressed at the end of treatment were to be followed with CT scans every 3 months for up to 2-year or until PD or initiation of another anticancer therapy. • Revised PK sample collection • Reduced the frequency of vital sign assessment in subsequent infusions of IMMU-132.
11 Apr 4, 2017	420	• Updated the vial size and reconstitution guidelines for IMMU-132 after a change in manufacturing.

The original statistical analysis plan (SAP) v1.0 was dated October 24, 2017 and was amended on March 14, 2018 (v2.0) after clinical database lock. Version 2.0 of the SAP served as the final SAP. The major changes in v2.0 included updating the sample size for the efficacy population (mTNBC Population) to 108 based on the enrollment, and, updating/revising various definitions/derivations for secondary/other endpoints, populations, and protocol violation categories.

8.1.2. Study Results

Compliance with Good Clinical Practices

According to the applicant, IMMU-132-01 was conducted in full conformance with the ethical principles of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) as required by the major regulatory authorities and in conformance with the principles set forth in the Declaration of Helsinki, Directive 2001/20/EC, as well as with applicable laws and regulations. Written informed consent was obtained from each study participant or their legal representative. The study protocols and amendments were approved by local Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

Financial Disclosure

According to the BLA submission, all investigators in Study IMMU-132-01 were assessed for equity interest, other significant payments, and other compensation by the Applicant as well as proprietary interest in this agent. Certification was provided by all 13 investigators listed for Study IMMU-132-01. No financial arrangements with investigators by the Applicant were reported, and none of the investigators disclosed a proprietary interest in the product or significant equity in the sponsor.

Patient Disposition

IMMU-132-01

A total of 420 patients enrolled in Study IMMU-132-01 (Phase 1, n=25; Phase 2, n=395), of whom a total of 148 had mTNBC. Among the 148 patients who had mTNBC, 131 patients received IMMU-132 10 mg/kg, and 108 of those patients had received 2 or more lines of therapy in the metastatic setting, prior to receiving IMMU-132 (efficacy population). Patient disposition for the cohorts of patients who comprise the efficacy population for this application is summarized included in Table 11 below.

Table 11. Patient Disposition for the mTNBC Cohort of IMMU-132-01

Disposition	mTNBC Target Population N=108
Discontinued therapy	91 (84.3)
Adverse event	3 (2.8)
Withdrawal of Consent	2 (1.9)

Investigator decision	6 (5.6)
Death	1 (0.9)
Other	1 (0.9)
Progressive disease	77 (71.3)
Missing	1 (0.9)
On therapy at cut-off date	17 (15.7)
Discontinued for reason other than PD	14 (13.0)

Source: *Reviewer Table; adsl.xpt. Data cut-off June 30, 2017*

Reviewer Comments: *While only 3 patients are recorded as having discontinued due to an adverse event, 13% discontinue for a reason other than progressive disease suggestive that those recorded as discontinuing due to an adverse event may be underestimating this number. Patients with mTNBC who have received two or more prior therapies are often quite ill and may have increased adverse events. At the time of the 90-Day Safety Update (cut-off December 1, 2017) 100 patients had discontinued treatment with most patients (n=86, 79.6%) discontinuing due to disease progression. Eight patients were continuing on therapy at that time.*

Protocol Violations/Deviations

In the study population of IMMU-132-01 where patients regardless of cancer type had received at least one dose of IMMU-132, a total of 11 (10.2%) patients had one or more major protocol violations.

Table **12** below demonstrates the incidence of major protocol violations by type.

Table 12. Protocol Deviations for Patients Who Received ≥1 dose of IMMU-132

Deviation Category	**Total Population n=420 n (%)**
Patients with ≥1 major protocol violation	11 (2.6)
Inclusion/exclusion criteria violated	5 (1.2)
• <2 weeks between prior therapy and start of IMMU-132 treatment	5 (1.2)
Prohibited therapy	7 (1.7)
• Anticancer therapy during IMMU-132 treatment	5 (1.2)
• Prophylactic use of growth factors or transfusions prior to Cycle 1	2 (0.5)
• Radiation during treatment with IMMU-132	1 (0.2)

Source: *Reviewer analysis using addv.xpt dataset & Table 13 on page 71 of the CSR*

In the mTNBC cohort from the IMMU-132-01 study, a total of 3 (2.8%) patients had one or more major protocol violations. Table 13 below demonstrates the incidence of major protocol violations by type.

Table 13. Protocol Deviations for the mTNBC Efficacy Population in IMMU-132-01

Deviation Category	**Efficacy Population**

	n=108 n (%)
Patients with ≥1 major protocol violation	3 (2.8)
Inclusion/exclusion criteria violated	1 (0.9)
• <2 weeks between prior therapy and start of IMMU-132 treatment	1 (0.9)
Prohibited therapy	3 (2.8)
• Anticancer therapy during IMMU-132 treatment	2 (1.9)
• Prophylactic use of growth factors or transfusions prior to Cycle 1	2 (1.9)

Source: *Reviewer analysis using addv.xpt dataset & Table 13 on page 71 of the CSR*

Reviewer Comments: *The incidence of protocol violations in the overall study was similar to that in the mTNBC efficacy cohort. The review of the CRFs and clinical site inspections revealed additional protocol violations. For example, 2 patients who were identified as responders, were noted to have radiation to new CNS lesions which were not documented as disease progression* (b) (6) *; these patients continued to receive IMMU-132 for additional cycles and were not documented as disease progression until a later date. Review of additional information regarding the treatment course of all patients who was identified as responders in the BLA submission (n=36), obtained through several information* (b) (4) *revealed the following:*

- *Patient* (b) (6) *had an off-protocol brain MRI completed that documented disease progression. The results of this scan were not recorded as disease progression and the brain MRI was not sent for independent central review (ICR) even though this patient had been selected to undergo response assessment by ICR.*

- *Patient* (b) (6) *underwent multiple thoracenteses until response was achieved.*

The overall impact of these protocol violations is that for the patients who experienced progression in the CNS and received radiation treatment to the CNS lesions, the applicant's report of duration of response did not reflect the progressive events, though there was no impact on the ORR. However, this finding raised concerns about the conduct of the study and the reporting of study findings in the BLA submission. For the patient who had multiple thoracenteses while continuing treatment with IMMU-132, went on to no longer require thoracenteses and to have a partial response.

Two patients (b) (6) *received other anticancer therapy (navelbine; taxotere, trastuzumab, pertuzumab) while on IMMU-132; however, since these patients were not identified as responders, this deviation did not impact the efficacy findings.*

There were 14 patients in the mTNBC population who received a waiver for enrollment. Five of these patients had bulky disease, two patients had a pregnancy test outside of the required window, two patients had extended screening periods, one patient did not meet baseline hematological parameters and had bulky disease, one patient had brain metastases, one patient did not receive a prior taxane, one patient requested that they receive day 8 on day 10, and one patient did not have at least 2 weeks since prior therapy or at least four weeks after surgery.

Table of Demographic Characteristics

Demographic data for the mTNBC efficacy cohort from IMMU-132-01 are included below in Table 14.

Table 14. Demographic Data for the mTNBC Efficacy Cohort of IMMU-132-01

Demographic Parameters	**mTNBC Efficacy Population N=108 n (%)**
Sex	
Male	1 (0.9)
Female	107 (99.1)
Age	
Mean years (SD)	54.2 (10.3)
Median (years)	55
Min, max (years)	31, 80
Age Group	
< 65 years	89 (82.4)
≥ 65 years	19 (17.6)
ECOG	
0	31 (28.7)
1	77 (71.3)
Race	
White	82 (75.9)
Black or African American	8 (7.4)
Asian	3 (2.8)
American Indian or Alaska Native	1 (0.9)
Native Hawaiian or Other Pacific Islander	0
Other	14 (13.0)
Ethnicity	
Hispanic or Latino	7 (6.5)
Not Hispanic or Latino	100 (92.6)
Region (optional)	
United States	108 (100)

Source: *Reviewer analysis using adsl.xpt dataset*

Reviewer Comments: *The patient population generally reflects the patients who would be receiving this therapy after approval. Most patients with mTNBC are younger than 65 and most patients are female. There were small numbers of African-American patients enrolled in this trial, though there is a higher incidence of TNBC among African-American patients (Lund 2009; Carey 2006). Most patients had an ECOG performance status of 1 which reflects that these patients have some debility from their disease and/or prior therapy for their disease.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease characteristics for the patients in the IMMU-132-01 mTNBC efficacy cohort are included in Table 15 below.

Table 15. Pretreatment Disease Characteristics of the mTNBC Efficacy Cohort

Pretreatment Disease Characteristic	IMMU-132-01 mTNBC Efficacy Cohort N=108 n (%)
Time since initial diagnosis (months) (n=102)	
Mean (Std Dev)	64.0 (58.8)
Median (Q1-Q3)	43.7 (27.9,89.1)
Min, Max	3.6, 413.5
Initial Diagnosis Disease Stage	
Stage 0-II	60 (55.6)
Stage III	32 (29.6)
Stage IV	12 (11.1)
Stage at Study Entry	
Metastatic	106 (98.1)
Unknown	2 (1.9)
Nature of disease	
Visceral	82 (75.9)
Other	26 (24.1)
Measurable Disease	
Yes	108 (100)
Brain Metastases	2 (1.9)
Creatinine > ULN	4 (3.7)
Hepatic Impairment defined as the presence of at least one of the following criteria: ALT > ULN, AST > ULN, or total bilirubin > ULN	26 (24.1)
Prior (neo)adjuvant chemotherapy (denominator is the 96 patients who did not have initial stage IV diagnosis)	88 (91.7)
Median number of prior therapies in the metastatic setting (range)	3 (2, 10)
Median number of prior cytotoxic chemotherapies in the metastatic setting (range)	2 (1, 8)
Prior chemotherapy in the metastatic setting	
Platinum	74 (68.5)
Gemcitabine	59 (54.6)
Taxane	56 (51.9)
Capecitabine	55 (50.9)
Eribulin	49 (45.4)
Anthracycline (doxorubicin and epirubicin)	28 (25.9)
Alkylating agent (cyclophosphamide or ifosfamide)	21 (19.4)

Vinorelbine	17 (15.7)
Ixabepilone	9 (8.3)
Prior endocrine therapy	25 (23.1)

Source: *Reviewer analysis using adsl.xpt & adcm.xpt*

Reviewer Comments: *Most patients in this study had received two prior chemotherapies, though there was one patient who had received only one prior chemotherapy but had also received a non-chemotherapy treatment option in the metastatic setting. Few patients had mild hepatic impairment, brain metastases, or a creatinine above the upper limit of normal. Most patients received a platinum (cisplatin or carboplatin) in the metastatic setting, and had received other agents such as taxanes, capecitabine, and gemcitabine that are used in this setting. Most patients (96, 88.9%) were diagnosed in the early stage setting and had received prior adjuvant chemotherapy. While all patients had biopsies consistent with hormone receptor negative disease in the metastatic setting, approximately 23% of patients had received prior endocrine therapy. All patients had measurable disease as this was an eligibility requirement given that the primary efficacy measurement was ORR by RECIST 1.1. The population overall was generally consistent with the US population that would be eligible for treatment based on the proposed indication.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance of sacituzumab govitecan was assessed as this agent was administered as an intravenous infusion by study personnel at each study site. For each patient infusion, the start and stop time were documented on the Case Report Form (CRF). Infusion interruptions and discontinuations were also documented.

Concomitant Medications

All patients in the mTNBC efficacy cohort were on concomitant therapies at some point during study participation. Concomitant therapies received by more than 20% of study participants are described in Table 16 below.

Table 16. Concomitant Medications Used in >30% of Patients in the mTNBC Efficacy Population

Concomitant therapy	**Efficacy Population n=108 n (%)**
≥ 1 therapy	108 (100)
Antiemetics and Antinauseants	105 (97.2)
Ondansetron	78 (72.2)
Prochlorperazine	53 (49.1)
Palonosetron	47 (43.5)
Fosaprepitant	42 (38.9)
Granesitron	26 (24.1)
Corticosteroids	79 (73.1)

Dexamethasone	78 (72.2)
Opioids	71 (65.7)
Oxycocodone	38 (35.2)
Drugs for Peptic Ulcer Disease and GERD	70 (64.8)
Famotidine	51 (47.2)
Omeprazole	27 (25.0)
Anxiolytics	70 (64.8)
Lorazepam	54 (50.0)
Vitamin and Mineral Supplements	69 (63.9)
Vitamin D	37 (34.3)
Other analgesics and antipyretics	64 (59.3)
Acetaminophen	39 (36.1)
Antihistamines	62 (57.4)
Diphenhydramine	53 (49.1)
Granulocyte Colony Stimulating Factor (incl. filgrastim & peg-filgrastim)	58 (53.7)
Antidiarrheals	52 (48.1)
Loperamide	45 (41.7)
Non-steroidal anti-inflammatory agents	49 (45.4)
Drugs to relieve constipation	46 (42.6)
Antibiotics	40 (37.0)
Antithrombotics (incl. alteplase for line anticoagulation &heparin flushes)	40 (37.0)
Antidepressants	33 (30.6)

***Source**: Reviewer analysis using adcm.xpt &Table 23 on page 83 of the CSR.*

***Reviewer comments:** All patients were on one or more concomitant therapies. The most common concomitant therapies were anti-nausea therapies. Corticosteroids were also common and could have been used as antiemetics as well as agents to prevent infusion-related reactions. The most common drug used for peptic ulcer disease/GERD was famotidine, an H2-antagonist that could have also been used to prevent infusion-related reactions. Over one-half of patients received G-CSF agents during their treatment. Approximately one-half of patients received antidiarrheals. This table demonstrates that there were multiple supportive therapies: antiemetics, steroids, antihistamines and H2 blockers, and G-CSF, that patients received in able to tolerate therapy. Additionally, review of the adcm.xpt dataset indicated that eleven patients (10.2%) received atropine to control the cholinergic adverse effects of the therapy which may have included abdominal cramping, diarrhea, diaphoresis, increased salivation, increased lacrimation, and visual changes. These data support the labeling recommendations regarding supportive care for neutropenia, nausea and vomiting, diarrhea, pretreatment medication to and prevent infusion-related reactions that is discussed in section 5 of the USPI. Use of these medications may improve the tolerability of study therapy and therefore possibly affect treatment efficacy.*

Efficacy Results – Primary Endpoint

The analysis of the primary efficacy endpoint of ORR per RECIST 1.1 as assessed by investigator was based upon the efficacy population (n=108) and a study cut of data of June 30, 2017; the results are shown in Table 17. The confirmed ORR was 33.3% (n=36; 95% CI: 24.6%, 43.1%) consisting of 3 complete responses (CRs, 2.8%) and 33 partial responses (PRs, 30.6%).

The median time to response was 2.0 months (range: 1.6, 13.5). During the review of the application, FDA requested that the applicant provide additional data to reflect longer follow-up for patients who were identified as responders in the original BLA submission (i.e., patients identified as responders based upon a data cut off date is June 30, 2017). The duration of response among these responders based upon a data cut-off date of December 1, 2017 is also shown in Table 17.

Table 17: Primary Analysis of Confirmed ORR by Investigator

	Efficacy Population (n=108)
Responders (CR+PR) n % (95% CI)	36 33.3% (24.6, 43.1)
CR, n (%)	3 (2.8)
PR, n (%)	33 (30.6)
Time to Response (months)	
Median (range)	2.0 (1.6, 13.5)
Duration of Response (months) DCO: 30 June 2017	
Median[1] (95% CI[2])	8.4 (4.9, 11.6)
Range	(1.4+, 24.6+)
≥3 months, n (%)	29 (80.6)
≥6 months, n (%)	15 (41.7)
≥9 months, n (%)	11 (30.6)
Duration of Response (months) DCO: 1 December 2017	
Median[1] (95% CI[2])	7.7 (4.9, 10.8)
Range	(1.9+, 30.4+)
≥3 months, n (%)	34 (94.4)
≥6 months, n (%)	20 (55.6)
≥9 months, n (%)	12 (33.3)
≥12 months, n (%)	6 (16.7)

[1] Kaplan-Meier estimate
[2] Brookmeyer and Crowley method with log-log transformation
+ denotes ongoing response
Source: *adrs.xpt & adtte.xpt from the original submission dated 5/18/18 and the final updated datasets submitted 10/8/18.*

Reviewer's Comment: *The BLA submission was based on a DCO of June 30, 2017. Based on the data in the submission, there were 15 patients with response durations censored due to data cutoff, including 7 patients with response durations censored at <3 months. Thus, the FDA requested updated data based on a DCO of 1 December 1, 2017 to get a more mature estimate of duration of response.*

In response to FDA's request for this additional data, the applicant noted that based on the new DCO, 23 of the 36 original responders had no additional efficacy evaluations and no change in efficacy outcome; however, the 13 remaining responders did. The updated data also included changes in dates of PD for three patients (b) (6) *identified by FDA review*

of the CRFs. Patients (b) (6) *and* (b) (6) *were part of the 23 patients with no additional efficacy evaluations; both were PD at the June DCO but their PD dates were updated to earlier dates. Patient* (b) (6) *was originally censored at the June DCO but FDA review determined it had a PD event. As discussed previously in this review, during clinical site inspections and data review it was determined that patients* (b) (6) *had imaging revealing progressive disease in the brain that was not originally considered progressive disease. The PD date for patient* (b) (6) *was changed to correspond with what was reported in the CRF.*

Confirmed ORR by RECIST 1.1 per Double-Read ICR

As specified in the SAP, independent central review (ICR) was performed on patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation; a total of 55 patients met these criteria. Results based on the double-read ICR under both DCO dates are shown in Table 18. The confirmed ORR was 32.4% (95% CI: 23.7%, 42.1%) consisting of 6 complete responses (CRs, 5.6%) and 29 partial responses (PRs, 26.9%).

The median time to response was 2.1 months (range: 1.6, 9.2). The Kaplan-Meier estimated median duration of response was 6.7 months (95% CI: 3.8, 11.3) based upon the June 30, 2017 DCO, and 9.1 months (95% CI: 4.6, 10.7) based upon the December 1, 2017 DCO.

Reviewer's Comment: *ICR was prespecified in the SAP but not in protocol. Initially ICR was based on single read (imaging charter 8/15/2016) and double read was added in the charter amendment (10/30/2017) after pre-BLA meeting (10/12/2017) per FDA's recommendation. The applicant initially performed a single-read ICR. In the October 2017 pre-BLA meeting, FDA notified the applicant of concerns regarding using a single blinded reviewer without adjudication for the BICR. Taking FDA's recommendation, the applicant amended their charter to include a double-read ICR with adjudication. The single-read ICR results are not reported in this review.*

To get updated data with a December DCO based on double-read ICR, the applicant noted that they reinitiated the blinded independent central read with the same 2 radiologists and adjudicator. In the updated results, they noted two additional partial responders, updating the new total number of responders to 37. However, the FDA review focused only on the original 35 responders per double-read ICR. Thus, the results shown in Table 18 *were adjusted accordingly to present time to response and duration of response for only the original 35 responders.*

Table 18: Sensitivity Analysis of Confirmed ORR by Double-Read ICR

	Efficacy Population n=108
Responders (CR+PR) n % (95% CI)	35 32.4% (23.7, 42.1)
CR, n (%)	6 (5.6)
PR, n (%)	29 (26.9)
Time to Response (months)	
Median (range)	2.1 (1.6, 9.2)

Duration of Response (months) DCO: June 30, 2017	
Median[1] (95% CI[2])	6.7 (3.8, 11.3)
Range	(1.4+, 22.8+)
≥3 months, n (%)	29 (82.9)
≥6 months, n (%)	15 (42.9)
≥9 months, n (%)	12 (34.3)
Duration of Response (months) DCO: December 1, 2017	
Median[1] (95% CI[2])	9.1 (4.6, 10.7)
Range	(3.0, 28.6+)
≥3 months, n (%)	35 (100.0)
≥6 months, n (%)	18 (51.4)
≥9 months, n (%)	15 (42.9)
≥12 months, n (%)	5 (14.3)

[1] Kaplan-Meier estimate
[2] Brookmeyer and Crowley method with log-log transformation
+ denotes ongoing response
Source: *adrs.xpt & adtte.xpt from the double-read ICR datasets submitted 6/29/18 & the final updated datasets submitted 10/8/18*

The response concordance between investigator and the double-read ICR is shown in Table 19. There was an overall concordance of 76% if comparing each response category but the concordance of responders vs. non-responders was higher at 92%. Note that of the 36 investigator-assessed responders, 33 were also responders by double-read ICR. The remaining 3 included 2 SD and 1 NA.

Table 19: Concordance between Investigator and Double-Read ICR Assessment of ORR

	Double-Read ICR					
Investigator	**CR**	**PR**	**SD**	**PD**	**NA**	**Total**
CR	2	1	0	0	0	3
PR	4	26	2	0	1	33
SD	0	2	13	2	1	18
PD	0	0	0	1	0	1
Total	6	29	15	3	2	55

Source: *adrs.xpt in original submission dated 5/18/18 & double-read ICR datasets submitted 6/29/18*

Reviewer Comment: *There was good concordance between the investigator and double-read ICR assessment of response. The double-read ICR assessment was based on a subgroup of patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation rather than the entire efficacy population. Given the inherent bias in evaluating response only among patients whom have been identified by investigators as responders or as having 20% tumor shrinkage (i.e. SD), FDA considers the partial review is inadequate to determine whether there is consistency in the ORR results across both assessment methods. As such, this reviewer recommends not including this information in product labeling. Instead, the applicant should provide the results of an independent assessment of ORR, that includes the entire efficacy*

population, and that is based upon the data cut off date of the original BLA submission (June 30, 2017), and also provide duration of response for these patients, in order to support labeling.

Exploratory Subgroup Analyses

Exploratory subgroup analyses of confirmed ORR by investigator assessment were conducted by age (<65, ≥65), race (Black or African American, White, Other), Trop-2 status (No/Weak Staining, Moderate/Strong Staining, Not Done), visceral disease (yes, no), liver disease (yes, no), and receiving at least 2 prior chemotherapies (yes vs. no). Results are shown in Table 20.

Table 20: Exploratory Subgroup Analyses

	n	# Responders	Confirmed ORR (95% CI)
Age group			
<65	89	29	32.6% (23.0, 43.3)
≥65	19	7	36.8% (16.3, 61.6)
Race			
Black or African American	8	3	37.5% (8.5, 75.5)
White	82	27	32.9% (22.9, 44.2)
Other	18	6	33.3% (13.3, 59.0)
Trop-2 Status			
No/Weak Staining	5	0	0% (0.0, 52.2)
Moderate/Strong Staining	57	23	40.4% (27.6, 54.2)
Not Done	46	13	28.3% (16.0, 43.5)
Visceral Disease			
Yes	82	23	28.0% (18.7, 39.1)
No	26	13	50.0% (29.9, 70.1)
Liver Disease			
Yes	45	11	24.4% (12.9, 39.5)
No	63	25	39.7% (27.6, 52.8)
Receiving at least 2 prior chemotherapies			
Yes	94	31	33.0% (23.6, 43.4)
No	14	5	35.7% (12.8, 64.9)

Source: *adrs.xpt & adsl.xpt Data cutoff date June 30, 2017.*

Reviewer Comment: *Response rates were generally consistent across all subgroups except for Trop-2 Status: No/Weak Staining which only had 5 patients with no responders and a wide confidence interval. Otherwise, no outlier subgroups were observed. All subgroup analyses presented are considered exploratory or hypothesis generating and no formal inference can be drawn. Additionally, in the case of Trop-2, testing was conducted with a test whose performance characteristics are unknown (see Section* 6.3.2*).*

Data Quality and Integrity

Refer to See section 4.1 regarding the OSI findings. In general, there was evidence of a lack of control, oversight, and management of the conduct of Study IMMU-132-01. The inspections also

revealed some discordance between source data (EMRs, patient clinical charts) and the information in the CRFs and datasets as previously described. Overall, he inspectional findings and this reviewer's review of the case report forms and datasets indicate that the datasets in the BLA were of reasonable quality and consistency. It was generally easy to recreate the results found in the study CSR.

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoints were time to response (TTR), duration of response (DOR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS)as assessed by the investigator.

TTR and DOR were described previously as related to the primary endpoint of confirmed ORR.

The investigator-assessed CBR (CR+PR+SD≥6 months) was 44.4% (95% CI: 34.9%, 54.3%),and 45.4% (95% CI: 35.8%, 55.2%), based on data cutoff date of June 30, 2017 and December 1, 2017, respectively.

The investigator assessed PFS showed the following:

- 84 (77.8%) patients had a PFS event with an estimated median PFS time of 5.6 months (95% CI: 4.8, 6.6) based on a data cutoff date of June 30, 2017.
- 94 (87.0%) patients had a PFS event with an estimated median PFS time of 5.5 months (95% CI: 4.1, 6.3) based on a data cutoff date of December 1, 2017.

There were 61 deaths (56.5%) with an estimated median survival time of 13.0 months (95% CI: 11.2, 14.4), and 77 deaths (71.3%) with an estimated median survival time of 13.0 months (95% CI: 11.2, 13.7), based on data cutoff date of June 301, 2017 and December 1, 2017, respectively.

Reviewer's Comment: *Because time to event endpoints such as PFS and OS are not interpretable in a single-arm study, the results of the analyses of these endpoints is considered exploratory/hypothesis generating.*

Dose/Dose Response

An analysis of dose and response was not conducted given that the efficacy analysis was based upon the subgroup of patients with mTNBC who had received 2 or more prior therapies for metastatic disease, and who received sacituzumab govitecan 10 mg/kg. Additionally, an analysis of efficacy in patients in the safety population who received doses other than 10 mg/kg was not possible as efficacy data for these patients were not included in the BLA.

Durability of Response

Duration of response is discussed with the assessment of the primary endpoint, ORR. Results of duration of response are shown in Table 17 and Table 18.

Persistence of Effect

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

There were no further analyses completed.

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

Not applicable as there is only a single clinical trial.

Primary Endpoints

Not applicable.

Secondary and Other Endpoints

Not applicable.

Subpopulations

Not applicable.

Additional Efficacy Considerations

Study IMMU-132-01 evaluated a relatively small number of patients with mTNBC, most of whom did not have evidence of CNS disease on study entry. Estimates of the incidence of brain metastases in patients with mTNBC vary with a recent analysis of SEER data estimating that approximately 10-15% of patients with mTNBC have brain metastases at the initial diagnosis of metastatic disease (Martin 2017). It is therefore unclear what the efficacy of sacitizumab govitecan may be in a post-market population that is likely to have higher incidence of brain metastases. Another consideration for efficacy the post-market setting is that TNBC is a molecularly heterogenous disease and it is unclear whether particular subpopulations of patients with mTNBC are deriving the differential benefit from treatment with sacituzumab govitecan.

Finally, the relationship between tumor *Trop-2* expression and response to therapy with sacituzumab govitecan is unclear. While data submitted in the BLA suggested that those tumors with *Trop-2* expression were experienced higher ORR than those patients whose tumors were deemed to have weak or no expression, the findings were exploratory, as was the *Trop-2* test itself.

8.1.4. Integrated Assessment of Effectiveness

The only study submitted to support the efficacy of sacituzumab govitecan in the treatment of metastatic TNBC in patients who have received at least two prior therapies for metastatic disease was IMMU-132-01. No integrated efficacy analysis was performed during this review.

Based on the data submitted from IMMU-132-01, sacituzumab govitecan demonstrates evidence of efficacy in patients with mTNBC who have received two prior therapies for metastatic disease. The ORR, along with supportive duration of response, is improved compared to that of available therapies. In the target mTNBC population (n=108), the study showed a confirmed ORR of 33.3% (95% CI: 24.6, 43.1) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment.

8.2. **Review of Safety**

8.2.1. **Safety Review Approach**

To support the safety evaluation of sacituzumab govitecan for this BLA, the Applicant submitted safety data from Study IMMU-132-01, a Phase 1/2 study of IMMU-132 (hRS7-SN38 antibody drug conjugate) in patients with epithelial cancer. The safety dataset consists of 420 patients who received at least one dose of study drug. Adverse events were assessed at baseline, during the study treatment period, and for at least 30 days after discontinuing study therapy. Laboratory studies were obtained at baseline, day 1 and 8 of each cycle, at the end of treatment, and during study follow-up. Hematology labs included a complete blood cell count with differential. Serum chemistries include liver function evaluation, renal function evaluation, and electrolytes. There were no clinical holds for safety during the development of sacituzumab govitecan.

Adverse event and therapy exposure datasets were used for these analyses. Where appropriate, narrative summaries and case report forms for serious adverse events were reviewed. Narratives and case report forms for all patient deaths within 30 days of discontinuing study therapy were reviewed as well.

Specific safety concerns, including infusion-related reactions, diarrhea, and neutropenia were reviewed as well. These events were further assessed by UGT1A1 mutation status given concern that there is increased risk of adverse events in patients who are not UGT1A1 *1 homozygotes.

Given the limited numbers of patients included in the safety database, analyses were conducted for both the overall safety population as well as for the mTNBC efficacy cohort. The reason for additionally conducting separate analyses in the efficacy cohort is that, unlike the overall cohort which had received at least one prior line of therapy, patients in the mTNBC efficacy cohort had received at least two prior therapies in the metastatic setting making them more heavily pretreated and potentially at increased risk of adverse events when compared to the overall study population.

Error! Reference source not found. includes the safety study submitted to the NDA as well as

the data cut-off dates for the Initial Submission and the 90-Day Safety Update.

Table 21. Summary of Safety Population Data Submitted with this BLA

Study Design	Population	No. Patients	Status	Data Cutoff at time of submission	Data Cutoff for Extended follow up
IMMU-132-01 Phase 1/2 open label, single arm study in patients with epithelial cancer	Patients with advanced epithelial cancer who had received at least one prior line of therapy	420	Ongoing	June 30, 2017	December 1, 2017

At the time of data cutoff of June 30, 2017, the safety database included 420 patients, including the 108 mTNBC patients who comprised the efficacy population (i.e., patients with mTNBC who received sacituzumab govitecan 10 mg/kg). Patients in the safety population received the following doses: 8 mg/kg (n=81), 10 mg/kg (n=327), 12 mg/kg (n=9), and 18 mg/kg (n=3). The 90-Day Safety Update provided cumulative safety information based upon a data cutoff date of December 1, 2017.

The tumor types that were represented in Study IMMU-132-01 are shown in the table below.

Table 22: Tumor Types included in Study IMMU-132-01

Tumor Type	All Population N=420 n (%)
Metastatic Triple-Negative Breast Cancer	144 (34.3)
Small Cell Lung Cancer	56 (13.3)
Non-Small Cell Lung Cancer	54 (12.9)
Urothelial Carcinoma	45 (10.7)
Colorectal Cancer	31 (7.4)
Metastatic HR positive Breast Cancer	20 (4.8)
Esophageal Cancer	19 (4.5)
Pancreatic Cancer	16 (3.8)
Epithelial Ovarian Cancer	8 (1.9)
Endometrial Cancer	7 (1.7)
Gastric Adenocarcinoma	5 (1.2)
Hormone Refractory Prostate Cancer	4 (1.0)
Glioblastoma Multiforme	3 (0.7)
Squamous Cell Carcinoma of the Head and Neck	3 (0.7)
Hepatocellular Carcinoma	2 (0.5)
Renal Cell Carcinoma	1 (0.2)

Source: *Reviewer analysis using adsl.xpt dataset*

8.2.2. Review of the Safety Database

Overall Exposure

The duration of exposure to sacituzumab govitecan in the overall safety population including the mTNBC is summarized in Table 23. As of the DCO of December 1, 2017, a total of 22 patients in the overall safety population, including 8 patients in the mTNBC efficacy analysis population, continued to receive sacituzumab govitecan.

Table 23. Exposure Summary for Safety Population (n=408)

Exposure Parameter	Safety Population n= 408	mTNBC Population n= 108		Overall n= 408
	Treatment Dose			
	8 mg	10 mg	8 mg	8 and 10 mg
Duration of Treatment (months)				
Mean (SD)	4.6 (5.9)	5.4 (5.8)	6.6 (6.7)	5.3 (5.8)
Median	3.0	3.7	5.1	3.5
Range	0–40.6	0–36	0–36	0–40.6
Number of months				
0 to <3	39 (48.1)	137 (41.9)	37 (34.3)	176 (43.1)
3 to <6	23 (28.4)	85 (26)	26 (24.1)	108 (26.5)
6 to <9	9 (11.1)	45 (13.8)	19 (17.6)	54 (13.2)
9 to <12	4 (4.9)	25 (7.6)	8 (7.4)	29 (7.1)
>= 12	5 (6.2)	33 (10.1)	16 (14.8)	38 (9.3)
Number of Cycles				
Mean (SD)	6.9 (7.9)	8 (7.9)	9.6 (9.1)	7.7 (7.9)
Median	5	6	8	6
Range	1–56	1–51	1–51	1–56
Doses Administered				
Mean (SD)	13.2 (15.5)	15.5 (15.7)	18.7 (18.1)	15.1 (15.7)
Median	10	11	15.5	11
Range	1–112	1–102	1–102	1–112
Dose Intensity				
Mean (SD)	84.7 (129.8)	97.7 (132.1)	90.5 (131.6)	95.1 (131.6)
Median	58.8	65.3	61.1	64.3
Range	21.4–964.8	29.6–1078	31.2–1078	21.4–1078

Source: *Reviewer analysis, supported by safety analytics team; adsl.xpt, adex.xpt*
Note: Analysis performed with planned treatment (TRT01P and TRTP).
[1]Three patients without treatment or analysis end-dates (IMMU-132-01-(b) (6), IMMU-132-01-(b) (6), and IMMU-132-01(b) (6)) were omitted from the analysis.

Dose Modifications

The analysis of dose modifications (dose delays, dose reductions, dose discontinuation was conducted based upon the overall safety population (n=408) and the mTNBC population (n=108). A summary results table is shown below.

Table 24: Summary Dose Modifications in Safety Population (n=408)

Dose Modifications	Safety Population n= 408		mTNBC Population n= 108	Overall n= 408
	Treatment Dose			
	8 mg	10 mg	8 mg	8 and 10 mg
Dose Reductions				
≥ 1 dose reduction	17 (21)	114 (34.9)	37 (34.3)	131 (32.1)
Mean (SD)	0.2 (0.5)	0.4 (0.7)		0.4 (0.6)
Range	0–2	0–3		0–3
Number of reductions				
1	15 (18.5)	88 (26.9)	26 (24.1)	103 (25.2)
2	2 (2.5)	22 (6.7)	10 (9.3)	24 (5.9)
3	0 (0)	4 (1.2)	1 (0.9)	4 (1)
Dose Delays	2 (2.5)	16 (4.9)	7 (6.5)	18 (4.4)

Source: *Reviewer analysis supported by safety analytics team; adsl.xpt, adex.xpt*
Note: Analysis performed with planned treatment (TRT01P and TRTP).
[1]Three patients without treatment or analysis end-dates (IMMU-132-01-(b) (6), IMMU-132-01-(b) (6), and IMMU-132-01-(b) (6)) were omitted from the analysis.

The median time to first dose reduction was similar in both the overall safety population (34 days [range 7, 419]) and in the mTNBC population (34 days [range 13, 280]). Dose reductions due to adverse events occurred in 32% of patients. The most common AE leading to dose reduction was neutropenia/ febrile neutropenia.

Reviewer comment: *It was determined during the review that there was missing information in the analysis datasets regarding adverse events which lead to dose modifications. Attempts were made to obtain clarification on the issue, including an information request sent on 1/2/19 requesting further information to support the proposed dose modification guidelines in labeling and requesting an updated ADAE dataset (cutoff 12/1/17) for the purpose of conducting an analysis. It was noted by FDA that previous ADAE datasets did not have a parameter which captured specific adverse events which lead to dose reduction; the datasets only included this information on dose interruptions and dose discontinuations.*

In response to FDA's request for information, Immunomedics stated that the case report forms (CRFs) captured the dose that patients received during each infusion, but information regarding the AE that led to dose reduction was not collected. In the response, Immunomedics provided an Excel file, based upon a manual medical review that examined AEs with onset date between prior dose and dose reduction. The frequency of each adverse event was tallied to estimate

specific AEs which occurred prior to the dose reduction in the efficacy population (n=108).

An analysis of adverse events led to dose reduction from this spreadsheet was limited by the absence of a dataset including these data, by the method by which the Applicant made a determination of which AE led to dose reductions, and by the absence of this information for the entire safety population. Based on the applicant's assessment, which indicated that a total of 36 patients experienced dose reductions (notably, one less patient than the analysis conducted based upon exposure dataset), the most common AE listed prior to dose reductions was neutropenia, including febrile neutropenia. This event was listed for 18 out of 36 patients (50%) in the spreadsheet.

In the absence of adequate data to conduct a more detailed analysis of specific adverse events leading to dose modifications, the information described in product labeling is limited and includes only neutropenia/febrile neutropenia as the most common adverse event leading to dose reduction.

Relevant characteristics of the safety population:

Demographic information for patients included in the safety database from the IMMU-132-01 study is included in Section 8.1.2 above. Demographic comparisons between the overall population and the mTNBC efficacy population are captured in Source: *Reviewer analysis with support from safety analytics team; adsl.xpt dataset*
below.

Table 25: Demographics of Patients Enrolled in Safety Population (n=408)

Demographic Parameter	**Safety Population n=408 %**	**mTNBC Population n=108 %**
Sex	100	100
Female	64.7	99.1
Male	35.3	0.9
Age Group	100	100
<65	64.7	82.4
>=65	35.3	17.6
ECOG Performance Status	100	100
Grade 0	27.2	28.7
Grade 1	72.8	71.3
Race	100	100
Black or African American	5.4	7.4
White	82.1	75.9
Other	12.5	16.7
Ethnicity	100	100

Hispanic or Latino	4.2	6.5
Not Hispanic or Latino	92.9	91.7
Other	2.5	0.9
Unknown/other	0.5	0.9

Source: *Reviewer analysis with support from safety analytics team; adsl.xpt dataset*

Reviewer Comment: *The demographic characteristics of patients in the mTNBC cohort were generally similar to the overall population; age was a notable exception with patients in the mTNBC cohort tending to be slightly younger than those in the overall study population. Another exception was that patients in the mTNBC cohort were more likely to have hepatic insufficiency and less likely to have a creatinine > ULN than those in the overall study population.*

Adequacy of the safety database:

The safety database of 420 patients treated in IMMU-132-01 is adequate. The age and sex of the patients treated in the mTNBC cohort is consistent with what is generally expected for patients with mTNBC. There was one male patient in the mTNBC cohort and there were additional male patients (149, 35.5%) in the overall safety population. Most patients were white (344, 81.9%). There were few African-American (24, 5.7%), Asian (17, 4.0%), or Native American (1, 0.2%) patients included in the overall safety database.

Reviewer Comment: *The overall safety database included more male patients than the mTNBC efficacy cohort due to the demographics of disease. The mTNBC cohort was younger than those in the overall safety database, again a reflection of differing disease epidemiology between tumor types. Baseline ECOG performance status was similar across the overall safety cohort and the mTNBC efficacy cohort. Patients in the overall safety cohort may have been less heavily pretreated as compared to the mTNBC efficacy cohort as patients were permitted to enroll in this study with at least one prior line of systemic therapy in the metastatic setting while those in the mTNBC cohort had received at least two prior lines of systemic therapy in the metastatic setting.*

Overall, the populations in the mTNBC cohort and the overall safety cohort are similar. Given the differences, however, analyses were performed and compared for each population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Case report forms (CRFs) were reviewed and compared to the datasets and patient narratives. The data in the CRFs and AE datasets were generally consistent with any exceptions noted during the course of the review. Overall the data quality for the study was generally acceptable.

While there were some discrepancies were noted throughout the course of the review, it does not appear that these discrepancies significantly impacted study results, specifically the ORR. Notably, the datasets submitted to the BLA were of adequate quality to facilitate FDA's analyses. However, as described in Section 8.2.2, the absence of key information to verify that the proposed dose modification guidelines in product labeling adequately mitigated the adverse

reactions in sacituzumab govitecan-treated patients in Study IMMU-132-01, represents a submission quality issue.

Categorization of Adverse Events

the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 was employed in IMMU-132-01, to characterize the adverse event (AE) terms and its severity; this was then mapped by the Applicant to corresponding terminology within MedDRA.

Preexisting conditions were defined as AEs that began prior to the first dose of study drug.

Treatment emergent AEs were defined as any AE beginning between the day of the first dose and 30 days after the last dose of study drug, or any preexisting condition that increased in CTCAE grade between the day of the first dose and 30 days after the last dose of study drug. A serious adverse event (SAE) was any AE during the study that resulted in death, initial or prolonged hospitalization, a life-threatening experience, persistent or significant disability, congenital anomaly or birth defect, or was considered significant for any other reason. Events may have been considered SAEs if they required surgical or medical intervention to prevent one of the previously listed outcomes. During the follow-up period, new AEs were documented if determined to be related to study therapy; otherwise only AEs leading to hospitalization, requiring IV or prescription anti-infectives, medications related to gastrointestinal (GI) events, or AEs leading to death were recorded.

The relationship of the AE to study treatment was assessed.

Reviewer Comments: *The Applicant used standard definitions for AE and SAE recording and reporting. In FDA's analyses, attribution of the relationship of events to study therapy was not considered given that this is a single-arm, open-label trial. Given this, the safety review was performed of all TEAEs regardless of investigator assessed attribution.*

Routine Clinical Tests

Routine laboratory testing included complete blood count with differential and blood chemistries including glucose, blood urea nitrogen , creatinine, total bilirubin, total protein, albumin, alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase (LDH), calcium, chloride, sodium, potassium, magnesium, phosphorus.

Laboratory studies were obtained on day 1 and 8 of each cycle, at the end of treatment, and during follow-up. Urinalysis, prothrombin time, partial thromboplastin time, and human anti-human antibodies (HAHA) were obtained at baseline, day 1 of even treatment cycles, at the end of treatment and at the end of study. For patients with positive HAHA testing, 2 additional monthly samples for HAHA were to be collected. Samples were collected for UGT1A1 mutation testing at study entry. See study schedule of assessments in section 8.1.1

Vital signs were collected with each infusion. For the first infusion, vital signs were collected

every 15 minutes for the first hour, every 30 minutes until the completion of the infusion, at completion, and 30 minutes after the end of the infusion. If no clinically relevant observations during the first infusion, vital signs were collected prior to the infusion, 30 minutes after the start of the infusion, and at infusion completion.

Physical examinations were performed on day 1 of cycle 1, day 1 of cycle 2, and then day 1 of ever even cycle.

Reviewer Comment: *The frequency of laboratory and clinical assessments was appropriate. Samples collected for UGT1A1 mutation testing were tested retrospectively. This is consistent with clinical practice as there are not currently recommendations to evaluate for this prospectively.*

8.2.4. Safety Results

Deaths

In the IMMU-132-01 study, at the time of the 90-Day Safety Update (December 1, 2017), there had been 20 deaths within 30 days of discontinuing study therapy in the overall safety population; 4 of these deaths occurred among patients in the mTNBC efficacy cohort. Narratives of each event and reviewer assessment are captured in Table 26 below.

Table 26. Death Narratives from IMMU-132-01

mTNBC Efficacy Cohort	
Patient ID	**Narrative**
(b) (6)	***Metastases to spine.*** 55-year-old white female with mTNBC with metastases to the liver and a malignant pleural effusion. The first and only dose of IMMU-132 (10 mg/kg) was given on (b) (6) On that date, the was noted to have lower extremity weakness, abdominal pain, and constipation. After receiving the infusion, the patient was sent to the hospital for evaluation. The patient was admitted to the hospital on (b) (6) MRI of the thoracic spine revealed a T11 spinal cord mass suspicious for metastatic disease and an MRI of the brain completed on (b) (6) demonstrated innumerable metastatic lesions to the brain with evidence of hemorrhage and vasogenic edema. The patient died on (b) (6) due to disease progression. No autopsy was performed. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression prior to the infusion which was confirmed during the hospital admission. It is not likely that study therapy contributed to this patient's death.*
(b) (6)	***Hypertension.*** 49-year-old white female with mTNBC with metastases to the lungs, hip, and left gluteal muscle. She received her first and only dose of IMMU-132 (10 mg/kg) on (b) (6) On the day of treatment, her creatinine was 2.13 and she was mildly hypokalemic with a potassium of 3.2 mEq/L. She was given 20 mEq of potassium. She died in her sleep on (b) (6) and

	the cause of death was recorded as hypertension. Of note, the patient was on multiple concomitant therapies including insulin, amlodipine, methadone, and promethazine. No autopsy was performed. The investigator did not consider the event to be related to study therapy. ***Reviewer Comments:*** *This patient had multiple comorbidities and multiple risk factors for death including the study therapy. Given that there was no autopsy, it is unclear whether this death may be related to study therapy as the patient could have had an arrhythmia due to renal failure and electrolyte imbalances, or due to being on multiple QT prolonging agents (methadone and promethazine).*
(b) (6)	***Neutropenia, hyponatremia, death.*** 40-year-old white female with mTNBC who received her first dose of IMMU-132 (10 mg/kg) on (b) (6) and received her last dose of IMMU-132 on (b) (6) TEAEs recorded included dyspepsia, fatigue, neuropathy, anemia, neutropenia, edema, difficulty swallowing, and shortness of breath. On (b) (6) the investigator discontinued the patient from study therapy due to clinical disease progression. On that same date, the patient had an SAE of hyponatremia recorded. The patient died on (b) (6) and the cause of death was attributed to disease progression. ***Reviewer Comments:*** *While the patient experienced multiple adverse events prior to discontinuing study therapy, this reviewer agrees that the cause of death was likely due to progression of the underlying disease as the patient had not received therapy for approximately 3 weeks prior to her death and had been discontinued from study therapy by the investigator for clinical evidence of disease progression; there was no radiographic confirmation of disease progression.*
(b) (6)	***Progressive Disease.*** 64-year-old white female with mTNBC who received her first dose of IMMU-132 (10 mg/kg) on (b) (6) She presented to clinic on (b) (6) (Cycle 1, Day 8) and was ill appearing and oxygen dependent. Two days prior to this, the patient had developed diarrhea which improved with use of loperamide. Laboratory studies demonstrated that she was neutropenic with an ANC of 0.19 X 1000/uL and in acute renal failure with a creatinine of 2.98 mg/dL. Her temperature was 100.9 F, and she was admitted for febrile neutropenia. She was hemodynamically unstable and initiated on pressors. She withdrew consent from the clinical trial on (b) (6) and was discharged to home hospice. She died at her home on (b) (6) While the investigator assessed the septic shock as life threatening and related to study therapy, her death was attributed to disease progression as she was in hospice care and not receiving disease directed therapy. ***Reviewer Comments:*** *While the events of febrile neutropenia and septic shock are likely related to study therapy, the timing of her death is not consistent with this being the primary cause of death as she survived for more than 14 days at home without treatment for septic shock. It is not clear that this patient's death was directly related to study therapy.*

(b) (6)	***Death.*** 55-year-old white female with mTNBC who received the first dose of IMMU-132 (10 mg/Kg) on (b) (6) She discontinued study therapy due to disease progression with documented progression of her liver lesions on repeat scans on (b) (6) She died on (b) (6) due to disease progression. ***Reviewer Comments:*** *This reviewer agrees that the cause of this patient's death was disease progression.*
Safety Population	
(b) (6)	***Embolism.*** 83-year-old white female with metastatic colon cancer. Past medical history included atrial fibrillation, spinal stenosis, and urosepsis. Initiated therapy with IMMU-132 (dose 8 mg/kg) on (b) (6) Cycle 1 day 8 was held due to neutropenia. She received her last dose of therapy on (b) (6) On the evening of (b) (6) the patient had abdominal pain and was noted to have left arm weakness. She collapsed and died. This event was attributed to a probable thromboembolic event given the patient's atrial fibrillation and cancer, however no imaging or other assessment was performed. This was not thought related to study therapy. ***Reviewer Comment:*** *This reviewer concurs that the clinical description sounds like a possible cerebrovascular accident that was likely related to the patient's history of atrial fibrillation. Additionally, the patient's metastatic malignancy increases her risk of similar events. While a definitive assessment is not possible, it is not likely that this event was related to study therapy.*
(b) (6)	***Anasarca, systemic inflammatory response syndrome.*** 52-year-old white male with metastatic esophageal cancer with metastases to the liver and bone. He was given his first dose of study therapy (8 mg/kg) on (b) (6) and the last dose was given on (b) (6) On (b) (6) the patient presented to the emergency room with edema, shortness of breath, non-productive cough, and wheezing and was noted to have a SAE of anasarca. His chest x-ray demonstrated bilateral pleural effusions. He was noted to be neutropenic at the time. Due to progressive dysphagia, a PEG tube was placed. His neutropenia and symptoms resolved and he was discharged on (b) (6) He received his last dose of IMMU-132 on (b) (6) On (b) (6) the patient presented to the emergency room with hypotension, a fever of 100.8 F, and confusion. His lung exam revealed crackles and his abdomen was distended with RUQ tenderness. He was neutropenic with an ANC of 0.5 x 1000/uL and his calcium was elevated at 10.4 mg/dL. CT scans demonstrated progression of disease. He was treated with broad spectrum antibiotics, however given the evidence of progressive disease, the patient's family transitioned the patient to hospice care and the patient died on (b) (6) ***Reviewer Comment:*** *While the study therapy may have contributed to this patient's death due to neutropenia and possible infection, the patient was also documented to have disease progression on imaging and had hypercalcemia, likely due to progressive malignancy.*

(b) (6)	***Cardiorespiratory arrest.*** 65-year-old female with metastatic small cell lung cancer who received 32 cycles of study therapy (8 mg/kg). Past medical history was significant for intermittent syncope, urinary retention, and a 30 pack year smoking history On (b) (6) (Cycle 32, Day 6), she reported not feeling well, lost bowel and bladder control, and collapsed. She was unable to be resuscitated by her brother or by EMS using CPR. She was taken to the ED and continued attempts at resuscitation were made including use of CPR and epinephrine. The patient was also given IV bicarbonate. Approximately 30 minutes after arrival to the ED and approximately 1 hour after the initial event, CPR was discontinued. Her last dose of study therapy had been administered on (b) (6) ***Reviewer Comment:*** *It is not clear that study therapy played a role in this patient's death. The patient had been on therapy for a notable period (>1 year). She had a prior SAE of abdominal pain for which she was hospitalized and the cause of her pain was determined to be constipation as her abdominal pain resolved with laxatives and bowel movements. Prior adverse events included fatigue, nausea, dyspnea, dizziness, dehydration, cough, and tachycardia, but no noted electrolyte abnormalities, seizures, chest pain, or other cardiac events. It is unclear what the actual cause of her cardiopulmonary arrest was, but given her significant smoking history, she could have had cardiovascular disease which may have led to a cardiac arrest or ruptured aortic aneurysm.*
(b) (6)	***Failure to thrive, pleural effusion, progressive disease.*** This was a 54-year-old white female with metastatic TNBC who received her first dose of IMMU-132 (8 mg/kg) on (b) (6) She discontinued study therapy on (b) (6) due to documented progressive disease. The patient presented to the hospital with respiratory failure and shortness of breath. The plan was to transfer to hospice care at discharge, however the patient died on (b) (6) prior to discharge. The death was attributed to progressive disease. ***Reviewer Comment:*** *This reviewer agrees that this death was due to disease progression and was not due to study therapy.*
(b) (6)	***Brain Metastasis.*** 69-year-old African-American female with metastatic small cell lung cancer. Her past medical history was significant for COPD, hypertension, osteoarthritis, hyperlipidemia, fatigue, neuropathy, dyspnea, anxiety, depression, and hyponatremia. She received her first dose of study therapy on (b) (6) (10 mg/kg). Her last dose of study therapy was received on (b) (6) On (b) (6) the patient had an episode of syncope. She was admitted to the hospital and on (b) (6) an MRI of the brain revealed too many brain metastases to count. She was started on dexamethasone and was evaluated for whole brain radiotherapy. During her simulation, she had an episode of respiratory distress and chest x-ray demonstrated bilateral pneumonia. She was transitioned to palliative care. She died on (b) (6) and the cause of death was attributed to disease progression. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to*

	disease progression. The patient had tolerated therapy for approximately 6 months without significant event and thus study therapy is unlikely to have contributed to this patient's death.
(b) (6)	***Pulmonary Embolism.*** 65-year-old white male who was diagnosed with stage IV pancreatic adenocarcinoma in (b) (6) Past medical history was significant for GERD, RUE DVT, peripheral neuropathy, partial blindness, ascites, peritoneal carcinomatosis, abdominal pain, loss of appetite, and constipation. He received his first and only dose of study therapy on (b) (6) (b) (6) (10mg/kg). On Day 7, (b) (6) the patient was admitted with melena and was admitted for a GI bleed. One week prior to the admission, he had undergone paracentesis with removal of 3 L of fluid. Upper endoscopy performed on Day 8 demonstrated severe esophagitis secondary to gastric outlet obstruction. On Day 12, the patient underwent stent placement to relieve the obstruction. On Day13, his course was complicated by the finding of a pulmonary embolism which was identified after the patient experienced progressive shortness of breath. CT pulmonary angiography demonstrated multiple pulmonary emboli. He had worsening pulmonary status, was trialed on BiPAP, and due to overall deterioration, it was confirmed that the patient was a DNR/DNI and the patient and family elected for comfort measures. The patient died on Day 14. Cause of death was reported as pulmonary embolism. No autopsy was performed. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to pulmonary embolism, a known risk associated with metastatic pancreatic adenocarcinoma. It is not likely that study therapy contributed to this patient's death.*
(b) (6)	***Acute Respiratory Distress.*** 72-year-old white male who was initially diagnosed with stage IV small cell lung cancer with a solitary brain metastasis in (b) (6) (b) (6) The patient's past medical history was significant for diabetes, hypertension, coronary artery disease, dysgeusia, anxiety, anorexia, hyponatremia, dyspnea, pleural effusions, and urinary frequency. The first dose of IMMU-132 (8 mg/kg) was administered on (b) (6) The last dose administered prior to the event was (b) (6) The patient developed worsening ability to swallow and was hospitalized on (b) (6) A PEG tube was placed. On (b) (6) the patient developed delirium due to hospitalization and pain medications. On (b) (6) the patient developed acute respiratory distress. CT pulmonary angiography demonstrated no evidence of a pulmonary embolism, but a new moderate to large pleural effusion and consolidation consistent with pneumonia. His respiratory status continued to decline and he was transitioned to hospice care. The patient died on (b) (6) (b) (6) and the death was attributed to progressive disease/acute respiratory distress. No autopsy was performed. ***Reviewer Comment:*** *This reviewer considers this death to be due to pneumonia vs. disease progression. Given the dysphagia preceding the events, it is possible that this patient had an aspiration event. The effusion could have been due to progressive disease as well and the dysphagia possibly due to CNS progression,*

	but there is no report of his CNS being evaluated. Whether due to acute pneumonia or disease progression, this reviewer agrees that it is not likely that study therapy contributed to this patient's death.
(b) (6)	***Hypoxia, progressive disease.*** 74-year-old male with metastatic small cell lung cancer. Additional comorbidities included atrial fibrillation, COPD, CAD, history of CVA, history of small cell lung cancer, hypomagnesemia, hypokalemia, abdominal aortic aneurysm. The patient initiated therapy with IMMU-132 (10 mg/kg) on (b) (6) Subsequently he developed a lower GI bleed on (b) (6) The dose of IMMU-132 was reduced to 7.5 mg/kg for subsequent doses. The last dose of therapy administered prior to the onset of hypoxia was on (b) (6) On (b) (6) he presented to the emergency department with shortness of breath. CT scan showed stable disease but possible multifocal pneumonia. On clinical exam, inspiratory and expiratory wheezing was noted. On (b) (6) the patient transferred to inpatient hospice. The patient died on (b) (6) and the cause of death was attributed to progressive disease. ***Reviewer Comment:*** *The reviewer agrees with the assessment. Given the patient's underlying comorbidities and disease, the patient was at increased risk for pneumonia, including post-obstructive pneumonia. It is not clear that study therapy played a role in this patient's death.*
(b) (6)	***Progressive disease.*** 65-year-old white male who was initially diagnosed with stage IV small cell lung cancer in (b) (6) with metastases to the bone, liver, and mediastinum. Past medical history was significant for anemia, peripheral vascular disease, hyperlipidemia, anxiety, chronic back pain, alcohol abuse, fatigue, weight loss, shortness of breath, kyphosis, and diverticulosis. The patient was treated with 28 doses of IMMU-132 (10 mg/kg) from (b) (6) to (b) (6) The enrolled in Hospice care on (b) (6) and died due to disease progression on (b) (6) No autopsy was performed. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. The reason for study discontinuation captured in the dataset was "Investigator Decision." The patient had previously tolerated therapy for approximately 10 months without difficulty. It is not likely that study therapy contributed to this patient's death.*
(b) (6)	***Aspiration pneumonia.*** 62-year-old white male with stage IV non-small cell lung cancer with a past medical history significant for hyperlipidemia, CAD, esophageal stenosis, hypertension, GERD, pneumonitis, and peripheral neuralgia. The first dose of IMMU-132 (10 mg/Kg) was administered on (b) (6) with the last dose administered on (b) (6) The patient was admitted to the hospital for nausea and dehydration on (b) (6) (b) (6) He had previously taken granisetron and prochlorperazine with limited improvement. He was given IV fluids and antiemetics and his symptoms improved. He was discharged on (b) (6) with improvement in symptoms,

	though his nausea was ongoing. The patient presented to the emergency department on (b) (6) with aspiration pneumonia. He was admitted with respiratory distress and chest x-ray demonstrated infiltrates. CT scan of the neck demonstrated persistent right supraclavicular mass and retropharyngeal swelling with new left supraclavicular lymphadenopathy. The patient was treated with broad spectrum antibiotics, but had nausea and clear emesis. On (b) (6) he had a cardiorespiratory arrest with PEA and received 6 rounds of CPR with two pushes of epinephrine and two pushes of naloxone. Multiple attempts at intubation were unsuccessful due to cervical lymphadenopathy and varices. Autopsy was performed and suggested that the underlying cause of death was due to metastatic lung cancer with post-obstructive sequalae. The Investigator and Sponsor considered the fatal event of aspiration pneumonia to possibly be related to IMMU-132. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was aspiration pneumonia, however in the setting of progressive cervical adenopathy, it is not clear that this event was related to study therapy. Given these findings, it is likely that this event was due to disease progression and not related to study therapy.*
(b) (6)	***Pneumonia.*** 54-year-old female with stage IV non-small cell lung cancer. Past medical history significant for dyspnea with hypoxia, fatigue, chest wall pain, lightheadedness, prolonged QTc, cough, depression, right pleural effusion, insomnia, anemia, and anxiety. Received a single dose of IMMU-132 (10 mg/kg) on (b) (6) Presented for cycle 1, day 8 on (b) (6) but study therapy withheld due to sinusitis/pneumonia with shortness of breath. Febrile and received a 10-day course of levofloxacin. On (b) (6) admitted for sepsis with respiratory failure and pneumonia. Chest x-ray demonstrated persistent right middle lobe consolidation and collapse and decreased right effusion. Had pulmonary edema and underwent thoracentesis with limited improvement. Permanently discontinued study therapy on (b) (6) (b) (6) due to disease progression. Transitioned to inpatient Hospice care on (b) (6) and died on (b) (6) The pneumonia was assessed as related to disease progression. No autopsy was performed. The Investigator and Sponsor attributed this fatal event to be unrelated to IMMU-132. ***Reviewer Comment:*** *This reviewer disagrees and considers this event as possibly related to study therapy. The cause of death as recorded in the datasets is due to adverse event, though the dataset indicates that the patient was discontinued from study therapy due to progressive disease. Given the risk of neutropenia associated with this therapy, it is possible that febrile neutropenia contributed to this patient's event. Review of the adlb.xpt dataset demonstrated that the neutrophil count was 1.3 x 10^9. While there were no additional labs available, it would be difficult to interpret subsequent laboratory results given the patient's sepsis and treatment with broad spectrum antibiotics. While it is not clear that*

	this patient's death is definite due to disease progression, it is possible that it may be given the known risk of neutropenia and infection associated with this therapy.
(b) (6)	***Hypoxia, pleural effusion, progressive disease.*** 53-year-old white male with metastatic non-small cell lung cancer. Past medical history was significant for depression, neuropathy, nausea, metastatic disease to the bone, fatigue, OSA, and hypertension. He was treated with his initial dose of IMMU-132 (10 mg/kg) on (b) (6) and received three subsequent doses at a dose reduction to 7.5 mg/kg. He received his last dose of study therapy on (b) (6) The patient was admitted to the hospital on (b) (6) at which time he was diagnosed with a right pleural effusion that was increasing in size. He additionally had a small left pleural effusion. Ultrasound guided thoracentesis of the left lung was performed and he underwent wire manipulation and declogging of right PleurX catheter. Symptoms improved' received 2 units of packed red blood cells on (b) (6) On (b) (6) admitted due to hypoxia and found to have aspiration pneumonia. He was septic and had evidence of acute kidney injury. Received broad spectrum antibiotics. On (b) (6) experienced clinical deterioration with worsening respiratory failure. Transitioned to comfort measures. Died on (b) (6) due to acute respiratory failure from progressive disease. The investigator and sponsor considered the events unrelated to study therapy. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression with worsening pulmonary effusions. He was not neutropenic with these events as he had received G-CSF and culture data revealed no organism. It is not likely that study therapy contributed to this patient's death.*
(b) (6)	***Neutropenic typhlitis, respiratory failure.*** 64-year-old white female with metastatic small-cell lung cancer with a past medical history significant for R pleural effusion, intermittent right headache, GERD, hypertension, gallstones, kidney stone, 50 pack year smoking history, cholecystitis, and anxiety. She received two doses of IMMU-132 (10 mg/kg) with the first dose on (b) (6) (b) (6). On cycle 1, day 5 (b) (6) the patient developed neutropenic typhlitis. Received broad spectrum antibiotics and antifungals. On (b) (6) (b) (6) symptoms improved, WBC was 9.3 x 1000/uL and ANC was 8.2 x 1000/uL. While the typhlitis resolved, the hypoxemia worsened. CT scan on (b) (6) (b) (6) demonstrated bilateral ground glass opacities and chest x-ray demonstrated a progressive alveolar filling process. Right thoracentesis performed on (b) (6) and it was considered that ARDS was the etiology. Received diuretics without evidence of improvement. Transitioned to comfort care measures and died on (b) (6) with the cause of death indicated as disease progression. No autopsy was performed. The neutropenic typhilitis event was considered severe and related to study

	therapy by both the Investigator and the Sponsor. The patient's respiratory failure was considered unrelated to study therapy. ***Reviewer Comment:*** *This reviewer disagrees and considers the event of respiratory failure due to ARDS as possibly related to study therapy. ARDS is known to be a sequela of sepsis or major illness and, in this case, may have been triggered by the patient's neutropenic colitis which both the Investigator and Sponsor agree was related to study therapy.*
(b) (6)	***Progressive Disease.*** 73-year-old white male who was initially diagnosed with stage IV urothelial cancer with metastases to the lymph nodes, lung, liver, adrenal gland, bone and subcutaneous tissue. Past medical history was significant for prostate cancer that was treated with curative intention with radiation therapy and ADT, colon polyps, history of smoking, fatigue, nocturia, depression, arthritis, neuropathy, decreased appetite, nausea, constipation and back pain. Received his first dose of study therapy on (b) (6) (dose 10 mg/kg) and received 10 total doses with the last dose received on (b) (6) CT scan completed on (b) (6) demonstrated progressive disease. The patient discontinued study therapy on (b) (6) and was transitioned to Hospice Care. The patient died on (b) (6) due to disease progression. No autopsy was performed. The Investigator and Sponsor considered this death due to disease progression. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. The patient had clinical evidence of progression on study imaging, was discontinued from study therapy, and was transition to Hospice care. It is not likely that study therapy contributed to this patient's death.*
(b) (6)	***Respiratory failure.*** 63-year-old white male with stage IV small cell lung cancer. Past medical history significant for coronary artery disease, GERD, hyperlipidemia, anxiety, inguinal hernia, type 2 diabetes mellitus, hypertension, cough, and headache. Received first dose of study therapy on (b) (6) and received 27 doses total: 11 doses of 10 mg/kg and 16 doses of 7.5 mg/kg. His last dose of study therapy was on (b) (6) Progressive disease was confirmed on (b) (6) The patient presented to a local emergency room on (b) (6) with shortness of breath. He was tachycardic and hypoxic with O_2 saturations of 82-91% on non-rebreather mask. PE protocol CT demonstrated no PE, but demonstrated evidence of progressive disease with bilateral ground glass opacities in the lungs, an increase in the size of the R lower lobe mass, an increase in the size of the hepatic metastases, and rising total bilirubin (total bilirubin 10.5 mg/dL). He was admitted for symptomatic care and was ultimately transitioned to comfort measures. The patient died on (b) (6) (b) (6) due to progressive disease. No autopsy was performed. Neither the sponsor nor the investigator considered this death as related to study therapy. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. It is not likely that study therapy contributed to this patient's*

	death.
(b) (6)	***Hyperbilirubinemia.*** 54-year-old white female with metastatic hormone receptor positive breast cancer with metastases to the lungs, liver and bone. Medical history was significant for GERD, hypercholesterolemia, diverticulosis, seasonal allergic rhinitis, and asthma. Received first dose of study therapy on (b) (6) (b) (6) (dose 10 mg/kg). On (b) (6) the dose was reduced to 7.5 mg/kg due to neutropenia. Received a total of 15 doses of study therapy with the last dose received (b) (6) On (b) (6) experienced elevated total bilirubin of 2.0 mg/dL. On (b) (6) (b) (6) the total bilirubin increased to 3.9 mg/dL. Admitted for further evaluation of hyperbilirubinemia in the setting of known hepatic metastases. Abdominal ultrasound performed on (b) (6) demonstrated mild central bile duct dilatation. On (b) (6) serum bilirubin was 7.7 mg/dL with direct bilirubin of 5.9 mg/dL. Assessed as likely related to known hepatic metastases. MRCP performed on (b) (6) and showed innumerable hepatic metastases that were not significantly changed since the prior CT scan on (b) (6) Gastroenterology consultation on (b) (6) indicated that "*given the constellation of progressive symptoms correlating with the initiation of IMMU-132, cholestatic pattern of LFTs, and the lack of dilatation and metastatic progression on imaging thus far, the most likely etiology of the patient's direct hyperbilirubinemia entail reaction to the patient's clinical trial drug.*" Liver biopsy recommended. Patient requested discharge from the hospital on (b) (6) (b) (6) and the punderwent IR-guided biopsy on (b) (6) revealed cholestatic liver with evidence of biliary ductal damage contributing to the elevated bilirubin. The end of treatment was (b) (6) and reason noted was progressive disease as the patient had rising tumor markers. Admitted on (b) (6) with grade 4 weakness and grade 2 confusion. Bilirubin had continued to rise. An autopsy was performed which revealed innumerable hepatic metastases that replaced approximately 80% of the hepatic parenchyma. The cause of death was considered progressive disease. Neither the investigator nor the sponsor considered this event related to study therapy. ***Reviewer Comment:*** *This reviewer agrees that the cause of death was due to disease progression. It is not likely that study therapy contributed to this patient's death.*

Reviewer Comments: *There was one death in the safety population due to neutropenic typhilitis. Given this, along with the incidence of neutropenia and diarrhea, a box warning for diarrhea and neutropenia is warranted. In the mTNBC cohort, there was one death that was not clearly attributable to disease. However, it was not clear whether the death may be related to study therapy as the patient had multiple comorbidities including renal failure and electrolyte imbalances that may have contributed to their death.*

Serious Adverse Events

Table 27. Serious Adverse Events in >2% patient by Descending Frequency in IMMU-132-01

Adverse Events	Safety Population n=408		mTNBC Population n=108	
	All Grade n (%)	Grade 3-4 n (%)	All Grade n (%)	Grade 3-4 n (%)
≥ 1 SAE	165 (40.5)	127 (31.1)	35 (32.4)	27 (25)
Infection*	34 (8.3)	30 (7.4)	10 (9.3)	9 (8.3)
Febrile Neutropenia	17 (4.2)	16 (3.9)	8 (7.4)	7 (6.5)
Respiratory Infection	15 (3.7)	11 (2.7)	3 (2.8)	3 (2.8)
Diarrhea	14 (3.4)	12 (2.9)	3 (2.8)	2 (1.9)
Dyspnea/Dyspnea exertional	11 (2.7)	9 (2.2)	4 (3.7)	2 (1.9)
Vomiting	11 (2.7)	8 (2)	7 (6.5)	6 (5.6)
Neutropenia*	9 (2.2)	9 (2.2)	2 (1.9)	2 (1.9)
Asthenia/Fatigue	6 (1.5)	5 (1.2)	1 (0.9)	1 (0.9)
Nausea	9 (2.2)	8 (2)	4 (3.7)	4 (3.7)
Intestinal Obstruction	2 (0.5)	2 (0.5)	0	0
Respiratory Failure/Hypoxia	7 (1.7)	2 (0.5)	0	0
Pulmonary Embolism/DVT/Embolism*	5 (1.2)	3 (0.7)	0	0
Pleural effusion	6 (1.5)	5 (1.2)	2 (1.9)	2 (1.9)
Sepsis/Septic Shock/Bacteremia	5 (1.2)	5 (1.2)	2 (1.9)	2 (1.9)
Abdominal Pain*	6 (1.5)	5 (1.2)	0	0
GastrointestinaI Bleeding*	3 (0.7)	2 (0.5)	0	0
Pain/Musculoskeletal pain*	9 (2.2)	8 (2)	2 (1.9)	1 (0.9)

Source: *FDA Reviewer Analysis with support from safety analytics team using adae.xpt dataset & reviewing Table 55 on page 128 of the CSR;* *******=pooled terms

Infection: Abdominal abscess; Atypical pneumonia; Body tinea; Bronchitis; Candida infection; Catheter site infection; Cellulitis; Clostridium difficile colitis; Clostridium difficile infection; Conjunctivitis; Cystitis; Device related infection; Diverticulitis; Escherichia bacteraemia; Escherichia infection; Escherichia urinary tract infection; External ear cellulitis; Eye infection viral; Folliculitis; Fungal infection; Fungal skin infection; Furuncle; Gastroenteritis; Gastroenteritis viral; Gastrointestinal infection; Herpes virus infection; Herpes zoster; Hordeolum; Influenza; Intervertebral discitis; Kidney infection; Liver abscess; Lower respiratory tract infection; Lung infection; Mastitis; Metapneumovirus infection; Mucosal infection; Oesophageal candidiasis; Oral candidiasis; Oral herpes; Peritonitis; Pleural infection; Pneumonia; Pneumonia haemophilus; Rectal abscess; Respiratory syncytial virus infection; Respiratory tract infection; Sepsis; Septic shock; Skin infection; Staphylococcal bacteraemia; Tooth abscess; Tooth infection; Upper respiratory tract infection; Urinary tract infection; Vaginal infection; Viral infection; Viral upper respiratory tract infection; Vulvovaginal mycotic infection; Vulvovaginitis; Wound infection
Neutropenia: Neutrophil count decreased; neutropenia
Abdominal Pain: abdominal pain upper; abdominal pain lower; abdominal distension; abdominal tenderness; abdominal discomfort; abdominal pain
Gastrointestinal Bleeding
Pain/MSK pain: Back pain; musculoskeletal pain; pain in extremity; musculoskeletal chest pain; bone pain; pain; neck pain; non-cardiac chest pain; arthralgia

Reviewer Comment: *The incidence of serious adverse events was similar in the overall safety population and in the mTNBC efficacy cohort. There was increased febrile neutropenia noted in*

the mTNBC cohort and this may be due to the population being more heavily pretreated than the overall safety population as at least two prior lines of systemic therapy were required for the mTNBC efficacy cohort. Additionally, there was a numerically greater incidence of nausea and vomiting.

Dropouts and/or Discontinuations Due to Adverse Effects

In the IMMU-132-01 safety population, 40/408 (9.8%) patients discontinued study therapy due to TEAEs. The most common reason to discontinue study treatment were fatigue (n=5;1.2%), pneumonia (n=4; 1.0%), diarrhea (n=3; 0.7%), pruritis (n=3; 0.7%), anemia (n=2; 0.5%), headache (n=2; 0.5%), neutropenia/febrile neutropenia.

In the IMMU-132-01 mTNBC efficacy cohort, 5 patients (4.6%) discontinued study therapy due to TEAEs. The most common reason specific adverse events that lead to discontinue study treatment were: hypertension (patient (b) (6)), anaphylaxis (patient (b) (6)), anorexia/fatigue (patient (b) (6)), hyponatremia ((b) (6)), and headache ((b) (6)).

Significant Adverse Events

The incidence of Grade 3 or 4 adverse events in the overall safety population (n=408) for IMMU-132-01 was 74.5% and for the mTNBC cohort (n=108) was 72.2%. The most common Grade 3 or 4 AEs were neutropenia (38.5% in the overall safety population and 41.7% in the mTNBC cohort), anemia (11.3% in the overall safety population and 11.1% in the mTNBC cohort), white blood cell count decreased (8.3% in the overall safety population and 11.1% in the mTNBC), fatigue (11.0% in the overall safety population and 8.3% in the mTNBC cohort), diarrhea (8.6% in the overall safety population and 8.3% in the mTNBC cohort), hypophosphatemia (5.6% in the overall safety population and 9.3% mTNBC cohort), nausea (5.6% in the overall safety population and 6.5% in the mTNBC cohort), vomiting (3.9% in the overall study population and 6.5% in the mTNBC cohort).

Reviewer Comment: *Overall, the incidence of the most common Grade 3-4 AEs was similar in the overall safety population and in the mTNBC population.*

Given the known toxicities associated with treatment with drugs containing irinotecan, and the observed incidence of GI and hematologic (neutropenia) adverse events, safety analyses focused on these toxicities and their complications, were performed. Six percent (6%) of patients in the overall study population and 9.3% of patients in the mTNBC cohort had at least one episode of febrile neutropenia. Ten patients (2.5%) had neutropenic colitis the overall safety population and four patients (3.7%) had neutropenic colitis in the mTNBC cohort.

Regardless of neutrophil count, eight patients (1.9%) had c difficile colitis demonstrating that, in addition to diarrhea being due to study therapy, that there was an increased risk of this particular infectious organism, likely due to antibiotic therapy due to previous infection/neutropenic fever, on this or other anticancer regimens.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) were assessed in the mTNBC efficacy cohort as well as in the overall safety population to characterize safety across a large patient sample. The overall safety population consisted of patients in Study IMMU-132-01 who received an initial sacituzumab dose of 8 or 10 mg/kg (n=408); patients who received >10 mg/kg as an initial dose in Study IMMU-132-01 were not included in the analyses of overall safety.

Safety analyses were based on all AEs, irrespective of investigator attribution to study drug. As this is a single-arm study and attribution is difficult to assess, adverse event tables included events regardless of investigator attribution to study therapy. Events in the safety population that received up to 10 mg/kg are below in Table 28 and events in the mTNBC efficacy population are below in **Error! Reference source not found.**. APPEARS THIS WAY ON ORIGINAL

Table 28. Most Common (≥10%[1]) Adverse Events in Safety Population (n=408)

Preferred Term*	**Safety Population n=408**				**Efficacy Population n=108**			
	All Grade		**Grade 3-4**		**All Grade**		**Grade 3-4**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
≥ 1 AE	407	99.8	287	70.3	108	100	76	70.4
Nausea	275	67.4	22	5.4	72	66.7	7	6.5
Diarrhea	253	62	35	8.6	67	62	9	8.3
Neutropenia*	220	53.9	156	38.2	69	63.9	45	41.7
Fatigue	214	52.5	39	9.6	55	50.9	8	7.4
Vomiting	178	43.6	16	3.9	53	49.1	7	6.5
Alopecia	173	42.4	1	0.2	39	36.1	1	0.9
Anemia	167	40.9	46	11.3	54	50	12	11.1
Infection*	166	40.7	42	10.3	54	50	13	12
Constipation	149	36.5	3	0.7	37	34.3	1	0.9
Decreased appetite	144	35.3	4	1	32	29.6	0	0
Pain/MSK pain *	142	34.8	9	2.2	52	48.1	1	0.9
Abdominal Pain*	113	27.7	12	2.9	27	25	1	0.9
Rash*	99	24.3	5	1.2	32	29.6	2	1.9
Dyspnea	84	20.6	18	4.4	20	18.5	3	2.8
Edema *	77	18.9	5	1.2	23	21.3	0	0
Cough	73	17.9	0	0	19	17.6	0	0
Weight decreased	69	16.9	1	0.2	15	13.9	0	0
Pyrexia	65	15.9	0	0	13	12	0	0
Dehydration	64	15.7	8	2	14	13	4	3.7
Dizziness	64	15.7	2	0.5	22	20.4	0	0
Headache	59	14.5	2	0.5	23	21.3	1	0.9
Urinary tract infection	51	12.5	6	1.5	22	20.4	3	2.8
Insomnia	48	11.8	0	0	15	13.9	0	0
Pruritus	47	11.5	2	0.5	17	15.7	0	0
Hyperglycemia	46	11.3	13	3.2	26	24.1	4	3.7
Upper respiratory tract	40	9.8	2	0.5	12	11.1	1	0.9

infection								
Dry skin	30	7.4	1	0.2	15	13.9	1	0.9
Dysgeusia	29	7.1	0	0	12	11.1	0	0
febrile neutropenia	24	5.9	22	5.4	10	9.3	9	8.3
Neuropathy peripheral	24	5.9	0	0	10	9.3	0	0

Source: *reviewer analysis using adae.xpt dataset.* Analysis excludes laboratory-based preferred terms. [1]In either the overall safety population or the efficacy population; MSK= Musculoskeletal; *= pooled terms.
Neutropenia: Neutrophil count decreased; neutropenia
Infection: Abdominal abscess; Atypical pneumonia; Body tinea; Bronchitis; Candida infection; Catheter site infection; Cellulitis; Clostridium difficile colitis; Clostridium difficile infection; Conjunctivitis; Cystitis; Device related infection; Diverticulitis; Escherichia bacteraemia; Escherichia infection; Escherichia urinary tract infection; External ear cellulitis; Eye infection viral; Folliculitis; Fungal infection; Fungal skin infection; Furuncle; Gastroenteritis; Gastroenteritis viral; Gastrointestinal infection; Herpes virus infection; Herpes zoster; Hordeolum; Influenza; Intervertebral discitis; Kidney infection; Liver abscess; Lower respiratory tract infection; Lung infection; Mastitis; Metapneumovirus infection; Mucosal infection; Oesophageal candidiasis; Oral candidiasis; Oral herpes; Peritonitis; Pleural infection; Pneumonia; Pneumonia haemophilus; Rectal abscess; Respiratory syncytial virus infection; Respiratory tract infection; Sepsis; Septic shock; Skin infection; Staphylococcal bacteraemia; Tooth abscess; Tooth infection; Upper respiratory tract infection; Urinary tract infection; Vaginal infection; Viral infection; Viral upper respiratory tract infection; Vulvovaginal mycotic infection; Vulvovaginitis; Wound infection
Pain/MSK pain: Back pain; musculoskeletal pain; pain in extremity; musculoskeletal chest pain; bone pain; pain; neck pain; non-cardiac chest pain; arthralgia
Abdominal Pain: abdominal pain upper; abdominal pain lower; abdominal distension; abdominal tenderness; abdominal discomfort; abdominal pain
Rash: rash; rash pruritic; rash papular; rash maculo-papular; rash macular; rash erythematous; rash generalised; hand dermatitis; dermatitis contact; dermatitis; dermatitis acneiform;
Edema: oedema; localised oedema; oedema peripheral; lymphoedema; pulmonary oedema; generalised oedema; testicular oedema; periorbital oedema; face oedema; tongue oedema

Reviewer Comments: *Safety findings were similar in the overall population and the mTNBC population. Cytopenias were increased in the mTNBC cohort, which may reflect that this cohort was required to have received at least 2 prior therapies when the overall safety population had received at least one prior therapy in the metastatic setting. Additionally, the overall safety population has a portion of patients who received 8 mg/kg rather than 10 mg/kg which may make the incidence of adverse events slightly lower in the overall group than in the mTNBC cohort. Patients who received doses greater than 10 mg/kg were not included in these analyses as they were not included in package labeling so as not to mislead prescribers that doses of greater than 10 mg/kg are safe.*

Laboratory Findings

Of interest were patients who had a grade 3-4 laboratory abnormality. The incidence of these abnormalities for the safety population is captured in Table 29 below.

Table 29. Grade 3-4 Laboratory Abnormalities in IMMU-132-01

Laboratory Parameter	Safety Population Grade 3-4 n (%)	Efficacy Population Grade 3-4 n (%)
Hematology		
Absolute Lymphocyte Count Decreased	110 (27.2)	28 (26.7)
Absolute Neutrophil Count Decreased	109 (27.0)	31 (29.5)

Leukocytes decreased	83 (20.6)	26 (24.8)
Platelets decreased	28 (6.9)	3 (2.9)
Hemoglobin decreased	26 (6.4)	7 (6.7)
Prolonged APTT	20 (5.2)	10 (9.7)
Chemistries		
Hyponatremia	34 (8.4)	5 (4.6)
Blood Glucose Increased	24 (5.9)	3 (2.9)
Hypokalemia	20 (5.0)	5 (4.8)
Elevated Alkaline Phosphatase	18 (4.5)	3 (2.9)
Hypernatremia	7 (1.7)	2 (1.9)
Hypophosphatemia	12 (3.0)	4 (3.7)
Hypermagnesemia	9 (2.4)	1 (1.2)
Hyperbilirubinemia	9 (2.3)	2 (1.9)
Elevated AST	9 (2.2)	4 (3.8)
Hypocalcemia	9 (2.2)	2 (1.9)
Hypercalcemia	9 (2.2)	3 (2.9)
Hypoalbuminemia	8 (2.0)	1 (1.0)
Hyperkalemia	8 (2.0)	2 (1.9)
Hypomagnesemia	3 (0.8)	2 (1.9)
Elevated ALT	6 (1.5)	2 (1.9)
Blood Glucose decreased	5 (1.2)	2 (1.9)
Creatinine increased	2 (0.5)	1 (1.0)

Source: *Reviewer analysis with the assistance of Clinical Analyst Yutao Gong; ADLB.xpt dataset; Data cut off Dec 17, 2018.*

Reviewer Comments: *The incidence of grade 3-4 neutropenia in the laboratory dataset is slightly lower than that of the adverse event dataset. Thirty three percent (n=137, 33.6%) of patients in the overall safety population received G-CSF support at some point during study therapy and 53.7% (n=58) of patients in the mTNBC cohort received g-csf support at some point during the study. At the time of amendment 7 (December 9, 2014), patients could receive growth factor support at any point in the study after cycle 1 day 1. This may have led to increased reporting by investigators and lower rates in the actual laboratory datasets. Additionally, it was noted that there was discordance in the lab dataset and the AE dataset regarding reporting dates as there were clinician reported events which did not correspond to laboratory dates. This is likely due to the CRFs having places for laboratory reporting associated with infusion dates while the adverse event reporting was captured on a separate form and permitted capture of events not directly linked to a study visit.*

Vital Signs

There were no relevant changes from baseline to the end of treatment for mean vital signs obtained in either the overall safety population or the mTNBC efficacy cohort.

It was noted that 30 minutes post infusion, 37% of patients (n=151) in the overall safety cohort had a decrease in systolic blood pressure from baseline of 20 mmHg or greater. At 60 minutes post infusion, this improved to 22% of patients (n=91) in the overall safety cohort.

Fifty-four patients had a decrease in SBP at the end of study therapy by ≥20 mmHg (13.2%) and 39 (9.6%) patients had an increase in SBP at the end of study therapy by ≥20 mmHg.

Bradycardia (defined as HR <60 AND change in HR of ≥20 beats per minute), an adverse event of interest given the cholinergic properties of sacituzumab govitecan and other irinotecan derivatives, at 30 minutes post-infusion was identified in 21 (5%) of patients.

Tachycardia (defined as HR >100 and change in HR of ≥20 beats per minute), at 30 minutes post-infusion was identified in 29 (7.1%) of patients.

Reviewer Comments: *While there were no significant changes in vital signs overall, there were changes in blood pressure and heart rate associated with infusions. Patients were not uniformly pre-treated with infusion reaction prevention medications in IMMU-132-01, however, as shown in the concomitant medication table, most patients received pretreatment steroids, acetaminophen, and/or H2 blockers. Given the findings from this study, the applicant proposed in the USPI that all patients should receive pre-infusion medications, that the infusion should be slowed or discontinued for infusion-related reactions and that sacituzumab govitecan should be permanently discontinued for severe infusion-related reactions. Additionally, the USPI includes the instructions for post-infusion monitoring for the initial infusion. Using SMQ, 148 patients (34.8%) had some event that may be considered and infusion related reaction. Of these, most patients were able to proceed with a slower rate of infusion without dose interruption or discontinuation, however 3 patients had a drug interruption and 3 patients discontinued study therapy due to these events.*

Electrocardiograms (ECGs)/QT

Single, 12-lead electrocardiograms were obtained at study screening/baseline, after completion of the infusion on Day 1 of every even numbered treatment cycle, at the end of treatment and at the end of study. ECGs were interpreted by investigators. Initially, investigators were only required to report abnormal readings.

The analysis of the incidence and severity of the effects sacituzumab goveitecan are limited by incomplete data. In the initial protocol, investigators were required only to record findings on the ECG if they were abnormal. Therefore, an assessment of the QTc interval was not performed for all patients as and for those patients for whom on-treatment ECG/QTc assessments are recorded in the analysis datasets (adeg.xpt), baseline values are missing for a significant proportion (202/408 (49.5%)). Given the small number of patients with complete information, the interpretation of study results is limited.

In the overall study population, 16 (7.2%, missing data on 202 patients) had increases had increases >500 ms in the QTc using Bazett's formula while 6 patients (2.7%, missing data on 202 patients) had increases >500 ms in the QTc using Fridericia's formula. In the mTNBC cohort, 7 patients (7.6%, data missing for 26 patients) had increases >500 ms in the QTc using Bazett's formula while 5 patients (6.1%, data missing for 26 patients) had increases >500 ms in the QTc using Fridericia's formula.

Reviewer Comments: *In general, a QTc of > 500 milliseconds (ms) or an increase in QTc of > 60 ms over baseline is thought to confer a higher risk of fatal arrhythmias like Torsade de Pointes. In Study IMMU-132-01, there is some evidence of mild prolongation of the QT interval. There were no ventricular arrhythmia events reported. Fifty-two patients (of 182 with baseline ECG, 28.6%) had a >30 QTc ≤60 milliseconds (ms) and 17 patients (9.3%) had a QTc increase of >60 ms. Whether this is due to study drug, electrolyte abnormalities or concomitant therapies is unclear. Given the risk of death due to underlying disease, the risk of QT prolongation is minimal. There will be further evaluation of the effect of this therapy on QT interval as part of the ongoing Phase 3 ASCENT study, IMMU-132-05.*

Immunogenicity

There were three patients who developed persistent human anti-human antibodies (HAHA) to study therapy: (b) (6) Review of the safety database for these patients did not reveal any clear safety issues related to this event.

Reviewer Comment: *None of the 3 patients who developed HAHA were responders in the efficacy analysis. Assessment of the relationship between HAHA and therapy efficacy is limited by the small number of patients included.*

8.2.5. Analysis of Submission-Specific Safety Issues

Nausea and Vomiting

Nausea and vomiting had a high incidence in this study population. Given the findings, labeling recommends premedication with antiemetics to reduce this risk. This risk is of concern in the setting of the additional risk of diarrhea all of these events can lead to dehydration, electrolyte abnormalities and decreased oral intake which can create additional risks in an ill population that may have some degree of poor oral intake at baseline.

Diarrhea

Diarrhea was frequent in this study population and as many as 10% of patients had Grade 3 diarrhea. As noted above, this can lead to dehydration, electrolyte abnormalities and decreased oral intake. Additionally, given the incidence of neutropenia, this can also lead to infection. This is noted as the incidence can be modified through the use of supportive care medications such as loperamide, treatments at the time of infusion such as atropine, and that both patients and providers should be advised of this risk so as to incorporate appropriate supportive care measures. Additionally, given that infections including *c difficile* were noted, appropriate infectious work up and treatment are also recommended.

Infusion-related reactions

Infusion related reactions including shortness of breath, rash, hypotension, and anaphylaxis were reported. Most patients received some type of premedication to prevent infusion reactions including steroids, antihistamines, H2 blockers, and/or acetaminophen. Labeling includes

instructions to reduce the infusion rate for grade 1 infusion reactions, to stop the infusion if a grade 2 reaction and consider restarting at a lower infusion rate when clinically stable, and to discontinue study therapy in the event of a grade 3 infusion related reaction.

Neutropenia

Neutropenia occurred in 63.9% of patients in the mTNBC cohort. The incidence of febrile neutropenia was low, however there were reports of neutropenic colitis and one death in the safety population occurred in the setting of this event. Over half of patients (53.7%) received growth factor support at some point during the study. Dose modifications for neutropenia are contained within the USPI.

UGT1A1 Mutation Status

The UGT1A1 gene is involved in metabolism of this drug. Of the safety population UGT1A1 status was known for 333/420 (79.3%) patients. Of these, 37/333 (11.1%) were homozygous for the *28 allele (decreased metabolism), 152/333 (45.6%) were heterozygous *1/*28 (possibly decreased metabolism), and 144/333 (43.2%) were homozygous for the *1 allele (normal metabolism). Of those in the mTNBC efficacy population, UGT1A1 status was known for 86/108 (79.6%) patients with 6/86 (7.0%) homozygous for the *28 allele, 37/86 (43.0%) heterozygous, and 43/86 (50.0%) homozygous for the *1 allele. Given the small sample size, there may be additional adverse events associated with UGT1A1 mutations that have not yet been identified. Table 30. Incidence of AEs by UGT1A1 Mutation Status in the Safety Population below captures AEs by UGT1A1 mutation status. As indicated in the table, the incidence of neutropenia is increased in those patients who are homozygous for *28/*28 as compared to the other subpopulations. This was consistent in analyses using the adlb.xpt dataset as well where the incidence of grade 4 neutropenia was 27% for patients who are homozygous for the *28 allele, 6% in patients heterozygous for the *28 allele, and 5% for patients with the wild-type allele. Additionally, there was a higher incidence of weight decreased and hypokalemia in those patients who are homozygous for the *28 allele.

At this time, it is not clear that prospective genotyping to dose this therapy based on UGT1A1 status is beneficial. Additional data will be collected in Study IMMU-132-05 to further characterize the differences in adverse event profiles.

Table 30. Incidence of AEs by UGT1A1 Mutation Status in the Safety Population

	UGT1A1 *1/*1 N=144	**UGT1A1 *1/*28 N=152**	**UGT1A1 *28/*28 N=37**
	All Grades n (%)	**All Grades n (%)**	**All Grades n (%)**
Any AE	144 (100)	151 (99.3)	37 (100)
Nausea	99 (68.8)	95 (62.5)	27 (73.0)
Neutropenia	74 (51.4)	87 (57.2)	26 (70.3)
Diarrhea	89 (61.8)	91 (59.9)	23 (62.2)

Fatigue/Asthenia	76 (52.8)	86 (56.6)	20 (54.1)
Anemia	63 (43.8)	60 (39.5)	20 (54.1)
Vomiting	70 (48.6)	58 (38.2)	21 (56.8)
Alopecia	61 (42.4)	63 (41.4)	13 (35.1)
Constipation	51 (35.4)	55 (36.2)	13 (35.1)
Decreased appetite	51 (35.4)	48 (31.6)	18 (48.6)
Rash[1]	34 (23.6)	39 (25.7)	7 (18.9)
Abdominal Pain[2]	36 (25.0)	37 (24.3)	12 (32.4)
Hyperglycemia	16 (11.1)	17 (11.2)	3 (8.1)
Cough	30 (20.8)	30 (19.7)	7 (18.9)
White blood cell count decreased	18 (12.5)	28 (18.4)	4 (10.8)
Headache	20 (13.9)	24 (15.8)	5 (13.5)
Hypomagnesemia	29 (20.1)	28 (18.4)	5 (13.5)
Dyspnea	31 (21.5)	27 (17.8)	6 (16.2)
Urinary Tract Infection	19 (13.2)	17 (11.2)	4 (10.8)
Dizziness	26 (18.1)	20 (13.2)	5 (13.5)
Respiratory Infection[3]	25 (17.4)	28 (18.4)	7 (18.9)
Edema[4]	20 (13.9)	32 (21.1)	5 (13.5)
Hypokalemia	20 (12.5)	27 (17.8)	12 (32.4)
Pruritis	18 (12.5)	20 (13.2)	6 (16.2)
Hypophosphatemia	23 (16.0)	19 (12.5)	2 (5.4)
Weight decreased	23 (16.0)	25 (16.0)	11 (29.7)
ALT increased	16 (11.1)	14 (9.2)	2 (5.4)
AST increased	16 (11.1)	13 (8.6)	2 (5.4)
Platelet count decreased/thrombocytopenia	10 (6.9)	11 (7.2)	3 (8.1)
Insomnia	14 (9.7)	23 (15.1)	3 (8.1)
Rhinorrhea/Nasal Congestion	16 (11.1)	21 (13.8)	2 (5.4)
Stomatitis/Esophagitis/Mucosal inflammation	11 (7.6)	15 (9.9)	3 (8.1)
Dehydration	21 (14.6)	25 (16.4)	7 (18.9)
Pyrexia	21 (14.6)	20 (13.2)	6 (16.2)
Blood Alkaline Phosphatase Increased	13 (9.0)	16 (10.5)	2 (5.4)

Source: *reviewer analysis using adae.xpt and adug.xpt datasets*
[1] Rash pooled terms: rash maculopapular, rash erythematous, rash generalized, dermatitis acneiform, skin disorder, skin irritation, skin exfoliation.
[2]Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness
[3]Respiratory infection: Viral upper respiratory infection, upper respiratory infection, influenza, pneumonia, pneumonia haemophilus, metapneumovirus, bronchitis
[4]Edema pooled terms: facial edema, generalized edema, peripheral edema.

8.2.6. **Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Not applicable. There was no COA data collected or assessed.

8.2.7. Safety Analyses by Demographic Subgroups

In the IMMU-132-01 study, 144/408 patients (35.3%) were ≥65 years old. In the mTNBC cohort, 19/108 patients (17.6%) were ≥65 years old. The most frequently reported TEAEs (≥10%) in patients ≥65 years are in Table 31 below.

Table 31. TEAEs ≥10% in patients ≥65 years

	Safety Population n=144			**Efficacy population n=19**		
	All Grades n (%)	**Grade 3 n (%)**	**Grade 4 n (%)**	**All Grades n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Diarrhea	96 (66.7)	10 (6.9)	-	14 (74)	1 (5)	-
Anemia	59 (41.0)	17 (11.8)	-	13 (68)	3 (16)	-
Fatigue, asthenia, malaise	85 (59.0)	19 (13.2)	-	10 (53)	2 (11)	-
Nausea	91 (63.2)	2 (1.4)	-	10 (53)	-	-
Neutropenia, neutrophil count decreased	79 (54.9)	46 (31.9)	24 (16.7)	13 (68)	7 (37)	3 (16)
Vomiting	49 (34.0)	1 (<1)	-	7 (37)	-	-
Decreased appetite	49 (34.0)	2 (1.4)	-	6 (32)	-	-
Alopecia	56 (38.9)	-	-	6 (32)	-	-
Constipation	48 (33.3)	-	-	9 (47)	-	-
Abdominal Pain[1]	32 (22.3)	4 (2.8)	-	2 (11)	-	-
Dyspnea, dyspnea exertional	30 (20.8)	8 (5.6)	1 (<1)	3 (16)	1 (5)	-
Weight decreased	30 (20.8)	-	-	4 (21)	-	-
Rash[2]	32 (22.2)	1 (<1)	-	5 (26)	-	-
Hypokalemia	26 (18.1)	6	1 (<1)	3 (16)	1 (5)	-
Hypomagnesemia	27 (18.8)	1 (0.7)	-	3 (16)	-	-
Edema[3]	28 (19.4)	-	-	3 (16)	-	-
Dizziness/Vertigo	26 (18.1)	1 (0.7)	-	3 (16)	-	-
Dehydration	24 (16.7)	-	-	2 (11)	-	-

Cough/productive cough	24 (16.7)	-	-	2 (11)	-	-
Back and MSK Pain	25 (17.4)	1 (0.7)	-	6 (32)	-	-
Respiratory Infection[4]	25 (17.4)	4	-	2 (11)	-	-
White blood count decreased	20 (13.9)	8 (5.9)	5 (3.5)	4 (21)	2 (11)	1 (5)
Insomnia	20 (13.9)	-	-	3 (16)	-	-
Pyrexia	17 (11.8)	-	-	1 (<1)	-	-
Hypophosphatemia	17 (11.8)	6	-	3 (16)	2 (11)	-
Pruritis/pruritis generalized	16 (11.1)	1 (<1)	-	2 (11)	-	-

Source: *reviewer analysis using adae.xpt dataset*
[1]*Abdominal pain, abdominal discomfort, abdominal pain upper, abdominal pain lower*
[2]*Rash, rash erythematous, rash maculo-papular, rash pruritic*
[3]*Facial oedema, localized oedema, oedema, oedema peripheral*
[4]*Influenza, Pneumonia, Atypical pneumonia, bronchitis, lower respiratory tract infection, metapneumovirus infection, pneumonia haemophilus, RSV infection, respiratory tract infection, upper respiratory tract infection, viral upper respiratory tract infection*

Reviewer Comments: *The incidence of diarrhea (66.7% for the safety population ≥65 compared to 62.0% for the safety population overall and 74% for the mTNBC cohort ≥65 as compared to 62.0% for the mTNBC cohort overall) and neutropenia (54.9% for the safety population ≥65 compared to 54.2% for the safety population overall and 68% for the mTNBC cohort ≥65 as compared to 63.9% for the mTNBC cohort overall) was numerically greater in older patients. The analysis and conclusions are limited by the small numbers of patients in this age range included. The tolerability appears to be generally similar to that of younger patients, though with an increased rate of adverse events. There are inadequate numbers of patients included to further explore safety in other population-based subgroups such as racial/ethnic or gender-based groups.*

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

See Pharmacology/Toxicology Review.

Human Reproduction and Pregnancy

No pregnancies were reported in IMMU-132-01. There were no exposures in pregnant or lactating women during this study.

Pediatrics and Assessment of Effects on Growth

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
No accidental overdoses were reported in Study IMMU-132-01.

Drug Abused Potential
There are no data available on the potential for abuse or dependence with sacituzumab govitecan.

Withdrawal and Rebound
There has been no formal study of withdrawal and/or rebound after treatment discontinuation of sacituzumab govitecan.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable. Sacituzumab govitecan does not have marketing authorization in any jurisdiction.

Expectations on Safety in the Postmarket Setting

Sacituzumab govitecan has been studied in a limited number of patients with refractory disease with a variety of epithelial tumor types and a limited number of patients with mTNBC who have received two or more prior therapies.

It is expected that there may be increased adverse events in the postmarketing setting as patients who have received two prior therapies for mTNBC are likely to have adverse effects from both their persistent disease as well as cumulative toxicities from prior therapies. Additionally, though there is an increased incidence of central nervous system metastases in patients with mTNBC, these patients were initially excluded from participation in this study. Even with the subsequent amendment to allow patients with stable CNS disease to participate, fewer than 2% of patients in the mTNBC efficacy cohort had evidence of CNS disease at the time of study entry. Given this, there may be differences in safety and efficacy of this agent when used in this population. Safety is being monitored in the Phase 3 ASCENT study which serves to further assess clinical benefit and will be evaluating this therapy against other available therapies for patients in a similar disease setting. This study will also be able to provide additional information regarding subpopulations such as those with alterations in the UGT1A1 gene that affect drug metabolism.

There are limited numbers of patients over the age of 75 in this study as well. This is somewhat consistent however with the epidemiology of this disease. No overall differences in safety were noted in this population in review of the safety database, though the incidence of neutropenia and diarrhea were numerically greater in older patients. Given this, monitoring of laboratory values and appropriate supportive care as advised in the general USPI for all patients is needed.

8.2.11. **Integrated Assessment of Safety**

The safety profile of sacituzumab govitecan for the treatment of patients with metastatic triple-negative breast cancer that has progressed on two or more prior lines of therapy is acceptable with adverse reactions managed through dose reductions and modifications, temporary treatment discontinuation, and/or standard medical care. Important safety signals identified in the course of the review of Study IMMU-132-01 include the increased risk of diarrhea, neutropenia, nausea and vomiting. An additional important risk is that of infusion related reactions. These risks have been conveyed in the USPI along with risk reduction and management strategies.

SUMMARY AND CONCLUSIONS

8.3. **Statistical Issues**

In general, there were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for the IMMU-132-01 study. The confirmed ORR was 33.3% (95% CI: 24.6, 43.1) in the target mTNBC population (n=108) with an estimated median duration of response of 7.7 months (95% CI: 4.9, 10.8) per local investigator assessment. Efficacy results based on blinded, independent, central review audit of the subgroup of patients with tumor scans showing CR, PR, or at least 20% shrinkage by local site evaluation were consistent with investigator assessment however, results per ICR should be interpreted with caution given that this was based

on assessment in a subgroup of patients. We reiterate that no inferential procedures were used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although PFS and OS results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm.

8.4. **Conclusions and Recommendations**

The clinical and statistical review teams viewed the efficacy results of Study IMMU-132-01 to be an improvement over available therapy for the treatment of patients with mTNBC who have received at least 2 therapies in the metastatic setting and consider the safety profile sacituzumab govitecan to be acceptable in the context of an incurable disease in a heavily pre-treated population. The risks described in this review are addressed in the proposed product labelling and are manageable by medical oncologists, with the implementation of monitoring, dose modifications, and supportive measures.

X X

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9 Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) or Special Government Employees (SGEs) for this application as there were no public health issues raised that would benefit from a public discussion or that required the expert opinions of the Committee. In addition, the safety profile of the drug is deemed acceptable for the indicated population of patients.

10 Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not submitted with the BLA. Included in the BLA was a request for a full waiver for the requirement to assess the safety and effectiveness of sacituzumab govitecan for the claimed indication under PREA based on necessary studies being impossible or highly impracticable due to the rarity of this indication in the pediatric population

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling negotiations were ongoing at the time of completing this Multi-disciplinary review. The table below summarizes significant changes to the proposed label made by FDA during the review.

DOP1 consulted with the FDA Office of Regulatory Policy (ORP) and Office of Chief Counsel (OCC) to evaluate the limited data submitted to this BLA by the Applicant related to SN-38 activity and the UGT1A1 metabolic pathway to determine information that may be inferred and used to support the TRODELVY prescribing information. Based on the ORP/OCC advice, DOP1 revised the TRODELVY prescribing information (b) (4) As advised by ORP/OCC, DOP1 focused the TRODELVY labeling information on the data provided in this BLA and the fundamental principles related to SN-38 activity and the UGT1A1 metabolic pathway that were important to fully characterize the safety and efficacy profile of TRODELVY, and to meet the requirements of 21CFR 201.56 and 201.57.

The draft labeling (prescribing information and patient labeling) with FDA's revisions were provided to the Applicant to address any remaining labeling-related issues.

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling** *(as of December 17, 2018)*
Highlights		
Boxed Warning	None.	FDA added a Boxed Warning for neutropenia and diarrhea. *See Full Prescribing Information (FPI), Boxed Warning below for more information.*
Indications and Usage	…	*See FPI, Indications and Usage.*
Dosage and Administration	…	FDA revised the information under this heading to add the following: • Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or SN-38. (2.1) • Do not administer as an intravenous push or bolus. (2.2) • (recommended dose) …until disease progression or unacceptable toxicity. (2.2) • Premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and

		vomiting is recommended. (2.2) • Monitor patients during the infusion and for at least 30 minutes after completion of infusion.
Dosage Forms and Strengths	…	Added "for reconstitution" to the product description.
Contraindications	None.	FDA revised to the following: • Severe hypersensitivity reaction to TRODELVY (4, 5.3).
Warnings and Precautions	Neutropenia: …	FDA moved the Warning and Precaution for Neutropenia into the Boxed Warning in Highlights.
	Hypersensitivity: (b) (6) …	FDA revised the information under this heading as follows: • Deleted (b) (6) • Added "Hypersensitivity reactions including severe anaphylactic reactions have been observed." • Added "Monitor patients for infusion-related reactions."
	Diarrhea: …	FDA moved the Warning and Precaution for Diarrhea into the Boxed Warning.
	None.	FDA added a Warning and Precaution for "Patients with Reduced UGT1A1 Activity".
	None.	FDA added a Warning and Precaution for "Embryo-Fetal Toxicity" to identify that TRODELVY can cause fetal harm and to advise patients of the risk to a fetus and to use contraception.
Adverse Reactions	…	FDA added "constipation", "rash", and "abdominal pain" to the list of common adverse reactions.
Drug Interactions	…	FDA removed (b) (6) maintained UGT1A1 inhibitors, and added UGT1A1 inducers to the "avoid concomitant use" statement.
Use in Specific Populations	…	FDA revised this section to move the pregnancy information to the Embryo-Fetal Warnings and Precaution. FDA added the following:

		• Females of Reproductive Potential: Verify pregnancy status prior to initiation of TRODELVY. (8.3)
Full Prescribing Information		
Boxed Warning	None.	FDA added a Boxed Warning for neutropenia and diarrhea. For neutropenia, advice to hold Trodelvy for ANC < 1500/mm^3 and periodic CBC monitoring, secondary prophylaxis, and anti-infective use for febrile neutropenia were added. For diarrhea, monitoring, fluid and electrolyte repletion, and advice on management of early and late diarrhea were added. This Boxed Warning was added in accordance with 21CFR201.57(c)(1) and the FDA Guidance for the Boxed Warning Sections of Labeling (IV.A) to highlight for prescribers neutropenia and diarrhea associated with TRODELVY "that is essential that it be considered in assessing the risks and benefits of the drug", "that can be prevented or reduced in frequency or severity by appropriate use of the drug", and "to highlight warning information that is especially important to the prescriber".
1. Indications and Usage	…	FDA removed (b) (6) since not required and added "adult" to clearly describe the indicated population. To the basis for accelerated approval statement, FDA added "duration for response" to tumor response rate.
2. Dosage and Administration	**2.1 Important Use Information** *(subsection added by FDA)*	FDA added this subsection and the following statement: **"Do NOT substitute TRODELVY for or use with other drugs containing irinotecan."**
	2.2 Recommended Dose and Schedule **…** <u>Premedication</u> …	FDA added "Do not administer as an intravenous push or bolus." … FDA agreed with the premedication regimens proposed with minor revisions to remove passive voice, redundant

		statements. (b) (6)
	2.3 Dose Modifications for Adverse Reactions …	FDA added a subsection for Infusion-related Reactions and information to slow or interrupt the infusion rate of TRODELVY, and to permanently discontinue TRODELVY for life-threatening infusion-related reactions. FDA revised the Dose Modifications Table (Table 1) to require a 25% dose reduction after the first occurrence of Grade 4 neutropenia $\geq$ 7 days or Grade 3 febrile neutropenia, revised the second dose reduction (b) (6) to 50%, and revised the third dose reduction (b) (6) (b) (6) to discontinuation of treatment. These revisions were to be consistent with how dose modifications were performed in the clinical trial.
	2.4 Preparation for Administration …	After reconstitution, FDA added "Use immediately to prepare a diluted TRODELVY infusion solution." At the beginning of the dilution process, FDA added "Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient's body weight. Withdraw this amount from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s)." FDA added the room temperature range and revised the time the diluted solution in the infusion bag can be stored (b) (4) (b) (4) to 4 hours prior to administration based on the data provided by the Applicant. FDA added a statement not to shake and to protect the diluted solution in the infusion bag from light.
4. Contraindications	None.	FDA added "TRODELVY is

		contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions (5.3)]*."
5. Warnings and Precautions		FDA revised the order of the Warnings and Precautions to reflect the relative clinical significance of TRODELVY's adverse reactions (i.e., 5.1 Neutropenia, 5.2 Diarrhea, 5.3 Hypersensitivity, 5.4 Nausea and Vomiting, 5.5 Patients with Reduced UGT1A1 Activity, 5.6 Embryo-Fetal Toxicity). FDA removed [redacted]
	5.1 Neutropenia *(FDA moved from 5.2)* …	FDA added "TRODELVY can cause severe or life-threatening neutropenia. Dose modifications may be required due to neutropenia *[see Dosage and Administration (2.3)]*." FDA removed [redacted] FDA moved dose modification information for neutropenia to subsection 2.3 (Table 1).
	5.2 Diarrhea *(FDA moved from 5.5)* …	FDA added "Neutropenic colitis was observed in [redacted]% of patients in the mTNBC co[redacted]rt and 1% of patients [redacted]" and "At the onset of diarrhea evaluate for infectious causes." FDA removed [redacted]

		[redacted]
	5.3 Hypersensitivity *(FDA moved from 5.1)* …	FDA added "TRODELVY can cause severe and life-threatening hypersensitivity." and revised [redacted] reactions to "anaphylaxis" reactions. FDA removed [redacted] FDA moved (and cross referenced) the infusion-related adverse reaction dose modification information to subsection 2.3. FDA revised the existing monitoring information for the first dose to require monitoring after all infusions as follows: "Observe patients closely for infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion [*see Dosage and Administration (2.3)*]. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use."
	5.4 Nausea and Vomiting …	FDA deleted [redacted] from the moderately emetogenic statement. FDA removed [redacted] FDA updated the incidence rates from [redacted]% (Grade 1-4) and [redacted] to 4% (Grade 3-4) vomiting based on the updated safety information reviewed.
	5.5 Patients with Reduced UGT1A1 Activity *(FDA moved from 5.3)* …	FDA added the following: • "In [redacted]% [redacted] of patients who received TRODELVY (up to 10 mg/kg on days 1 and 8 of a 21-day

		cycle) and had retrospective UGT1A1 genotype results available, the incidence of Grade 4 neutropenia was (b) (6)% in patients homozygous for the UGT1A1*28 allele (b) (6)% in patients heterozygous for the UGT1A1*28 allele (b) (6) and (b) (6)% in patients homozygous for the wild-type allele (b) (6) *[see Clinical Pharmacology (12.4)]."* • "The appropriate dose for patients who are homozygous for UGT1A1*28 is not known and should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2.3)]*."
	5.6 Embryo-Fetal Toxicity …	FDA removed (b) (6) FDA added the following: • "Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*." • "Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY." • "Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months

		(b) (6) the last dose."
6. Adverse Reactions	**6.1 Clinical Trials Experience** …	FDA added a paragraph to describe the safety population used in Warnings and Precautions (n=408 patients) treated with TRODELVY for mTNBC and other malignancies who had received prior systemic therapeutic regimens for advanced disease. As discussed above, only patients who received doses up to 10 mg/kg were included in the safety population (n=408) to be consistent with the approved dosage regimen. *See Section 8.2.4 of this review for more information.* In this section (and throughout the prescribing information), FDA removed (b) (6) FDA removed (b) (6) FDA revised the incidence rate of serious adverse reactions by removing (b) (6). This changed overall SARs (b) (6) to 31%; increased the incidence rates of vomiting (6%) and nausea (3%); and required the addition of colitis (3%) and sepsis (2%) not previously included in this section. *See Section 8.2.4 of this review for more information.* FDA removed the statement (b) (6)

		FDA revised the adverse reactions leading to discontinuation (b) (6) (b) (6)% of patients and added (b) (6) to the existing ARs. FDA added a statement to identify that (b) (6)% of patients experienced an adverse reaction leading to treatment interruption (with (b) (6)% due to neutropenia) and a statement that 33% of the patients treated with TRODELVY required dose reductions. FDA revised the Adverse Reactions table (Table 2) to increase the incidence of nearly every Grade 1-4 and Grade 3-4 adverse reaction (b) (6) . FDA added ARs for mucositis, hypokalemia, peripheral neuropathy, dysgeusia, urinary tract infection, respiratory infection, cough, dyspnea, and insomnia based on the FDA Clinical Safety review findings. FDA required the addition of Table 3 Laboratory Abnormalities to provide the clinically relevant laboratory abnormalities observed for mTNBC patients treated with TRODELVY in the IMMU-132-01 trial. FDA deleted (b) (6)
	6.2 Immunogenicity …	FDA added immunogenicity and anti-sacituzumab govitecan antibodies results to this subsection based on FDA review.

		See Section 6.3.1 of this review for more information.
7. Drug Interactions	[redacted] (b) (4) …	FDA removed statements [redacted] (b) (6) FDA revised this section to remove statements [redacted] (b) (6) FDA revised the information related to UGT1A1 inhibitors to add a statement that administration of TRODELVY may increase the incidence or severity of adverse reactions due to potential increase in systemic exposure to SN-38. FDA removed [redacted] (b) (6) FDA revised [redacted] (b) (6) to UGT1A1 inducers [redacted] (b) (6) FDA added a statement to avoid administering TRODELVY with UGT1A1 inducers. *See Section 6.3.2 of this review for more information on SN-38 data submitted in this BLA and how known UGT1A1 inhibition or induction activity impacts the safety and efficacy profile of TRODELVY.*
8. Use in Specific Populations	**8.1 Pregnancy** …	Risk Summary FDA removed information [redacted] (b) (6)

		(b) (6) [redacted] FDA revised can cause (b) (6) to "teratogenicity" and "embryo-fetal lethality" when administered to pregnant women. FDA added that there are no available data in pregnant women to inform the drug associated risk. FDA added "TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells" and "females of reproductive potential" to the potential risk to the fetus statement. <u>Data</u> *Animal Data* FDA revised the proposed information to condense, clarify, and add the following statement: "TRODELVY can cause teratogenicity and/or embryo-fetal lethality. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells." FDA removed information (b) (6) [redacted] *See Section 5 of this review for more information.*
	8.2 Lactation …	<u>Risk Summary</u> FDA agreed to the proposed risk summary with minor revisions. (b) (6) [redacted] *See Section 5 of this review for more information.*

	8.3 Females and Males of Reproductive Potential …	FDA agreed with pregnancy testing and contraception information with revisions to the required time to use effective contraception after the final dose for females (i.e., (b) (6) revised to 6 months) and males (i.e., 3 months revised (b) (6)). *See Section 5 of this review for more information.*
	(b) (6) ..	FDA deleted this subsection and statements (b) (6)
	8.6 Hepatic Impairment (b) (6)	FDA revised this section to the following: "No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin less than or equal to 1.5 ULN and AST/ALT < 3 ULN). The exposure of sacituzumab govitecan - hziy in patients with mild hepatic impairment (bilirubin less than or equal to ULN and AST greater than ULN, or bilirubin greater than 1.0 to 1.5 ULN and AST of any level; n=12) was similar to patients with normal hepatic function (bilirubin or AST less than ULN; n=45). The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established. TRODELVY has not been tested in patients with serum bilirubin > 1.5 ULN, or AST and ALT > 3 ULN, or AST and ALT > 5 ULN and associated with liver metastases."
11. Description	…	FDA removed (b) (6)

		FDA added the route of administration "for intravenous use" to be consistent with the requirements in 21CFR201.57.
12. Clinical Pharmacology	**12.1 Mechanism of Action** …	FDA revised Section 12.1 to limit the information in this section to a concise summary of the established mechanism of action of sacituzumab govitecan-hziy and to avoid speculative and unsupported claims and general information that is educational in nature.
	12.2 Pharmacodynamics *(FDA added this subsection)*	FDA added "Exposure-response relationships and the time course of pharmacodynamics response are unknown sacituzumab govitecan – hziy."
	12.3 Pharmacokinetics …	Throughout this subsection, FDA removed information (b) (6) *See Section 6.3.1 of this review for more information* (b) (6) FDA agreed with the Applicant's information related to pharmacokinetics for absorption and distribution of sacituzumab govetican-hziy with minor revisions, reformatting, and removal of references (b) (6) <u>Elimination</u> FDA removed (b) (6) <u>Specific Populations</u> FDA added this subsection to provide information on the lack of effect on TRODELVY pharmacokinetics for age

		or race. FDA added a statement regarding the lack of data for patients with varying degrees of renal impairment. FDA added data from TRODELVY use in patients with mild hepatic impairment and a statement regarding the lack of data for patients with moderate or severe hepatic impairment that may result in an increase in SN-38 concentrations in patients with decreased hepatic function. <u>Drug Interaction Studies</u> FDA agreed that no studies of sacituzumab govetican-hziy have been conducted and added "Inhibitors or inducers of UGT1A1 are expected to increase or decrease SN-38 exposure, respectively." *See Section 6.3.2 of this review for more information.*
	12.4 Pharmacogenomics *(FDA added this subsection)*	FDA added this subsection due to the increased risk of neutropenia and other TRODELVY-related adverse reactions in individuals who are homozygous for the UGT1A1*28 allele. *See Section 6.3.2 of this review for more information.*
13. Nonclinical Toxicology	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** **…**	FDA agreed with the proposed information that sacituzumab govetican-hziy was clastogenic in nonclinical *in vitro* studies and not mutagenic in *an in vitro* Ames assay with minor revisions. FDA moved the statement related to rapidly dividing cells and potential to cause embryotoxicity and teratogenicity to subsection 8.1. FDA added "In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan - hziy on Day 1

		and Day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the human recommended dose of 10 mg/kg based on body weight)."
		(b) (6) [redacted]
14. Clinical Studies	**…**	FDA accepted the IMMU-0132 study description with minor revisions. FDA added the following: "Patients with bulky disease, defined as a mass >7 cm, were not eligible. Patients with treated brain metastases not receiving high dose steroids (>20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert's disease were excluded." FDA agreed with the IMMU-0132 demographic and baseline disease information proposed with minor revisions and the added the following clinically relevant information: "Seventy-five percent had visceral disease, 42% had hepatic metastases, and 2% had brain metastases. Twelve patients (11%) had Stage IV disease at the time of initial diagnosis." FDA agreed to the prior systemic therapy information in the metastatic setting with the addition of "carboplatin or cisplatin (69%)", "paclitaxel or docetaxel (52%)", and "doxorubicin (24%), vinorelbine (16%), cyclophosphamide (19%), and ixabepilone (8%)" to fully characterize this information. FDA removed (b) (6) [redacted]

		(b) (6) FDA removed (b) (6) FDA revised the Efficacy Results table (Table 5) for IMMU-0132 to add complete responses (CRs) (2.8%) and Partial Responses (PRs) (30.6%) and the range and % duration of response at 6 months and 12 months. FDA removed (b) (6) (*see Section 8.1.1, Statistical Analysis Plan, for more information).* (b) (6)
15. References	…	FDA revised outdated references to the current reference for the safe handling of cytotoxic drugs.
16. How Supplied/ Storage and Handling	…	FDA revised this section to include the dosage formulation and identifying characteristics required by 21 CFR 201.58(c)(17). FDA added "(store) in the original carton to protect from light until time of

		reconstitution". FDA added "TRODELVY is a cytotoxic drug. Follow applicable special handling and disposal procedures[1]."
17. Patient Counseling Information	…	FDA added the following required statement: "*Advise the patient to read the FDA-approved patient labeling (Patient Information)".* FDA reordered this section to reflect the new order of the Warnings and Precautions to reflect the relative clinical significance of counseling topics and information provided. FDA revised the Embryo-Fetal Toxicity information and added: "Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*." FDA removed (b) (6)

11.2. Patient Labeling

At the time of this review, the Patient Information for TRODELVY was under review and negotiation with the Applicant. The following is a summary of major revisions made to the Patient Information during this review:

- FDA added the "What is the most important information I should know about TRODELVY?" section to be consistent with the Boxed Warning information for severe neutropenia and diarrhea in the prescribing information.
- To the "What is TRODELVY?" section, added:
  - "It is not known if TRODELVY is safe and effective in people with moderate or severe liver problems."
  - "It is not known if TRODELVY is safe and effective in children."
  - "Do not receive TRODELVY if you have had a severe allergic reaction to TRODELVY. Ask your healthcare provider if you are not sure." to be consistent with revisions to the Contraindications in the prescribing information.

- To the "Before receiving TRODELVY, tell your healthcare provider about all of your medical conditions, including if you:" added information regarding UGT1A1 toxicities, liver problems, and revised the information related to pregnancy and contraception to be consistent with revisions to Section 8 of the prescribing information.
- To the "How will I receive TRODELVY?" section, added information related to the risks of infusion-related reactions.
- To the "What are the possible side effects of TRODELVY?" section:
    - Revised to advise patients to contact their healthcare provider if swelling of mouth, tongue, or throat occur.
    - (b) (6)
    - Added side effects for "constipation", "stomach (abdominal) pain", and "rash" consistent with the prescribing information and FDA clinical safety review.

See the OPDP/DMPP review filed under this BLA for more information.

12 Risk Evaluation and Mitigation Strategies (REMS)

None.

13 Postmarketing Requirements and Commitment

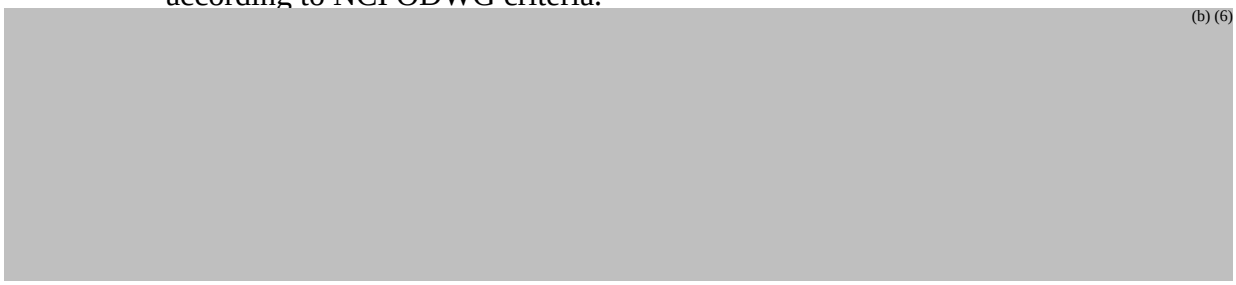
The following Postmarketing Requirements (PMR) were recommended by the review team; however, at the time of this review, negotiations for PMR/PMCs were not completed.

Chemistry, Manufacturing, and Controls

- Given the unresolved deficiencies with regards to the CMC review, the review team had not yet made a determination regarding the need for PMRs/PMCs.

Clinical Pharmacology

- PMR
  - Submit the final report from clinical trial IMMU-132-05 titled "An International, Multi-Center, Open-Label, Randomized, Phase III Trial of Sacituzumab Govitecan versus Treatment of Physicians Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments" a summary of all safety analyses and corresponding patient-level data related to the impact of UGT1A1 genotype on toxicity as obtained under the trial protocol.
  - Submit the final report of the substudy characterizing the QT interval prolongation potential of sacituzumab govitecan under trial IMMU-132-05, titled "An International, Multi-Center, Open-Label, Randomized, Phase III Trial of Sacituzumab Govitecan versus Treatment of Physicians Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments".
  - Conduct a trial in patients with moderate hepatic impairment to select an adequate starting dose in this patient population. The study should be an open-label, non-randomized, dose-escalation study in patients with moderate hepatic impairment according to NCI ODWG criteria.



Clinical

- PMR:
  - Submit the progression free survival data and report from clinical trial IMMU-132-05, An International, Multi-Center, Open-Label, Randomized, Phase III Trial of Sacituzumab Govitecan versus Treatment of Physicians Choice in Patients with Metastatic Triple-Negative Breast Cancer Who Received at Least Two Prior Treatments

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

Julia A. Beaver, MD
Director, Division of Oncology Products 1

18 Office Director (or designated signatory authority)

Richard Pazdur, MD
Director, Office of Oncology Center of Excellence, OCE and
Director (acting), Office of Hematology and Oncology Products

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents review of the clinical portion of the application under the OCE. My signature also represents a non-approval/complete response recommendation for this BLA under CDER.

19 Appendices

19.1. References

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19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): IMMU132-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 13		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the	Yes ☐	No ☐ (Request explanation

reason:		from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages].

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Four analytes were measured to characterize the PK of IMMU-132: total antibody (hRS7 and hRS7-SN38), unconjugated SN-38, SN-38 glucuronide, and total SN-38. An average drug-to-antibody ratio of 8 along with the concentration of SN-38 (unconjugated and total) and SN-38G were used to calculate the concentration IMMU-132. The amount of IMMU-132 was estimated using the following formula:

$$\frac{(8 * 392\ AMU)}{161{,}000\ AMU} = \frac{concentration\ of\ bound\ SN - 38}{X}$$

Where (8*392 atomic mass units (AMU)) refers to the molecular weight of SN-38 (392 AMU) multiplied by the fixed DAR of 8; 161,000 AMU refers to the molecular weight of the 8-loaded ADC; concentration of bound SN-38 (ng/mL) is calculated by subtracting the concentrations of measured free SN-38 and free SN-38G from measured total SN-38, and X is the estimated IMMU-132 concentration.

Free SN-38 and SN-38G

Free SN-38 and SN-38G were extracted from human serum by solid-phase extraction under yellow light and were quantified by reverse phase high-performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS), using SN-38-d3 and SN-38G-13C6 as internal standards. The method was validated in serum of the range of 1.00 to 500 ng/mL and was demonstrated to show acceptable precision, accuracy, selectivity, linearity, and stability.

	Acceptance Criteria	**Method Performance**
Matrix – Human Serum		
Anticoagulant – NA		
Assay Volume	50 µL	
Selectivity		
Analyte – Free SN-38 and SN-38G	Interferences at ≤ 20.0% LLOQ (at least 5 of 6 screened)	Complies (6 lots interference – free)
Internal Standard – SN-38-d_3 and SN-38G-^{13}C6	Interferences at ≤ 5.0% mean IS (at least 5 of 6 screened)	Complies (6 lots interference – free)
Conversion Efficiency Evaluation (Carboxylate Form to Lactone Form)	There are no criteria for this evaluation.	84.6% Low QC 86.5% high QC

Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be ≤ 15% over all 6 lots	Complies
Hemolytic Effect Evaluation	± 15.0% Bias; ≤ 15.0% CV	Complies
Lipemic Effect Evaluation	± 15.0% Bias; ≤ 15.0% CV	Complies
Carry-Over	≤ 20.0% LLOQ, ≤ 5.0% mean IS	Complies
SN-38		
Linearity		
Weighting		$1/x^2$
Bias at LLOQ	± 20.0% Bias	-0.7%
Bias above LLOQ	± 15.0% Bias	-3.9 to 2.7%
Bioanalytical Range	1.00 to 500 ng/mL	Complies
Precision		
Intra-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	4.3 to 7.7% (LLOQ); 1.2 to 5.2% (above LLOQ)
Inter-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	5.6% (LLOQ); 1.7 to 4.4% (above LLOQ)
Accuracy		
Intra-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	5.6 to 8.0% (LLOQ); -2.3 to 7.1% (above LLOQ)
Inter-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	6.6% (LLOQ); -1.1 to 4.8% (above LLOQ)
Dilution (2x, 5x)		
Precision	≤ 15.0% CV	1.8%, 1.8%
Accuracy	± 15.0% Bias	2.0%, -1.5%
	Acceptance Criteria	**Method Performance**
SN-38G		
Linearity		
Weighting		$1/x^2$
Bias at LLOQ	± 20.0% Bias	-1.0%
Bias above LLOQ	± 15.0% Bias	-2.2 to 2.0%
Bioanalytical Range	1.00 to 500 ng/mL	Complies
Precision		
Intra-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	4.3 to 8.2% (LLOQ); 1.6 to 3.2% (above LLOQ)
Inter-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	5.9% (LLOQ); 2.0 to 2.9% (above LLOQ)
Accuracy		
Intra-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	6.7 to 10.4% (LLOQ); 1.0 to 4.8% (above LLOQ)
Inter-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	9.0% (LLOQ); 1.2 to 3.7% (above LLOQ)

Dilution (2x, 5x)		
Precision	≤ 15.0% CV	2.7%, 1.6%
Accuracy	± 15.0% Bias	1.4%, -0.8%
Stability		
Matrix (in polypropylene tubes)		
Freeze/Thaw (-20°C/ ice-water bath)	± 15.0% Bias; ≤ 15.0% CV	Stable for 3 cycles
Freeze/Thaw (-70°C/ ice-water bath)	± 15.0% Bias; ≤ 15.0% CV	Stable for 4 cycles
Bench-top (ice-water bath)	± 15.0% Bias; ≤ 15.0% CV	Stable up to 6 hours
Whole Blood	% change must be within ± 15.0% with % CVs ≤ 15.0%.	Not performed due to the nature of matrix.
Evaluation of Free SN-38 and Free SN-38G Stability in the Presence of the hRS7-SN-38 (ADC) in Human		
Freeze/Thaw (-70°C/ ice- water bath)	Report % Change as is	9.7% after 4 cycles
Bench-top (ice-water bath)	Report % Change as is	9.7% after 3.0 hours 19.4% after 6.0 hours
Conversion Efficiency	Reported as is	84.6% at low QC level 86.5% at high QC level
Processed Matrix glass		
Autosampler (Ambient)	± 15.0% Bias; ≤ 15.0% CV	Stable for 2 days 23 hours
Refrigeration	± 15.0% Bias; ≤ 15.0% CV	Stable for 2 days 23 hours
Individual Sample Re-injection	± 15.0% Bias; ≤ 15.0% CV	Reproducible
	Acceptance Criteria	**Method Performance**
Whole Batch Re-injection Integrity (Duration 4 days 10 hours)	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ)	Reproducible
Column Ruggedness	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ)	Reproducible
Extraction Recovery		
Free SN-38	Report as found	Overall 64.1%
SN-38G	Report as found	Overall 51.5%
SN-38-d3	Report as found	Overall 69.5%
SN-38G-$^{13}C_6$ (IS)	Report as found	Overall 60.4%
Solution Stability in Glass		
SN-38 in DMSO (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38 in DMSO (refrigerated temp)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
SN-38G in Methanol (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours

SN-38G in Methanol (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
SN-38-d3 in DMSO (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Taken as the same as SN-38
SN-38-d3 in DMSO refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
SN-38G-$^{13}C_6$ Methanol (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Taken as the same as SN-38G
SN-38G-$^{13}C_6$ Methanol (refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
Solution, Working glass		
SN-38-d_3 (IS) in 20/80 MeOH/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38-d_3 (IS) in 20/80 MeOH/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
SN-38G-$^{13}C_6$(IS) in 20/80 MeOH/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38G—$^{13}C_6$(IS) in 20/80 MeOH/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
SN-38 Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
	Acceptance Criteria	**Method Performance**
SN-38 Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
SN-38G Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38G Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days

Abbreviations: ADC = antibody-drug conjugate (hRS7-SN-38); CV = coefficient of variation; DMSO = dimethylsulfoxide; IS = internal standard; LLOQ = lower limit of quantification; MF = matrix factor; NA = not applicable; QC = quality control; RT = room temperature

Total SN-38

Total SN-38 is defined as the combined amounts of free SN-38 in solution (unbound to the ADC [hRS7-SN-38]) and acid-dissociated SN-38. Following hydrolysis, total SN-38 was extracted from human serum by protein precipitation, then LC-MS/MS with SN-38-d3 as an internal standard. The precision, accuracy, selectivity, recovery, and stability were validated over the range of 5.00 to 2500 ng/mL in human serum.

	Acceptance Criteria	**Method Performance**
Matrix – Human Serum		
Anticoagulant – NA		
Assay Volume	50 µL	
Selectivity		
Analyte – Total SN-38	Interferences at ≤20.0% LLOQ (at least 5 of 6 screened)	Complies (6 lots interference – free)
Internal Standard – SN-38-d3	Interferences at ≤5.0% mean IS (at least 5 of 6 screened)	Complies (6 lots interference – free)
Evaluation of SN-38G Conversion During Hydrolysis	There are no criteria for this evaluation.	2.8%
Matrix Effect (6 spiked matrix lots)	the % CV for IS Normalized MF must be ≤ 15.0% over all 6 lots	Complies
Hemolytic Effect Evaluation	± 15.0% Bias; ≤ 15.0% CV	Complies
Lipemic Effect Evaluation	± 15.0% Bias; ≤ 15.0% CV	Complies
Carry-Over	≤ 20.0% LLOQ, ≤ 5.0% mean IS	Complies
Linearity		
Weighting		$1/x^2$
Bias at LLOQ	± 20.0% Bias	-0.4%
Bias above LLOQ	± 15.0% Bias	-1.9 to 2.6%
Bioanalytical Range	5.00 to 2500 ng/mL	Complies
Precision		
Intra-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	6.7 to 7.5% (LLOQ); 0.9 to 5.1% (above LLOQ)
Inter-assay	≤ 20.0% CV (LLOQ); ≤ 15.0% CV (above LLOQ)	8.8% (LLOQ); 3.0 to 3.9% (above LLOQ)
Accuracy		
Intra-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	1.5 to 13.9% (LLOQ); -1.6 to 6.9% (above LLOQ)
Inter-assay	± 20.0% Bias (LLOQ); ± 15.0% Bias (above LLOQ)	5.8% (LLOQ); -0.6 to 4.9% (above LLOQ)
Dilution (2x, 5x, 10x)		
Precision	≤ 15.0% CV	2.5%, 2.6%, 2.9%
Accuracy	± 15.0% Bias	-0.9%, 5.3%, 4.4%
Stability		
Matrix (in polypropylene tubes)		
Freeze/Thaw (-80°C/ ice- water bath)	± 15.0% Bias; ≤ 15.0% CV	7 cycles

Bench-top – RT	± 15.0% Bias; ≤ 15.0% CV	Stable for 6.0 hours
Bench-top Stability Under Hydrolysis Conditions	± 20.0% Bias; ≤ 20.0% CV	Stable for 21 hours
Hydrolysis recovery evaluation	Report as is	112.8%
	Acceptance Criteria	**Method Performance**
3 cycle Freeze/Thaw (-80°C/ ice-water bath)	Report % Change as is	-0.5%
Bench-top (ice-water bath)	Report % Change as is	-0.5%
Processed Matrix in glass		
Autosampler (Ambient)	± 15.0% Bias; ≤ 15.0% CV	Stable for 3 days 1 hour
Refrigeration	± 15.0% Bias; ≤ 15.0% CV	Stable for 3 days 1 hour
Individual Sample Re-injection	± 15.0% Bias; ≤ 15.0% CV	Reproducible
Whole Batch Re-injection Integrity (Duration 5 days 2 hours)	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ)	Reproducible
Column Ruggedness and System- to-System Ruggedness (5000 to 5500)	± 20.0% Bias; ≤ 20.0% CV (LLOQ) ± 15.0% Bias; ≤ 15.0% CV (above LLOQ)	Reproducible
Extraction Recovery		
SN-38	Report as found	Overall 79.5%
SN-38-d3	Report as found	Ongoing
Solution Stability (in Glass)		
SN-38 in DMSO (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38 in DMSO (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
SN-38 Glucuronide in Methanol (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38 Glucuronide in Methanol (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
SN-38-d3 in DMSO (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Taken as the same as SN-38
SN-38-d3 in DMSO (refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
Solution, Working		
SN-38-d3 (IS) in Acetonitrile (RT)	Loss of 15.0% is meaningful, ≤ 15.0% CV	Stable for 21.5 hours
SN-38-d3 (IS) in Acetonitrile (refrigerated temperature)	Not applicable	1-year stability can be assigned and evaluated thereafter in yearly increments
SN-38 Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours

SN-38 Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days
	Acceptance Criteria	**Method Performance**
SN-38 Glucuronide Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (RT)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 22.75 hours
SN-38 Glucuronide Spike in 50/50 ACN/10 mM Ammonium Acetate, pH 4.2 (refrigerated temperature)	Loss of 10.0% is meaningful, ≤ 15.0% CV	Stable for 21 days

Abbreviations: ACN = acetonitrile; CV = coefficient of variation; DMSO = dimethylsulfoxide; IS = internal standard; LLOQ = lower limit of quantification; MF = matrix factor; NA = not applicable; RT = room temperature

Total Antibody (hRS7-IgG and hRS7-SN-38)

hRS7-IgG represents the antibody portion of the ADC, with or without the SN-38 moiety attached. As assay to detect all versions of hRS7-IgG in serum (with or without SN-38 or drug linker groups attached) was validated for system suitability, accuracy, precision, dynamic range of quantification, selectivity, specificity, linearity, matrix interference, and stability from 374 to 3049 ng/mL. The antibody was prepared for analysis on a standard binding plate detected using an electrochemiluminescence assay with Southern Anti-Human IgG-Fc JDC-10 as the primary detection antibody and Sulfo-Tag streptavidin as the secondary detection antibody.

PARAMETER	EXPERIMENTAL DESIGN	TARGET SPECIFICATION	VALIDATION RESULTS
STANDARDS (System Suitability) 374-3049 ng/mL (Anchor Point at 258 ng/mL) *(Anchors points at 4120 & 5150 ng/mL dropped)*	# of Standard Level: 9 + 3 anchor points # of Batch Runs: 6 or more # of Replicate Wells/Point: 2	Accuracy: 80.0 to 120.0% Precision: CV ≤20.0% (Except at LLOQ Accuracy and Precision ≤25.0%)	Accuracy: 91.8 - 108.8% CV: 2.8 - 6.5%
Within and Between Run Accuracy and Precision of hRS7-lgG and hRS7-SN38 (A&P)			
374 ng/mL	LLOQ level VS	CV ≤25.0% %RE ≤ ±25.0%	Intra-assay CV: 5.63% Inter-assay CV: 8.3% RE: 8.1%
1030 ng/mL	Low QC level VS	CV ≤ 20.0% %RE ≤ ±20.0%	Intra-assay CV: 4.46% Inter-assay CV: 7.7% RE: 0.2%
1545 ng/mL	Mid QC level VS	CV≤ 20.0% %RE ≤ ±20.0%	Intra-assay CV: 5.89% Inter-assay CV: 8.0% RE: 12.2%

2287 ng/mL	High QC level VS	CV≤ 20.0% %RE ≤ ±20.0%	Intra-assay CV: 2.84% Inter-assay CV: 5.4% RE: 15.6%
3049 ng/mL	ULOQ level VS	CV≤ 25.0% %RE ≤ ±25.0%	Intra-assay CV: 2.25% Inter-assay CV: 3.9% RE: -4.2%
		Total Error ≤ ±30.0% (≤±40.0% at LLOQ, ULOQ)	Total Error: 8.0 - 21.0%
DILUTION LINEARITY	Ultra-High Concentration of hRS7-IgG and hRS7-SN-38 (1030 µg/mL in pooled human serum) Dilutions # of Sample: ≥1 sample # of Dilutions: 9 # of Replicate Wells/Dilution Level: 2	For results between LLOQ and ULOQ, dilution corrected concentration Accuracy: 80.0 to 120.0%, Precision: CV of ≤20.0% Minimum acceptable dilution is highest dilution that meets acceptance.	For dilutions between the ULOQ and the LLOQ: **Batch 010:** 1:2000 (1:100,000 Post-MRD) 1:2000 %AR: 91.8%
SELECTIVITY	Individual human serum samples spiked between LQC and LLOQ of hRS7-IgG and hRS7-SN-38 (374 ng/mL pre-MRD). # of Samples: ≥10 Individual human plasma samples (spiked and unspiked)	Relative Recovery: 75.0 to 125.0% with a precision of ≤20.0% in at least 80.0% of samples tested.	**Batch 007:** 374 ng/mL 91.6-147.3 %AR 8/10 samples passing criteria
PARAMETER	**EXPERIMENTAL DESIGN**	**TARGET SPECIFICATION**	**VALIDATION RESULTS**
MATRIX INTERFERENCE	# of Matrix: ≥3 (Normal, Hemolyzed and Lipemic) # of Dilutions/Matrix: 3 # of Replicate Wells/Dilution Level: 2	Percent change for hemolytic/lipemic must be ≤20.0% in at least 66.7% of samples analyzed with a precision of ≤20.0%.	**Batch 009:** 474, 1545, 2266 ng/mL **Normal**: 103.2 - 118.7%AR **Hemolytic**: 90.5 - 101.4%AR **Lipemic**: 99.4-103.4%AR
FREEZE/THAW (MINIMUM 5 CYCLES IN MATRIX) **(~-80°C/RT)**	Matrix: human serum 2 QC levels # of Samples ≥3 Aliquots at each level per condition # of Replicate Wells/Aliquot: 2	Accuracy: 80.0 to 120.0% of nominal concentration Precision: CV ≤20.0% Passing Rate: At least 66.7% (2 out of 3) overall and 50.0% at each level	**5 F/T: B009**: HQC: 113.0 - 115.8%AR LQC: 89.6 - 95.0%AR

ANALYTE STABILITY **BENCH-TOP (>16 HOURS IN MATRIX)**	Matrix: human serum 2 QC levels # of Samples ≥3 Aliquots at each level per condition # of Replicate Wells/Aliquot: 2	Accuracy: 80.0 to 120.0% of nominal concentration Precision:CV≤20.0% Passing Rate: At least 66.7% (2 out of 3) overall and 50.0% at each level	***17.75 hours B008:** *HQC: 120.4 - 123.0%AR LQC: 103.8 - 109.9%AR **Fails acceptance criteria* ***15 hours B010:** *HQC: 111.4 - 126.1%AR LQC: 98.3 - 106.1%AR **Fails acceptance criteria* **8 hours B011:** HQC: 111.4 - 122.2%AR LQC: 101.9 - 110.2%AR
REFRIGERATION STABILITY (≥24 HOURS IN MATRIX)	Matrix: human serum 2 QC levels # of Samples ≥3 Aliquots at each level per condition # of Replicate Wells/Aliquot: 2	Accuracy: 80.0 to 120.0% of nominal concentration Precision: CV≤20.0% Passing Rate: At least 66.7% (2 out of 3) overall and 50.0% at each level	**>24 hours:** 24 hours B008: HQC: 107.5 -119.1%AR LQC: 101.4-104.7%AR
LONG-TERM STORAGE	2 QC levels As needed # of Sample ≥3 Aliquots at each level per condition # of Replicate Wells/Aliquot: 2	Accuracy: 80.0 to 120.0% nominal concentration. Precision: CV ≤20.0% Pass Rate of Stability Samples: At least 66.7% (2 of 3 overall) and 50% at each level	Ongoing

Abbreviations: A&P = accuracy and precision; AR = analytical recovery; CV = coefficient of variation; HQC = high quality control; LLOQ = lower limit of quantification; LQC = low quality control; MRD = minimal required dilution; QC = quality control; RE = relative error; ULOQ = upper limit of quantification; VS = validation sample

19.4.2. Population PK and/or PD Analyses

The sponsor conducted exposure-toxicity and exposure-response assessments of sacituzumab-govitecan (IMMU-132) using sparse PK data collected from the mTNBC target population of study IMMU-132-01 (110 patients). However, only 57 patients contributed data to PPK and ER analysis. The value of these ER analyses was limited due to the small sample size.

APPLICANTS' PK/PD ANALYSIS

Objectives

The objectives of the applicant's population PK and exposure-response analysis were:

- To characterize the PK of IMMU-132 and metabolites in patients with mTNBC from the Phase I/II Study IMMU-132-01.
- To characterize the exposure-response relationships for IMMU-132 metabolites and AEs, specifically gastrointestinal (GI; nausea/vomiting and diarrhea), and hematologic in terms of neutropenia.

- To characterize the exposure-response relationships for IMMU-132 metabolites and efficacy (local tumor shrinkage ≥30%, progression-free survival [PFS], overall survival [OS]).

Methods

Four analytes were measured in serum as described in **Table 32**: total antibody (denoted for this analysis as IgG), free SN-38, SN-38 glucuronide (SN-38G), and total SN-38. In the Phase I portion of the study, serum samples were to be collected to measure concentrations within approximately 30 minutes from the end of the infusion (i.e., peak) and then before each subsequent infusion (i.e., trough). In the Phase II portion of the study, serum samples were to be collected pre-infusion, 30 minutes and 3 to 4 hours after the end of the first infusion, and on Days 1, 2, 3, and 7, for a maximum of 7 samples per patient after a single dose (e.g., either after infusion 1, 3, or 5).

Table 32: Moieties Included in PopPK Models

Analyte	Description	Quantification/Calculation Method	Other Names
IMMU-132	Antibody drug conjugate (ADC) that comprises SN-38, a topoisomerase I inhibitor, coupled by a linker (CL2A) to the humanized monoclonal antibody hRS7	Calculated from concentrations of total SN-38, free SN-38, and SN-38G according to Equation 1. Represented as the amount in compartment 1 of the IMMU-132 model.	hRS7-SN-38, ADC, sacituzumab govitecan, hRS7-CLA2-SN-38
Conjugated SN-38	Portion of SN-38 that remains conjugated to the hRS7 antibody IgG in serum at the time of sample collection	Conjugated SN-38 is not measured, but is represented in the Total/Free SN-38 model as the (unmeasured) amount in compartment 1. It is assumed for modeling purposes that administered SN-38 dose is entirely conjugated.	Not applicable
IgG	Total antibody; comprised of unconjugated hRS7-IgG plus hRS7-SN-38	Quantified by assay as described in VIMME1706E1. Represented as the amount in compartment 2 of the IgG model.	IgG1κ, total antibody
Free SN-38	Cytotoxic payload and active metabolite; not covalently bound to ADC	Quantified by assay as described in VIMME1700E2. Represented as the amount in compartment 2 in the Total/Free SN-38 model.	Not applicable
SN-38G	SN-38 glucuronide; inactive metabolite of SN-38 not	Quantified by assay as described in VIMME1700E2. Represented as the amount in compartment 4 in the SN-38 glucuronide model. Compartment 4,	Not applicable

Source: Table 1 of the applicant's PPK and ER report

PPK Analysis: NONMEM® version 7.3 was used for all pharmacokinetic model development. In all cases, traditional forward addition/backward elimination method was used for model selection.

Four pharmacokinetic models were developed. First, a model of IMMU-132 was developed independently of other analytes. A separate model for both total SN-38 and free SN-38 was then developed. Subsequently, a model for SN-38G was developed by extending the total SN-38/free SN-38 model. The parameters of the total SN-38/free SN-38 model were fixed, and the model and parameters of the SN-38G model were added, with SN-38G being a metabolite of free SN-38. In addition, a model for the IgG component (total antibody) of IMMU-132 was developed independently of the other models.

Nonlinear models (target-mediated disposition and saturable clearance models) and linear models, with one and two compartments, were examined for IMMU-132 and IgG. Linear models (one and two compartment) were examined for SN-38 free, SN-38 total and SN-38G.

Pre-specified covariate hypotheses were defined in the analysis plan. These included:

The clearance of IMMU-132 is target mediated
The clearance of IMMU-132 is dose-dependent (Michaelis-Menten)
Body weight is a predictor of Volume
Body weight is a predictor of Clearance
Race is a predictor of Clearance
UGT1A1 status is a predictor of Clearance

Exposure-Response Analysis: R version 3.3.1 or higher was used for all logistic regression and Kaplan-Meier analysis. Analyses conducted include:

Toxicity:

Logistic Regression of nausea/vomiting (any grade) by first cycle (days 1-21) area under the curve (AUC) of: IgG, total SN- 38, free SN-38, SN-38G
Logistic Regression of diarrhea (any grade) by first cycle (days 1-21) AUC of: IgG, total SN-38, free SN-38, SN-38G
Logistic Regression of neutropenia (any grade) by first cycle (days 1-21) AUC of: IgG, total SN-38, free SN-3, SN-38G
Logistic Regression of neutropenia (any grade) by first cycle (days 1-21) by peak concentrations of: IgG, total SN-38, free SN-38
Logistic Regression of any dose reduction by first cycle (days 1-21) AUC of: IgG, total SN-38, free SN-38
Logistic Regression of any dose reduction by last cycle, AUC of IgG, total SN-38, free SN-38
Logistic Regression of any dose delay during first cycle, AUC of: IgG, total SN-38, free SN-38

Efficacy:

Logistic Regression of response (local tumor shrinkage of ≥30%) by first cycle (AUClast i.e., up to 3 weeks, which is the duration of a cycle) AUC of: IgG, total SN-38, free SN-38
Kaplan–Meier with OS and PFS by quartiles of AUC (IgG, total SN-38, free SN-38)

PPK Results

IMMU-132:

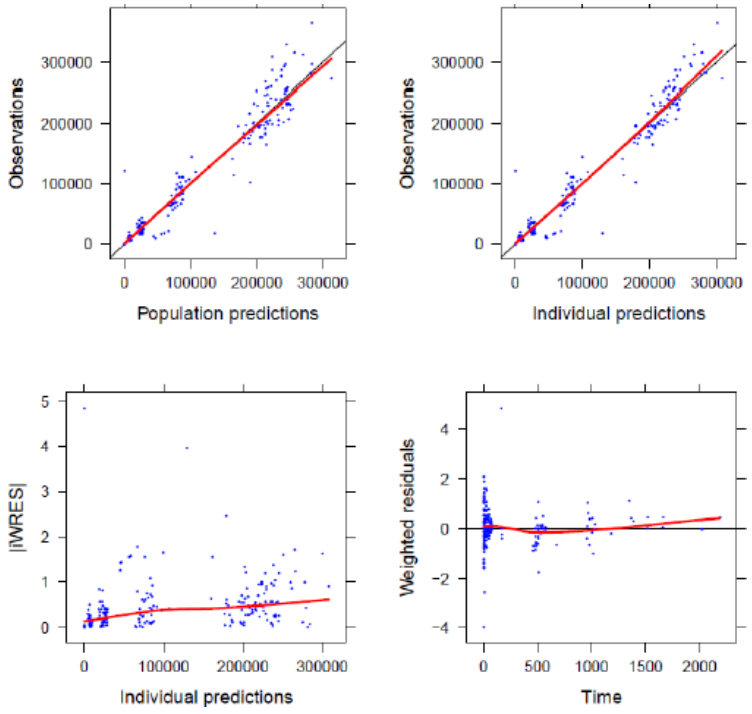
The final model for IMMU-132 was a one-compartment model. This model included a fixed (not estimated) allometric scaling component on clearance of 0.75. Race-other and weight were found to be significant predictors of IMMU-132 clearance and volume of distribution respectively. However, the typical value of clearance estimated in Race-other patients was only ~5% lower than the clearance in other race categories, and is therefore not clinically significant.
The effect of UGT1A1 could not be adequately tested as 35 of 57 patients did not have UGT1A1 status recorded. The data did not support either saturable clearance or target-mediated clearance. The PK estimates are listed in
Table 33. Goodness of fit plots are shown **in Figure 12**.

Table 33: IMMU-132 Final PK Model Parameter Estimates

Parameter	Description (Units)	Originally Calculated IMMU-132 Concentrations (Incorrect, no SN-38G accounted for)		Correctly Calculated IMMU-132 Concentrations (Accounts for total SN-38, free SN-38, and SN-38G)	
		Estimate	%RSE	Estimate	%RSE
THETA(1)	CL (L/h)	0.132	0.0057	0.134	0.360
THETA(2)	V (L)	2.72	2.33	2.72	2.27
THETA(3)	Additive Error on SD	25200	2.57	25000	2.32
THETA(4)	Proportional Error (%CV)	9.25	27.2	9.95	23.3
THETA(5)	Weight on V	0.415	30.4	0.426	29.5
THETA(6)	Other Race on CL	0.913	0.002	0.947	23.2

Source: Table 4 of the applicant's PPK and ER report

Figure 12: Goodness of Fit Plot for the Final Pharmacokinetic Model for IMMU-132



Source: Figure 3 of the applicant's PPK and ER report

IGG:

The final model for IgG described a linear two-compartment model. The model had a first-order input from the IMMU-132 dose. It is recognized that the IgG assay detects total antibody (i.e., both IgG bound to SN-38 and unbound IgG). Therefore, this model is not strictly correct. However, the model described the data well. In contrast to most monoclonal antibodies, the IgG for IMMU-132 demonstrated two-compartment pharmacokinetics. Covariate relationships found to be statistically significant include:

- A negative effect of albumin on IgG clearance, where a higher albumin predicts a lower clearance
- A positive relationship between aspartate aminotransferase (AST) and IgG clearance, where a higher AST predicts a higher clearance.

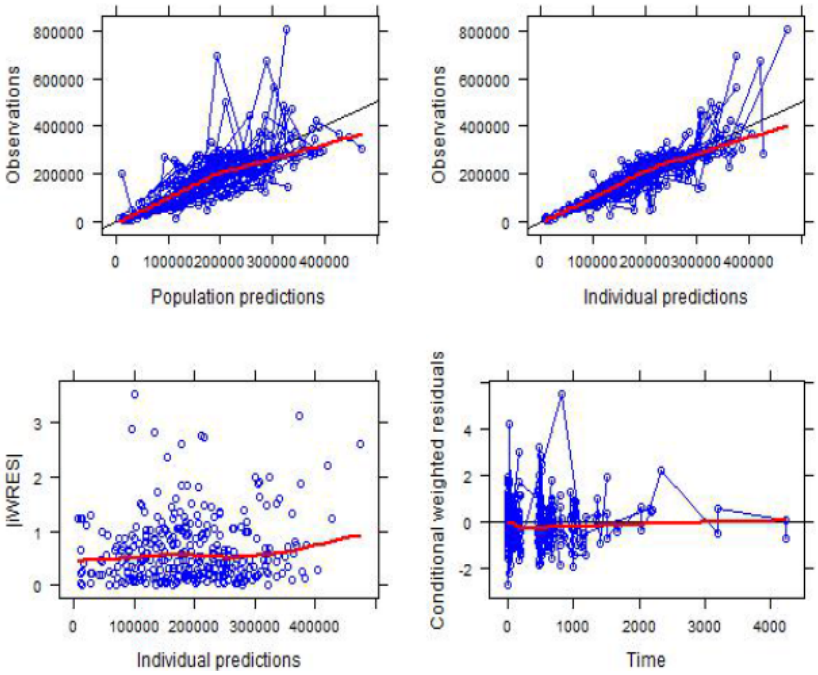
The effect of UGT1A1 could not be adequately tested as 35 of 57 patients did not have UGT1A1 status recorded. The data did not support either saturable clearance or target-mediated clearance. The PK estimates are listed in **Table 34**. Goodness of fit plots are shown in **Figure 13**.

Table 34: IGG Final PK Model Parameter Estimates

Parameter	Description (Units)	Estimate	Standard error	%RSE
THETA(1)	Volume of distribution (L)	1.44	0.285	19.8
THETA(2)	Clearance (L/hr)	0.0143	9.17E-04	6.4
THETA(3)	K IMMU-132-> IgG (1/hr)	0.699	0.162	23.2
THETA(4)	K23 (1/hr)	0.272	0.116	42.6
THETA(5)	K32 (1/hr)	0.205	0.0394	19.2
THETA(7)	CL~ALB	-1.390	0.347	25.0
THETA(8)	CL~AST	0.461	0.1164	25.2

Source: Table 10 of the applicant's PPK and ER report

Figure 13: Goodness of Fit Plot for the Final Pharmacokinetic Model for IGG



Source: Figure 7 of the applicant's PPK and ER report

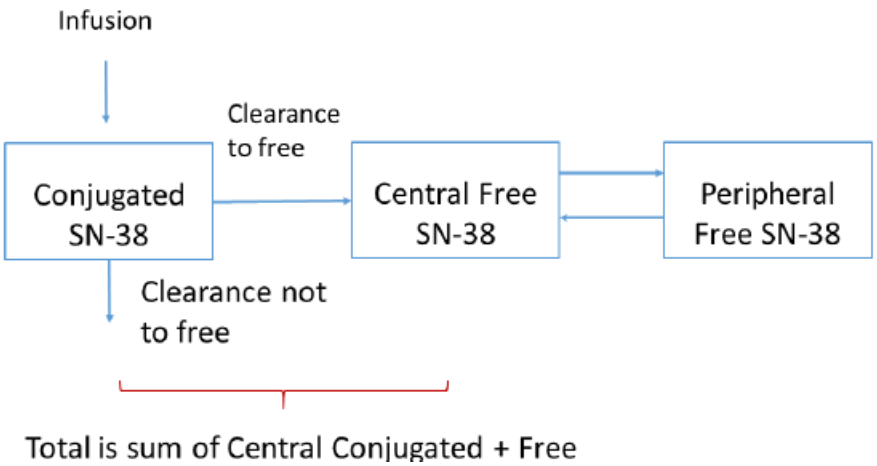
Total and Free SN-38:
The final model for total SN-38/free SN-38 described a linear model with one compartment for conjugated SN-38 and two compartments (central and peripheral) for free SN-38 (**Figure 14**). Total SN-38 was the sum of the conjugated SN-38 and the free SN-38. Two covariates were found to be statistically significant:

- A negative effect of albumin on conjugated SN-38 clearance, where a higher albumin predicted a lower clearance.
- A negative effect of albumin on conjugated SN-38 volume of distribution, where a higher albumin predicted a lower volume of distribution.

The effect of UGT1A1 could not be adequately tested as 35 of 57 patients did not have UGT1A1 status recorded. The PK estimates are listed in **Table 35**. Goodness-of-fit plots are shown in

Figure 15.

Figure 14: Structural model for Total and Free SN-38



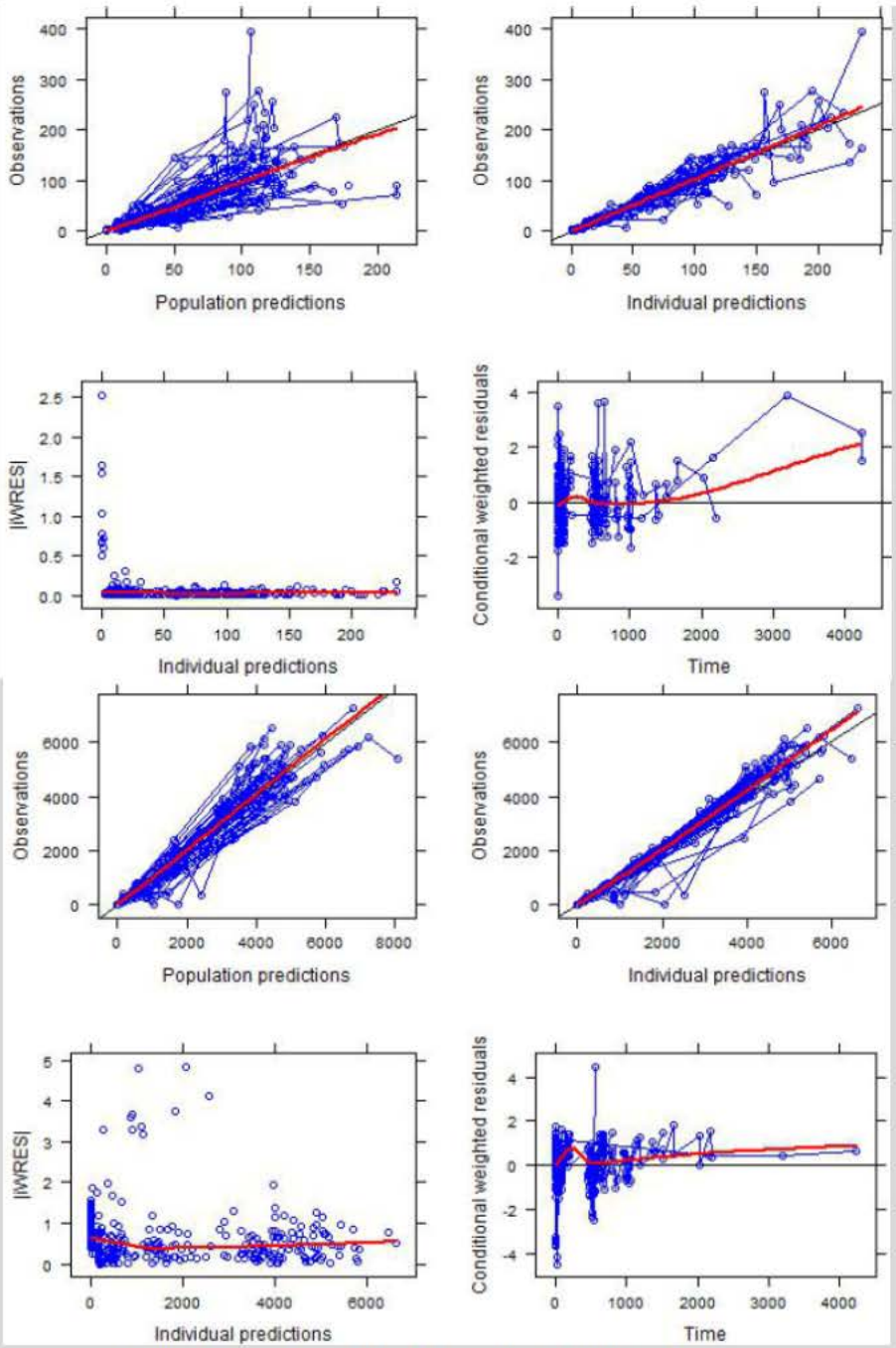
Source: Figure 12 of the applicant's PPK and ER report

Table 35: Total and Free SN-38 Final PK Model Parameter Estimates

Parameter	Description (Units)	Estimate	Standard error	%RSE
THETA(1)	Volume, conjugated and free (L)	146	4.25	2.9
THETA(2)	Conjugated SN-38 clearance ->Free (L/hr)	6.09	0.378	6.2
THETA(3)	Free SN-38 clearance (L/hr)	171	13.2	7.7
THETA(4)	Conjugated SN-38 clearance, not to Free	0.606	0.278	45.9
THETA(5)	K23 (1/hr)	0.358	0.0642	17.9
THETA(6)	K32 (1/hr)	0.0898	0.0167	18.6
THETA(7)	Conjugated SN-38 clearance ~albumin	-0.595	0.171	28.7
THETA(8)	Central volume ~ albumin	-0.317	0.162	51.3

Source: Table 16 of the applicant's PPK and ER report

Figure 15: Goodness of Fit Plot for the Final Pharmacokinetic Model for Free SN-38 (Upper Four Panels) and Total SN-38 (Lower Four Panels)



Source: Figures 13 and 14 of the applicant's PPK and ER report

SN-38G

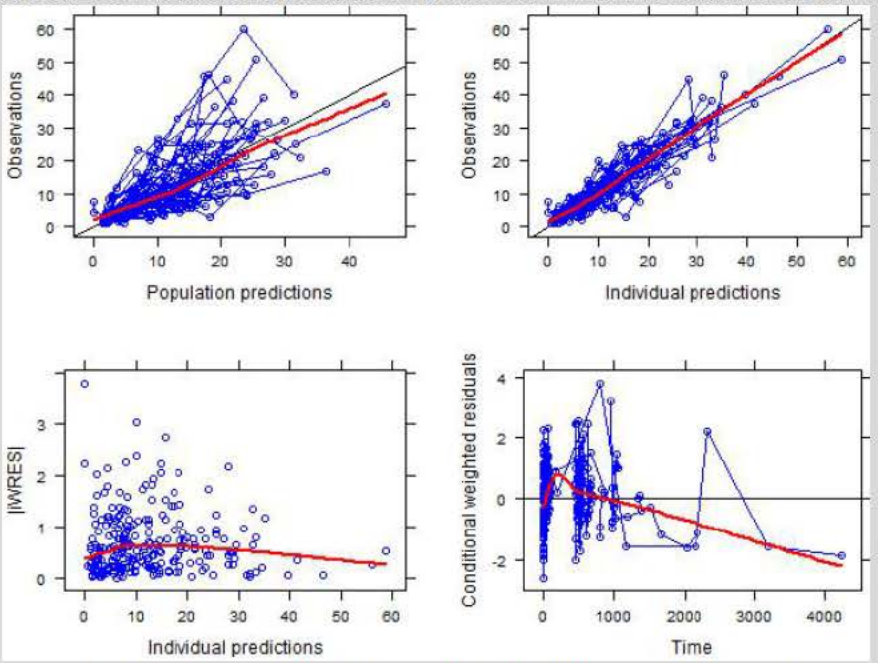
The SN-38G model was appended to the total SN-38/free SN-38 model. This model included a fraction of the free SN-38 being metabolized to SN-38G by a first-order process. SN-38G is then eliminated by a first-order process. A single compartment was described for SN-38G. No covariates were found to be statistically significant in the SN-38G model. The effect of UGT1A1 could not be adequately tested as 35 of 57 patients did not have UGT1A1 status recorded. The PK estimates are listed in **Table 36**. Goodness of fit plots are shown in Figure 16.

Table 36: SN-38G Final PK Model Parameter Estimates

Parameter	Description (Units)	Estimate	Standard error	%RSE
THETA(1)	Volume, conjugated SN-38 (L)	146	NA	NA
THETA(2)	Conjugated SN-38 clearance ->Free SN-38 (L/Hr)	6.07	NA	NA
THETA(3)	Free SN-38 clearance (L/HR)	171	NA	NA
THETA(4)	Conjugated SN-38 clearance, not to Free SN-38	0.619	NA	NA
THETA(5)	K23 (1/hr)	0.368	NA	NA
THETA(6)	K32 (1/hr)	0.0921	NA	NA
THETA(7)	Conjugated SN-38 clearance ~albumin power	-0.596	NA	NA
THETA(8)	Central volume ~ albumin	-0.316	NA	NA
THETA(9)	Fraction -> Glucuronide	7.54E-2	0.0115	15.3
THETA(10)	Glucuronide clearance (L/hr)	79.1	16.1	20.4

Source: Table 25 of the applicant's PPK and ER report

Figure 16: Goodness of Fit Plot for the Final Pharmacokinetic Model for SN-38G



Source: Figure 19 of the applicant's PPK and ER report

Exposure-Response Results

Toxicity:

- The AUC (1st cycle, defined as AUClast i.e., up to 3 weeks, which is the duration of a cycle) of free SN-38 was correlated with increased probability of observing nausea/vomiting of any grade.

- The AUC (1st cycle) of total SN-38 was correlated with the increased probability of diarrhea of any grade.
- AUC (1st cycle) of total SN-38 was correlated with a decreased risk of dose delay, but this result is potentially spurious due to a lack of correction for multiple comparisons.
- The C_{max} (1st cycle) of total SN-38 was correlated with increased probability of neutropenia in the first cycle.
- The AUC (1st cycle) of IgG was correlated with increased probability of diarrhea of any grade.

The results are listed in **Table 37.**

Efficacy:

- No apparent correlation between probability of complete/partial response (CR/PR; as defined by tumor shrinkage of ≥30%) at any point in the trial and AUC (1st cycle) of total SN-38, free SN-38 and SN-38G was observed.
- IgG AUC quartiles had statistically different OS and PFS probability outcomes, using a significance level of 0.05. The highest values of IgG AUC (Q4) were correlated with improved OS and PFS.
- Increased free SN-38G AUC (1st cycle) was correlated with decreased OS.

The exposure-ORR results are listed in **Table 38.** OS and PFS versus quartiles of AUClast (1st cycle only) for IgG, free SN-38, total SN-38, and SN-38G results are listed in **Table 39**.

Table 37: Parameter Estimates for Exposure-Toxicity Analysis

Event (DV)	Analyte	Exposure estimate (IDV)	Slope	Intercept	P Value for slope
Nausea/Vomiting in 1st cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	7.75e−9	-0.422	0.492
	Total SN-38	AUC (1st cycle)	8.17e−6	−1.35	0.139
	Free SN-38	AUC (1st cycle)	0.0003*	−2.06	0.009
	SN-38G	AUC (1st cycle)	−6.40e−5	0.215	0.791
Diarrhea in 1st cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	3.17e−8*	−2.91	0.016
	Total SN-38	AUC (1st cycle)	1.16e−5*	−2.80	0.045
	Free SN-38	AUC (1st cycle)	1.12e−4	−1.42	0.249
	SN-38G	AUC (1st cycle)	0.000326	−1.24	0.202
Neutropenia in 1st cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	6.93e−9	−1.80	0.603
	IgG	Cmax (1st cycle)	6.07e−6	−3.12	0.224
	Total SN-38	AUC (1st cycle)	4.88e−6	−2.22	0.388
	Total SN-38	Cmax (1st cycle)	0.000899*	−5.53	0.0257
	Free SN-38	AUC (1st cycle)	0.000122	−2.16	0.255
	Free SN-38	Cmax (1st cycle)	0.00966	−2.56	0.146
	SN-38G	AUC (1st cycle)	−0.000213	−0.973	0.527
Dose reduction in 1st cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	−3.82e−8	−0.115	0.198
	Total SN-38	AUC (1st cycle)	−1.32e−5	−0.258	0.333
	Free SN-38	AUC (1st cycle)	−0.000639	0.97	0.116
Dose reduction by last cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	1.07e−8	−1.52	0.366
	Total SN-38	AUC (1st cycle)	−5.32e−6	0.167	0.362
	Free SN-38	AUC (1st cycle)	3.28e−5	−0.990	0.739
Dose delay in 1st cycle (1-YES; 0-NO)	IgG	AUC (1st cycle)	2.26e−10	−0.282	0.985
	Total SN-38	AUC (1st cycle)	−0.0000132*	2.11	0.05
	Free SN-38	AUC (1st cycle)	−0.000117	0.511	0.270

(p≤0.05)

DV- Dependent variable

IDV- Independent variable

Source: Appendix 10 Table 1 of applicant's PPK and ER Analysis

Table 38: Parameter Estimates for Exposure-ORR Analysis

Event (DV)	Analyte	Exposure estimate (IDV)	Slope	Intercept	P Value for slope
CR/PR in the trial (1-YES; 0-NO)	IgG	AUC (1st cycle)	1.65e−10	−0.867	0.989
	Total SN-38	AUC (1st cycle)	−3.38e−06	−0.265	0.559
	Free SN-38	AUC (1st cycle)	6.92e−05	−1.32	0.484

(p≤0.05)

CR- Complete response

PR- Partial response

DV- Dependent variable

IDV- Independent variable

Source: Appendix 10 Table 2 of applicant's PPK and ER Analysis

Table 39: Parameter Estimates for Exposure-PFS/OS Analysis

Statistical test	Overall Survival p-value	Progression-free Survival p-value
IgG AUC	0.00044*	0.011*
Total SN-38 AUC	0.11	0.67
Free SN-38 AUC	0.13	0.27
Free SN-38G AUC	0.0096*	0.36

* = Statistically significant p-value, using a significance level of 0.05

Source: Table 31 of applicant's PPK and ER Analysis

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20.1. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

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