CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761115Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Metastatic Triple-Negative Breast Cancer

Recommendation: Approval

BLA 761115
Integrated Quality Assessment: Review #2
Review Date: April 17, 2020

Drug Name/Dosage Form	Trodelvy lyophilate
Strength/Potency	180 mg/vial
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Indication	Indicated, (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/Sponsor	Immunomedics

Product Overview

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 cross-linker (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. IMMU-132 drug product is manufactured as a 180 mg lyophilized powder in single-dose vials. IMMU-132 is indicated as a monotherapy for the treatment of adult patients with mTNBC who have received at least two prior therapies for metastatic disease.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
mAb intermediate/Drug Substance Drug Product Immunogenicity	Andrea Siegel mAb/DS/DP Brian Janelsins Immunogenicity	OBP/DBRR1
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Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
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Statistics	Joyce Cheng/Mallorie Fiero	OB/DBV

a. Names
   i. Proprietary Name: Trodelvy
   ii. Trade Name: Trodelvy
   iii. Non-Proprietary/USAN: sacituzumab govitecan
   iv. CAS name: 1491917-83-9
   v. Common name: IMMU-132
   vi. INN Name: sacituzumab govitecan
   vii. Compendial Name: not yet assigned
   viii. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI P09758 (TROP2_HUMAN); SN38 [hRS7-SN38]

b. Pharmacologic category: Therapeutic recombinant humanized anti-human Trop2 monoclonal antibody (IgG1, kappa) drug conjugated to SN-38

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761115.103	12/2/2019 (BLA resubmission)
761115.104 response to OPMA IR #1	12/19/2019 (Manufacturing Schedule)
761115.105	12/20/2019 (Batch analysis for DS lot #S19I026)
761115.106 response to OBP IR #2	1/6/2020
761115.107	1/14/2020 (Revised Manufacturing Schedule due to Potential (b) (4))
761115.109 response to OPMA IR #3	1/16/2020 (FEI number and testing at (b) (4))
761115.110 response to OPMA IR #4	1/31/2020 (Update Form FDA 356h)
761115.111	2/11/2020 ((b) (4) Investigation Summary)
761115.112 response to OPMA IR #5	2/13/2020 (Bioburden and Endotoxin Qualification)
761115.113	2/18/2020 (mAb intermediate stability update)
761115.116 response to OBP IR #6 and OPMA IR #7	2/27/2020
761115.120 response to OBP IR #8	3/30/2020
761115.123 follow-up response to OBP IR #6	4/1/2020 ((b) (4) method transfer report)
761115.125 response to OBP IR #9	4/8/2020
761115.126 response to OBP IR #10	4/10/2020
761115.128 response to OBP IR #11	4/15/2020

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		

(b) (4)	III		(b) (4)	3	N/A	
	III			3	N/A	
	II			3	N/A	

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available;6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

3. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation: Approval

The Office of Product Quality (OPQ), CDER, recommends approval of STN 761115 for Trodelvy (Sacituzumab Govitecan) manufactured by Immunomedics Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Trodelvy (Sacituzumab Govitecan) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under the conditions specified in the package insert.

b. Summary of Complete Response issues

None

c. Benefit/Risk Considerations

The proposed indication for IMMU-132 is for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who received at least 2 prior therapies for metastatic disease. mTNBC is a prevalent type of metastatic breast cancer defined by the lack of expression of the estrogen receptor, progesterone receptor, and HER2/neu. mTNBC is estimated to affect 20,000 patients annually in the US. Currently chemotherapy is the only option for treating mTNBC. However, the outcomes for chemotherapy in this patient population are often poor due to resistance of cancer cells to chemotherapeutic treatment and aggressive disease progression. Therefore, there is an unmet medical need for new therapies for managing mTNBC.

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 the initial BLA review cycle, it was determined that 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 poor and do not comply with GMPs, leading to major deficiencies in establishing a well-controlled process that is necessary for assuring product safety, efficacy and consistency to meet the intended drug product performance. Refer to the Complete Response Letter (CRL) issued to Immunomedics Inc. on January 17, 2019.

In response to the CRL, 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 CRL were adequately addressed in the BLA resubmission and provide overall assurance of the manufacture of a consistent, safe, pure and potent product.

d. Environmental Assessment or Claim of Categorical Exclusion: A claim of categorical exclusion from environmental assessment according to 21 CFR 25.31 (c) was provided. Immunomedics states that to their knowledge, per 21 CFR 25.15(d), no extraordinary circumstances exist.

A categorical exclusion for IMMU-132 is acceptable per 21 CFR 25.15(d), 25.31(b), and 25.31(c).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps:

1. Perform 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.

2. 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.

3. Develop an assay (e.g., icIEF) that is capable of providing quantitative control of (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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Note that Table 1 describes CQAs intrinsic to sacituzumab govitecan.

Section C describes the hRS7 (sacituzumab) and CL2A-SN-38 (govitecan) drug substance intermediates. Other product related CQAs typically included in Section A for unconjugated mAbs, as well as process related CQAs are in Section C, Table 3. Product- and process-related CQAs for CL2A-SN-38 are in Section C, Table 4.

Table 1: API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Target Binding (Potency)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes	(b) (4)	Binding assay was (b) (4) Data were provided to support that the assay can detect a change in the binding activity of IMMU-132 DS and DP, should there be any.
Cytotoxicity (Potency)	Impact on safety and efficacy	Quality of DSIs (hRS7 and SN-38) (b) (4) processes, and fraction pooling criteria. (b) (4)		Cytotoxicity assay was (b) (4)
DAR (Quantity)	Impact on safety and efficacy Impact on the SN-38 payload amount	(b) (4) processes, DS and DP storage		
Intact IgG (Purity)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes		

			(b) (4)	
Heavy and Light Chain (Purity)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes (b) (4)		
heavy-light chain (HL) (Product Variant)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes (b) (4)		(b) (4)
Aggregate (Dimer and Higher Order) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety	Quality of hRS7 DSI, (b) (4) processes		
(b) (4) (Product Impurity)	Impact on safety	(b) (4) processes, DS and DP storage		

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			(b) (4)	

B. Drug Substance [sacituzumab govitecan] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and clarity (General)	Impact on safety and immunogenicity	(b) (4) process	(b) (4)	
Protein Quantity (General)	Impact on efficacy	Concentration of mAb DSI, (b) (4) step		
Identity	Impact on safety and efficacy	Intrinsic to molecule. Quality of DSIs (sacituzumab and SN-		

(General)		38) (b) (4) processes
pH (General)	Impact on safety	Excipients
Residual Solvents (Impurity)	Impact on safety	(b) (4) process
Elemental Impurities (Impurity)	Impact on safety	SN-38 DSI
Endotoxin (Contaminant)	Impact on safety and purity	Raw materials or contamination during manufacturing
Bioburden (Contaminant)	Impact on safety, purity, and efficacy (degradation of modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing

(b) (4)

a. Description
Sacituzumab govitecan is a humanized IgG1κ, anti-Trop 2 mAb (hRS7) that is covalently linked to the cytotoxic agent SN-38 (the active metabolite of irinotecan) via a cleavable linker (CL2A). Sacituzumab govitecan has a drug to antibody ratio (DAR) average of 7.0 – 7.5 SN-38 to 1 mAb.

b. Mechanism of action
Sacituzumab govitecan binds Trop-2 expressed on cancer cells and delivers SN-38 to the tumor upon the cleavage of CL2A linker. The CL2A linker is designed to be cleavable, which allows the release of SN-38 over time at the site of the tumor. After internalization of sacituzumab govitecan into the tumor cells, SN-38 is released and 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.

c. Potency Assay
There are two potency assays: a cell-based binding assay (see description in Section C for the mAb intermediate) and a cell-based cytotoxicity assay. In the cytotoxicity assay, Trop-2 expressing PC-3 cells are incubated with serial dilutions of sacituzumab govitecan reference standard, test samples and an hRS7 control for five days. After five days, the tetrazolium dye MTT is added to the cells and is reduced by viable cells to a formazan product, resulting in a colorimetric signal that is directly proportional to the number of living cells. Dose-response curves are generated and the 50% effective concentration (EC_{50}) values of the sample and reference standard are obtained by non-linear regression analysis (sigmoidal dose-response algorithm) using the software. Relative potency is calculated as the percent EC_{50} of the test specimen compared to that of the reference standard. Data are reported as the average of 4 plates. The cytotoxicity assay was optimized and validated to reduce assay variability and to support the monitoring of assay performance and reference standard (RS) stability by qualifying the use of IMMU-132 DS batch CN 1905102 as an assay control.

d. Reference material(s)
Currently a single-tier reference standard (RS) system is used. (b) (4)

(b) (4)

A post-market commitment will be issued for establishing a two-tiered RS system by

qualifying a PRS.

e. Critical starting materials or intermediates
The hRS7 (sacituzumab) and CL2A-SN-38 (govitecan) drug linker are described in Section C.

f. Manufacturing process summary

g. Container closure

h. Dating period and storage conditions:
The dating period for the IMMU-132 DS is (b) (4) months when stored at ≤ (b) (4) °C, (b) (4)

C. Drug Substance Intermediates

Sacituzumab govitecan is manufactured from the monoclonal antibody (hRS7, sacituzumab) DSI and the small molecule/linker (CL2A-SN-38) DSI.

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for the sacituzumab DSI CQAs that derive from the mAb manufacturing process and general mAb attributes.

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for the SN-38 DSI CQAs that derive from the drug/linker manufacturing process and general drug/linker attributes.

Table 3: MAb Intermediate (IMMU-132, sacituzumab) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
(b) (4)				

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a. Description
hRS7 (sacituzumab) is a humanized IgG1κ, monoclonal antibody that recognizes Trop-2 and is produced in a proprietary host cell line derived from the (b) (4) cell line. It has an average molecular weight of ~148131.1 Da (lacking C-terminal lys, a predominant glycoform of G0F on both H chains), and a pI of ~8.8 It has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds and 12 intrachain disulfide bonds. It has the typical N-linked glycan structures at position N301.

b. Mechanism of action
hRS7 (sacituzumab) binds Trop-2 and serves as the targeting molecule for sacituzumab govitecan. It was shown to have low levels of ADCC activity and no CDC activity.

c. Potency Assay
The binding of sacituzumab to Trop-2 is measured by a cell-based binding assay. The PC-3 cell line expressing Trop-2 is allowed to adhere to wells of a microtiter plate. Dilutions of the reference standard and samples are added to the wells. Bound antibody is detected by the addition of HRP-conjugated goat anti-human IgG Fcγ specific antibody, which binds to the cell-bound hRS7 and is detected using 3,3',5,5'-Tetramethylbenzidine (TMB) by measuring absorbance at 450 nm. The data are fitted to a 4-parameter logistic fit and processed by PLA software. Similarity of reference standard and test sample dose response curves is required prior to calculation of binding. Results are calculated as an average of 5 plates and reported as relative to the reference standard. In response to the CRL Letter, the binding assay was optimized and validated to reduce assay variability and to support the monitoring of assay performance and RS stability by qualifying the use of hRS7 IgG batch CN 1809199 as a Cell Binding Assay Control (CBAC).

d. Reference material(s)
Currently, there is a Primary Reference Standard (PRS) and Working Reference Standard (WRS). (b) (4)

Upon qualification, the current WRS batch (b) (4) will be qualified against PRS batch (b) (4) to form the basis of a two-tiered reference standard system.

e. Critical starting materials or intermediates

(b) (4)

f. Manufacturing process summary

The commercial manufacturing process starts with (b) (4)

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions: The dating period for the mAb DSI is (b) (4) months when stored at (b) (4) °C.

Table 4: Drug/Linker CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
(b) (4)				

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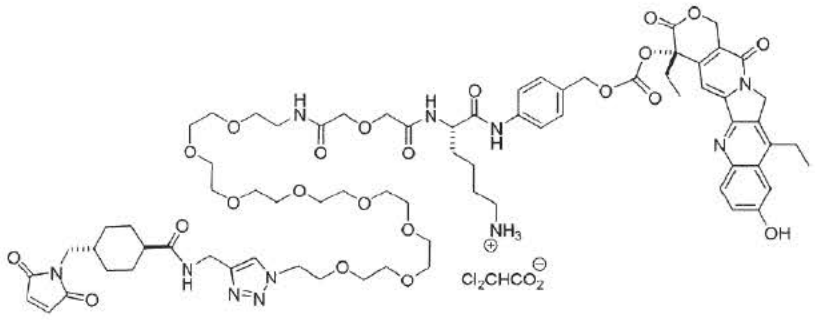
a. Description
CL2A-SN-38, the drug linker DSI, is an off-white to yellow solid with an average mass of 1609.554 Da. It is a dichloroacetate salt.



b. Mechanism of action
The SN-38 drug is a topoisomerase inhibitor and is the active metabolite of irinotecan. SN-38 prevents religation of DNA single-strand breaks by binding to topoisomerase I-DNA complex. The cytotoxicity of SN-38 is believed to be due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the topoisomerase-I-DNA-SN-38 complex, which prevents repair of the double stranded breaks. The CL2A linker provides intermediate conjugate stability in serum, is attached to the hydroxyl group on the lactone ring of SN-38 and contains a short polyethylene glycol moiety (b) (4) In the low pH environment of lysosomes, and in the tumor microenvironment, the carbonate bond between the linker and SN-38 is cleaved, releasing the active form of SN-38.

c. Strength
Assay is determined by HPLC analysis. Acceptance criteria are ≥ (b) (4) %. (b) (4) %.

d. Reference material(s)
Appropriately characterized.

e. Critical starting materials or intermediates
SN-38

f. Manufacturing process summary
Manufacture of the CL2A-SN36 intermediate involves (b) (4)

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions
For both SN-38 and CL2A-SN-38, a retest period of (b) (4) months at (b) (4) temperature was assigned and is justified based on the 24-month long term condition data.

D. Drug Product [Sacituzumab Govitecan] Quality Summary

Table 5 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 5: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other notes
Appearance (powder cake)	Measure of purity, impact on product safety and immunogenicity	DP manufacture Input materials, BDS, Lyophilization and Stoppering step.	(b) (4)	
Appearance reconstituted solution; color and opalescence, visible particulates	Measure of purity, impact on product safety and immunogenicity	DP manufacture Input materials, BDS, Lyophilization and Stoppering step.		
Sub-visible particulates (General)	Impact on product safety and efficacy	DP manufacture Input materials, BDS and (b) (4) step		

Reconstitution time (General)	Impact on product quality	DP manufacture Lyophilization and Stoppering step	(b) (4)	(b) (4)
pH (as reconstituted DP) (General)	Impact on product stability and conformation	DS manufacture Input materials and BDS		
Protein Quantity (General)	Impact on efficacy	DP manufacture BDS and the Filling and Partial Stoppering step.		
Content Uniformity	Impact on efficacy	DP manufacture Filling and Partial Stoppering step		
(b) (4) (General)	Impact on product safety, immunogenicity and therapeutic dose	DP manufacture (b) (4) Lyophilization and Stoppering step		(b) (4)
Osmolality (General)	Potential impact on therapeutic dose	DS manufacture Input materials and BDS		
Polysorbate 80 (General)	Impact on product quality	(b) (4) step		
Identity	Impact on safety and	Intrinsic to molecule.		

	efficacy	Quality of DS	(b) (4)	
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contaminants could be introduced throughout DP manufacturing process and through raw materials		
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing		
Container Closure Integrity (Contaminant)	Safety (Failure in closure integrity may lead to contamination through a loss of sterility) or evaporation/leakage (impacting concentration or content)	May be impacted by storage conditions.		

a. Potency and Strength
Trodelvy is supplied as sacituzumab govitecan for injection, 180 mg/vial drug product, an off-white to yellowish powder cake.

b. Summary of Product Design
Trodelvy is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP providing a targeted concentration of 10 mg/mL solution and a deliverable volume of 18 mLs.

c. List of Excipients
- 2-(N-morpholino) ethane sulfonic acid (MES) (b) (4) pH 6.5 – 77.3 mg/vial
- Trehalose dihydrate – 154.0 mg/vial
- Polysorbate 80 – 1.8 mg/vial

d. Reference material(s)
Same as for DS

e. Manufacturing Process
(b) (4)

(b) (4)

f. Container Closure
DP is stored in 50 mL (b) (4) colorless clear glass vials, sealed with elastomeric (b) (4) lyophilization stoppers (b) (4) and aluminum overseals with flip-off overseals.

g. Expiration Date & Storage Conditions: The dating period for DP is 24 months when stored at 2 – 8°C, protected from light.

E. Novel Approaches/Precedents

MES is a novel excipien (b) (4) There are no safety concerns related to MES.

F. Any Special Product Quality Labeling Recommendations:
Not applicable

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G. Establishment Information:

MAB INTERMEDIATE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
mAb intermediate Manufacture Release and stability	Immunomedics, Inc. 300 The American Road Morris Plains, NJ 07950	115350605 1000526871	Withhold pending the firm's adequate response to objectionable conditions.	(b) (4)	The firm is acceptable
Manufacture, release testing and release of CL2A-SN-38	Johnson Matthey Pharmaceutical Services 25 Patton Road Devens, MA 01434-3803	055774186 2018076	The last inspection of the firm was a surveillance inspection conducted on Sep 02, 2016 with a VAI outcome. The firm has acceptable (b) (4) profile.	N/A	The firm is acceptable
(b) (4)	(b) (4)	(b) (4)	The last inspection of the firm was a	N/A	The firm is acceptable

(b) (4)			surveillance inspection conducted on (b) (4) (b) (4) with a VAI outcome. The firm has acceptable (b) (4) profile.		
DRUG SUBSTANCE/ DRUG PRODUCT					
(b) (4) DP manufacture Release and stability	BSP Pharmaceuticals SpA Via Appia Km 65,561 Latina Scalo Latina, Italy 04013	857007830 3007255826	The PLI for this BLA was conducted Sep 13- 21, 2018 and concluded with initial VAI outcome and recommendation of the BLA for approval.	A 3-item FDA 483 was issued to the firm (b) (4) The firm's response to the FDA-483 observations is deemed adequate.	The firm is acceptable

Prior Inspection History

The compliance status and inspectional history of DSI, DS and DP manufacturing and testing facilities are provided in the table below.

Site Name/ Address	FEI #	Responsibility	Profile/Inspection History
Johnson Matthey Pharma Services, 25 Patton Road, Devens MA 01434, USA	2018076	Manufacture, testing and release of CL2A-SN-38	(b) (4) • 9/2/2016: surveillance inspection, VAI • 12/2/2013: PAI for (b) (4) profile and surveillance inspection, NAI • 11/7/2011: surveillance inspection, VAI

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(b) (4)

Immunomedics, Inc., 300 The American Road, Morris Plains, New Jersey 07950, USA	1000526871	Manufacture, testing and release of hRS7 IgG1K (b) (4) DP Testing of assay by UPLC	CBI • 8/14/2018: PLI for BLA 761115, withhold • 1/23/2003: surveillance inspection, VAI • 3/6/2001: surveillance inspection, VAI
BSP Pharmaceuticals S.p.A., Via Appia km 65,561, 04013 Latina Scalo (LT), ITALY	3007255826	Manufacture (conjugation (b) (4)) of sacituzumab govitecan (IMMU-132) (b) (4) Manufacture of drug product, Quality Control and Release testing of drug product	CBI, SVL • 9/21/2018: PLI for BLA 761115 covering CBI and SVL profiles, VAI • 12/16/2016: surveillance inspection for SVL and SVS profiles, VAI • 6/26/2015: surveillance inspection, VAI

(b) (4)

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(b) (4)

H. Facilities: Approvable

III. Lifecycle Knowledge Management

a. Drug Substance Intermediate (hRS7 mAb)

i. Protocols approved:
- MCB and WCB stability protocol
- (b) (4) Protocols
- PRS and WRS re-qualification protocol
- Post-approval stability protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: A post-approval inspection of the facility (Immunomedics Inc., Morris Plains, New Jersey) should be performed to verify that the observations identified during the pre-license inspection were adequately addressed.

b. Drug/Linker

i. Protocols approved:
- Post-approval stability protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

c. Drug Substance

i. Protocols approved:
- PRS and WRS re-qualification protocol
- Post-approval stability protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

d. Drug Product

i. Protocols approved:
- DP container closure leachable study protocol
- Post-approval stability protocol

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_			
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_ _)		X	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements		X	
18.	SPOTS (Special Products On-line Tracking System)		X	
19.	USAN Name Assigned	X		

20.	Other_				
Quality Considerations					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process	x		
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements			x	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial Analytical Procedures	Drug Product	x		
32.		Excipients	x		
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel	x		
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other				

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/s/

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KATHLEEN A CLOUSE STREBEL
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ZHIHAO PETER QIU
04/17/2020 05:09:09 PM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

BLA STN 761115

Sacituzumab govitecan-hziy, injection for intravenous use
TRODELVY

Immunomedics, Inc.

CMC Technical Report

Andrea Siegel, Ph.D., Biologist
Willie Wilson, Ph.D., Team Leader
Qing Zhou, Ph.D., Review Chief

Division of Biotechnology Review and Research I

OBP CMC Review Data Sheet

1. **BLA#:** STN 761115
2. **Review Date:** April 17, 2020
3. **Primary Review Team:**
   a. Product Quality Team: Andrea Siegel (OBP/DBRR1 mAb/DS/DP), Brian Janelsins (OBP/DBRR1 Immunogenicity), Maxwell Van Tassell (OPMA/DBM Microbiology), Rohit Tiwari (ONDP/DNDAP1)
   b. OBP Labeling: Scott Dallas
   c. Facilities: Wayne Seifert (OPMA/DBM)
   d. RBPM: Anh-Thy Ly (OPRO/DRBPM1)
   e. Medical Officer: Sakar Wahby (DO1)
   f. Clinical Pharmacology: Salaheldin Hamed, Pengfui Song (OCP/DCPV)
   g. Pharm/Tox: Kimberly Ringgold, Tiffany Ricks (DHOT)
   h. Statistics: Joyce Cheng, Mallorie Fiero (OB/DBV)
   i. Cross-disciplinary Team Lead: Christy Osgood (DO1)
   j. Application Technical Lead: Willie Wilson (OBP/DBRR1)
   k. RPM: Jeannette Dinin (DO1)

4. **Major GRMP Deadlines:**

Planning Meeting:	December 16, 2019
Mid-Cycle Meeting:	February 24, 2020
Wrap-up Meeting:	March 12, 2020
Primary Review Due:	April 3, 2020
Secondary Review Due:	April 10, 2020
PDUFA Action Date:	June 2, 2020

5. **Communications with Sponsor and OND:**

Communication/Document:	Date:
Information Request 2	12/26/2019
Teleconference to discuss the revised hRS7 manufacturing schedule	1/13/2020
Information Request 6	2/18/2020
Information Request 8	3/26/2020
Teleconference to discuss the 483 and the (b) (4) qualification strategy	3/31/2020
Information Request 9	4/6/2020
Information Request 10	4/9/2020

6. **Submission Reviewed:**

Submission:	Date Received:	Review Completed (yes or no)
761115/SD-103 CR Response	12/02/2019	Yes
761115/SD-105 New IMMU-132 DS lot	12/20/2019	Yes
761115/SD-106	1/6/2020	Yes

Response to IR-2		
761115/SD-107 Updated manufacturing schedule at Immunomedics	1/14/2020	yes
761115/SD-109 Updated 3.2.S.2.1-hRS7	1/16/2020	yes
761115/SD-110 Updated 3.2.S.2.1-IMMU-132	1/31/2020	yes
761115/SD-111 Update on (b) (4) testing of (b) (4) hRS7	2/11/2020	yes
761115/SD-112 Updated 3.2.S..2.1-hRS7	2/13/2020	yes
761115/SD-113 Updated 3.2.S.2.5-hRS7 2019 comparability report and 3.2.S.7 with 2019 PPQ hRS7 Stability data	2/18/2020	yes
761115/SD-116 Response to IR-6	2/27/2020	yes
761115/ SD-120 Response to IR-8	3/30/2020	yes
761115/SD-123 Method transfer of (b) (4) to BSP	4/1/2020	yes
761115/SD-125 Response to IR-9	4/8/2020	yes
761115/SD-126 Response to IR-10	4/11/2020	yes
761115/SD-127 Response to IR-11	4/15/2020	yes

7. Drug Product Name/Code/Type:

a. Proprietary Name:	Trodelvy
b. Trade Name:	Trodelvy
c. Non-Proprietary Name/USAN:	sacituzumab govitecan
d. CAS Name:	1491917-83-9
e. Common Name:	IMMU-132
f. INN Name:	sacituzumab govitecan
g. Compendial Name:	not yet assigned
h. OBP systematic name:	CONJ: MAB HUMANIZED (IGG1) ANTI P09758 (TROP2_HUMAN); SN-38 [hRS7-SN-38]
i. Other names:	immunoglobulin G1-kappa anti-[Homo sapiens TACSTD2, M1S1, GA7331, GA733-1, EGP-1, TROP2)] humanized monoclonal antibody conjugated to 7-ethyl-10-hydroxycamptothecin, SN-38, via a maleimide-type cleavable linker, CL2A, (carbonate group, self-immolative 4-aminobenzyl alcohol and cathepsin-B-cleavable dipeptide Phe-Lys) and containing a triazoline group and a spacer PEG (n=8)

8. Pharmacological Category: immunoglobulin G1-kappa anti-Trop2 humanized monoclonal antibody conjugated to SN-38 via a CL2A linker.

9. Dosage Form: Lyophilate

10. Strength/Potency:

(i): The concentration/strength of the Drug Product: 180 mg/vial. The concentration when reconstituted is 10 mg/mL.
(ii): Type of potency assay(s): Trop-2 binding assay, cytotoxicity assay

11. Route of Administration: intravenous

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)			Letters for each were Provided in Section 1.4.1	Type III, N/A
			Provided in Section 1.4.1	N/A
			Provided in Section 3.2.S.5-IMMU-132	N/A
			Provided in Section 3.2.S.6-IMMU-132	Type III, N/A
			Provided in Section 3.2.S.6-IMMU-132	Type III, N/A
			Provided in Section 3.2.S.6-IMMU-132	Type III, N/A
			Provided in Section 1.4.1	Type III, N/A
			Provided in Section 1.4.1	Type III, N/A
			Provided in Section 1.4.1	Type II, N/A

13. Inspectional Activities:

A pre-license inspection (PLI) was conducted at Immunomedics, Inc., Morris Plains, NJ (FEI: 1000526871). The hRS7 IgG1κ antibody intermediate of sacituzumab govitecan is manufactured, tested and released at the facility. The inspection was conducted on March 2-10, 2020 by ORA (Guerlain Ulysse), OPMA (Wayne Seifert), and OBP (Willie Wilson and Andrea Siegel) reviewers. The PLI covered the following Quality Systems: Quality Procedures, Facilities and Equipment, Production

Processes and Contamination Prevention, and Laboratory Controls. A 10-item Form FDA 483 was issued during the inspection related to:

(b) (4)

The recommendation for the classification of the inspection is VAI, with a post-approval inspection to be requested.

14. Consults Requested by OBP: None.

15. Quality by Design Elements:
The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application resubmission support the conclusion that the manufacture of sacituzumab govitecan is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in the manufacturing have been sufficiently validated, and a consistent product has been manufactured from the multiple production runs presented. It is recommended that sacituzumab govitecan be approved for human use under conditions specified in the package insert.

I recommend an expiry of 24 months for sacituzumab govitecan DP when stored at 2 – 8ºC, protected from light.

I recommend an expiry of (b) (4) months for sacituzumab govitecan DS when stored at ≤ (b) (4) ºC, (b) (4)

I recommend an expiry of (b) (4) months for sacituzumab drug substance intermediate (DSI) when stored at (b) (4) C.

II. List of Deficiencies to be Communicated

None

III. List of Post-Marketing Commitments/Requirements

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion

A claim for categorical exclusion under 21 CFR 25.31 (c) was made. The sponsor stated that sacituzumab govitecan is a biologic product composed of naturally occurring substances conjugated to such a minute amount of a chemical agent, including CL2A-SN38, as to be insignificant to the environment. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review was performed by Scott Dallas, OBP.

VI. Review of Common Technical Document- Quality Module 3.2

BLA 761115 is resubmitted for approval of sacituzumab govitecan. The initial BLA 761115 submission for sacituzumab govitecan was not approvable, and a complete response (CR) letter was sent on January 17, 2019. CMC Type A meetings were held on May 2, 2019 and September 27, 2019 to clarify the contents of the CR response. Immunomedics submitted additional data and manufactured new process qualification lots to address the deficiencies in the CR letter as reviewed in Section 1.11. Numerous updates were made to BLA 761115 in the resubmission including revalidation and transfer of many of the analytical methods for hRS7 IgGκ, IMMU-

132 DS, and IMMU-132 DP release and stability. Additional batch analysis, stability and viral clearance data was provided, and editorial corrections were made throughout the resubmission.

The following sections were updated in the resubmission:

- 1.14 Labeling
- 3.2.S hRS7 IgG1 – Immunomedics
    - 3.2.S.2 Manufacture
        - 3.2.S.2.1 Manufacturer(s)
        - 3.2.S.2.2 Description of Manufacturing Process and Process Controls
        - 3.2.S.2.3 Control of Materials
        - 3.2.S.2.4 Controls of Critical Steps and Intermediates
        - 3.2.S.2.5 Process Validation and/or Evaluation
        - 3.2.S.2.6 Manufacturing Process Development
    - 3.2.S.3 Characterization
    - 3.2.S.4 Control of Drug Substance
    - 3.2.S.5 Reference Standards or Materials
    - 3.2.S.6 Container Closure System
    - 3.2.S.7 Stability
- 3.2.S IMMU-132 DS – BSP
    - 3.2.S.1.3 General Properties
    - 3.2.S.2 Manufacture
        - 3.2.S.2.1 Manufacturers
        - 3.2.S.2.2 Description of Manufacturing and Manufacturing Controls
        - 3.2.S.2.6 Manufacturing Process Development
    - 3.2.S.3 Characterization
    - 3.2.S.4 Control of Drug Substance
    - 3.2.S.5 Reference Standards or Materials
    - 3.2.S.6 Container Closure
    - 3.2.S.7 Stability
- 3.2.S IMMU-132 DP – BSP
    - 3.2.P.2 Pharmaceutical Development
    - 3.2.P.3 Manufacture
    - 3.2.P.5 Control of Drug Product
    - 3.2.P.8 Stability
- 3.2.A Appendices
    - A.2.2.4.3 Viral Clearance Study
- 3.2.R Regional Information (USA)
    - Batch records provided

VII. Review of Immunogenicity Assays- Module 5.3.1.4

The immunogenicity review was conducted by Brian Janelsins and can be referenced in Panorama. PMCs will be issued for the commitments regarding the assays to detect anti-drug antibodies (ADA) and neutralizing antibodies (NAb).

1.11 Information Amendment Not Covered Under Module 2 or 5 Responses to Deficiencies Stated in the Complete Response Letter

Andrea Siegel

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Willie Wilson

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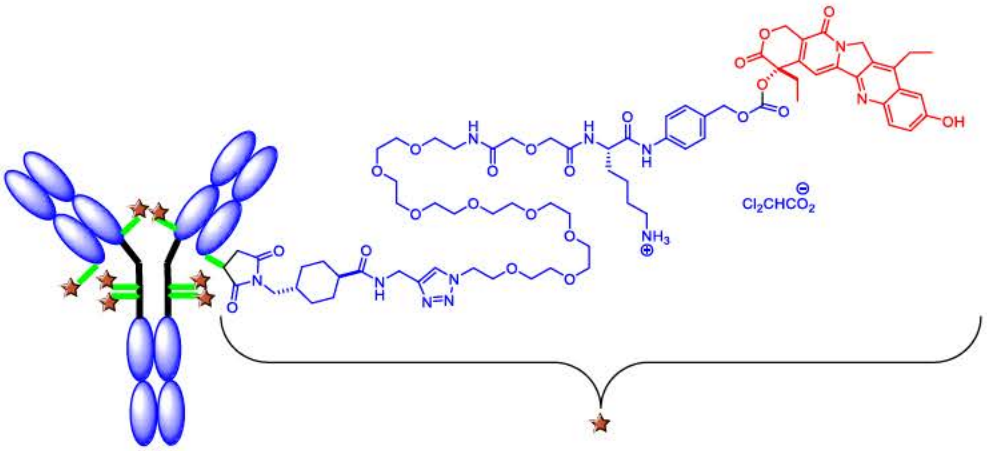
DRUG SUBSTANCE

Review Summary: *This BLA is recommended for approval from the review of drug-linker (small synthetic molecule chemistry) perspective. The following review only covers the synthetic drug CL2A-SN38.*

Product Background: The ADC drug product (IMMU-132, sacituzumab govitecan) is comprised of the humanized antibody, hRS7 IgG1κ, that is directed against Trop-2, the trophoblastic cell surface antigen, the linker, CL2A, and the payload, SN-38. SN-38 is a potent tropoisomerase I inhibitor and used clinically for several malignancies.

BLA: 761115

Chemical Name and Structure: *immunoglobulin G1-kappa anti-[Homo sapiens TACSTD2, M1S1, GA7331, GA733-1, EGP- 1, TROP2)] humanized monoclonal antibody conjugated to 7-ethyl-10-hydroxycamptothecin, SN-38,via a maleimide-type cleavable linker, CL2A, (carbonate group, self-immolative 4-aminobenzyl alcohol and cathepsine-B-cleavable dipeptide Phe-Lys) and containing a triazoline group and a spacer PEG (n=8)*



Applicant Name/DMF Holder: ***Immunomedics, Inc.***

List Submissions being reviewed (table): SN 0097

Highlight Key Outstanding Issues from Last Cycle: not applicable

Concise Description Outstanding Issues Remaining: none

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Ali Al Hakim

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotech Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

To: Administrative File, **STN 761115-ORIG-1-RESUB-103**
From: Maxwell Van Tassell, Ph.D.
Through: Candace Gomez-Boughton, Ph.D., Acting Quality Assessment Lead
Subject: Review of Original BLA Resubmission
Applicant: Immunomedics, Inc.
US License: 1737
Product: Trodelvy (sacituzumab govitecan)
Indication: Metastatic triple-negative breast cancer
Dosage: Powder for solution for IV infusion (180 mg)
Facilities: Immunomedics, Inc., Morris Plains, NJ (FEI # 1000526871)
BSP Pharmaceuticals SpA, Latina Scalo, Italy (FEI # 3007255826)
Receipt Date: 12/02/2019
Action Date: 4/10/2020

Recommendation for Approvability: STN 761115-ORIG-1-RESUB-103 was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for approval.

Review Summary

Immunomedics, Inc. submitted 351(a) BLA 761115 in eCTD format on 18 May 2018 to license the manufacture of Trodelvy (sacituzumab govitecan) for treatment of patients with metastatic triple-negative breast cancer who (b) (4) received at least two prior therapies for metastatic disease. A Complete Response Letter (CRL) was subsequently provided to the applicant 17 January 2019. This resubmission was submitted on 02 Dec 2019 to address the deficiencies listed in the CRL.

There were no approvability items in the CRL pertaining to product quality microbiology for the drug substance (DS) or drug product (DP). However, there were two additional comments in the CRL pertaining to the DS manufacturing process, as described in the 29 October 2018 assessment memo by Reyes Candau-Chacon, Ph.D., and one additional comment pertaining to the DP manufacturing process, as described in the 10 January 2019 assessment memo by Jessica Hankins, Ph.D. The Product Quality Microbiology additional comments in the CRL were as follows:

(b) (4)

This review contains the assessment of the changes made in the BLA resubmission, from a product quality microbiology and sterility assurance perspective.

Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
eCTD 0097	12/02/2019	BLA Resubmission
eCTD 0099	12/20/2019	Additional CMC Information
eCTD 0100	01/06/2020	Response to Product Quality IR
eCTD 0103	01/16/2020	Response to Facility IR

Product Quality Microbiology Assessment

MODULE 1

1.14 LABELING

Reconstituted DP solution must be diluted immediately for preparation of the final dosage form. Diluted solution in the infusion bag should be used immediately or stored at 2-8°C for no more than 4 hours.

Reviewer Comment

The post-dilution storage time was reduced (b) (4) *to 4 hours in the resubmission to account for the lack of microbial challenge studies supporting storage of > 4 hours.*

SATISFACTORY

3.2.S DRUG SUBSTANCE – HRS7 IGG1 - IMMUNOMEDICS

Reviewer Comment

The humanized monoclonal antibody (mAb) hRS7 IgG1κ (sacituzumab) is expressed in a recombinant (b) (4) *cell line. Sacituzumab has no known independent biological activity, but is a DS-intermediate for conjugation with a cytotoxic drug to form the final DS antibody-drug conjugate (ADC).*

S.2 MANUFACTURE

(b) (4)

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Candace Gomez-Broughton

Digitally signed by Candace Gomez-Broughton
Date: 3/12/2020 11:22:00AM
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First Approval for Metastatic Triple-Negative Breast Cancer

Recommendation: Complete Response

BLA 761115
Integrated Quality Assessment: Review #1
Review Date: 1/11/2019

Drug Name/Dosage Form	Trodelvy lyophilate
Strength/Potency	180 mg/vial
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Indication	Indicated, (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/Sponsor	Immunomedics

Product Overview

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
mAb intermediate/Drug Substance Drug Product Immunogenicity	Andrea Siegel mAb/DS Willie Wilson DP Brian Janelsins Immunogenicity	OBP/DBRR1
SMD intermediate/Drug Substance Drug Product	Rohit Tiwari	ONDP/DNDAP1
Facilities	Ephrem Hunde	OPF/DIA
Microbiology	Reyes Candau-Chacon DS Jessica Hankins DP	OPF/DMA
Business Regulatory Process Manager	Anh-Thy Ly	OPRO/DRBPM1
Team Lead ONDP	Suong Tran	ONDP/DNDAP1
Team Lead Microbiology	Patricia Hughes	OPF/DMA
Team Lead Facilities	Peter Qiu	OPF/DIA
Labeling	Dallas Scott/Vicky Borders-Hemphill	OBP
Application Technical Lead	Qing Zhou	OBP/DBRR1

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	Jeannette Dinin	DOP1
Cross-disciplinary Team Lead	Lola Fashoyin-Aje	DOP1
Medical Officer	Lynn Howie/Gwen	DOP1
Pharm/Tox	Kimberly Ringgold/Tiffany Ricks	DHOT
Clinical Pharmacology	Salaheldin Hamed/Pengfui Song	OCP/DCPV
Statistics	Joyce Cheng/Lijun Zhang	OB/DBV

a. Names
   i. Proprietary Name: Trodelvy
   ii. Trade Name: Trodelvy
   iii. Non-Proprietary/USAN: sacituzumab govitecan
   iv. CAS name: 1491917-83-9
   v. Common name: IMMU-132
   vi. INN Name: sacituzumab govitecan
   vii. Compendial Name: not yet assigned
   viii. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI P09758 (TROP2_HUMAN); SN-38 [hRS7-SN-38]

b. Pharmacologic category: Therapeutic recombinant humanized anti-human Trop2 monoclonal antibody (IgG1, kappa) drug conjugated to SN38

Submissions Reviewed:

SUBMISSION(S) REVIEWED	DOCUMENT DATE
761115.0	5/18/2018 (Original Submission)
761115.2 response to IR #1	6/4/2018 (detailed manufacturing schedule)
761115.6 response to IR #2	6/13/18 (validation plans, mAb intermediate and DS, micro and PQ)
761115.9 response to IR #3	6/27/18 (DP micro)
761115.15 response to IR #4	7/16/17 (mAb intermediate and DS PQ)
761115.20 response to IR #5	7/25/2018 (mAb intermediate and DS micro)
761115.21 response to IR #6	7/30/18 (mAb intermediate and DS PQ)
761115.24 Updates to Module 3	8/3/2018 (to reflect responses to IRs 2, 4 and 6: mAb intermediate DS and Appendices)
761115.25 response to IR #7	8/8/2018 (DP micro and PQ)
761115.29 Updates to Module 3	8/14/2018 (to reflect responses to IR 7, DP and Appendices)
761115.34 response to IR #8	8/27/18 (mAb intermediate, DS and DP PQ (methods)
761115.35 Updates to Module 3	8/31/18 (remaining DS and DP PPQ lots)
761115.36 response to IR #9	8/31/18 (immunogenicity and DP PQ)
761115.37 response to IR #10	9/7/2018 (DP micro)
761115.38 Updates to Module 3	9/7/2018 (remaining drug linker PPQ lots, updated stability all, response to IR 9 in-use stability)
761115.42 Updates to Module 3	9/12/18 (to reflect DP IRs)
761115.46 additional response to IR #8	9/20/2018 (follow-up to item 1 regarding host cell DNA and item 3 regarding stability indicating ability of release methods

761115.46 response to IR #11	9/26/18 (drug-linker intermediate)
761115.52 response to IR #12	10/5/18 (DP micro follow up to Q12 in IR#10)
761115.56 response to IR #12 and updates to Module 3	10/12/18 (drug-linker intermediate, DS and DP micro)
761115.57 response to IR #12 and updates to Module 3	10/19/18 (mAb intermediate)
761115.59 response to IR #13 and updates to Module 3	11/2/18 (DP micro)
761115.61 response to IR #13	11/13/18 (facilities – 3rd party data integrity investigation plan)
761115.62	11/15/18 comparability proposal to support that (b) (4) lots used in the clinical studies will support use of (b) (4) commercial lots.
761115.63	11/19/18 hRS7 manufacturing 3rd party oversight protocol
761115.64 Response to IR #14	11/20/18 (mAb intermediate, DS and DP)
761115.66 Response to IR #14	11/23/18 (mAb intermediate, DS and DP)
761115.67 Comparability study	11/28/18 (response to concerns raised during the 11/2/18 F2F meeting that clinical and commercial lots may not be the same
761115.68 Response to IR #15	12/6/18 (immunogenicity)
761115.69 Response to IR #5 Q2b	12/10/18 (DS micro)
761115.70 Response to IR #1 Q3e	12/11/18 (mAb intermediate (b) (4))
761115.71 Response to IR #14 Q4 and 16	12/17/18 (shipping validation mAb intermediate and DP
761115.72	12/18/18 (comparability protocol mAb intermediate)
761115.76 (Response to IR #16)	12/27/18 (mAb intermediate, DS and DP, DS micro)
761115.81 (Response to IR #17)	1/10/19 (mAb intermediate and DS specs, DS micro, DP micro)

Teleconferences with Sponsor:

Date	Topic(s)
Tcon #1 6/22/18	Clarification regarding filing deficiencies sent in IR #3, 6/20/18
Tcon #2 7/26/18	Discussion of Q15 from IR #3 and Q9 and 20 from IR #6
Tcon #3 8/23/18	Discussion of IR #8 Q13, assay validations and updating IND 115621 with current CMC information
Tcon #4 9/6/18	Discussion of microbial retention study (DP micro), LC/MS calculations for DAR, and WCB
Tcon #5 10/4/18	Discussion of amended response to Immunomedics 483, DS/DP potency assay and follow up in (b) (4) study.
Tcon #6 10/10/18	Follow up discussion regarding the Request for Information related to the Immunomedics 483 response
Tcon #7 11/15/18	Discussion of operating ranges, dosage strength and label claim, MCB (b) (4) data, (b) (4) validation and microbial safety, cytotoxicity assay, and (b) (4) integrity
Tcon #8 11/16/18	Discussion of audit protocol

Tcon #9 11/29/18	Discussion regarding dosage strength, master cell bank, cell cytotoxicity assay, comparability plan.
Tcon #10 12/13/18	Discussion regarding dosage strength, submission of updates from PAI Form 483 Observations, Status of Retrospective DI Report, Comparability Report, and Prospective DI Report.
Tcon #11 12/20/18	Discussion regarding Audit report, the methodology and data used to set the control limits for hRS7 and IMMU-132 PRS stability testing, proposed assay controls for potency assays.
Tcon #12 1/9/19	Discussion of specifications and updates needed to Module 3

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		
	III			3	N/A		

(b) (4)	III	(b) (4)	3	N/A		
	III		3	N/A		

[1] Action codes for DMF Table: 1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows: 2 – Reviewed previously and no revision since last review; 3 – Sufficient information in application; 4 – Authority to reference not granted; 5 – DMF not available;6 – Other (explain under "Comments")

[2] Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

3. CONSULTS: None

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation: Complete Response

The Office of Product Quality (OPQ), CDER, has completed review of STN 761115 for Trodelvy (Sacitumumab Govitecan) manufactured by Immunomedics Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Trodelvy is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life.

From a CMC standpoint, the Office of Biotechnology Products (OBP), OPQ, CDER is recommending that a Complete Response letter be issued to Immunomedics Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

The Division of Inspection Assessment (DIA), OPF, OPQ is recommending that a Complete Response letter be issued to Immunomedics Inc., to outline the deficiencies noted below and the information and data that will be required to support approval.

b. Summary of Complete Response issues (OBP and DIA)

1. During a recent inspection of the Immunomedics, Inc., (FEI 1000526871) manufacturing facility for BLA 761115, our field investigators observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

2. Per 21 CFR 601.20 (c) "No product shall be licensed if any part of the process of or relating to the manufacture of such product...would impair the assurances of continued safety, purity, and potency…".
   a. Reference is made to the information and data provided to the Agency in response to Form 483 and the Agency's information request (IR) dated July 18, 2018 (b) (4)

[redacted] (b) (4)

is not validated to ensure the manufacture of a product with continued safety, purity, and potency. Provide information and data to support [redacted] (b) (4)

b. Reference is made to manufacturing information provided during the pre-license inspection at Immunomedics Inc. (Morris Plains, NJ), and in response to the Agency's IR dated Oct 3, 2018. The data provided demonstrate [redacted] (b) (4)

3. Reference is made to the information and data provided in response to the Agency's IR dated Oct 3, 2018 and Dec 14, 2018, and in multiple communications through teleconferences with the Agency [redacted] (b) (4)

To support a well-controlled and consistent commercial production [redacted] (b) (4)

provide adequate data and information to confirm [redacted] (b) (4)

that is currently intended for commercial manufacture. Additionally, provide a root cause analysis, supported by appropriate documentation, for the observed trend [redacted] (b) (4)

4. Reference is made to the information and data provided in response to the Agency's IR dated Aug 17, 2018 and in multiple communications through teleconferences with the Agency [redacted] (b) (4)

(b) (4)

Provide adequate information and data to support the testing strategy (b) (4) Additionally, as committed in response to the Agency's IR dated Nov 13, 2018, implement appropriate assay controls (b) (4)

5. Reference is made to the information and data provided in response to the Agency's IR dated Nov 13, 2018 and Jan 5, 2019 (b) (4) Revise the specifications, as appropriate, and provide information and data (b) (4)

(b) (4)

(b) (4)

[redacted]

6. Reference is made to the information provided in response to the Agency's IR dated Nov 13, 2018 (b) (4)

[redacted]

7. Reference is made to the information and data provided in response to the Agency's IR dated Dec 14, 2018 and Jan 5, 2019 (b) (4) [redacted] The information provided is insufficient to support the following (b) (4)

(b) (4) Provide additional information and data (b) (4)

hRS7 antibody intermediate

(b) (4)

IMMU-132 DS

(b) (4)

8. Reference is made to the information provided in response to the Agency's information request dated Jan 5, 2019 (b) (4)

9. Regarding method validation:

(b) (4)

10. Reference is made to the information provided in response to the Agency's IR dated Nov 13, 2018 concerning hRS7 antibody intermediate and IMMU-132 DP shipping validation. As conveyed in the IR, the shipping validation studies submitted in the BLA are insufficient (b) (4)

Provide detailed information (e.g., study conditions and justification) and data (e.g., product quality data from the same hRS7 and IMMU-132 DP lots prior to and after the shipping) generated to allow for an assessment on the potential impact of shipping on hRS7 and IMMU-132 DP quality and to support the validation of all shipping routes,

modes of transportation and shipping containers intended for commercial use.

Additional Comments (OBP and DMA)

1. Reference is made to the information and data provided in response to the Agency's information requests (IRs) dated Nov 13, 2018 and Jan 5, 2019 concerning the qualification of the hRS7 and IMMU-132 reference standards. FDA recommends that Immunomedics develop a two-tiered reference material system that is composed of primary and working reference standards derived from different hRS7 and IMMU-132 lots to support the product lifecycle. As described in ICHQ6B, an appropriately characterized primary reference material that is representative of production and clinical materials can be used to calibrate or qualify a working reference material and contributes to mitigating the risk of drift in quality attributes over time. Use of a working or secondary reference material calibrated against a single primary reference material for routine release and stability testing of commercial lots provides additional assurance that commercially manufactured product is representative of the clinical trial material. Implementation of a two-tiered reference material should also consider the long-term stability of the primary reference material when evaluating storage temperatures. The primary reference material should be stored under conditions that prevent product degradation to the greatest extent possible. (b) (4)

2. Reference is made to the information and data provided in response to the Agency's IR dated Dec 14, 2018. (b) (4)

3. Reference is made to the information and data provided in response to the Agency's IR dated Dec 14, 2018 (b) (4)

4. [redacted] (b) (4)

5. [redacted] (b) (4)

The acceptance criteria should contain quantitative limits based on scientific knowledge, structure-function characterization study results, existing manufacturing, non-clinical study, and clinical study experience.

6. Reference is made to the information provided in response to the Agency's IR dated July 18, 2018 and December 14, 2018 [redacted] (b) (4)

Regarding Immunogenicity:

7. Insufficient information and data were provided (b) (4) Address the following unresolved issues:

(b) (4)

8. (b) (4) (see Additional Comment 7).

Regarding Product Quality Microbiology (DS and DP):

(b) (4)

[redacted]

c. Benefit/Risk Considerations

The proposed indication for IMMU-132 is for the treatment of patients with metastatic triple-negative breast cancer (mTNBC) who received at least 2 prior therapies for metastatic disease. mTNBC is a prevalent type of metastatic breast cancer defined by the lack of expression of the estrogen receptor, progesterone receptor, and HER2/neu. mTNBC is estimated to affect 20,000 patients annually in the US. Currently chemotherapy is the only option for treating mTNBC. However, the outcomes for chemotherapy in this patient population are often poor due to resistance of cancer cells to chemotherapeutic treatment and aggressive disease progression. Therefore, there is an unmet medical need for new therapies for managing mTNBC.

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

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, are demonstrated to be poor and presented serious violations of GMPs, leading to lack of appropriate validation of the commercial manufacturing process and poor manufacturing capability (see CR comments above), which contribute to the lack of assurance of the manufacture of a consistent, safe, pure and potent product.

The extensive problems with the CMC section of this BLA reflect potential disadvantages for manufacturing development that come with a Breakthrough Therapy Designation (BTD). BTD is granted on the basis of preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints for a serious or life-threatening condition. The

Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics acknowledges that a sponsor may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program and also describes expectations for pre-BLA discussions a sponsor should have with the Agency regarding product development in preparation for submission of a BLA and the extent of information and data that should be submitted to the BLA.

There were two CMC pre-BLA meetings for sacituzumab govitecan; a Written Responses Only meeting dated 3/17/2017 and a face-to-face meeting on January 3, 2018. A variety of topics were discussed including process characterization and the validation strategy.

Information provided in the first pre-BLA meeting package indicated that the mAb intermediate manufactured at Immunomedics would be used for clinical trials and to support commercial launch and the manufacture of commercial lots of the mAb intermediate would be transferred (b) (4) The Agency advised Immunomedics that data from process development studies to support their control strategy and the validation of the manufacturing process for the mAb intermediate that will be used for commercial launch is required for licensure. Immunomedics took steps to prepare their facility for commercial use and to provide data to support licensur (b) (4)

Overall, the OPQ review of manufacturing and controls has identified 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 (see CR comments above).

The technical assessments for OBP (including hRS7 antibody intermediate, drug substance, drug product quality and immunogenicity assays), ONDP (including drug-linker product quality), DMA (including drug substance and drug product quality microbiology), and (b) (4) facility are located as separate documents in Panorama.

d. Environmental Assessment or Claim of Categorical Exclusion: A claim of categorical exclusion from environmental assessment according to 21 CFR 25.31 (e) was provided. Immunomedics states that to their knowledge, per 21 CFR 25.15(d), no extraordinary circumstances exist.

The claim for a categorical exclusion is acceptable per 21 CFR 25.31(b).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps: Not applicable

II. Summary of Quality Assessments

A. CQA Identification, Risk and Lifecycle Knowledge Management

Note that Table 1 describes CQAs intrinsic to sacituzumab govitecan.

Section C describes the hRS7 (sacituzumab) and CL2A-SN38 (govitecan) drug substance intermediates. Other product related CQAs typically included in Section A [redacted] (b) (4) as well as process related CQAs are in Section C, Table 3. Product- and process-related CQAs for CL2A-SN38 are in Section C, Table 4.

Table 1: API CQA Identification, Risk and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Target Binding (Potency)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes	(b) (4)	
Cytotoxicity (Potency)	Impact on safety and efficacy	Quality of DSIs (hRS7 and SN38 (b) (4) processes, and fraction pooling criteria. (b) (4)		
DAR (Quantity)	Impact on safety and efficacy Impact on the SN-38 payload amount	(b) (4) processes, DS and DP storage		
Intact IgG (Purity)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes		

			(b) (4)
Heavy and Light Chain (Purity)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes (b) (4)	
heavy-light chain (HL) (Product Variant)	Impact on safety and efficacy	Quality of hRS7 DSI, (b) (4) processes (b) (4)	
Aggregate (Dimer and Higher Order) (Product Variant)	Impact on biological activity, immunogenicity, PK/PD, and safety	Quality of hRS7 DSI, (b) (4) processes	
(b) (4) (Product Impurity)	Impact on safety	(b) (4) processes, DS and DP storage	

			(b) (4)	

B. Drug Substance [sacituzumab govitecan] Quality Summary

CQA Identification, Risk and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
Visual Appearance: color and clarity (General)	Impact on safety and immunogenicity	(b) (4) process	(b) (4)	
Protein Quantity (General)	Impact on efficacy	Concentration of mAb DSI, (b) (4) step		
Identity	Impact on safety and efficacy	Intrinsic to molecule. Quality of DSIs (sacituzumab and SN-		

(General)		38) (b) (4) processes
pH (General)	Impact on safety	Excipients
Residual Solvents (Impurity)	Impact on safety	(b) (4) process
Elemental Impurities (Impurity)	Impact on safety	(b) (4)
Endotoxin (Contaminant)	Impact on safety and purity	Raw materials or contamination during manufacturing
Bioburden (Contaminant)	Impact on safety, purity, and efficacy (degradation of modification of the product by contaminating microorganisms)	Raw materials or contamination during manufacturing

(b) (4)

a. Description
Sacituzumab govitecan is a humanized IgG1, κ anti-Trop 2 mAb (hRS7) that is covalently linked to the cytotoxic agent SN38 (the active metabolite of irinotecan) via a cleavable linker (CL2A). Sacituzumab govitecan has a drug to antibody ratio (DAR) average of 7.0 – 7.5 SN38 to 1 mAb.

b. Mechanism of action
Trop-2 is overexpressed on various epithelial cancer cells and has been linked to aggressive malignancy with an overall poor prognosis. Sacituzumab govitecan binds Trop-2 expressed on cancer cells and delivers SN38 to the tumor upon the cleavage of CL2A linker. The CL2A linker is designed for intermediate stability, which allows the release of SN38 over time at the site of the tumor. After internalization of sacituzumab govitecan into the tumor cells, SN38 is released and 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.

c. Potency Assay
There are two potency assays: a cell-based binding assay (see description in Section C for the mAb intermediate) and a cell-based cytotoxicity assay. In the cytotoxicity assay, Trop-2 expressing PC-3 cells are incubated with serial dilutions of sacituzumab govitecan reference standard, test samples and an hRS7 control for five days. After five days, the tetrazolium dye MTT is added to the cells and is reduced by viable cells to a formazan product, resulting in a colorimetric signal that is directly proportional to the number of living cells. Dose-response curves are generated and the 50% effective concentration (EC_{50}) values of the sample and reference standard are obtained by non-linear regression analysis (sigmoidal dose-response algorithm) using software. Relative potency is reported as the percent EC_{50} of the test specimen compared to that of the reference standard.

The cytotoxicity assay is shown (b) (4) (see CR comments).

d. Reference material(s)
Currently there is only a Primary Reference Standard (PRS). (b) (4)

(b) (4)

(b) (4)

See additional comments.

e. Critical starting materials or intermediates
The hRS7 (sacituzumab) and CL2A-SN38 (govitecan) drug linker are described in Section C.

f. Manufacturing process summary

(b) (4)

g. Container closure

(b) (4)

h. Dating period and storage conditions: Not applicable due to CR.

C. Drug Substance Intermediates

Sacituzumab govitecan is manufactured from the monoclonal antibody (hRS7, sacituzumab) DSI and the small molecule/linker (CL2A-SN38) DSI.

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for the sacituzumab DSI CQAs that derive from the mAb manufacturing process and general mAb attributes.

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for the SN38 DSI CQAs that derive from the drug/linker manufacturing process and general drug/linker attributes.

Table 3: MAb Intermediate (Immu-132, sacituzumab) CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
(b) (4)				

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

a. Description
hRS7 (sacituzumab) is a humanized IgG1, κ monoclonal antibody that recognizes Trop-2 and is produced in a proprietary host cell line derived from the (b) (4) cell line. It has an average molecular weight of ~148131.1 Da (lacking C-terminal lys, a predominant glycoform of G0F on both H chains), and a pI of ~8.8 It has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds and 12 intrachain disulfide bonds. It has the typical N-linked glycan structures at position N301.

b. Mechanism of action
hRS7 (sacituzumab) binds Trop-2 and serves as the targeting molecule for sacituzumab govitecan. It was shown to have low levels of ADCC activity and no CDC activity.

c. Potency Assay
The binding of sacituzumab to Trop-2 is measured by a cell-based binding assay. The PC-3 cell line expressing Trop-2 is allowed to adhere to wells of a microtiter plate. Dilutions of the reference standard and samples are added to the wells. Bound antibody is detected by the addition of HRP-conjugated goat anti-human IgG Fcγ specific antibody, which binds to the cell-bound hRS7 and is detected using 3,3',5,5'-Tetramethylbenzidine (TMB) by measuring absorbance at 450 nm. The data are fitted to a 4-parameter logistic fit and processed by PLA software. Similarity of reference standard and test sample dose response curves is required prior to calculation of binding. Results are reported relative to the reference standard.

d. Reference material(s)
Currently there is only a Primary Reference Standard (PRS). (b) (4) It has been used for release and stability testing for the mAb DS1 clinical materials and will be used for routine testing of the commercial materials.

e. Critical starting materials or intermediates
(b) (4)

f. Manufacturing process summary
The commercial manufacturing process starts with (b) (4)

g. Container closure

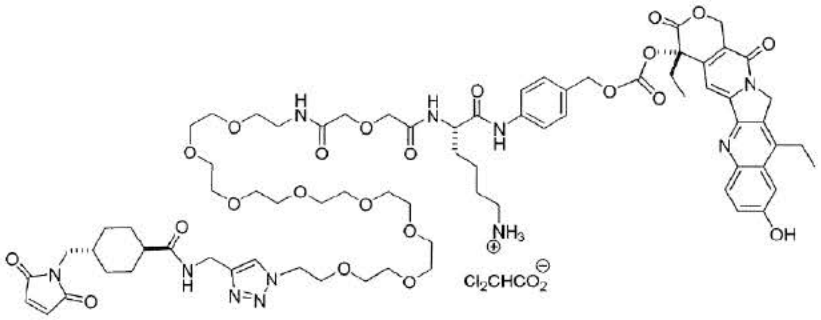
h. Dating period and storage conditions: Not applicable due to CR.

Table 4: Drug/Linker CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other
(b) (4)				

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

a. Description
CL2A-SN38, the drug linker DSI, is an off-white to yellow solid with an average mass of 1609.554 Da. It is a dichloroacetate salt.



b. Mechanism of action
The SN-38 drug is a topoisomerase inhibitor and is the active metabolite of irinotecan. SN38 prevents religation of DNA single-strand breaks by binding to topoisomerase I-DNA complex. The cytotoxicity of SN38 is believed to be due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the topoisomerase-I-DNA-SN-38 complex, which prevents repair of the double stranded breaks. The CL2A linker provides intermediate conjugate stability in serum, is attached to the hydroxyl group on the lactone ring of SN-38 and contains a short polyethylene glycol moiety [redacted] (b) (4) In the low pH environment of lysosomes, and in the tumor microenvironment, the carbonate bond between the linker and SN-38 is cleaved, releasing the active form of SN-38.

c. Strength
Assay is determined by HPLC analysis. Acceptance criteria are ≥ [redacted] (b) (4) %.
[redacted] (b) (4) %.

d. Reference material(s)
Appropriately characterized.

e. Critical starting materials or intermediates
SN-38

f. Manufacturing process summary
Manufacture of the CL2A-SN36 intermediate involves [redacted] (b) (4)

[redacted] (b) (4)

g. Container closure

[redacted] (b) (4)

h. Dating period and storage conditions

For both SN-38 and CL2A-SN38, a retest period of [redacted] (b) (4) months at [redacted] (b) (4) temperature was assigned and is justified based on the 24-month long term condition data.

D. Drug Product [Sacituzumab Govitecan] Quality Summary

Table 5 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 5: Drug Product CQA Identification, Risk, and Lifecycle Knowledge Management

CQA (Type)	Risk	Origin	Control Strategy	Other notes
Appearance (powder cake)	Measure of purity, impact on product safety and immunogenicity	DP manufacture Input materials, BDS, Lyophilization and Stoppering step.	(b) (4)	
Appearance reconstituted solution; color and opalescence, visible particulates	Measure of purity, impact on product safety and immunogenicity	DP manufacture Input materials, BDS, Lyophilization and Stoppering step.		
Sub-visible particulates (General)	Impact on product safety and efficacy	DP manufacture Input materials, BDS and the (b) (4) step		

Reconstitution time (General)	Impact on product quality	DP manufacture Lyophilization and Stoppering step	(b) (4)
pH (as reconstituted DP) (General)	Impact on product stability and conformation	DS manufacture Input materials and BDS	
Protein Quantity (General)	Impact on efficacy	DP manufacture BDS and the Filling and Partial Stoppering step.	
Content Uniformity	Impact on efficacy	DP manufacture Filling and Partial Stoppering step	
(b) (4) (General)	Impact on product safety, immunogenicity and therapeutic dose	DP manufacture (b) (4) Lyophilization and Stoppering step	
Osmolality (General)	Potential impact on therapeutic dose	DS manufacture Input materials and BDS	
Polysorbate 80 (General)	Impact on product quality	(b) (4) step	
Identity	Impact on safety and	Intrinsic to molecule.	

			(b) (4)
	efficacy	Quality of DS	
Endotoxin (Contaminant)	Safety, purity, and immunogenicity	Contaminants could be introduced throughout DP manufacturing process and through raw materials	
Sterility (Contaminant)	Safety risk to patients (infection) Efficacy (degradation or modification of the product by microorganisms or their byproducts)	Contaminants could be introduced throughout DP manufacturing	
Container Closure Integrity (Contaminant)	Safety (Failure in closure integrity may lead to contamination through a loss of sterility) or evaporation/leakage (impacting concentration or content)	May be impacted by storage conditions.	

a. Potency and Strength
Trodelvy is supplied as sacituzumab govitecan for injection, 180 mg/vial drug product, an off-white to yellowish powder cake.

b. Summary of Product Design
Trodelvy is reconstituted with 20 mL of 0.9% Sodium Chloride Injection, USP providing a targeted concentration of 10 mg/mL solution and a deliverable volume of 18 mLs.

c. List of Excipients
- 2-(N-morpholino) ethane sulfonic acid (MES) (b) (4) pH 6.5 – 77.3 mg/vial
- Trehalose dihydrate – 154.0 mg/vial
- Polysorbate 80 – 1.8 mg/vial

d. Reference material(s)
Same as for DS

e. Manufacturing Process

(b) (4)

(b) (4)

f. Container Closure
DP is stored in 50 mL (b) (4) colorless clear glass vials, sealed with elastomeric (b) (4) lyophilization stoppers (b) (4) and aluminum overseals with flip-off overseals.

g. Expiration Date & Storage Conditions: Not applicable due to CR.

E. Novel Approaches/Precedents

MES is a novel excipien (b) (4) There are no safety concerns related to MES.

F. Any Special Product Quality Labeling Recommendations:
Not applicable due to CR.

G. Establishment Information

OVERALL RECOMMENDATION:					
MAB INTERMEDIATE					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**PRELIMINARY ASSESSMENT**	**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
mAb intermediate Manufacture Release and stability	Immunomedics, Inc. 300 The American Road Morris Plains, NJ 07950	115350605 1000526871	PLI conducted August 6-14, 2018 and initial recommendation is withhold approval.	Observations during PLI include (b) (4)	Withhold (the firm is not acceptable).
DRUG INTERMEDIATE					
Manufacture, release testing and release of CL2A-SN38	Johnson Matthey Pharmaceutical Services 25 Patton Road Devens, MA 01434-3803	055774186 2018076	The last inspection of the firm was a surveillance inspection conducted on Sep 02, 2016 with a VAI outcome. The firm has acceptable (b) (4) profile.	NA	The firm is acceptable
(b) (4)	(b) (4)	(b) (4)	The last inspection of the firm was a	NA	The firm is acceptable

(b) (4)	(b) (4)	(b) (4)	surveillance inspection conducted on (b) (4) (b) (4) with a VAI outcome. The firm has acceptable (b) (4) profile.		
DRUG SUBSTANCE/ DRUG PRODUCT					
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**		**INSPECTIONAL OBSERVATIONS**	**FINAL RECOMMENDATION**
(b) (4) DP manufacture (b) (4)	BSP Pharmaceuticals SpA Via Appia Km 65,561 Latina Scalo Latina, Italy 04013	857007830 3007255826	The PLI for this BLA was conducted Sep 13- 21, 2018 and concluded with initial VAI outcome and recommendation of the BLA for approval.	A 3-item FDA 483 was issued to the firm (b) (4) The firm's response to the FDA-483 observations is deemed adequate.	The firm is acceptable.

Prior Inspection History

The compliance status and inspectional history of DSI, DS and DP manufacturing and testing facilities are provided in the table below.

Site Name/ Address	FEI #	Responsibility	Profile/Inspection History
Johnson Matthey Pharma Services, 25 Patton Road, Devens MA 01434, USA	2018076	Manufacture, testing and release of CL2A-SN38	(b) (4) • 9/2/2016: surveillance inspection, VAI • 12/2/2013: PAI for (b) (4) profile and surveillance inspection, NAI • 11/7/2011: surveillance inspection, VAI
(b) (4)			
Immunomedics, Inc., 300 The American Road, Morris Plains, New Jersey 07950, USA	1000526871	Manufacture, testing and release of hRS7 IgG1κ; (b) (4) DP Testing of assay by UPLC	CBI • 8/14/2018: PLI for BLA 761115, withhold • 1/23/2003: surveillance inspection, VAI • 3/6/2001: surveillance inspection, VAI

BSP Pharmaceuticals S.p.A., Via Appia km 65,561, 04013 Latina Scalo (LT), ITALY	3007255826	Manufacture (conjugation and [redacted] (b) (4) of sacituzumab govitecan (IMMU-132) (b) (4) Manufacture of drug product, Quality Control and Release testing of drug product	CBI, SVL • 9/21/2018: PLI for BLA 761115 covering CBI and SVL profiles, VAI • 12/16/2016: surveillance inspection for SVL and SVS profiles, VAI • 6/26/2015: surveillance inspection, VAI

[redacted]

H. Facilities: Not approvable. See CR comments.

III. Lifecycle Knowledge Management

a. Drug Substance Intermediate (hRS7 mAb)

i. Protocols approved: Not applicable due to CR

ii. Outstanding review issues/residual risk: See CR comments and additional comments

iii. Future inspection points to consider: A re-inspection of the facility (Immunomedics Inc., Morris Plains, New Jersey) is needed to verify the findings related to data manipulation/integrity, and manufacturing capability.

b. Drug/Linker

i. Protocols approved: None

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider: None

c. Drug Substance

i. Protocols approved: Not applicable due to CR

ii. Outstanding review issues/residual risk: See CR comments and additional comments

iii. Future inspection points to consider: None

d. Drug Product

i. Protocols approved: Not applicable due to CR

ii. Outstanding review issues/residual risk: See CR comments and additional comments

iii. Future inspection points to consider: None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist	Yes	No	N/A
	Product Type			
1.	Recombinant Product	X		
2.	Naturally Derived Product		X	
3.	Botanical		X	
4.	Human Cell Substrate/Source Material		X	
5.	Non-Human Primate Cell Substrate/Source Material		X	
6.	Non- Primate Mammalian Cell Substrate/Source Material	X		
7.	Non-Mammalian Cell Substrate/Source Material		X	
8.	Transgenic Animal Sourced		X	
9.	Transgenic Plant Sourced		X	
10.	New Molecular Entity	X		
11.	PEPFAR Drug		X	
12.	PET Drug		X	
13.	Sterile Drug Product	X		
14.	Other_____			
	Regulatory Considerations			
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application (#_____)		X	
16.	Comparability Protocol(s)		x	
17.	End of Phase II/Pre-NDA Agreements tem)		X	
18.	SPOTS (Special Products On-line Tracking System		X	
19.	USAN Name Assigned	X		

20.	Other_____				
Quality Considerations					
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process	x		
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements			x	
27.	Real Time Release Testing (RTRT)			X	
28.	Parametric Release in lieu of Sterility Testing			X	
29.	Alternative Microbiological Test Methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial Analytical Procedures	Drug Product	x		
32.		Excipients	x		
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel	x		
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other _____				

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Qing Zhou

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BLA STN 761115
Product Sacituzumab govitecan
Manufacturer Immunomedics

OBP CMC Review Data Sheet

1. BLA#: 761115

2. Review Date: May 18, 2018-January 11, 2019

3. Primary Review Team: [list names, as applicable, e.g.]:
   a. Product Quality Team: Andrea Siegel (OBP/DBRR1 mAb/DS), Willie Wilson (OBP/DBRR1 DP), Brian Janelsins (OBP/DBRR1 Immunogenicity), Marjorie Shapiro (OBP/DBRR1), Rohit Tiwari (ONDP/DNDAP1), Charles Jewell (ONDP), Jessica Hankins (OPF/DMA DP), Reyes Candau-Chacon (OPF/DMA DS), Patricia Hughes (OPF/DMA)
   b. OBP Labeling: Dallas Scott, Vicky Borders-Hemphill (OBP)
   c. Facilities: Ephrem Hunde (OPF/DIA), Peter Zhihao Qiu (OPF/DIA)
   d. RBPM: Anh-Thy Ly (OPRO/DRBPM1)
   e. Medical Officer: Lynn Howie (DOP1)
   f. Clinical Pharmacology: Salaheldin Hamed, Pengfui Song (OCP/DCPV)
   g. Pharm/Tox: Kimberly Ringgold, Tiffany Ricks (DHOT)
   h. Statistics: Joyce Cheng, Lijun Zhang (OB/DBV)
   i. Cross-disciplinary Team Lead: Lola Fashoyn-Aje (DOP1)
   j. Application Technical Lead: Qing Zhou (OBP/DBRR1)
   k. RPM: Jeannette Dinin (DOP1)

4. Major GRMP Deadlines:

   a. Filing Meeting: July 9, 2018
   b. Mid-cycle meeting: September 17, 2018
   c. Wrap-up meeting: November 15, 2018
   d. Primary review due: January 4, 2019
   e. Secondary review due: January 7, 2019
   f. PDUFA action date: January 18, 2019

5. Communications with Sponsor and OND:

Communication/Document:	Date:
Information Request 1	May 25, 2018
Information Request 2	June 4, 2018
Information Request 4	June 27, 2018
Information Request 6	July 18, 2018
Information Request 8	August 17, 2018
Information Request 12	October 3, 2018
Information Request 14	November 13, 2018
Information Request 16	December 14, 2018

6. Submission Reviewed:

Submission:	Date Received:	Review Completed (yes or no)
STN 761115/3 for IR-1	June 4, 2018	Yes
STN 761115/6 for IR-2	June 13, 2018	Yes
STN 761115/16 for IR-4	July 16, 2018	Yes
STN 761115/22 for IR-6	July 30, 2018	Yes
STN 761115/35 for IR-8	August 27, 2018	Yes
STN 761115/39	September 7, 2018	Yes
STN 761115/47 response to T-con on August 23, 2018	September 20, 2018	Yes
STN 761115/58 for IR-12	October 19, 2018	Yes
STN 761115/63 Comparability plan	November 15, 2018	Yes
STN 761115/65 and 70 for IR-14	November 20 and 23, 2018	Yes
STN 761115/71 Comparability plan	November 28, 2018	Yes
STN 761115/74 (b) (4) study	December 11, 2018	Yes
STN 761115/75 Shipping validation Master Plan	December 17, 2018	Yes
STN 761115/76 Comparability Interim Report	December 18, 2018	Yes
STN 761115/80 for IR-16	December 27, 2018	Yes
IR-17 Response (email attachment) for specifications	January 8, 2019	Yes
32s73-stability-data_mAb-08Jan2019 update (email attachment) for hRS7 icIEF specification	January 9, 2019	Yes

7. Drug Product Name/Code/Type:
   a. Proprietary Name
   b. Trade Name: Trodelvy
   c. Non-Proprietary Name/USAN: sacituzumab govitecan
   d. CAS Name: 1491917-83-9
   e. Common Name: IMMU-132
   f. INN Name: sacituzumab govitecan
   g. Compendial Name: not yet assigned
   h. OBP systematic name (refer to OPQ-SOP-OBP-3006): CONJ: MAB HUMANIZED (IGG1) ANTI P09758 (TROP2_HUMAN); SN-38 [hRS7-SN-38]
   i. Other names: immunoglobulin G1-kappa anti-[*Homo sapiens* TACSTD2, M1S1, GA7331, GA733-1, EGP-1, TROP2)] humanized monoclonal antibody conjugated to 7-ethyl-10-hydroxycamptothecin, SN-38, via a maleimide-type cleavable linker, CL2A, (carbonate group, self-immolative 4-aminobenzyl alcohol and cathepsin-B-cleavable dipeptide Phe-Lys) and containing a triazoline group and a spacer PEG (n=8)

8. Pharmacological Category: immunoglobulin G1-kappa anti-Trop2 humanized monoclonal antibody conjugated to SN-38 via a CL2A linker.

9. Dosage Form: Lyophilate

10. Strength/Potency:
(i): The concentration/strength of the Drug Product: 180 mg/vial. The concentration when reconstituted is 10 mg/mL.
(ii): Type of potency assay(s): Trop-2 binding assay, cytotoxicity assay

11. Route of Administration: intravenous

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4)				Type III, N/A
				N/A
				N/A
				Type III, N/A
				Type III, N/A
				Type III, N/A
				Type III, N/A
				Type III, N/A

13. Inspectional Activities: A pre-approval inspection of the drug substance intermediate manufacturing facility was conducted at Immunomedics, Inc. in Morris Plains, NJ (FEI: 1000526871) from August 6, 2018 to August 14, 2018. Reyes Candau-Chacon, Madushini Dharmasena, Gunther Boekhoudt, and Rajiv Srivastava conducted the inspection. A pre-approval inspection of the drug substance and drug product manufacturing facility was conducted at BSP Pharmaceuticals S.p.A. in Latina Scalo LT, Italy (FEI: 3007255826) from September 13, 2018 to September 20, 2018. Reyes Candau-Chacon, Jessica Hankins, Rachel Novak, and Ephrem Hunde conducted the inspection. Refer to the Establishment Inspection Reports for details regarding the 483 observations and recommendations.

14. Consults Requested by OBP: None.

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Summary of Quality Assessments

I. Primary Reviewer Summary Recommendation: Complete Response.

II. List of Deficiencies to be Communicated
Refer to the Integrated Quality Assessment Memo for the summary of complete response issues and additional comments to be communicated to Immunomedics.

III. List of Post-Marketing Commitments/Requirements: Not applicable.

IV. Review of Common Technical Document- Quality Module 1

A. Environmental Assessment of Claim of Categorical Exclusion (1.12.14)

Immunomedics claims a categorical exclusion from an environmental assessment under 21 CFR 25.3(e) for BLA 761115.

Reviewer comment: *This is acceptable.*

V. Future Inspection Items for Immunomedics

(b) (4)

[redacted]

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Marjorie Shapiro

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products
Division of Biotechnology Review and Research I

Memorandum

STN:	BLA 761115 (SDN 1, May 18, 2018)
Subject:	Immunogenicity Assay Review
Review/Revision Date:	January 04, 2019
Primary Reviewer:	Brian Janelsins, Ph.D. (DBRR I)
Secondary Reviewer:	Qing Zhou, Ph.D. (DBRR I)
RBPM:	Anh-Thy Ly, Pharm.D.
Applicant:	Immunomedics, Inc.
Product:	IMMU-132, sacituzumab govitecan (hRS7-SN38 ADC)
Indication:	Treatment of patients with metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. Prior therapy should have included a taxane in either the adjuvant or the metastatic setting
Dose Regimen and Route of Admin:	10 mg/kg by intravenous infusion once weekly on Days 1 and 8 of continuous 21-day treatment cycles
PDUFA Goal Date:	January 18, 2019
Proprietary Name:	Trodelvy

RECOMMENDATION

Insufficient information and data were provided to support the suitability of the immunogenicity assay that was used to detect the presence of binding anti-drug antibodies in clinical samples. Therefore, the immunogenicity data generated from the clinical study to support the BLA may not be reliable.

EXECUTIVE SUMMARY

Immunomedics is seeking licensure for IMMU-132 as a biologic product under the 351(a) pathway. In support of the BLA, Immunomedics performed immunogenicity analysis of patients enrolled in a Phase I/II study (IMMU-132-01), which is a multi-center, open-label, uncontrolled basket trial, including dose escalation, performed in patients of various epithelial cancers (i.e., mTNBC, NSCLC, SCLC, and UC). At the time of BLA submission, immunogenicity analysis was on-going; however, immunogenicity data have been generated from over 625 samples from slightly over 100 patients in the mTNBC target population and provided in the BLA submission. (b) (4)

During the course of the review, numerous issues related to the validation of the binding ADA assay were identified (discussed below), and

information requests (IRs) were communicated to Immunomedices on August 28, 2018 and November 28, 2018 to address these issues. The information and data provided in response to the IRs [August 31, 2018 (SDN 37), December 06, 2018 (SDN 72)] did not adequately address the issues to support the suitability of the binding ADA assay for its intended purpose (b) (4) Because these issues are unlikely to impact the approvability of the BLA, considering the product, indication, and nature of the observed ADA responses, these issues will be included in the Complete Response Letter as "additional comments" for Immunomedics to address by the next review cycle. Refer to the end of the review for a draft list of the two additional comments to be communicated in the Complete Response Letter.

REVIEW

Note: *Reviewer Comments are indicated by italic font. The tables are copied directly from the submission.*

Section 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

(b) (4)

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Qing Zhou

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BLA STN 761115

Sacituzmab Govetican
(TRODELVY)

Immunomedics, Inc.

Drug Product CMC Technical Report

Willie Wilson, Ph.D., Chemist
Qing (Joanna) Zhou, Ph.D., Team Lead

Division of Biotechnology Review and Research I

OBP CMC Review Data Sheet

1. **BLA#:** STN 761115

2. **REVIEW DATE:** January 11, 2019

3. **PRIMARY REVIEW TEAM:**

Medical Officer:	Lynn Howie
Pharm/Tox:	Tiffany Ricks, Kimberly Ringgold
Product Quality Team:	Andrea Siegel (DS Reviewer), Willie Wilson (DP Reviewer), Brian Janelsins (Immunogenicity Reviewer), Joanna Qing Zhou (ATL), Marjorie Shapiro (OBP), Rohit Tiwari (ONDP), Charels Jewell (ONDP), Jessica Hankins (DMA), Reyes Candau-Chacon (DMA), Patricia Hughes (DMA)
Facilities:	Ephrem Hunde (DIA), Peter Zhihao Qiu (DIA)
Clinical Pharmacology:	Salaheldin Hamed, Pengfei Song
Genomics:	Rosane Charlab Orbach, Sarah Dorff
Statistics:	Joyce Chenc, Lijun Zhang
OBP Labeling:	Scott Dallas
Labeling:	William Pierce
OBP RBPM:	Ahn-Thy Ly
RPM:	Jeanette Dinin

4. **MAJOR GRMP DEADLINES**

Filing Meeting:	July 9, 2018
Mid-Cycle Meeting:	September 17, 2018
Wrap-Up Meeting:	November 15, 2018
Primary Review Due:	January 4, 2019
Secondary Review Due:	January 4, 2019
PDUFA Action Date:	January 14, 2019

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
Information Request 1	May 25, 2018
Information Request 2	June 4, 2018
Information Request 4	June 27, 2018
Information Request 6	July 18, 2018
Information Request 8	August 17, 2018
Information Request 12	October 3, 2018
Information Request 14	November 14, 2018
Information Request 16	December 14, 2018
Information Request 17	January 4, 2019

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed
STN 761115/0 (Original submission)	5/18/18	Yes
STN 761115/2 (Response to IR1)	6/4/18	Yes
STN 761115/6 (Response to IR2)	6/13/18	Yes
STN 761115/15 (Response to IR4; mAb intermediate and DS PQ)	7/16/18	Yes
STN 761115/21 (Response to IR6; mAb intermediate and DS PQ)	7/30/18	Yes
STN 761115/24 (Updates to Module 3)	8/3/18	Yes
STN 761115/29 (Updates to Module 3)	8/14/18	Yes
STN 761115/34 (Response to IR8; mAb intermediate, DS and DP PQ methods)	8/27/18	Yes
STN 761115/35 (Updates to Module 3)	8/31/18	Yes
STN 761115/38 (Updates to Module 3)	9/7/18	Yes
STN 761115/42 (Updates to Module 3)	9/12/18	Yes
STN 761115/46 (Additional Response to IR8)	9/20/18	Yes
STN 761115/57 (Response to IR12, Updates to Module 3, mAb intermediate)	10/19/18	Yes
STN 761115/62 (Comparability proposal to support (b) (4) lots used in the clinical studies are comparable to (b) (4) commercial lots)	11/15/18	Yes
STN 761115/64 (Response to IR14)	11/20/18	Yes
STN 761115/66 (Response to IR14)	11/23/18	Yes
STN 761115/67 (Comparability Study)	11/28/18	Yes
STN 761115/70 (Response to IR1 Q3e)	12/11/18	Yes
STN 761115/71 (Response to IR14 Q4 and 16)	12/17/18	Yes
STN 761115/72 (Comparability protocol mAb intermediate)	12/18/18	Yes
STN 761115/76 (Response to IR16)	12/27/18	Yes
STN 761115/81 (Response to IR17)	1/10/19	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: TRODELVY
b. Trade Name: TRODELVY
c. Non-Proprietary/USAN: sacituzumab govetican
d. CAS name: 1491917-83-9
e. Common name: IMMU-132
f. INN Name: sacituzumab govetican
g. Compendial Name: N/A
h. OBP systematic name: CONJ: MAB HUMANIZED (IGG1) ANTI P09758 (TROP2_HUMAN); SN-38 [hRS7-SN-38]

i. Other Names: N/A

8. **PHARMACOLOGICAL CATEGORY:** Human IgG1k antibody against Trop-2 conjugate to a topoisomerase I inhibitor (SN-38) with a hydrolysable spacer

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**
- The sacituzumab govetican Drug Product is supplied as a 180 mg lyophilized cake in a single-use vial
- Potency is defined as the percent K_D relative to the reference standard, using a cell-based ELISA assay that measures the ability of sacituzumab govetican to bind to the Trop-2 positive human prostate adenocarcinoma cell line (PC-3). Potency is also defined as the percent EC_{50} relative to reference standard, using a cell-based bioassay that measure the ability of sacituzumab govitican to induce cytotoxicity upon binding to PC-3 cells.

11. **ROUTE OF ADMINISTRATION:** Intravenous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Letters for each were Provided in Section 1.4.1	Type III, N/A
			Provided in Section 1.4.1	N/A
			Provided in Section 3.2.S.5-IMMU-132	N/A
			Provided in Section 3.2.S.6-IMMU-132	Type III, N/A

(b) (4)	Provided in Section 3.2.S.6-IMMU-132	Type III, N/A
	Provided in Section 3.2.S.6-IMMU-132	Type III, N/A
	Provided in Section 1.4.1	Type III, N/A
	Provided in Section 1.4.1	Type III, N/A

13. **INSPECTIONAL ACTIVITIES**

A pre-license inspection (PLI) for the manufacture of the hRS7 IgG1 antibody intermediate of sacituzumab govetican was conducted. Inspection of the Immunomedics, Inc., Morris Plains, NJ facility (FEI: 1000526871) was conducted from August 6, 2018 to August 14, 2018 by ORA (Rajiv Srivastava), DMA (Reyes Candau-Chacon and Madushini Dharmasena) and OBP (Gunther Boekhoudt) reviewers. The site is responsible for manufacturing, testing and release of hRS7 IgG1 antibody intermediate. The PLI covered the following five Quality Systems: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. Eleven 483 items were issued during the inspection. The issues were related to:

- Quality control unit lacks authority to investigate critical deviations of approved procedures. Specifically, the discovery of a data integrity breach in 2/2018 did not trigger a deviation
- No assurance that samples and batch records from process validation and commercial batches manufactured prior to the data integrity breach were not impacted
- Inadequate retesting procedure (b) (4)
- Inadequate raw material sampling and testing program

- Lack of procedures for inventory audit trail and for tracking and reconciliation of raw materials
- Inadequate maintenance and monitoring of differential pressure between GMP areas
- Inadequate facility design
- No signed Quality Agreement between firm and (b) (4)
- No procedure in place for the trending of (b) (4) results
- Inadequate investigations and CAPA implementations
- Inadequate deviation initiation and closing times

The recommendation for the classification for the inspection is withhold.

A PLI for the manufacture of sacituzumab govetican drug substance and drug product was conducted. Inspection of the BSP Pharmaceuticals S.p.A., Latina Scalo LT, Italy facility (FEI: 3007255826) was conducted from September 13, 2018 to September 20, 2018 by DIA (Ephrem Hunde), DMA (Reyes Candau-Chacon and Jessica Hankins) and OBP (Rachel Novak) reviewers. The site is responsible for the manufacture (conjugation (b) (4)), (b) (4) The site is also responsible for the manufacture and release of drug product. The PLI covered the following five Quality Systems related to drug substance and drug product manufacturing: Quality Procedures, Facilities and Equipment, Materials Management, Production Processes and Contamination Prevention, and Laboratory Controls. Three 483 items were issued at the end of the inspection. The issues were related to discrepancies between the information included in the BLA (b) (4) (b) (4) (b) (4) The recommendation for the classification of the inspection is VAI.

14. **CONSULTS REQUESTED BY OBP:** None

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
X	Design of Experiments
X	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Design of Experiments studies were performed as part of process development.

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation: Complete Response

The data submitted in this Biologics License Application do not adequately support the conclusion that the manufacture of sacituzumab govetican is well-controlled and leads to a product that is pure and potent.

II. List of Deficiencies to be Communicated

Refer to the Integrated Quality Assessment document for a list of the deficiencies to be conveyed in the Complete Response Letter.

III. List of Post-Marketing Commitments/Requirement

Not applicable due to CR

IV. Review of Common Technical Document-Quality Module 1

Environmental Assessment or Claim of Categorical Exclusion:
A claim for categorical exclusion under 21 CFR 25.31 (c) was made. To the sponsor's knowledge, no extraordinary circumstances exist relative to this action.

V. Primary Container Labeling Review

The CMC labeling review was performed by Scott Dallas, OBP.

VI. Review of Common Technical Document-Quality Module 3.2.P

This technical report contains the review of the information provided for sacituzumab govetican drug product (Section 3.2.P). The sacituzuamb govetican drug product (DP) is manufactured at BSP Pharmaceuticals S.p.A., Latina Scalo, Italy. The DP manufacturing process consists of (b) (4)

(b) (4)

Refer to the DS CMC Technical Report for review of information provided for hRS7 IgG1 (3.2.S – hRS7 IgG1), sacituzumab govetican DS (3.2.S – IMMU-132 DS), adventitious agents safety evaluation (3.2.A) and the method validation package and batch records (3.2.R).

VII. Review of Immunogenicity Assays – Module 5.3.1.4

The review of the immunogenicity assays was performed by Brian Janelsins and is provided in the Immunogenicity Technical Report.

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DESCRIPTION OF DRUG PRODUCT

3.2.P DRUG PRODUCT

Reviewer Comment: *Refer to the Drug Substance CMC Review Technical Report for references made to information, data and reviewer comments related to Module 3.2.S of the BLA submission.*

3.2.P.1 Description and Composition of the Drug Product

Sacituzumab govitecan drug product (DP) is a lyophilized presentation which contains 180 mg of active pharmaceutical ingredient (API), 77.3 mg of 2-(*N*-morpholino) ethane sulfonic acid (MES) (b) (4) pH 6.5, 154.0 mg of trehalose dihydrate, and 1.8 mg of polysorbate 80 per (b) (4) (b) (4) glass vial. Vials are stoppered with elastomeric rubber stoppers and sealed with aluminum seals. Trehalose dihydrate and polysorbate 80 meet USP compendial requirements; API and MES (b) (4) meet in-house quality standards. Lyophilized DP is reconstituted with 20 mL of normal saline to achieve a 10 mg/mL solution. The reconstituted solution is further diluted with normal saline (not exceeding 500 mL) to achieve 1.1 – 3.4 mg/mL DP solution for i.v. infusion.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

(b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

(b) (4)

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Qing Zhou

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Jessica Hankins, Ph.D.
Branch Chief: Patricia Hughes, Ph.D.

BLA:	761115
Applicant:	Immunomedics, Inc.
US License Number:	1737
Submission Reviewed:	Original BLA
Product:	Sacituzumab govitecan (Trodelvy)
Indication:	Metastatic triple-negative breast cancer who have (b) (4) received at least 2 prior therapies for metastatic disease
Dosage Form:	Powder for solution for intravenous infusion (180 mg)
Manufacturing Sites:	BSP Pharmaceuticals SpA Via Appia Km 65,561 Latina Scalo Latina Italy (FEI 3007255826)
FDA Receipt Date:	05/18/2018
Action Date:	01/18/2019

Conclusion and Approvability Recommendation

The drug product portion of this BLA, as amended, is recommended for approval from a product quality microbiology and sterility assurance perspective.

The following additional comment should be communicated to the applicant:

(b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0000	05/18/18	Original BLA
0009	06/27/18	Response to IR
0025	08/03/18	Response to IR
0029	08/14/18	Response to IR
0035	08/31/18	Updated Module 3
0037	09/07/18	Response to IR
0038	09/07/18	Updated Module 3
0042	09/12/18	Updated Module 3
0051	10/05/18	Response to IR
0056	10/12/18	Response to IR
0059	11/02/18	Response to IR
0064	11/20/18	Response to IR
0076	12/27/18	Response to IR
0081	TBD	Response to IR

Module 1

1.14 Labeling

The drug product (DP) is an antibody drug conjugate for intravenous infusion, supplied as a lyophilized powder in single-use vials containing 180 mg/vial. The recommended dose is 10 mg/kg once weekly. The first infusion is administered over 3 hours and all subsequent infusions are administered over 1-2 hours.

The DP is reconstituted with 20 mL 0.9% sodium chloride, USP. The reconstituted DP is then further diluted into the infusion bag containing 0.9% sodium chloride, USP.

Reviewer comment: At the time of submission, the Section 2.3 of the label indicated that the (b) (4) *An IR was sent to the applicant requesting microbial challenge data to support the storage conditions of the diluted DP. During label negotiations, the Agency modified the label to indicate that the reconstituted DP should be used immediately to prepare the infusion solution. Additionally, the label was updated to indicate that the diluted solution in the infusion bag should be used immediately. If it is not used immediately, the reconstituted infusion bag may be stored at room temperature for up to 4 hours prior to administration.*

SATISFACTORY

Module 3.2

P.1 Description and Composition of the Drug Product

Each vial contains 180 mg of DP which is reconstituted in 20 mL sodium chloride, USP. The reconstituted DP solution is further diluted with sodium chloride injection, USP to obtain a concentration of 1.1-3.4 mg/mL in a solution for infusion.

Reviewer comment: The applicant states that the reconstituted DP concentration is 10 mg/mL; however, 180 mg DP in 20 mL sodium chloride is equivalent to 9 mg/mL. The applicant stated in sequence 0009 that based on discussions with FDA in January 2018, the label claim was changed to 180 mg/vial (b) (4) *Additional discussions with OBP led to the applicant* (b) (4) *The review of the dosage strength for label claim is deferred to OBP.*

The composition of the DP is described below (copied and pasted from the submission):

Table 1 Composition of the drug product

Component	Amount per vial[1]	Function	Quality Standard	Amount in reconstituted solution
Sacituzumab govitecan	180 mg	active ingredient	In-house	10 mg/mL
2-(*N*-morpholino)ethane sulfonic acid (MES) (b) (4) pH 6.5	77.3 mg[2]	(b) (4)	In-house	(b) (4)
Trehalose dihydrate	154.0 mg[2]		Eur. Ph. USP-NF JP	
Polysorbate 80	1.8 mg		Eur. Ph. USP-NF	
(b) (4)				

The DP is packaged in a (b) (4) clear glass vial and stoppered with an elastomeric stopper.

SATISFACTORY

P.2 Pharmaceutical Development

Microbiological Attributes

The DP is (b) (4)

CCI of the stopper/vial combination was validated using the microbial ingress study. (b) (4)

(b) (4)

The results met the acceptance criteria,

(b) (4)

The results are provided in Table 24 of section P.2

(b) (4)

Reviewer comment: The microbial ingress method validation report (b) (4) *was presented initially in P.3.3 of the BLA (report CC-PO286.16, sequence 0009).*

(b) (4)

SATISFACTORY

(b) (4)

SATISFACTORY

P.3 Manufacture

P.3.1 Manufacturers

The DP manufacturing site listed below serves as the site for fill/finish, bulk packaging, batch release, and stability testing.

BSP Pharmaceuticals S.p.A.
Via Appia km 65561
04013 Latina Scalo (LT) Italy
FEI# 3007255826

P.3.3 Description of the Manufacturing Process and Process Controls

Description of Manufacturing Process

(b) (4)

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Jessica Hankins

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Patricia Hughes Troost

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
WO Bldg 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: October 29, 2018
To: Administrative File, STN 761115/0
From: Reyes Candau-Chacon, Ph.D., Reviewer, OPQ/OPF/DMA/BIV
Through: Patricia Hughes, Ph.D., Branch Chief, OPQ/OPF/DMA/BIV
Subject: New Biologic License Application (BLA)
US License: 1737
Applicant: Immunomedics, Inc.
Facilities: Immunomedics, Inc., 300 The American Road, Morris Plains, NJ (FEI # 1000526871)
BSP Pharmaceuticals SpA, Via Appia Km 65,561, Latina Scalo, Italy (FEI # 3007255826)
Product: sacituzumab govitecan
Dosage: powder for solution for IV infusion (180 mg)
Indication: Treatment of patients with metastatic triple-negative breast cancer (mTNBC) who (b) (4) received at least two prior therapies for metastatic disease
Due date: PDUFA date January 19, 2019 (Primary reviews due November 5, 2018)

Recommendation for Approvability: The drug substance section of BLA 761115 is recommended for approval from a microbial control and microbiology product quality perspective. The following additional comments should be included in the Complete Response letter:

(b) (4)

Review Summary

Immunomedics, Inc submitted BLA 761115 to license sacituzumab govitecan and the associated antibody intermediate, drug substance and drug product manufacturing processes.

BLA 761115 was submitted in eCTD on May 18, 2018. This review contains the assessment of the manufacturing process of sacituzumab govitecan antibody intermediate and bulk drug substance from a microbiological quality perspective. For review of drug product aspects of the application, please see the review by Dr. Hankins.

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Reyes Candau-Chacon

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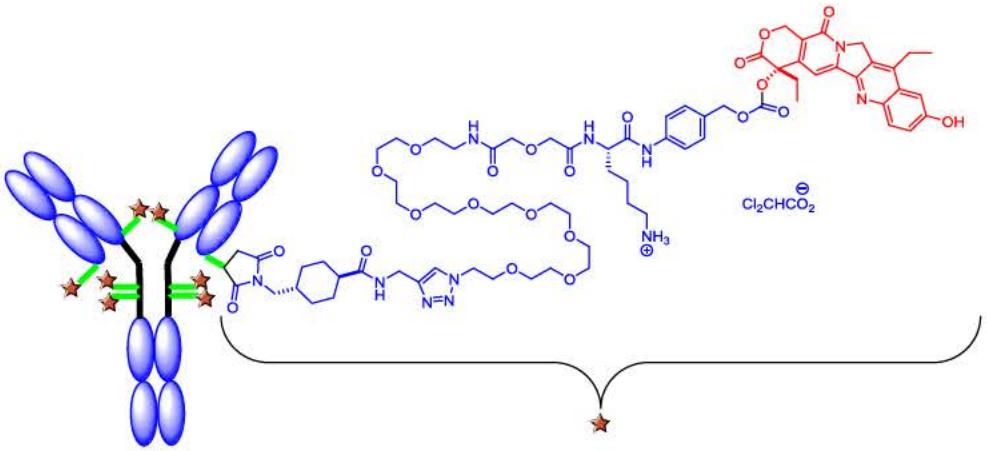
DRUG SUBSTANCE

Review Summary: This BLA is recommended for approval from the review of drug-linker (small synthetic molecule chemistry) perspective. The following review only covers the synthetic drug SN38 and linker CL2A information.

Product Background: The ADC drug product (IMMU-132, sacituzumab govitecan) is comprised of the humanized antibody, hRS7 IgG1κ, that is directed against Trop-2, the trophoblastic cell surface antigen, the linker, CL2A, and the payload, SN-38. SN-38 is a potent tropoisomerase I inhibitor and used clinically for several malignancies. The mechanism of the IMMU-132 is based on the specific targeting of Trop-2 which results in an enrichment of SN-38 in the tumor milieu. It is also hypothesized that SN-38 can be released from the ADC extracellularly, which then efficiently enter and kill either targeted or bystander cancer cells. The ability to release the payload without the requirement of internalization is both a unique property and an essential aspect of its mechanism of action as per the applicant. Because of its moderate cytotoxicity, normal cells that might take up low levels of the released SN-38 are expected to be mostly unaffected. Further, only the dividing cells will be damaged by SN-38. Thus, various quiescent normal tissues that express Trop-2 and might be targeted to some extent by sacituzumab govitecan are expected to be spared.

BLA: 761115

Chemical Name and Structure: *immunoglobulin G1-kappa anti-[Homo sapiens TACSTD2, M1S1, GA7331, GA733-1, EGP- 1, TROP2)] humanized monoclonal antibody conjugated to 7-ethyl-10-hydroxycamptothecin, SN-38,via a maleimide-type cleavable linker, CL2A, (carbonate group, self-immolative 4-aminobenzyl alcohol and cathepsine-B-cleavable dipeptide Phe-Lys) and containing a triazoline group and a spacer PEG (n=8)*



Applicant Name/DMF Holder: ***Immunomedics, Inc.***

IMMU-132 drug substance is medium greenish to yellow solution with an average drug to antibody ration (DAR) of 7.0-7.5. The IMMU-132 DS manufacture involves (b) (4)

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Su (Suong) Tran

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BLA MANUFACTURING FACILITY ASSESSMENT

Application ID	BLA 761115 Resub 103
Drug Product Name	sacituzumab govitecan (Immu-132)
Strengths	180 mg
Dosage Form	Powder for solution for infusion
Administration Route	intravenous
Indication	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 Name	Immunomedics, Inc.
US License Number	1737
Application Type	351 (a)

I. Manufacturing Summary

Facility Assessment Recommendation: Approval

Assessment Summary:

Adequate descriptions of equipment, facilities, utilities, environmental controls, and the cleaning and contamination control strategy were provided for antibody intermediate (hRS7 IgG1k) manufacture at Immunomedics, Inc. FEI: 1000526871, IMMU-132 DS manufacture at BSP Pharmaceuticals SpA, FEI: 3007255826, conjugate site and the same facility for drug product manufacture (b)(4) The final dosage form is within a glass 50cc vial with elastomer closure and aluminum crimp.

IMMU-132 is a Trop-2 antibody-drug conjugate (ADC) that comprises SN-38, a topoisomerase I inhibitor, couples to the humanized anti-Trop-2 monoclonal antibody hRS7 IgG1k by a hydrolysable spacer, a drug-to-antibody ratio of 7-8:1.

All proposed manufacturing and testing facilities are acceptable based on their acceptable compliance status and recent inspection coverage. This submission is recommended for approval from a facility standpoint.

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
BLA 761115 Resub 103	12/02/2019

Highlight Key Issues from Last Cycle and Their Resolution: Withhold approval for the PLI conducted at antibody intermediate (hRS7 IgG1k) manufacturer Immunomedics, Inc. FEI: 1000526871. Resolution is re-inspection, see following assessment.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No
Choose lifecycle consideration topic(s)	None

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Immunomedics, Inc. 300 The American Road Morris Plains, New Jersey 07950	1000526871	Manufacture, release and stability testing site for the antibody intermediate. CL2A-SN38, antibody intermediate, (b) (4) DP batch release. Antibody intermediate (b) (4) control testing. Cell bank storage. DS and DP release and stability testing via cell binding testing. CBI	Approve - Based on PAI/PLI
BSP Pharmaceuticals SpA Via Appia Km 65,561 Latina Scalo, Latina Italy 04013	3007255826	(b) (4) DP: Fill & finish, bulk packaging, QC, batch release, release and stability testing. Final DP I.D. testing. CBI SVL	Approve - Based on PAI/PLI
Johnson Matthey Pharmaceutical Services 25 Patton Road Devens, Massachusetts 01434-3803	2018076	Manufacture, testing and release of CL2A-SN38. (b) (4)	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			No Evaluation Necessary
			Approve - Based on Previous History
			Approve - Based on

[redacted] (b) (4)	Previous History
	Approve - Based on Previous History
	Approve - Based on Previous History
	No Evaluation Necessary
	Approve - Based on Previous History
	No Evaluation Necessary

II. Drug Product Manufacturing

1. Batch Formula

Table 1 Composition of the drug product

Component	Amount per vial[1]	Function	Quality Standard	Amount in reconstituted solution
Sacituzumab govitecan	180 mg	active ingredient	In-house	10 mg/mL
2-(*N*-morpholino)ethane sulfonic acid (MES) (b) (4) pH 6.5	77.3 mg[2]	(b) (4)	In-house	(b) (4)
Trehalose dihydrate	154.0 mg[2]		Eur. Ph. USP-NF JP	
Polysorbate 80	1.8 mg		Eur. Ph. USP-NF	
[redacted]				(b) (4)

Taken from 3.2.P.1, *"Description and Composition of the Drug Product (IMMU-132 DP, BSP)"*

Wayne Seifert

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Zhong Li

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: January 10, 2019
To: Administrative File, STN 761115
From: Ephrem Hunde, Ph.D., Chemical Engineer, CDER/OPQ/OPF/DIA
Endorsement: Zhihao Peter Qiu, Ph.D., Branch 1 Chief, CDER/OPQ/OPF/DIA
Subject: New Biologic License Application (BLA)
US License: To be assigned
Applicant: Immunomedics, Inc.
Mfg Facility: Drug Substance: Immunomedics, Inc., Morris Plains, NJ (FEI:1000526871)
BSP Pharmaceuticals S.p.A., Latina Scalo, Italy (FEI 3007255826)
Drug Product: BSP Pharmaceuticals S.p.A., Latina Scalo, Italy (FEI 3007255826)
Product: sacituzumab govitecan (IMMU-132), powder for solution for infusion
Dosage: 180 mg strength
Indication: Triple negative malignant neoplasm of breast (disorder).
Due Date: 1/18/2019

RECOMMENDATION: This submission is not recommended for approval from a facilities assessment perspective. During a recent inspection of the Immunomedics, Inc., (FEI 1000526871) manufacturing facility for this BLA, our field investigators observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

SUMMARY

BLA 761115 was submitted by Immunomedics, Inc., which provided information and data to support the manufacture of sacituzumab govitecan (IMMU-132), a lyophilized DP for solution for intravenous injection. IMMU-132 is a Trop-2-directed antibody-drug conjugate (ADC) that comprises SN-38, a topoisomerase I inhibitor, coupled to the humanized anti-Trop-2 monoclonal antibody hRS7 IgG1κ by a hydrolysable spacer, at a drug-to-antibody ratio of 7-8:1.

The production of sacituzumab govitecan involves the manufacture of (b) (4)

The DP is formulated as lyophilizate (180 mg/vial) for reconstitution in saline and intravenous administration. Sacituzumab govitecan solution is lyophilized in (b) (4) colorless, 50-mL clear glass vials. The vials are closed by 20 mm elastomeric (b) (4) stopper, and sealed with 20 mm aluminum flip-off overseal.

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Ephrem Hunde

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Zhihao Peter Qiu

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