

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761115Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 24, 2020

To: Jeannette Dinin
Regulatory Project Manager
Division of Oncology 1 (DO1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRODELVY (sacituzumab govitecan-hziy)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761115

Applicant: Immunomedics, Inc.

1 INTRODUCTION

On December 2, 2019, Immunomedics, Inc. submitted for the Agency’s review, a Complete Response in response to an Agency Complete Response letter dated January 17, 2019 for their Original Biologic License Application (BLA) 761115 TRODELVY (sacituzumab govitecan-hziy) for injection. With this resubmission, the Applicant proposes the following indication for TRODELVY (sacituzumab govitecan-hziy) for injection: for the treatment of patients with metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

We note that the Division of Medication Error Prevention and Analysis (DMEPA) found the proposed the nonproprietary suffix “-hziy” acceptable on January 21, 2020. Additionally, DMEPA found the proposed proprietary name, TRODELVY, acceptable on February 21, 2020.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Oncology 1 (DO 1) on March 17, 2020, for DMPP to review the Applicant’s proposed Patient Package Insert (PPI) for TRODELVY) sacituzumab govitecan-hziy for injection.

2 MATERIAL REVIEWED

- Draft TRODELVY (sacituzumab govitecan-hziy) for injection PPI received on December 2, 2019, and received by DMPP on March 17, 2020.
- Draft TRODELVY (sacituzumab govitecan-hziy) Prescribing Information (PI) received on December 2, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on March 17, 2020.
- Agency Complete Response Letter dated January 17, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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SHARON R MILLS
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03/24/2020 02:49:04 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 21, 2020
Requesting Office or Division: Division of Oncology 1 (DO1)
Application Type and Number: BLA 761115
Product Name and Strength: Trodelvy (sacituzumab govitecan-hziy) For Injection, 180 mg/vial
Applicant/Sponsor Name: Immunomedics, Inc.
OSE RCM #: 2018-957-4
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on February 19, 2020 for Trodelvy. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Trodelvy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Gao, T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 19. RCM No.: 2018-957-3.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 19, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761115
Product Name, Dosage Form, and Strength:	Trodely (sacituzumab govitecan-hziy) For Injection, 180 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Immunomedics, Inc.
FDA Received Date:	December 2, 2019
OSE RCM #:	2018-957-3
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Immunomedics submitted a response to the Complete Response (CR) letter for BLA 761115 on December 2, 2019. As part of the review process for Trodelvy (sacituzumab govitecan-hziy) For Injection, the Division of Oncology 1 (DO1) requested that we review the proposed Trodelvy prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Immunomedics previously submitted BLA 761115, which was received on May 18, 2018. We previously completed three label and labeling review/memos for BLA 761115. However, BLA 761115 received a Complete Response letter on January 17, 2019 due to product quality issues.^a

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a Dinin, J on behalf of Pazdur, R. Complete Response for BLA 761115. Silver Spring (MD): FDA, CDER, OHOP (US); 2019 Jan 17.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Since our last review, we noted that there are no changes to the proposed container labels and carton labeling. However, during this review cycle, we learned that the product is cytotoxic from the review team and since cytotoxic products require special handling procedures, we recommend adding the statement "CAUTION: Cytotoxic Agent" to the principal display panel.

We reviewed the proposed PI and noted that it could be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Trodelvy PI, container labels and carton labeling could be improved for clarity. We provide specific recommendations in Section 4.1 and Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section

- a. In Section 2.2 Recommended Dose and Schedule, consider revising the statement [REDACTED] (b) (4) to "Administer infusion over 1 to 2 hours..." for clarity.
- b. In Section 2.4 Preparation for Administration, consider revising [REDACTED] (b) (4) to "more frequently if the patient's body weight changed by more than 10%" for clarity. We recommend [REDACTED] (b) (4) to prevent misinterpretation and confusion.
- c. In Section 2.4 Preparation for Administration, consider revising "concentration of 1.1-3.4 mg/mL" to "concentration of 1.1 to 3.4 mg/mL" for clarity.

4.2 RECOMMENDATIONS FOR IMMUNOMEDICS, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container label & Carton Labeling)

1. Add the statement in bolded font on the principal display panel, "CAUTION: Cytotoxic Agent". Cytotoxic products require special handling procedures.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trodelvy received on December 2, 2019 from Immunomedics, Inc..

Table 2. Relevant Product Information for Trodelvy	
Initial Approval Date	N/A
Nonproprietary Name	sacituzumab govitecan-hziy
Indication	treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.
Route of Administration	Intravenous
Dosage Form	For Injection
Strength	180 mg/vial
Dose and Frequency	10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity.
How Supplied	Carton of 1 single-dose vial
Storage	Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution. Do not freeze.
Container Closure	(b) (4) colorless, clear glass 50-mL vial sealed with an aluminum flip-off overseal, 20 mm Dark Grey

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 26, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Trodelvy. Our search identified 3 previous reviews^{b,c,d}, and we confirmed that our previous recommendations were implemented.

^b Gao, T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 24. RCM No.: 2018-957.

^c Gao, T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 7. RCM No.: 2018-957-1.

^d Gao, T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jan 3. RCM No.: 2018-957-2.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Trodelvy labels and labeling submitted by Immunomedics, Inc..

- Container label received on December 2, 2019
- Carton labeling received on December 2, 2019
- Prescribing Information (Image not shown) received on December 2, 2019, available from <\\cdsesub1\evsprod\bla761115\0097\m1\us\114-labeling\draft\labeling\draft-labeling-text-tc.docx>

G.2 Label and Labeling Images

Container label



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^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: January 3, 2019
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: BLA 761115
Product Name and Strength: Trodelvy (sacituzumab govitecan-hziy) For Injection, 180 mg/vial
Applicant/Sponsor Name: Immunomedics, Inc.
FDA Received Date: January 2, 2019
OSE RCM #: 2018-957-2
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Trodelvy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 DISCUSSION

Immunomedics stated that they intend to use MMMYYYY as the expiration date format instead of the previously recommended format (e.g., YYYY-MMM-DD or YYYY-MMM) on the container labels and carton labeling.^b Since the proposed expiration date format consists of the 3-letter abbreviated alphabetical characters for the month (MMM) and the 4-digit year (YYYY), we find this proposed expiration date format acceptable from a medication error perspective.

^a Gao, T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 7. RCM No.: 2018-957-1.

^b BLA 761115: Response to FDA Request for Information Dated December 13, 2018. Serial Number 0078. Morris Plains (NJ): Immunomedics, Inc. 2019 Jan 2. Available at <\\cdsesub1\evsprod\bla761115\0078\m1\us\111-information-amendment\response-to-fda-labelling-rfi-sn0077-02jan2019.pdf>.

3 CONCLUSION

The revised container label and carton labeling for Trodelvy are acceptable from a medication error perspective. We have no further recommendations at this time.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 17, 2018

To: Julia Beaver, MD
Director
Division of Oncology Products 1 (DOP 1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kevin Wright, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TRODELVY (sacituzumab govitecan-xxxx¹)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: BLA 761115

Applicant: Immunomedics, Inc.

¹ At the time of this review, the four letter suffix for the established name has not been determined and xxxx is being used as a placeholder.

1 INTRODUCTION

On May 18, 2018, Immunomedics, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761115 for TRODELVY (sacituzumab govitecan-xxxx) for injection. The Applicant seeks Accelerated Approval of TRODELVY (sacituzumab govitecan-xxxx) for injection for the treatment of patients with metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease, under 21 CFR Part 314, Subpart E.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 1 (DOP 1) on June 14, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRODELVY (sacituzumab govitecan-xxxx) for injection. On December 9, 2018, DOP-1 clarified by email that they have determined a PPI will suffice as patient labeling for TRODELVY (sacituzumab govitecan-xxxx) for injection.

2 MATERIAL REVIEWED

- Draft TRODELVY (sacituzumab govitecan-xxxx) for injection PPI received on May 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 3, 2018.
- Draft TRODELVY (sacituzumab govitecan-xxxx) for injection Prescribing Information (PI) received on May 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on December 3, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI, is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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12/17/2018

KEVIN WRIGHT
12/17/2018

LASHAWN M GRIFFITHS
12/17/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: December 17, 2018

To: Julia Beaver, M.D., Director
Division of Oncology Products 1 (DOP1)

Jeannette Dinin, Regulatory Project Manager, (DOP1)

William Pierce, PharmD, Associate Director for Labeling, DOP1

From: Kevin Wright, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, PharmD, MBA, Team Leader, OPDP

Subject: OPDP Labeling Comments for Trodelvy™ (sacituzumab govitecan-xxxx) for injection, for intravenous use

BLA: 761115

In response to DOP1's consult request dated June 14, 2018 , OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), carton labeling and container label for original BLA submission for Trodelvy™ (sacituzumab govitecan-xxxx) for injection, for intravenous use (Trodelvy).

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP1(Jeannette Dinin) on December 3, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 21, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Kevin Wright at (301) 796-3621 or kevin.wright@fda.hhs.gov.

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/s/

KEVIN WRIGHT
12/17/2018

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 7, 2018
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: BLA 761115
Product Name and Strength: Trodelvy (sacituzumab govitecan-hziy)^a For Injection, 180 mg/vial
Applicant/Sponsor Name: Immunomedics, Inc.
FDA Received Date: November 21, 2018
OSE RCM #: 2018-957-1
DMEPA Safety Evaluator: Tingting Gao, PharmD
DMEPA Team Leader (Acting): Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 1 (DOP1) requested that we review the revised container label and carton labeling for Trodelvy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 DISCUSSION

The revised Trodelvy container label and carton labeling are unacceptable from a medication error perspective due to the following reasons:

- The dosage form is not located below the nonproprietary name.
- The route of administration statement lacks prominence on the Trodelvy container label and is not present on the carton labeling.

^a The proposed nonproprietary name (sacituzumab govitecan-hziy) is only conditionally accepted for this product until the application is approved; see Mena-Grillasca, C. Nonproprietary Name Suffix for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 26. OSE RCM No.: 2018-1844.

^b Gao T. Label and Labeling Review for Trodelvy (BLA 761115). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 24. RCM No.: 2018-957.

- The Usual Dosage statement is missing.
- The reconstitution instructions lack prominence.
- The expiration date format should be revised to YYYY-MMM in accordance with the recommendations provided in *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*.

3 CONCLUSION

The revised Trodelvy container label and carton labeling are unacceptable from a medication error perspective. We provide specific recommendations for Immunomedics in Section 4 below.

4 RECOMMENDATIONS FOR IMMUNOMEDICS, INC.

We recommend the following be implemented prior to approval of this BLA:

A. Container label

1. Add the dosage form "For Injection" immediately below the nonproprietary name on the principal display panel to clarify the dosage form for this product. Delete the (b) (4) statement (b) (4)
2. Relocate the route of administration statement "For intravenous infusion only" below the strength statement (180 mg per vial) to increase the prominence of the route of administration statement.
3. Add the "Usual Dosage: See prescribing information." statement on the side panel in accordance with 21 CFR 201.55.
4. As currently presented on the side panel, the reconstitution instructions ("Slowly inject 20 mL of 0.9% Sodium Chloride Injection...") lack prominence. Add "Reconstitution:" at the beginning so that the sentence reads:

Reconstitution: Slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each vial. Gently swirl and allow to dissolve for up to 15 minutes. The resulting concentration will be 10 mg/mL.

5. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to

separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

B. Carton labeling

1. Relocate the dosage form “For Injection” immediately below the nonproprietary name on the principal display panel to clarify the dosage form for this product.
2. Add the route of administration statement “For intravenous infusion only” below the strength statement (180 mg per vial) in accordance with 21 CFR 201.100(b)(3).
3. Add the “Usual Dosage: See prescribing information.” statement on the side panel in accordance with 21 CFR 201.55.
4. As currently presented on the side panel, the reconstitution instructions (“Slowly inject 20 mL of 0.9% Sodium Chloride Injection...”) lack prominence. Add “Reconstitution:” at the beginning so that the sentence reads:

Reconstitution: Slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each vial. Gently swirl and allow to dissolve for up to 15 minutes. The resulting concentration will be 10 mg/mL.

5. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date. See *Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act-Questions and Answers*. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 24, 2018
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	BLA 761115
Product Name and Strength:	Trodely (IMMU-132) ^a For Injection, 180 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Immunomedics, Inc.
FDA Received Date:	May 18, 2018 and July 20, 2018
OSE RCM #:	2018-957
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader (Acting):	Sevan Kolejian, PharmD, MBA

^a Since the proper name for IMMU-132 has not yet been determined, the developmental code name, IMMU-132, is used in this review to refer to this product. The proposed proprietary name, Trodely, is only conditionally accepted for this product until the application is approved.

1 REASON FOR REVIEW

As part of this BLA, this review evaluates the proposed Trodelvy prescribing information (PI), container label, and carton labeling to identify areas of vulnerability that could lead to medication errors in response to a consult request from Division of Oncology Products 1 (DOP1).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 PRESCRIBING INFORMATION

We reviewed the proposed Trodelvy PI and determined that the PI may be improved to promote the safe use of the proposed product.

3.2 CONTAINER LABEL AND CARTON LABELING

We reviewed the proposed Trodelvy container label and carton labeling and determined that they may be improved to promote the safe use of the proposed product. Additionally, we note that the labels and labeling contains the term, (b) (4) which is not consistent with the draft guidance^b and we defer to the Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term for Trodelvy labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

The proposed Trodelvy PI, container label and carton labeling may be improved to promote safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section (b) (4) Preparation for Administration

a. Under "Dilution", add the following as the first step for dilution:

"Calculate the required volume of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to patient's body weight. Withdraw this amount from the vial(s) using a syringe."

4.2 RECOMMENDATIONS FOR IMMUNOMEDICS, INC

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container Label and Carton Labeling)

1. On September 12, 2018^c, you were notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for your product in an Advice Letter. Add "-xxxx" as a placeholder after your nonproprietary core name throughout your labels and labeling until you are notified of the suffix that will be designated for your product. Once you receive our notification of the four-letter distinguishing suffix that will be designated for your product, revise your labels and labeling accordingly and resubmit those materials to the application.
2. Revise the dosage form to read "For Injection".

^b Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2018. Available from <https://www.fda.gov/downloads/Drugs/Guidances/UCM468228.pdf>

^c Harris, D. General Advice Letter for BLA 761115. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 SEP 12.

B. Container Label

1. Add the statement “Discard unused portion” immediately after the statement “Single-dose vial”.
2. Relocate the route of administration statement “For intravenous infusion only” to the principal display panel in accordance with the Draft Guidance^d.
3. Consider adding the statements “slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each vial. Gently swirl and allow to dissolve for up to 15 minutes. The resulting concentration will be 10 mg/mL.” to the side panel of the container label. The concentration after reconstitution will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.

C. Carton Labeling

1. Revise the carton labeling to add the statements “slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each vial. Gently swirl and allow to dissolve for up to 15 minutes. The resulting concentration will be 10 mg/mL.” to the carton labeling. These instructions will inform persons responsible for preparing the product what type and volume of diluent should be used for reconstitution, and the amount of drug contained in each milliliter once reconstituted.

^d Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trodelvy received on July 20, 2018 from Immunomedics, Inc.

Table 2. Relevant Product Information for Trodelvy	
Initial Approval Date	N/A
Active Ingredient	sacituzumab govitecan-xxxx
Indication	treatment of patients with metastatic triple-negative breast cancer (mTNBC) who previously received at least two prior therapies for metastatic disease
Route of Administration	Intravenous
Dosage Form	For Injection
Strength	180 mg/vial
Dose and Frequency	10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles.
How Supplied	Carton containing one single-dose vial
Storage	Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) (b) (4) Do not freeze.
Container Closure	Sacituzumab govitecan solution is lyophilized in (b) (4) colorless, clear glass 50-mL vials (b) (4). The vials are closed by elastomeric (b) (4) stopper 20 mm, (b) (4) and sealed with an aluminum flip-off overseal, 20 mm Dark Grey, (b) (4).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Trodelvy labels and labeling submitted by Immunomedics, Inc.

- Container label received on May 18, 2018
- Carton labeling received on May 18, 2018
- Prescribing Information (Image not shown) received on July 20, 2018

G.2 Label and Labeling Images

Container label



1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TINGTING N GAO
10/24/2018

SEVAN H KOLEJIAN
10/24/2018

Clinical Inspection Summary

Date	October 23, 2018
From	Lauren Iacono-Connors, Ph.D., Reviewer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Division of Clinical Compliance Evaluation
To	Jeannette Dinin, Regulatory Project Manager Lynn Howie, Clinical Reviewer Division of Oncology Products 1
BLA #	761115
Applicant	Immunomedics, Inc.
Drug	Trodelvy (Sacituzumab govitecan; IMMU-132)
NME	Yes
Therapeutic Classification	Antibody Drug Conjugate
Proposed Indication	Metastatic Triple Negative Breast Cancer
Consultation Request Date	May 24, 2018 (Submission date: May 18, 2018)
Summary Goal Date	October 15, 2018
Action Goal Date	November 5, 2018
PDUFA Date	January 18, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study IMMU-132-01 was submitted to the Agency in support of BLA 761115. Seven clinical sites, Dr. Aditya Bardia, M.D. (Site 255), Dr. Jordan David Berlin, M.D. (Site 252), Dr. Allyson Ocean, M.D. (Site 111), Dr. Rebecca Moroosse, M.D. (Site 204), Dr. Wells Messersmith, M.D. (Site 254), Dr. Ebenezer Kio, M.D. (Site 181), Dr. Kevin Kalinsky, M.D. (Site 259), the study sponsor, Immunomedics, Inc., and CRO (b) (4) were selected for audit.

There were no significant inspectional findings for clinical investigators Dr. Aditya Bardia, Dr. Jordan David Berlin, Dr. Allyson Ocean, Dr. Rebecca Moroosse, Dr. Wells Messersmith, Dr. Ebenezer Kio, Dr. Kevin Kalinsky, the study sponsor, Immunomedics, Inc., and CRO (b) (4). The data from Study IMMU-132-01 submitted to the Agency in support of BLA 761115, appear reliable.

II. BACKGROUND

Immunomedics, Inc., seeks approval to market Sacituzumab govitecan (IMMU-132) for the treatment of individuals with metastatic, triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. The key clinical study supporting this application is Study IMMU-132-01.

Additional Background Information Regarding Confidential Informants:

Extensive information was received by the Agency from multiple confidential informants (whistleblower/s) since the original FACTS Assignment Memo was issued on June 1, 2018. Allegations, in part, suggested GCP compliance violations had occurred at the study sponsor and clinical investigator sites that may have affected the integrity of the study data and subject safety and welfare. Because of these allegations, three additional clinical sites (254, 181, and 259) were added to the inspection plan with instructions to not pre-announce inspections that had not yet been initiated.

The allegations related to GCP compliance are summarized below:

1. There were inconsistencies between data found in source documents, CRFs, and data listings submitted to the application.
2. Allegations suggested that changes in copies of CRFs were not always reported to the sponsor or represented in the application submitted to the FDA. The CRFs were not electronic. Briefly, clinical monitors collected top and second copy sheets from the CRFs; however, the third copy left at the clinical sites many times was not legible, contained subsequent edits, or new information added. Allegations suggested that these changes were not always reported to the sponsor or represented in the application submitted to the FDA.
3. The sponsor used Microsoft Access as the platform for the study clinical database, which does not support audit trails for data entry, changes, and attribution.
4. There were many protocol waivers granted by the sponsor. However, those granting waivers did not always have the qualifications or authority to make waiver decisions.
5. There was no clinical monitoring plan for this study and monitoring quality was inconsistent or lacking. In many cases, no monitoring visit reports were provided to the sponsor by the clinical monitors. Further, the sponsor did not take corrective action and did not pursue missing reports associated with monitoring site visits.
6. IP quality at the time of receipt at clinical sites, use, and disposition was also a concern. Allegations suggested that IP may have experienced temperature excursions in transport; however, it was suggested that the sponsor approved use of the IP.

Study IMMU-132-01

The following overview of the Study IMMU-132-01 is intended as background context for interpreting the inspectional findings.

Study IMMU-132-01, the key study supporting this application, is a Phase I/II, open-label, uncontrolled, multicenter basket trial with dose-escalation in the Phase I part of the study and expansion cohorts in the Phase II part. The focus of these inspections is a subset of 108 study subjects in the Phase 1/2 study who have metastatic Triple Negative Breast Cancer (mTNBC). The mTNBC target population of 108 subjects' data was analyzed for safety and efficacy in

direct support of the application. The study was conducted under IND 122694.

Study IMMU-132-01, is entitled, “A Phase I/II study of IMMU-132 (hRS7-SN38 antibody drug conjugate) in patients with epithelial cancer”.

Study Period:

Date of first subject enrolled: December 17, 2012

Data cut-off date for analysis: June 30, 2017

Primary efficacy endpoint: Objective response (achievement of complete response [CR] plus partial response [PR]) in the study population as determined by clinical investigators and an independent, central imaging review committee per RECIST 1.1.

Objectives of Inspections:

Phase I: To evaluate the safety and tolerability of IMMU-132 as a single agent administered in 3-week treatment cycles, in previously treated patients with advanced epithelial cancer. To determine a maximum acceptable dose and select cancer types for continued expanded study in Phase II.

Phase II: To evaluate the safety and efficacy of IMMU-132 administered in 3-week treatment cycles, at a dose selected in Phase I.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # and # of Subjects (mTNBC)	Inspection Date	Final Classification
CI: Dr. Aditya Bardia, M.D. (Site 255) Massachusetts General Hospital 55 Fruit Street Boston, MA 02114	Protocol: IMMU-132-01 Subjects: 52	August 13 -17, 2018	*VAI
CI: Dr. Jordan David Berlin, M.D. (Site 252) Vanderbilt University-Ingram Cancer Center 222 Pierce Ave Nashville, TN 37232	Protocol: IMMU-132-01 Subjects: 23	August 16 - September 10, 2018	NAI
CI: Dr. Allyson Ocean, M.D. (Site 111) Weill Cornell Medical College 1305 York Avenue, 12th Floor New York, NY 10065	Protocol: IMMU-132-01 Subjects: 19	August 6 -10, 2018	NAI

Name of CI, Site #, Address	Protocol # and # of Subjects (mTNBC)	Inspection Date	Final Classification
CI: Dr. Rebecca Moroose, M.D. (Site 204) Orlando Health, Inc. 1400 South Orange Ave. Orlando, FL 32806	Protocol: IMMU-132-01 Subjects: 9	June 26 - July 2, 2018	NAI
CI: Dr. Wells Messersmith, M.D. (Site 254) University of Colorado Cancer Center 1665 Aurora Court Aurora, CO 80045	Protocol: IMMU-132-01 Subjects: 10	September 12 - 17, 2018	NAI
CI: Dr. Ebenezer Kio, M.D. (Site 181) Goshen Center for Cancer Care 200 High Park Avenue Goshen, IN 46526	Protocol: IMMU-132-01 Subjects: 2	August 20-23, 2018	NAI
CI: Dr. Kevin Kalinsky, M.D. (Site 259) Columbia University 161 Fort Washington Avenue New York, NY 10032	Protocol: IMMU-132-01 Subjects: 7	September 4-7, 2018	NAI
Sponsor: Immunomedics, Inc. POC: Diane Whitely 300 The American Road Morris Plains, NJ 07950	Protocol: IMMU-132-01 Site Numbers: All Clinical Sites with mTNBC subjects	June 14, 2018 through August 1, 2018 (Intermittently)	*VAI
CRO: (b) (4) (Conducted the Central Review of Radiologic Imaging) POC: (b) (4)	Protocol: IMMU-132-01 Site Numbers: All Clinical Sites with mTNBC subjects	(b) (4)	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Aditya Bardia, M.D. (Site 255)

The site enrolled 52 subjects into the mTNBC cohort. Records reviewed during this inspection included but was not limited to: Institutional Review Board (IRB) documentation, Informed Consent Forms (ICF's), investigator agreements, financial disclosures, and subject source records. Review included protocol compliance for mTNBC subjects included in the BLA with focus on the subjects whose results showed they were responders. Review specifically focused on the primary endpoint of RECIST 1.1 determinations of objective response. Review also included random review of adverse events and inclusion/exclusion criteria compliance. Two protocol deviations were found for two subjects where source records showed progression; however, the study site did not report progression.

A Form FDA 483 Inspectional Observations was issued to Dr. Bardia with the following observation: An Investigation was not conducted in accordance with the investigational plan. Specifically, Subjects # [REDACTED] (b) (6) had brain MRI's indicating new lesions; however, the study site did not report progressive disease.

The protocol defines progressive disease (PD) as per RECIST 1.1. Per RECIST 1.1, the definition for PD includes the appearance of one or more new lesions.

Subject [REDACTED] (b) (6) had a MRI on [REDACTED] (b) (6) indicating potential brain metastasis (new lesion). Subject [REDACTED] (b) (6) was treated with radiation for the brain metastasis. The study site reported a response determination of Partial Response on March 28, 2017.

Subject [REDACTED] (b) (6) had a MRI on [REDACTED] (b) (6) indicating potential brain metastasis (new lesion). Subject [REDACTED] (b) (6) was treated with radiation for the brain metastasis. The study site reported a response determination of Partial Response on March 2, 2016.

OSI Reviewer Notes: These two protocol violations were discussed at length with DOP1 Clinical Reviewer, Dr. Lynn Howie, who also participated in the inspection of Dr. Bardia. The MRI brain scans were conducted while the subjects were on study. The scans were not considered part of the study and, as such, were not reported to the sponsor or included in data listings submitted to the application. DOP1 issued an IR, dated September 18, 2018, to the sponsor requesting, "subject-level information for responders that includes all imaging obtained during the course of the study (both scheduled and unscheduled); narrative summaries of each of these imaging assessments (e.g. if not per protocol, why imaging was obtained); and an indication of whether the imaging assessment was submitted for central review." The sponsor's response, dated September 24, 2018, stated, in part, that they found no additional instances of failure of a clinical site to document and report to the sponsor all scheduled and unscheduled MRIs/CT scans and the associated tumor responses based on their re-review of study subjects. The sponsor also indicated that the additional MRI scans for Subjects [REDACTED] (b) (6) had since been sent to the CRO, [REDACTED] (b) (4)

The inspectional observations noted above should not have importantly impacted overall study outcomes or placed subjects at undue risk.

Notwithstanding the inspectional observations noted above, the inspection revealed no significant deficiencies. With two exceptions, the primary efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

2. Dr. Jordan David Berlin, M.D. (Site 252)

The site screened 53 subjects and enrolled 46 subjects, of which 23 subjects were in the mTNBC cohort; 20 of those received study treatment. A record review was done for 14 mTNBC subjects. At the time of this inspection 3 mTNBC subjects remained on study. Records reviewed during the inspection included informed consent documents, monitoring logs, delegation logs, enrollment logs, ethics committee correspondence and approvals, sponsor and monitor correspondence, investigator agreements, AE reports, IP accountability, and source documentation. Source documentation was specifically reviewed to verify efficacy and safety assessments. In addition, key source documents were reviewed for verification of inclusion/exclusion criteria, clinical test results, cycle dates, study drug infusion date, dosage/dosage administration time, PK and human anti-human antibodies (HAHA) collection and target lesion/non-target lesions assessments by the clinical investigator. No apparent discrepancies were noted.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

3. Dr. Allyson Ocean, M.D. (Site 111)

The site screened 22 subjects for the mTNBC cohort and enrolled 19 subjects. At the time of this inspection 15 subjects were deceased, three subjects were in follow-up, and one subject was actively receiving treatment. A record review was done for 12 enrolled subjects. Records reviewed during the inspection included, but were not limited to: informed consent forms, monitoring logs, delegation logs, enrollment logs, IRB correspondence and approvals, sponsor correspondence, adverse events, serious adverse events, case report forms, drug accountability records, and source documentation. A 100% review of all subjects' source documents was conducted for informed consents, primary and secondary efficacy endpoints, protocol deviations, concomitant medications, inclusion/exclusion criteria compliance, AEs and SAEs. A review of 30% of subjects' laboratory data was also conducted.

For three subjects, there were discrepancies found between primary efficacy endpoint source documents, the corresponding CRF, and the data listings submitted to the application.

Specifically,

Subject (b) (6) was found to have a new equivocal lesion (sternum, sclerotic [non-target]) and was reported on the RECIST worksheet for Cycle 6 (b) (6) scans. On the Cycle 8 scans, the non-target lesion on the RECIST worksheet was evaluated as “stable/incomplete”. However, the CRF recorded the non-target lesion as “non-progressive disease/non-complete response”.

Per RECIST 1.1 guidelines, if a new lesion is equivocal, treatment can continue, and a follow-up evaluation can be done to clarify if it represents new disease. If repeat scans confirm there is a new lesion present, then progression should be declared. Because the RECIST worksheet for Cycle 8 notes that the non-target lesion is equivocal at Cycle 6 and stable/incomplete at Cycle 8, the response of non-complete response/non-progressive disease recorded in the CRF for Cycle 8 is correct.

Subject (b) (6) had two target lesions noted on the baseline (b) (6) Response Assessment CRF (page 14); right chest wall nodule and left inguinal lymph node. The corresponding Response Assessment CRF pages for Cycle 3 (b) (6), Cycle 6 (b) (6) and Cycle 9 (b) (6), listed a single target lesion; “R breast”. The RECIST worksheet for the subject’s baseline scan listed a single lesion; “skin R breast lesion.” Finally, the radiology report for the baseline scan noted the baseline target lesion as “right chest wall nodule.”

During the inspection the reading radiologist confirmed that the right chest wall nodule in the radiology report and the right breast skin lesion on the RECIST worksheet are the same lesion; Subject (b) (6) had had a mastectomy. For clarification, the subject’s chart has been updated with this information. Finally, the second target lesion on the baseline CRF page 14, “left inguinal lymph node,” was entered in error and was a non-target lesion noted on the baseline non-target CRF page 15.

Subject (b) (6) had a new equivocal non-target lesion on the Cycle 3 (b) (6) Response Assessment as recorded on the RECIST worksheet. The corresponding CRF page for the visit shows the subject’s overall response as progression. However, the subject’s Cycle 6 (b) (6) Response Assessment RECIST worksheet shows that the non-target lesion is stable/incomplete and the CRF page for that visit shows the subject’s overall response as complete response.

The clinical investigator explained that the new equivocal non-target lesion that appeared on the subject’s Cycle 3 imaging was initially listed on the CRF as progression due to the size of the lesion. However, the clinical investigator did not note this lesion as progression in her notes and had requested a biopsy to confirm the status of the lesion. The biopsy confirmed that the lesion was benign breast tissue. In addition, the treating physician referenced the new lesion as non-malignant at Subject (b) (6)’s subsequent follow-up office visit.

OSI Reviewer Notes: Based upon the information provided during the inspection of Site 111, the Cycle 3 Response Assessment in the CRF for [REDACTED]^{(b) (6)} should not have been assessed as progression. A Data Clarification Form (DCF), was sent to the sponsor in December 2017, after the data cut-off date; June 30, 2017. However, the correction was not included in the data listings submitted to the application to support clinical site inspections.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no over reporting or under reporting of AEs, SAEs, or protocol deviations.

4. Dr. Rebecca Moroose, M.D. (Site 204)

The site screened 28 subjects and enrolled 22 subjects, of which 9 subjects were in the mTNBC cohort and received study treatment. A record review was done for 17 subjects. Records reviewed during the inspection included IRB documentation, informed consents, CRFs, line listings submitted to the application and source documents that consisted of study worksheets and medical records which contained biopsy results, laboratory results, primary and secondary efficacy endpoints including progression free survival and overall survival, AE reporting, concomitant medications, imaging and infusion records. There were 4 serious adverse events for the 9 subjects that were mTNBC subjects. Three of the four SAEs were indicated to be likely related to the test article. No discrepancies were noted.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

5. Dr. Wells Messersmith, M.D. (Site 254)

Sixteen subjects were screened, and sixteen subjects were enrolled into the mTNBC cohort. A record review was done for 10 subjects. All 10 of these subjects were eventually discontinued from the study due to disease progression.

Records reviewed during the inspection included IRB documentation, informed consents, CRFs, line listings submitted to the application and source documents found at the site. Data verification focused on protocol compliance, determination of primary and key secondary efficacy endpoints including time-to-response and overall survival and AE reporting. No discrepancies were noted.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

6. Dr. Ebenezer Kio, M.D. (Site 181)

The site enrolled and treated five subjects in the mTNBC cohort. A record review was done for the two subjects [REDACTED]^{(b) (6)} who were included in the patient population that met the requirements for inclusion in the application for the study; they signed informed consent documents before [REDACTED]^{(b) (6)} had received two prior therapies in a metastatic setting, and received an IP dose of 10 mg/kg in the study. Records reviewed during the inspection included, but were not limited to: informed consent forms, monitoring logs, delegation logs, enrollment logs, IRB correspondence and approvals, sponsor correspondence and waivers, adverse events, serious adverse events, case report forms, drug accountability records and source documentation.

It was noted during the inspection that the upper and lower limits of normal for certain laboratory tests didn't always match between the BIMO data listings submitted to the application and the source documents found at the site. In some cases, laboratory test results on source documents were flagged as high but reported as normal on the data listings submitted to the application. For example, Subject [REDACTED]^{(b) (6)} alanine aminotransferase (ALT), dated [REDACTED]^{(b) (6)} was reported as 'normal' in the BIMO data listings submitted to the application to be used in support of clinical site inspections; Table J1, "Listing of Laboratory Testing Performed for Safety Monitoring", but was flagged as high in the source documentation found at the site.

In response to this observation, during the inspection, the sponsor communicated to the site the following explanation with regards to these differences:

"Listings in the CSR and the BIMO listings used local laboratory normal ranges when available unless the programmed outputs contained a missing normal range, ..., where missing, normal reference ranges were used based on a publication in the NEJM (N Engl J Med 2004; 351:1548-63.). The BIMO listing was generated using SI units. The displays in the CSR, listings were generated using both conventional units and SI units." The sponsor also indicated that they are "currently looking into how often the normal reference ranges from the NEJM were applied to local lab values."

OSI Reviewer Notes: The discrepancies noted during this inspection appeared to be borderline normal/abnormal depending upon the method of conversion of the test limits used by the sponsor and should not have placed subjects at undue risk.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

7. Dr. Kevin Kalinsky, M.D. (Site 259)

The site screened nine subjects for the mTNBC cohort and enrolled eight subjects. One subject withdrew informed consent prior to receiving study drug. At the time of this inspection there was one subject in follow-up. The inspection covered subject

eligibility, informed consent, IRB correspondence and approvals, sponsor correspondence, study monitoring, adverse events, concomitant medications, case report forms, protocol deviations, disease response data, study drug accountability, and the training of study staff. Review of 100% of the informed consent documents revealed that all study subjects signed the informed consent document prior to undergoing any study activities. Source documents reviewed included: results of laboratory tests; subject physical exams; electrocardiogram results; CT and MRI reports; disease response assessment reports; concomitant medications; and adverse event reports. The subject source data was consistent with the data listings submitted to the application.

Photocopies of skin lesion photos (body rash) and caliper measurements were found in subject research files for two mTNBC cohort subjects on the study (Subject (b) (6) and Subject (b) (6)). During the inspection the clinical investigator was informed that the Informed Consent Form did not include information related to the use of subject photographs that could be included in their research files. There was also no IRB approval for the use of photographs in this research study.

The clinical site provided a copy of an email, dated September 6, 2018, from the Executive Director, Human Research Protection Office, Columbia University to the Executive Director of the Clinical Trials Office, Columbia University. The email, in part, stated that... *'while the consent form does not describe photographs will be taken of the skin with caliper providing a measurement, it does include a statement that most of the exams, tests, and procedures you will have are part of the usual approach for your condition.'* Dr. Kalinsky stated that he would discuss the use of photocopies of pictures with senior management at Columbia University Medical Center.

The inspection revealed no significant deficiencies. The efficacy endpoint data were verifiable with the source records maintained at the site. There was no evidence of under-reporting of AEs.

8. Sponsor: Immunomedics, Inc.

The inspection of Immunomedics, Inc., focused on the control, oversight, and management of the conduct of Study IMMU-132-01. This inspection covered the following elements of the sponsor's operation: protocol and amendments, organization and personnel, FDA Forms-1572, and financial disclosure forms, patient protection/Institutional Review Board (IRB) communications, monitoring procedures and activities, test article integrity, test article accountability, data collection and handling, and adverse experience/effects Reporting.

With respect to clinical monitoring of Study IMMU 132-01, Immunomedics, Inc. employed Clinical Research Associates (CRAs) from within their company and CRAs hired from (b) (4) whom Immunomedics utilized as their own employees to monitor the activities at the clinical sites. Site Initiation Reports (SIRs) from each of the 15 clinical sites are used by the sponsor to document that the

clinical site has obtained the appropriate training and IRB approvals to conduct the clinical trial. However, the inspection revealed that the sponsor did not have SIRs on file for five of the 15 clinical sites (Sites #: 068, 261, 263, 264 and 265). Sponsor staff informed that they could not confirm whether Immunomedics staff had lost the reports, or if the reports were never completed by the monitors. Likewise, interim clinical site monitoring activities were to be documented in the Interim Site Monitoring Visit Reports (IMVRs) for each of the 15 clinical sites. However, two IMVRs for Site 132 were missing from the monitoring records maintained by the sponsor, and an additional 17 IMVRs for six clinical sites were dated more than 60 days after the completion of the IMVs. Study staff explained that the [reports] were expected to be signed by the sponsor within 30 days. Immunomedics, Inc., did not prepare or finalize a study-specific Monitoring Plan to provide written guidance for monitoring activities. Immunomedics, Inc., did have an SOP for monitoring activities and report writing. Two versions of the SOP were in effect during this study, one dated September 29, 2011 and another October 31, 2016; both versions called for the IMVRs to be signed within "one month" of the monitoring visit.

OSI Reviewer Notes: In a written response to the inspectional observations, Immunomedics, Inc., stated that gaps in monitoring existed during the conduct of IMMU-132-01 and that they are already in the process of revising processes and procedures to improve clinical monitoring in accordance with regulations and industry standards. The sponsor further stated that the deficiencies noted were not evidence of intentional neglect or failure to recognize the importance of monitoring as a measure to not only ensure trial integrity but more importantly ensure the safety of subjects enrolled on the clinical trial. The sponsor believes that the monitoring visits did occur and that the monitoring reports were likely misplaced.

Nonetheless, the inspectional observations indicate a poorly executed clinical monitoring program that demonstrates the sponsor's inability to maintain continuous control, oversight, and management of the conduct of Study IMMU-132-01. Inspectional findings of 7 clinical sites, representing a majority of enrolled study subjects, found only minor study conduct and GCP compliance issues, therefore, obviating the potential impact of poor clinical monitor controls on overall study outcomes.

A Note to File [REDACTED] (b) (4) was found the Trial Master File reporting that, [REDACTED] (b) (4)

OSI Reviewer Notes: In a written response to the Form FDA 483, dated August 20, 2018, Immunomedics, Inc., explained that they had requested [REDACTED] (b) (4)

(b) (4)

(b) (4)

In the written response to the Form FDA 483, dated August 20, 2018, Immunomedics described a corrective action plan, that if implemented, may minimize these deficiencies moving forward.

Inspectional observations included the finding that while electronic records are used, they do not meet systems validation and audit trail requirements to ensure that they are trustworthy, reliable, and generally equivalent to paper records. Specifically, Immunomedics, Inc., utilized the computer program Microsoft Access to record data from each of the clinical site's paper Case Report Forms (CRFs), from inception through May of 2017 for the reporting of clinical data to FDA. Microsoft Access is not validated for this use, so there was no audit trail to monitor use and change controls.

OSI Reviewer Notes: In a written response to the Form FDA 483, dated August 20, 2018, Immunomedics, Inc., stated that they agreed with the inspectional observation and in 2016, they recognized the need to insure the utilization of a regulatory compliant application for entering, housing, and cleaning Study IMMU-132-01 trial data. ClinPlus Data Management Software was selected to meet this need and Immunomedics, Inc., contracted (b) (4) the application vendor, to install the software, develop the trial application and migrate the data from the Microsoft Access database to ClinPlus Data Management Software. After the final migration of the data, the ClinPlus Database Management data files were compared to the original source data to insure data accuracy. Subsequently, Case Report Forms (CRFs) brought in-house after the migration to ClinPlus were entered directly into the ClinPlus application using double key entry.

The clinical site inspectional findings of seven clinical sites, representing a majority of enrolled study subjects, found that most data found in source documents verified the data listings submitted to the application, therefore, obviating the potential impact of limited data management systems.

The inspectional observations summarized above describe deficiencies that suggest the sponsor did not demonstrate consistent control, oversight, and management of the

conduct of Study IMMU-132-01. However, it does not appear that these inspectional observations importantly effected overall study outcomes or have placed subjects at undue risk.

The data from this sponsor, associated with Study IMMU-132-01, submitted to the Agency in support of BLA 761115, appear reliable.

9. CRO: [REDACTED] (b) (4)

This inspection was issued to review the conduct of one clinical study (IMMU-132-01), performed in support of BLA 761115. The inspection focused primarily on assessing the accuracy of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO. Documents reviewed during this inspection included but were not limited to: organizational chart, master service agreements, task orders, charters, standard operating procedures, training and qualifications, transmittal forms, RECIST determinations, radiologist Case Report Form's (CRF's), and adjudication determinations.

[REDACTED] (b) (4) had agreements in place with the sponsor, Immunomedics, Inc. Task orders and a charter were in place. Immunomedics, Inc., retrospectively sent imaging to [REDACTED] (b) (4) for review. Immunomedics, Inc., chose which scans for which subjects were sent to [REDACTED] (b) (4) [REDACTED] (b) (4) conducted RECIST review of subject scan timepoints and presented Immunomedics, Inc., with subject scan timepoint overall responses per RECIST 1.1. [REDACTED] (b) (4) was not contracted to evaluate or determine any of the study endpoints.

Initially, Immunomedics, Inc., contracted [REDACTED] (b) (4) to conduct single reads of scans. Subsequently, Immunomedics, Inc., contracted [REDACTED] (b) (4) to conduct double reads (Radiologist #1 and Radiologist #2) with adjudication where needed. A total of 81 subjects' scans were sent to [REDACTED] (b) (4) from Immunomedics, Inc., which included multiple timepoint scans for each of the 81 subjects. A data audit was conducted comparing [REDACTED] (b) (4) results to Immunomedics, Inc., data listings submitted to the application for use in conducting BIMO inspections. [REDACTED] (b) (4) [REDACTED] (b) (4) processes were consistent. However, there were discrepancies noted with Immunomedics, Inc., data listings. Briefly, the Immunomedics, Inc., data listings for use in conducting BIMO inspections showed results for Radiologist #1 for all subject scans.

The BIMO data listings only included Radiologist #1 results when [REDACTED] (b) (4) had determined Radiologist #2 results were the adjudicated results, therefore making the Immunomedics, Inc., data listings incorrect for all [REDACTED] (b) (4) Radiologist #2 adjudicated results. In addition, [REDACTED] (b) (4) sent Immunomedics, Inc., results for all 81 subjects' records received. However, Immunomedics, Inc., data listings show results for only 55 subjects in two of the data listings with Independent Review Committee (IRC) RECIST data and only 52 subjects in one of the data listings with IRC RECIST data. Data from IRC RECIST Radiologist #1 matched the

Immunomedics, Inc., data listings. At the time of this inspection, it was unclear as to why the sponsor didn't include the tumor response assessments.

Immunomedics, Inc., submitted a total of 25 of 81 subjects for single read only review by (b) (4). The following is a list of the 25 subjects submitted to (b) (4) (b) (4) for single read only:



For the remaining 56 subjects (b) (4) conducted double reads with adjudication as needed. Of the 56 subjects sent to (b) (4) for double read and adjudication (where needed) a total of 41 subjects were sent for adjudication. A total of 18 of 41 subjects that were sent for adjudication had Reader 2 adjudicated results as final.

OSI Reviewer Notes: The above findings were discussed with DOP1 MO Lynn Howie and CDTL MO Lola Fashoyin-Aje on several occasions in September and October 2018. Lynn Howie informed that updated datasets were submitted to the application that included both (b) (4) Readers (1 and 2) tumor response determinations and adjudication results. This was provided by the sponsor in response to an IR, however, the "BIMO" Site specific data listings by subject were not updated. Therefore, the inspection of (b) (4) could only verify data generated for Reader#1 during the inspection. The FDA field investigator found that Reader#1 tumor response source records were consistent with that reported in the BIMO data listings submitted to the application. No deficiencies were noted.

An IR was sent to the sponsor requiring explanation as to why 81 subjects' scans were submitted to (b) (4) for radiology assessment and that only ~55 subjects' efficacy data were submitted to the application. Immunomedics, Inc., responded that the 55 subjects were mTNBC patients who were part of the pre-defined efficacy population and were included in BLA listing 16.2.6.6.2 ["Response Evaluation Criteria in Tumors (RECIST) by ICR Assessment (Target mTNBC Population)"].

Of these 55 subjects 52 had target lesions and were included in BLA listing 16.2.6.2.2 ["Target Lesions – ICR Assessment (Target mTNBC Population)"], and 3 subjects who had target lesions defined by local assessment but did not have target lesions defined by the ICR were excluded from this listing. Of the remaining 26 subjects out of 81, 17 were lung cancer patients and nine were other triple-negative breast cancer subjects

who did not meet the pre-defined criteria for the efficacy population (e.g., not enrolled at 10 mg/kg dose level and/or fewer than 2 prior courses of therapy for metastatic disease). The sponsor's response clarifies the discrepancy noted during the CRO inspection and is consistent with datasets included in the application.

Assessment of the CRO's conduct of the Charter-Specified CRO responsibilities found no deficiencies.

{ See appended electronic signature page }

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAUREN C IACONO-CONNORS
10/24/2018

SUSAN D THOMPSON
10/24/2018

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10/24/2018



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 26, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Jeannette Dinin, RPM
DOP1

Subject: QT-IRT Consult to BLA 761115 / IND 122694

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 06/29/2018 regarding the Division's QT related question. The QT-IRT reviewed the following materials:

- [Sponsor's ECG report](#) and [CSR for Study IMMU-132-01](#); and
- [Previous QT-IRT review](#) under IND 122694 dated 04/25/2017 in DARRTS.

1. QT-IRT Responses

Question from the Division: This BLA contains a report summarizing the potential electrocardiographic effects of sacituzumab govetican (IMMU-132) along with cardiac event narratives. The applicant is not making any QTc prolongation claims in the proposed label. Do you agree with the applicant's proposal?

QT-IRT's response to the Division: The data submitted are inconclusive as to whether sacituzumab govetican causes QTc prolongation to inform the USPI. It is our opinion that including any specific warnings about QTc prolongation is not needed at this time and we will revisit this recommendation when the data from study IMMU-132-05 are submitted and reviewed. We had previously agreed that the characterization of QTc will come from a substudy in IMMU-132-05 which is still ongoing.

1. The ECG data collected in Study IMMU-132-01 cannot be used to to exclude large mean increases (>20 ms) in the QTcF interval due to the following limitations:
 - a. There was lack of centralized ECG acquisition and interpretation.
 - b. As per the protocol, ECG assessments were to be done at baseline and after completion of infusion on Day 1 of every even numbered treatment cycle (Cycle 2, Cycle 4 etc.). However, it is not known whether the post-dose ECGs were collected at the same time post-infusion across individuals and visits to derive the mean QTc effects.
 - c. The ECGs were not collected at any other time point to inform if there are any potential delayed effects. Furthermore, there is no PK information available. Thus, it is not clear whether the observed QTc effect is concentration-dependent, or an indirect effect (e.g., due to electrolyte imbalance) or merely an artifact of assessment methodology (the first post-baseline measurement is quite far in time from baseline measure).
2. In Study IMMU-132-01, there were no baseline and on-treatment ECGs in ~50% patients. Overall, in the subset of 184 patients with available ECG data, 2.7% patients had QTcF >500 ms and 4.7% patients had increase in baseline >60 ms. A majority of these cases of QTc prolongation are confounded by other risk factors or concomitant medications that are known to prolong the QTc interval. It is difficult to determine whether there is a causal relationship to IMMU-132.
3. The sponsor did not evaluate the ability of SN-38 to inhibit the hERG channel.

2. BACKGROUND

Product Information

IMMU-132 (sacituzumab govitecan) is an antibody-drug conjugate being developed for treatment of cancer by Immunomedics. The drug is comprised of SN-38 (the active metabolite of irinotecan) conjugated to hRS7, a humanized antibody targeting the Trop-2 antigen expressed on many solid epithelial cancers.

Reviewer's comments: Irinotecan (Camptosar) was approved in the US in 1996. At the highest irinotecan dose of 300 mg/m² q3w, the mean SN-38 C_{max} is around 50 ng/mL. The free C_{max} of SN-38 is ~111 ng/mL at the first dose of 10 mg/kg of IMMU-132. Therefore, further assessment of the QT effect of SN-38 within IMMU-132 is needed.

Details of the study in current submission

IMMU-132-01, a Phase I/II open-label study, enrolled a total of 420 patients with various metastatic cancers who had received at least one prior therapy for their metastatic disease by the cutoff for submission to FDA for consideration of accelerated approval in triple-negative breast cancer. All patients had received IMMU-132 administered by IV administration on days 1 and 8 of a 21-day treatment cycle to be repeated until progression of disease requiring treatment discontinuation or unacceptable toxicity.

Current analysis of adverse events has revealed no overt pattern of clinical cardiovascular toxicity, consistent with the limited evidence of any cardiac effects of irinotecan, whose active metabolite is SN-38, as reported in the Camptosar package insert.

A formal electrocardiogram (ECG) study of IMMU-132 has not been conducted as yet, although a formal ECG sub-study has been included in IMMU-132-05, an ongoing Phase III study.

However, in IMMU-132-01, routine ECG safety monitoring was conducted for patient safety. During this study, 12-lead ECGs were recorded with local ECG equipment in each patient at baseline (up to 28 days before the first dose) and then on the first day of every even numbered treatment cycles. Automated readings were over-read by the local PI and the results were recorded in the study Case Report Form (CRF). On review of these forms, the Sponsor noted occasional instances of QT prolongation and requested an outside review to determine if the incidence of QT prolongation is different from what would be expected in this oncology population. This, therefore, is an ad hoc analysis that was not originally planned.

Sponsor's position and summary of available data

Given the totality of the available cardiac data, there is no contraindication to continued development of IMMU-132.

Modest mean increases during treatment with IMMU-132 of PR (4.65 msec overall) and QTcF (9.62 msec overall) were observed in this analysis.

There were no reported deaths or arrhythmias related to QT or PR prolongation in this study.

In most patients in this study alternative explanations for QT prolongation and other cardiac adverse effects were present. QT prolongation was not judged to be definitely related to IMMU-132 in any case and was thought to be possibly related in only 4 cases (0.95% of all enrolled subjects). None of the other cardiac adverse effects were judged to be related, probably related or possibly related to IMMU-132.

Sponsor's QTc Analysis

Categorical frequencies of normal and three progressively abnormal ranges of QTcF at baseline, and at any time during treatment, are summarized in Table 3, with the percentage based upon the number of subjects with QTcF numerical data at baseline (n=205) and on treatment (n=220).

Table 3: QTcF and dQTcF Categories at Baseline and on Treatment Among Patients with QTcF Numerical Data

Category (msec)	Baseline N	On Treatment N* (%)
≤ 450	194 (94.6)	210 (95.5)
> 450, ≤ 480	10 (4.9)	52 (23.6)
> 480, ≤ 500	1 (0.5)	11 (5.0)
> 500	0 (0)	6 (2.7)
Increase > 30, ≤ 60	-	32 (14.5)
Increase > 60	-	9 (4.1)
> 500 and increase > 60	-	3 (1.4)

*Number of patients with an instance of an ECG meeting Category criteria; categories are not mutually exclusive. As a result, the sum (323) is greater than the number of individual patients (220)

15 patients had QTcF prolongation as an adverse effect. Those with prolonged QT are summarized in Sponsor's Table 5.

Table 5: Fifteen Patients with Prolonged QT Events

ID	Specific Risk Factor	Con Med Risk	Timing	Relatedness according to Medical Review	Baseline QTc	N ECG on Rx (% with QTcF > 480 msec)	Search Criterion **
(b) (6)	MI, CRF		On Rx	Possibly related	unk	5 (60)	A, B
	Con med, MI	ondansetron, fentanyl, morphine, hydrocodone	On Rx	Probably unrelated	wnl	0 (0)*	C
	CHF, Con med	oxycodone	On Rx	Unrelated	487 msec	3 (66.7)	B
	HypoMg, HypoK	codeine, ondansetron	On Rx	Probably unrelated	unk	3 (33.3)	B
	Con med	ondansetron, hydrocodone, metoclopramide	On Rx	Probably unrelated	wnl	4 (25)	B
	Con med	hydrocodone	On Rx	Possibly related	wnl	4 (25)	B
	Con med	ondansetron, oxycodone	On Rx	Probably unrelated	470 msec	2 (50)	B
	Con med	granisetron	On Rx	Possibly related	unk	3 (66.7)	B
	Con med	hydrocodone	On Rx	Probably unrelated	wnl	0 (0)*	A
	Con med	ondansetron	On Rx	Probably unrelated	wnl	8 (12.5)	B
	None		On Rx	Possibly related	wnl	3 (66.7)	B
	HypoMg, HypoK	ondansetron	On Rx	Unrelated	wnl	2 (50)	B
	None		LTFU	Unrelated	wnl	3 (33.3)	B
	Con med	palonosetron	On Rx	Probably unrelated	wnl	8 (12.5)	A, B
	Con med	ondansetron	FSE	Unrelated	wnl	1 (100)	B

MI=myocardial infarction, CRF=chronic renal failure, CHF=congestive heart failure, Con med=concomitant medication, HypoMg=hypomagnesemia, HypoK=hypokalemia, On Rx=during treatment with immu-132, LTFU=long term follow-up (3 weeks after last infusion), FSE=final study evaluation (2 weeks after last infusion), unk=unknown, wnl= within normal limits

* - these cases had diagnostic statements indicating QT prolongation, but no QTcF value ≥ 480 msec in the database

** - see Table 4 for search criterion

The table below summarizes the number of patients with one or more selected cardiac safety events which may potentially be associated with QT prolongation and related ventricular arrhythmias. There were no events of sudden death, torsade de pointes or ventricular

arrhythmias, including ventricular fibrillation and ventricular flutter. In 3 of the 7 patients who experienced syncope, the events were assessed as serious adverse events and were related to current AEs of hypotension, neutropenia and hypokalemia. None of the patient reported QTc prolongation.

Patient ^{(b) (6)}, who sustained a cardio-respiratory arrest, was a 64-year-old White female with a 5-year history of stage III small-cell lung cancer who experienced loss of consciousness at home on Day 6 of Cycle 32 (8 mg/kg). She was brought to the Emergency Room where resuscitation attempts were unsuccessful. The most recent response evaluation prior to her death, done at Cycle 28, indicated stable disease. Electrocardiograms during the study were assessed by the investigator as “abnormal, not clinically significant;” QT intervals were normal.

Table 2.1 Selected Cardiac Safety Treatment-Emergent Adverse Events by MedDRA Preferred Term (Overall Safety Population)

MedDRA Preferred Term	8mg/kg (N=81)	10mg/kg (N=327)	12mg/kg (N=9)	18mg/kg (N=3)	Overall (N=420)
	n (%)	n (%)	n (%)	n (%)	n (%)
Syncope	0 (0.0)	7 (2.1)	0 (0.0)	0 (0.0)	7 (1.7)
Electrocardiogram QT prolonged	1 (1.2)	2 (0.6)	0 (0.0)	0 (0.0)	3 (0.7)
Seizure	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (0.2)
Cardio-respiratory arrest	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Sudden death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Torsade de pointes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular arrhythmias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular flutter	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Protocol IMMU-132-01 Clinical Study Report Table 14.3.1.13.1

Reviewer’s comments:

- The ability of SN-38 to inhibit hERG channel was not assessed.
- Cases of QTc prolongation are confounded by other risk factors (e.g. electrolyte abnormalities) known to prolong the QTc interval. It is difficult to determine from these data whether there is a causal relationship to IMMU-132.
- As per the sponsor, IMMU-132, total SN-38, and free SN-38 are most often cleared almost entirely within 3 days. So negligible accumulation is expected with multiple dosing (administration on Day 1 and Day 8 in each 21-day cycle).
- There was no PK data reported and the sponsor did not report any C-QT analysis to evaluate whether there is any concentration dependent effect for data from Study IMMU-132-01.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DHANANJAY D MARATHE
07/26/2018

CHRISTINE E GARNETT
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