# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

# 761115Orig1s000

| | |
|---|---|
| ***Trade Name:*** | Trodelvy |
| ***Generic or Proper Name:*** | sacituzumab govitecan-hziy |
| ***Sponsor:*** | Immunomedics, Inc |
| ***Approval Date:*** | April 22, 2020 |
| ***Indication:*** | For the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease. |

BLA 761115

**BLA ACCELERATED APPROVAL**

Immunomedics, Inc
Attention: Diane Whiteley
Vice President, Regulatory Affairs
300 The American Road
Morris Plains, NJ 07950

Dear Ms. Whiteley:

Please refer to your biologics license application (BLA) dated May 18, 2018, received May 18, 2018, and your amendments, submitted under section 351 of the Public Health Service Act for Trodelvy™ (sacituzumab govitecan-hziy) for injection, 180 mg/vial.

We acknowledge receipt of your amendment dated November 30, 2019, received December 2, 2019, which constituted a complete response to our January 17, 2019, action letter.

## LICENSING

We have approved your BLA for Trodelvy™ (sacituzumab govitecan-hziy) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Trodelvy™ under your existing Department of Health and Human Services U.S. License No. 1737. Trodelvy™ is indicated for the treatment of adult patients with metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies for metastatic disease.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture sacituzumab drug substance intermediate at Immunomedics Inc. in Morris Plains, NJ, USA. The CL2A-SN38 drug substance intermediate will be manufactured at Johnson Matthey Pharma Services in Devens, MA, USA. Sacituzumab govitecan-hziy drug substance and drug product will be manufactured, filled, and bulk packaged at BSP Pharmaceuticals S.p.A. in Latina Scalo, Italy. The final formulated product will be labeled and packaged at (b) (4) You may label your product with the proprietary name Trodelvy™ and will market it in single-dose vials, 180 mg/vial, for injection.

## DATING PERIOD

The dating period for Trodelvy™ shall be 24 months from the date of manufacture when stored at 2 - 8 °C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C (b) (4) The dating period for your sacituzumab drug substance intermediate shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your sacituzumab drug substance intermediate, drug substance, and drug product under 21 CFR 601.12.

## FDA LOT RELEASE

You are not currently required to submit samples of future lots of Trodelvy™ to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Trodelvy™ or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

## APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761115**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for sacituzumab govitecan-hziy was not referred to an FDA advisory committee because it did not raise significant safety or efficacy issues that were unexpected for a biologic of this class or in the intended population.

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such a clinical trial with due diligence. If the postmarketing clinical trial fails to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 20, 2020. This requirement, along with required completion dates, is listed below.

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

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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| Final Protocol Submission: | 08/2019 (completed) |
| Trial Completion: | 04/2020 |
| Final Report Submission: | 10/2020 |

Submit clinical protocols to your IND 122694 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

## REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of risk for increased hematologic toxicities in patients homozygous for the UGT1A1*28 allele, increased toxicities in patients with moderate hepatic impairment, and QT interval prolongation receiving sacituzumab govetecan-hziy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these signals.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

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

The timetable you submitted on April 20, 2020, states that you will conduct this study according to the following schedule:

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| Final Protocol Submission: | 08/2019 (completed) |
| Trial Completion: | 04/2020 |
| Final Report Submission: | 10/2020 |

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

The timetable you submitted on April 17, 2020, states that you will conduct this study according to the following schedule:

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

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

The timetable you submitted on April 20, 2020, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | 08/2019 (completed) |
| Trial Completion: | 03/2020 |
| Final Report Submission: | 12/2020 |

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 122694 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3504-5 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.

Final Report Submission: 12/2022

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

Final Report Submission: 03/2021

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

Final Report Submission: 06/2021

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

Final Report Submission: 11/2020

3504-9 Develop and validate a sensitive assay for the detection of neutralizing antibodies (NAb) to sacituzumab govitecan for accurate detection of NAb to sacituzumab govitecan in the presence of drug levels that are expected to be present in the serum or plasma at the time of patient sampling. The NAb assay procedures and method validation report will be submitted in the final report to the BLA.

Final Report Submission: 12/2020

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

Final Report Submission: 06/2020

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

Final Report Submission: 10/2020

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

Final Report Submission: 06/2020

Submit clinical protocols to your IND 122694 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

## PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry.[4]

## REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

**MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at FDA.gov.[5]

**POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jeannette Dinin, Regulatory Project Manager, at 240-402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, MD
Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[5] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

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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.**

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/s/

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RICHARD PAZDUR
04/22/2020 10:25:04 AM