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RESEARCH**

APPLICATION NUMBER:

761115Orig1s000

OTHER ACTION LETTERS



BLA 761115

COMPLETE RESPONSE

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(a) of the Public Health Service Act for sacituzumab govitecan powder for solution for infusion, intravenous, 180 mg.

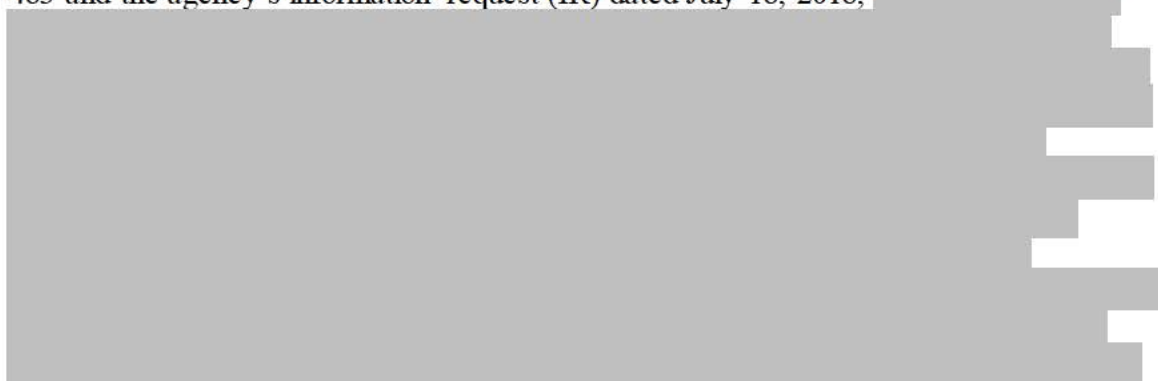
We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Per 21 CFR 601.20 (c) "No product shall be licensed if any part of the process of or relating to the manufacture of such product...would impair the assurances of continued safety, purity, and potency...".

1. Reference is made to the pre-license inspection at Immunomedics Inc. (Morris Plains, NJ) and subsequent communications between Immunomedics and the Agency:

a. Reference is made to the information and data provided to the agency in response to Form 483 and the agency's information request (IR) dated July 18, 2018, (b) (4)



(b) (4) to ensure the manufacture of a product with continued safety, purity, and potency.

In your resubmission, provide information and data to support (b) (4)

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

In your resubmission, provide evidence to support (b) (4)

2. Reference is made to the information and data provided in response to the agency's IR dated October 3, 2018 and December 14, 2018, and in multiple communications through teleconferences with the agency (b) (4)


To support a well-controlled and consistent commercial production (b) (4) in your resubmission, provide adequate data and information in your resubmission to confirm (b) (4) that is currently intended for commercial manufacture. Additionally, provide a root cause analysis, supported by appropriate documentation, for the observed trend (b) (4)

3. (b) (4)

(b) (4)



In your resubmission, provide adequate information and data to support the testing strategy (b) (4) Additionally, as committed in your response to the agency's IR dated November 13, 2018, implement appropriate assay controls (b) (4)



4. Reference is made to the information and data provided in response to the agency's IR dated November 13, 2018 and January 5, 2019 (b) (4)





(b) (4)






(b) (4)





In your resubmission, revise the specifications, as appropriate, and provide information and data  (b) (4)



5. Reference is made to the information provided in response to the agency's IR dated November 13, 2018,  (b) (4)
- 

6. Reference is made to the information and data provided in response to the agency's IRs dated December 14, 2018 and January 5, 2019,  (b) (4)

 The information provided is insufficient to support the following
(b) (4) Provide additional information and data  (b) (4)

(b) (4)

hRS7 antibody intermediate

(b) (4)

IMMU-132 DS

(b) (4)

7. Reference is made to the information provided in response to the agency's IR dated January 5, 2019,

(b) (4)

(b) (4)

8. Regarding method validation:

(b) (4)

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

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you continue to develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

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

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of labeling, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version, at the time of the resubmission. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling, as attached, based on our proposed revisions.

PROPRIETARY NAME

Please refer to correspondence dated August 30, 2018, which addresses the proposed proprietary name, Trodelvy. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

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

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Product Quality

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

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

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

4. [REDACTED] (b) (4)

5. [REDACTED] (b) (4)

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

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

Additionally, insufficient details were provided in response to the IR conveyed on December 14, 2018 (Drug Product Question #1) [REDACTED] (b) (4)

Immunogenicity

7. Insufficient information and data were provided [REDACTED] (b) (4)

Address the following unresolved issues:

[REDACTED] (b) (4)

(b) (4)



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

Product Quality Microbiology

9.  (b) (4)
10.  (b) (4)
11.  (b) (4)

Labeling

12.

(b) (4)

To support this labeling, in your resubmission, provide a new full BICR evaluation of ORR for the entire efficacy population, based upon the data cutoff date in original BLA submission (June 30, 2017), and provide duration of response based upon the original data cutoff date and the extended follow-up data cutoff date (December 1, 2017).

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," December 2017 at: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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 Hematology & Oncology Products
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Labeling
Carton/Container Labeling

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

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/

RICHARD PAZDUR
01/17/2019 04:19:47 PM