BLA 761145/S-007

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Attention: Melanie Rothschild, MBA
Associate Director, Regulatory Affairs
920 Route 202 South
Raritan, NJ 08863

Dear Ms. Rothschild:

Please refer to your supplemental biologics license application (sBLA), dated November 11, 2020, received November 12, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Darzalex Faspro (daratumumab and hyaluronidase-fihj) injection.

This Prior Approval supplemental biologics application provides for a new indication for Darzalex Faspro for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior therapy including lenalidomide and a proteasome inhibitor.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the Food and Drug Administration (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] that is identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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

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.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(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.

Since Darzalex Faspro (daratumumab and hyaluronidase-fihj) was approved on May 1, 2020, we have become aware through clinical trial data of an increased risk of severe and serious adverse events, including severe neutropenia among U.S. racial and ethnic minority patients with relapsed or refractory multiple myeloma. We have also become aware through postmarketing data of severe and fatal infusion-related reactions associated with the administration of daratumumab postmarketing setting. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

[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.

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 the known serious risk of increased severe and serious adverse events, severe neutropenia and fatal infusion-related reactions.

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 this serious risk.

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

4074-1 Conduct a clinical study to further characterize the exposure of daratumumab (D) subcutaneous (SC), the increased risk of severe and serious adverse events, including severe neutropenia, and efficacy among U.S. racial and ethnic minority patients with relapsed or refractory multiple myeloma. Include an assessment of the PK, PD, safety, and efficacy of daratumumab SC in combination with other agents including pomalidomide and dexamethasone (Pd) in U.S. racial and ethnic minority patients including Black and Asian patients with relapsed or refractory multiple myeloma in the final study report. The population pharmacokinetic and exposure-response analyses for both efficacy and safety should be updated.

The timetable you submitted on June 2, 2021 states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	03/2022
Study Completion:	07/2025
Final Report Submission:	01/2026

4074-2 Conduct a prospective, observational single-arm study to assess the risk of severe (Grades 3-4) and fatal infusion-related reactions (IRRs) in patients treated with intravenous (IV) or sub-cutaneous (SC) daratumumab. Evaluate the incidence of severe and fatal IRRs, and collect information, including a full description of clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of IRRs and other potential associated risk factors. Specify case definitions, validation methods, and procedures

for all study outcomes. Submit interim reports of the data collected from the study annually until the study is completed.

The timetable you submitted on June 30, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2021
Final Protocol Submission:	06/2022
Interim Report Submission #1:	01/2024
Interim Report Submission #2:	01/2025
Study Completion:	01/2026
Final Report Submission:	07/2026

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 the protocol(s) to your IND 125541, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) 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)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

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

[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.

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 COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4074-3 Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access programs, real-world evidence, and other sources to further characterize the safety and efficacy of daratumumab (SC) in combination with pomalidomide and dexamethasone among U.S. racial and ethnic minority patients with multiple myeloma.

The timetable you submitted on June 2, 2021, states that you will conduct this study according to the following schedule:

Draft Analysis Submission:	02/2022
Final Analysis Submission:	06/2022
Study Completion:	07/2025
Final Report Submission:	01/2026

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry "*Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]"

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Kimberly Scott, Senior Regulatory Project Manager, at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

KIMBERLY L SCOTT
07/09/2021 03:58:04 PM

NICOLE J GORMLEY
07/09/2021 04:05:15 PM