BLA 761145/S-002

ACCELERATED APPROVAL

Janssen Biotech, Inc.
Attention: Melanie Rothschild, MBA
Associate Director, Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Ms. Rothschild:

Please refer to your supplemental Biologics license application (sBLA), dated September 9, 2020, received September 9, 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 license application provides for a new indication for the treatment of patients with light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

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.

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

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.

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.

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 clinical trial with due diligence. If postmarketing clinical trials fail 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 January 13, 2021. This requirement, along with required completion dates, is listed below.

[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.

This postmarketing study is subject to the reporting requirements of 21 CFR 601.70:

3951-1	Submit the final study report and datasets from a randomized clinical trial to verify and further characterize the clinical benefit and safety of daratumumab subcutaneous for the treatment of patients with AL amyloidosis. This submission should include the final analysis and datasets of progression free survival or overall survival results.	
	Draft Protocol Submission:	10/2017
	Final Protocol Submission:	10/2017
	Trial Completion:	12/2024
	Final Report Submission:	06/2025

Submit clinical protocols to your IND 125541 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)**."

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 was approved on May 1, 2020, we have become aware of serious cardiovascular adverse events and cardiac toxicity identified from clinical trials of patients with newly diagnosed AL amyloidosis. We have also become aware of increased rates of hematological toxicities, infection, hemorrhage, serious adverse events and increased dose exposures in African American patients with AL amyloidosis identified from clinical trials. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 signal of serious risk of cardiovascular adverse events and cardiac toxicity. Additionally, 505(k)(1) of the FDCA will not be sufficient to assess the signal of serious risks of increased rates of adverse events and to determine appropriate dose adjustment of Darzalex Faspro SC in U.S. racial and ethnic minority patients with AL amyloidosis.

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 clinical trials (rather than nonclinical or observational studies) will be sufficient to assess these signals.

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

3951-2 Conduct clinical trials in newly diagnosed and relapsed/refractory AL amyloidosis to assess (1) all serious cardiovascular adverse events on study treatment; (2) all deaths on study treatment and; (3) the risk factors for cardiac toxicity and the adequacy of monitoring in at least 100 patients treated with daratumumab subcutaneous for at least 6 months. Data from clinical trials in patients with relapsed / refractory AL amyloidosis will be considered supportive. Characterize the incidence, clinical presentation, management and outcome of these events and identify those that represent major adverse cardiovascular events; namely nonfatal myocardial infarction, cardiac failure and arrhythmia, or fatal cardiovascular adverse events and events of sudden death. Also, identify hospitalizations for unstable angina, coronary revascularization procedures, and serious adverse events of heart failure. Include an evaluation of potential mitigation strategies for cardiac toxicity. The interim report should contain results from the first completed clinical trial.

The timetable you submitted on January 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2021
Final Protocol Submission:	04/2022
Trial Completion:	08/2025
Interim Report Submission:	04/2024
Final Report Submission:	02/2026

Submit datasets with the final report.

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]

[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.

3951-3 Conduct a clinical trial to assess the safety of daratumumab subcutaneous (SC) among U.S. racial and ethnic minorities including African American patients with AL amyloidosis given the higher pharmacokinetic (PK) exposure and hematologic toxicity rates (neutropenia, lymphopenia, thrombocytopenia and anemia). This study should characterize the exposure (including PK data), safety, and efficacy of daratumumab SC.

The timetable you submitted on January 13, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2021
Final Protocol Submission:	12/2021
Trial Completion:	12/2023
Final Report Submission	06/2024

Submit datasets with the final report.

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.[4]

Submit the protocols 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)"**.

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

[4] 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.

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.

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.*[5]*"*

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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

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

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/s/

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