BLA 761061/S-021

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Attention: Jenna Giacchi, MS
Associate Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Jenna Giacchi:

Please refer to your supplemental biologics license application (sBLA), dated and received March 11, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tremfya (guselkumab) injection.

This Prior Approval supplemental biologics license application provides for the treatment of adult patients with moderately to severely active ulcerative colitis. This supplement also provides for three new drug presentations:

- 200 mg/20 mL (10 mg/mL) single-dose vial
- 200 mg/2 mL single-dose prefilled pen (Tremfya Pen)
- 200 mg/2 mL single-dose prefilled syringe

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 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] that is identical to the enclosed labeling (Prescribing Information, Instructions

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

for Use, and Medication Guide) 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).

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*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761061/S-021**." Approval of this submission by FDA is not required before the labeling is used.

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 studies requirement for ages less than 2 years. This is because necessary studies are impossible or highly impracticable, as ulcerative colitis is rarely diagnosed in patients less than 2 years of age.

[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 are deferring submission of your pediatric studies for ages 2 to <18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the FDCA. These required studies are listed below.

4696-1 Conduct a one-year, randomized, open-label induction, double-blind maintenance, parallel-group, multicenter study to assess the pharmacokinetics, safety, and efficacy of Tremfya (guselkumab) in pediatric patients 2 to <18 years of age with moderately to severely active ulcerative colitis.

Final Protocol Submission: 04/2025
Study Completion: 07/2028
Final Report Submission: 01/2029

4696-2 Conduct a long-term extension study to evaluate the long-term safety of Tremfya (guselkumab) in patients 2 to <18 years of age with moderately to severely active ulcerative colitis who participated in postmarketing requirement 4696-1. This Study can be conducted as a part of postmarketing requirement 4696-1.

Final Protocol Submission: 04/2025
Study Completion: 02/2030
Final Report Submission: 08/2030

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 140330, with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal 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 identify an unexpected serious risk of adverse reactions associated with long-term exposure to guselkumab (e.g., malignancy, autoimmune disease) or an unexpected serious risk of adverse reactions which occur infrequently (e.g., opportunistic infections, neurologic or demyelinating disease, gastrointestinal events [including hepatic]) in patients with inflammatory bowel disease. Additionally, we have determined that analyses of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of maternal, fetal, or infant toxicity due to exposure to guselkumab during pregnancy or due to the presence of guselkumab in human milk during lactation.

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.

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

4696-3 Complete the treatment and evaluation of subjects enrolled in the ongoing CNTO1959UCO3001 (QUASAR), CNTO1959UCO3004 (ASTRO), CNTO1959CRD3001 (GALAXI), and CNTO1959CRD3004 (GRAVITI) studies. Follow subjects in these studies for 5 years unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable. Adverse events (including, but not limited to, malignancy, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal [including hepatic] or hematologic adverse events) will continue to be collected throughout the long-term extensions.

The timetable you submitted on August 29, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2025
Study Completion:	03/2030
Final Report Submission:	03/2031

4696-4 Collect data from prospective pregnancy exposure registry/registries, preferably disease-based multiproduct pregnancy registry/registries, using a registry-based cohort study design to compare the maternal, fetal, and infant outcomes of women with inflammatory bowel disease exposed to guselkumab during pregnancy with unexposed comparator population(s). Align the U.S. protocol with protocols(s) outside the U.S. to reach the target sample size, if applicable. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortion, stillbirths, pregnancy terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on August 29, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2025
Study Completion: 06/2030
Final Report Submission: 06/2031

4696-5 Conduct a retrospective cohort study using claims or electronic medical record data or a case control study with confirmation based upon review of data from medical records to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births, neonatal deaths, and infant infections in women exposed to guselkumab regardless of indication during pregnancy compared to an unexposed control population.

The timetable you submitted on August 29, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2025
Study Completion: 06/2030
Final Report Submission: 06/2031

4696-6 Perform a lactation study (milk only) in lactating women who have received guselkumab, regardless of indication, to measure concentrations of guselkumab in breast milk using a validated assay.

The timetable you submitted on August 29, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	03/2026
Study Completion:	09/2027
Final Report Submission:	09/2028

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 clinical protocol(s) to your IND 140330 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all 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(a)(1) 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(a)(1) 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.

[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.

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

We remind you of your postmarketing commitment:

4695-1 Perform a supplemental low endotoxin recovery (LER) study to examine the effects [redacted] on endotoxin recovery using 3 batches of [redacted] mg/mL guselkumab [redacted] to verify [redacted] for the DP manufacturing process has no impact on endotoxin recovery.

The timetable you submitted on August 23, 2024 states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2025

Submit clinical protocols to your IND 140330 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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/subjects 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

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]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

[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

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).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

If you have any questions, contact Andrew Chi, PharmD, Regulatory Project Manager, at (301) 796-8597 or email at andrew.chi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Erica Lyons, MD
Associate Director for Therapeutic Review
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use:
    - 200 mg/2 mL Prefilled Syringe
    - 200 mg/2 mL Prefilled Pen
    - 100 mg/mL Prefilled Syringe (version dated December 2017)
    - One-Press Patient Controlled Injector (version dated June 2023)
- Carton and Container Labeling

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/

ERICA M LYONS
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