

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA761061Orig1s021

Name: Tremfya (guselkumab) injection

- 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

Sponsor: Janssen Biotech, Inc.

Approval Date: September 11, 2024

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BLA761061Orig1s021
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA761061Orig1s021

APPROVAL LETTER

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>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

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>.

U.S. Food and Drug Administration

Silver Spring, MD 20993

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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 of hold time at 15-25°C on endotoxin recovery using 3 batches of 20 mg/mL guselkumab FVP spiked with RSE or CSE and stored at 20-25°C to verify that the longest duration 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](https://www.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
09/11/2024 08:16:34 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA761061Orig1s021

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TREMFYA safely and effectively. See full prescribing information for TREMFYA.

TREMFYA® (guselkumab) injection, for subcutaneous use
TREMFYA® PEN (guselkumab) injection, for subcutaneous use
TREMFYA® (guselkumab) injection, for intravenous use

Initial U.S. Approval: 2017

RECENT MAJOR CHANGES	
Indications and Usage (1.3)	09/2024
Dosage and Administration (2.1, 2.4, 2.5, 2.6)	09/2024
Warnings and Precautions (5.2, 5.3, 5.4)	09/2024

INDICATIONS AND USAGE

TREMFYA is an interleukin-23 antagonist indicated for the treatment of adult patients with:

- moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.1)
- active psoriatic arthritis (1.2)
- moderately to severely active ulcerative colitis (1.3)

DOSAGE AND ADMINISTRATION

- Complete all age-appropriate vaccinations as recommended by current immunization guidelines prior to treatment initiation. (2.1)

Recommended Dosage

Plaque Psoriasis

- 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. (2.2)

Psoriatic Arthritis

- 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. TREMFYA can be used alone or in combination with a conventional DMARD (e.g., methotrexate). (2.3)

Ulcerative Colitis

- **Induction:** 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8. (2.4)
- **Maintenance:** 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. Use the lowest effective recommended dosage to maintain therapeutic response. (2.4)

DOSAGE FORMS AND STRENGTHS

Subcutaneous Injection (3)

- Injection: 100 mg/mL in a single-dose One-Press patient-controlled injector.
- Injection: 200 mg/2 mL in a single-dose prefilled pen (TREMFYA PEN).
- Injection: 100 mg/mL in a single-dose prefilled syringe.
- Injection: 200 mg/2 mL in a single-dose prefilled syringe.

Intravenous Infusion (3)

- Injection: 200 mg/20 mL (10 mg/mL) solution in a single-dose vial.

CONTRAINDICATIONS

Serious hypersensitivity reactions to guselkumab or to any of the excipients. (4)

WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis, may occur. (5.1)
- **Infections:** TREMFYA may increase the risk of infection. Do not initiate treatment with TREMFYA in patients with clinically important active infection until the infection resolves or is adequately treated. If such an infection develops, discontinue TREMFYA until the infection resolves. (5.2)
- **Tuberculosis (TB):** Evaluate for TB prior to initiating treatment with TREMFYA. (5.3)
- **Immunizations:** Avoid use of live vaccines. (5.4)

ADVERSE REACTIONS

Most common adverse reactions associated with TREMFYA are:

- **Plaque Psoriasis and Psoriatic Arthritis (≥1%):** upper respiratory infections, headache, injection site reactions, arthralgia, bronchitis, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. (6.1)
- **Ulcerative Colitis**
- **Induction (≥2%):** respiratory tract infections. (6.1)
- **Maintenance (≥3%):** injection site reactions, arthralgia, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

TREMFYA is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

1.2 Psoriatic Arthritis

TREMFYA is indicated for the treatment of adult patients with active psoriatic arthritis.

1.3 Ulcerative Colitis

TREMFYA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluations and Immunizations Prior to Treatment Initiation

- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA [see *Warnings and Precautions* (5.3)].
- Complete all age-appropriate vaccinations according to current immunization guidelines [see *Warnings and Precautions* (5.4)].

2.2 Recommended Dosage for Plaque Psoriasis

TREMFYA is administered by subcutaneous injection. The recommended dosage is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

2.3 Recommended Dosage for Psoriatic Arthritis

TREMFYA is administered by subcutaneous injection. The recommended dosage is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

TREMFYA may be administered alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD) (e.g., methotrexate).

2.4 Recommended Dosage for Ulcerative Colitis

Induction:

The recommended induction dosage of TREMFYA is 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8 [see *Dosage and Administration* (2.6)].

Maintenance:

The recommended maintenance dosage of TREMFYA/TREMFYA PEN is:

- 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or
- 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter.

Use the lowest effective recommended dosage to maintain therapeutic response.

2.5 Preparation and Administration Instructions for Subcutaneous Injection

- Administer TREMFYA/TREMFYA PEN subcutaneously. Each prefilled syringe, One-Press injector, or Prefilled Pen is for one time use in one patient only. Instruct patients to inject the full amount (1 mL or 2 mL), which provides 100 mg or 200 mg of TREMFYA.
- TREMFYA/TREMFYA PEN is intended for use under the guidance and supervision of a healthcare professional. TREMFYA/TREMFYA PEN may be administered by a healthcare professional, or a patient/caregiver may inject after proper training on correct subcutaneous injection technique.
- Before injection, remove TREMFYA/TREMFYA PEN from the refrigerator and allow to reach room temperature (30 minutes) without removing the needle cap.
- Inject into the front of the thighs, the lower abdomen except for the 2 inches around the navel, or the back of the upper arms (healthcare professional or caregiver only).
- Do not inject TREMFYA/TREMFYA PEN into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis [see *Instructions for Use*].
- The TREMFYA/TREMFYA PEN *Instructions for Use* contains more detailed patient instructions on the preparation and administration of TREMFYA/TREMFYA PEN [see *Instructions for Use*].
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.
- Inspect TREMFYA/TREMFYA PEN visually for particulate matter and discoloration prior to administration. TREMFYA/TREMFYA PEN is a clear and colorless to light yellow solution that may contain small translucent particles. Do not use if the liquid contains large particles, is discolored or cloudy. TREMFYA/TREMFYA PEN does not contain preservatives; therefore, discard any unused product remaining in the prefilled syringe, One-Press injector, or Prefilled Pen.

2.6 Preparation and Administration Instructions for Intravenous Infusion (Ulcerative Colitis)

Preparation Instructions:

1. Withdraw and then discard 20 mL of the 0.9% Sodium Chloride Injection from the 250 mL infusion bag which is equal to the volume of TREMFYA to be added.
2. Withdraw 20 mL of TREMFYA from the vial and add it to the 250 mL intravenous infusion bag of 0.9% Sodium Chloride Injection for a final concentration of 0.8 mg/mL. Gently mix the diluted solution. Discard the vial with any remaining solution.
3. Visually inspect the diluted solution for particulate matter and discoloration before infusion. Infuse the diluted solution over a period of at least one hour.
4. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein binding filter (pore size 0.2 micrometer).
5. Do not infuse TREMFYA concomitantly in the same intravenous line with other medicinal products.
6. Dispose any unused medicinal product in accordance with local requirements.

Administration Instructions:

- TREMFYA solution for intravenous infusion must be diluted, prepared, and infused by a healthcare professional using aseptic technique. TREMFYA does not contain preservatives. Each vial is for one time use in one patient only.

- Inspect TREMFYA visually for particulate matter and discoloration prior to administration. TREMFYA is a clear and colorless to light yellow solution that may contain small translucent particles. Do not use if the liquid contains large particles, is discolored, or is cloudy.

Storage of Diluted Solution:

- The diluted infusion solution may be kept at room temperature up to 25°C (77°F) for up to 10 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 10 hours after the dilution in the infusion bag.
- Do not freeze.
- Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

TREMFYA/TREMFYA PEN is a clear and colorless to light yellow solution.

Subcutaneous Injection

- Injection: 100 mg/mL in a single-dose One-Press patient-controlled injector.
- Injection: 200 mg/2 mL in a single-dose prefilled pen (TREMFYA PEN).
- Injection: 100 mg/mL in a single-dose prefilled syringe.
- Injection: 200 mg/2 mL in a single-dose prefilled syringe.

Intravenous Infusion

- Injection: 200 mg/20 mL (10 mg/mL) solution in a single-dose vial.

4 CONTRAINDICATIONS

TREMFYA is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipients [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with post market use of TREMFYA. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue TREMFYA and initiate appropriate therapy.

5.2 Infections

TREMFYA may increase the risk of infection. In clinical trials in subjects with plaque psoriasis, infections occurred in 23% of subjects in the TREMFYA group versus 21% of subjects in the placebo group through 16 weeks of treatment. Upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections occurred more frequently in the TREMFYA group than in the placebo group [see *Adverse Reactions (6.1)*]. The rate of serious infections for the TREMFYA group and the placebo group was $\leq 0.2\%$. A similar risk of infection was seen in placebo-controlled trials in subjects with psoriatic arthritis and ulcerative colitis. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing TREMFYA. Instruct patients to seek medical help if signs or symptoms of clinically important

chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TREMFYA until the infection resolves.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA. Initiate treatment of latent TB prior to administering TREMFYA. In clinical trials, 105 subjects with plaque psoriasis, 71 subjects with psoriatic arthritis, and 31 subjects with ulcerative colitis with latent TB who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop active TB. Monitor patients for signs and symptoms of active TB during and after TREMFYA treatment. Consider anti-TB therapy prior to initiating TREMFYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Do not administer TREMFYA to patients with active TB infection.

5.4 Immunizations

Avoid use of live vaccines in patients treated with TREMFYA. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with TREMFYA, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [*see Contraindications (4) and Warnings and Precautions (5.1)*]
- Infections [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plaque Psoriasis

In clinical trials, a total of 1823 subjects with moderate-to-severe plaque psoriasis received TREMFYA. Of these, 1393 subjects were exposed to TREMFYA for at least 6 months and 728 subjects were exposed for at least 1 year.

Data from two placebo- and active-controlled trials (PsO1 and PsO2) in 1441 subjects (mean age 44 years; 70% males; 82% white) were pooled to evaluate the safety of TREMFYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 8 weeks).

Weeks 0 to 16:

In the 16-week placebo-controlled period of the pooled clinical trials (PsO1 and PsO2), adverse events occurred in 49% of subjects in the TREMFYA group compared to 47% of subjects in the placebo group and 49% of subjects in the U.S. licensed adalimumab group. Serious adverse events occurred in 1.9% of subjects in the TREMFYA group (6.3 events per 100 subject-years of follow-up) compared to 1.4% of subjects in the placebo group (4.7 events per 100 subject-years of follow-up), and in 2.6% of subjects in U.S. licensed adalimumab group (9.9 events per 100 subject-years of follow-up).

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA group than in the placebo group during the 16-week placebo-controlled period.

Table 1: Adverse Reactions Occurring in $\geq 1\%$ of Subjects through Week 16 in PsO1 and PsO2

	TREMFYA^a 100 mg N=823 n (%)	Adalimumab^b N=196 n (%)	Placebo N=422 n (%)
Upper respiratory infections ^c	118 (14.3)	21 (10.7)	54 (12.8)
Headache ^d	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions ^e	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis ^f	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections ^g	9 (1.1)	0	0
Herpes simplex infections ^h	9 (1.1)	0	2 (0.5)

^a Subjects receiving 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter

^b U.S. licensed adalimumab

^c Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.

^d Headache includes headache and tension headache.

^e Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.

^f Gastroenteritis includes gastroenteritis and viral gastroenteritis.

^g Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.

^h Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

Adverse reactions that occurred in $< 1\%$ but $> 0.1\%$ of subjects in the TREMFYA group and at a higher rate than in the placebo group through Week 16 in PsO1 and PsO2 were migraine, candida infections, and urticaria.

Specific Adverse Reactions

Infections

Infections occurred in 23% of subjects in the TREMFYA group compared to 21% of subjects in the placebo group.

The most common ($\geq 1\%$) infections were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of TREMFYA.

Elevated Liver Enzymes

Elevated liver enzymes were reported more frequently in the TREMFYA group (2.6%) than in the placebo group (1.9%). Of the 21 subjects who were reported to have elevated liver enzymes in the TREMFYA group, all events except one were mild to moderate in severity and none of the events led to discontinuation of TREMFYA.

Safety through Week 48

Through Week 48, no new adverse reactions were identified with TREMFYA use and the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment.

Psoriatic Arthritis

TREMFYA was studied in two placebo-controlled trials in subjects with psoriatic arthritis (748 subjects on TREMFYA and 372 subjects on placebo). Of the 748 subjects who received TREMFYA, 375 subjects received TREMFYA 100 mg at Week 0, Week 4, and every 8 weeks thereafter and 373 subjects received TREMFYA 100 mg every 4 weeks. The overall safety profile observed in subjects with psoriatic arthritis treated with TREMFYA is generally consistent with the safety profile in subjects with plaque psoriasis with the addition of

bronchitis and neutrophil count decreased. In the 24-week placebo-controlled period, combined across the two studies, bronchitis occurred in 1.6% of subjects in the TREMFYA q8w group and 2.9% of subjects in the TREMFYA q4w group compared to 1.1% of subjects in the placebo group. Neutrophil count decreased occurred in 0.3% of subjects in the TREMFYA q8w and 1.6% of subjects in the TREMFYA q4w group compared to 0% of subjects in the placebo group. The majority of events of neutrophil count decreased were mild, transient, not associated with infection and did not lead to discontinuation.

Ulcerative Colitis

TREMFYA was studied up to 12 weeks in subjects with moderately to severely active ulcerative colitis in a randomized, double-blind, placebo-controlled induction study (UC1) and a randomized, double-blind, placebo controlled, induction dose-finding study (UC3; NCT04033445). Long-term safety up to 44 weeks was evaluated in subjects who responded to induction therapy in a randomized, double-blind, placebo-controlled maintenance study (UC2) [see *Clinical Studies (14.3)*].

In the induction studies (UC1 and UC3), 522 subjects received at least one dose of the TREMFYA intravenous induction regimen (i.e., 200 mg at Week 0, Week 4, and Week 8). Clinical response was defined as a decrease in modified Mayo score (mMS) of $\geq 30\%$ and ≥ 2 points from baseline with either a ≥ 1 decrease from baseline in rectal bleeding subscore (RBS) or RBS of 0 or 1. In the maintenance study (UC2), subjects who achieved clinical response after 12 weeks of TREMFYA intravenous induction treatment were randomized and received either TREMFYA 100 mg every 8 weeks (with the first dose given at Week 4 of UC2) or TREMFYA 200 mg every 4 weeks (with the first dose given at Week 0 of UC2), by subcutaneous (SC) injection for up to an additional 44 weeks.

Respiratory tract infections occurred in $\geq 2\%$ of subjects treated with TREMFYA and at a higher rate than placebo (8.8% TREMFYA-treated subjects vs. 7.3% placebo-treated subjects) through Week 12 in the induction studies (UC1 and UC3). Respiratory tract infections included COVID-19, influenza, nasopharyngitis, respiratory tract infection, upper respiratory tract infection, and viral respiratory tract infection.

Adverse reactions that occurred in $\geq 3\%$ of subjects treated with TREMFYA and at a higher rate than placebo through Week 44 in the maintenance study (UC2) are shown in Table 2.

Table 2: Adverse Reactions Occurring in $\geq 3\%$ of Subjects through Week 44 in UC2

	TREMFYA^a 100 mg Subcutaneous Injection N=186 n (%)	TREMFYA^a 200 mg Subcutaneous Injection N=190 n (%)	Placebo N=192 n (%)
Injection site reactions ^b	2 (1.1)	17 (8.9) ^c	2 (1)
Arthralgia	8 (4.3)	15 (7.9)	13 (6.8)
Upper respiratory tract infection	6 (3.2)	13 (6.8)	8 (4.2)

^a Subjects receiving TREMFYA 100 mg at Week 16 and every 8 weeks thereafter or TREMFYA 200 mg at Week 12 and every 4 weeks thereafter.

^b Injection site reactions include administration site pain, injection site hematoma, injection site hemorrhage, injection site hypersensitivity, injection site erythema, injection site pain, injection site pruritus, injection site rash, injection site reaction, and injection site urticaria.

^c TREMFYA 200 mg was administered as two 100 mg injections.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval of TREMFYA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to TREMFYA exposure.

Immune system disorders: Hypersensitivity, including anaphylaxis [see *Warnings and Precautions (5.1)*]

Skin and subcutaneous tissue disorders: Rash [see Warnings and Precautions (5.1)]

7 DRUG INTERACTIONS

7.1 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , interferon) during chronic inflammation.

Results from an exploratory drug-drug interaction study in subjects with moderate-to-severe plaque psoriasis suggested a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 but the interaction potential cannot be ruled out for drugs metabolized by CYP2D6. However, the results were highly variable because of the limited number of subjects in the study.

Upon initiation of TREMFYA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to TREMFYA during pregnancy. Patients should be encouraged to enroll in the registry by visiting www.mohtertobaby.org/ongoing-study/tremfya-guselkumab, by calling 1-877-311-8972, or emailing MotherToBaby@health.ucsd.edu.

Risk Summary

Available data from literature, post-marketing reports, and ongoing pregnancy registry with TREMFYA use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, TREMFYA may be transmitted from the mother to the developing fetus.

In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 18 times the exposure (AUC) in humans administered 200 mg intravenously and 32 times the exposure (AUC) to the 200 mg dose given subcutaneously. Neonatal deaths in monkeys were observed at 4 to 18 times the exposure (AUC) in humans administered 200 mg intravenously and 7 to 32 times the exposure (AUC) to the 200 mg dose given subcutaneously (*see Data*). The clinical significance of these nonclinical findings is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab from the beginning of organogenesis to parturition at a dose (50 mg/kg) resulting in exposures (AUC) 18 times the exposure in humans administered 200 mg intravenously and 32 times the human exposure at 200 mg given subcutaneously. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (4 times the exposure (AUC) in humans administered 200 mg intravenously and 7 times the exposure (AUC) at 200 mg given subcutaneously) and three monkeys administered guselkumab at 50 mg/kg/week (18 times the exposure (AUC) in humans administered 200 mg intravenously and 32 times the exposure (AUC) following a 200 mg subcutaneous dose). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and the extent of systemic exposure in the breastfed infant to guselkumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA and any potential adverse effects on the breastfed infant from TREMFYA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of TREMFYA in pediatric patients (less than 18 years of age) have not been established.

8.5 Geriatric Use

Of the 4303 subjects with plaque psoriasis, psoriatic arthritis, or ulcerative colitis exposed to TREMFYA, a total of 240 subjects were 65 years or older, and 23 subjects were 75 years or older. Clinical studies of TREMFYA, within each indication, did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of guselkumab were observed based on age [*see Clinical Pharmacology (12.3)*].

11 DESCRIPTION

Guselkumab, an interleukin-23 antagonist, is a human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody. Guselkumab is produced in a mammalian cell line using recombinant DNA technology and has an approximate molecular weight of approximately 147 kDa.

TREMFYA[®] (guselkumab) injection is a sterile, preservative free, clear, and colorless to light yellow solution.

TREMFYA for Subcutaneous Injection

Available as a 100 mg/mL solution in a 1 mL or 2 mL glass prefilled syringe, in a 2 mL prefilled pen, or in a 1 mL One-Press patient-controlled injector for subcutaneous use.

Each TREMFYA 1 mL prefilled syringe or One-Press patient-controlled injector delivers 100 mg guselkumab, L-histidine (0.6 mg), L-histidine monohydrochloride monohydrate (1.5 mg), polysorbate 80 (0.5 mg), sucrose (79 mg) and water for injection at pH 5.8.

Each TREMFYA 2 mL prefilled syringe or prefilled pen (TREMFYA PEN) delivers 200 mg guselkumab, L-histidine (1.2 mg), L-histidine monohydrochloride monohydrate (3 mg), polysorbate 80 (1 mg), sucrose (158 mg) and water for injection at pH 5.8.

TREMFYA for Intravenous Infusion

Available as 10 mg/mL solution in a 20 mL single-dose vial for intravenous use.

Each TREMFYA 20 mL vial delivers 200 mg guselkumab, EDTA disodium dihydrate (0.4 mg), L-histidine (11.3 mg), L-histidine monohydrochloride monohydrate (26.6 mg), L-methionine (8 mg), polysorbate 80 (10 mg), sucrose (1700 mg) and water for injection at pH 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guselkumab is a human monoclonal IgG1 λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

12.2 Pharmacodynamics

In evaluated subjects with plaque psoriasis, guselkumab reduced serum levels of IL-17A, IL-17F and IL-22 relative to pre-treatment levels based on exploratory analyses of the pharmacodynamic markers.

In evaluated subjects with psoriatic arthritis, serum levels of acute phase proteins C-reactive protein, serum amyloid A and IL-6, and Th17 effector cytokines IL-17A, IL-17F and IL-22 were elevated at baseline. Serum levels of these proteins measured at Week 4 and Week 24 were decreased compared to baseline following guselkumab treatment at Week 0, Week 4 and every 8 weeks thereafter.

The relationship between these pharmacodynamic markers and the mechanism(s) by which guselkumab exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Guselkumab exhibited linear pharmacokinetics in healthy subjects and subjects with plaque psoriasis following subcutaneous injections. In subjects with plaque psoriasis, following subcutaneous administration of 100 mg of TREMFYA at Weeks 0 and 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.

The pharmacokinetics of guselkumab in subjects with psoriatic arthritis was similar to that in subjects with plaque psoriasis. Following subcutaneous administration of 100 mg of TREMFYA at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.

Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks or 200 mg TREMFYA every 4 weeks in subjects with ulcerative colitis, mean steady-state trough serum guselkumab concentrations were approximately 1.4 mcg/mL and 10.7 mcg/mL, respectively.

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean ($\pm$ SD) maximum serum concentration of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose. The absolute

bioavailability of guselkumab following a single 100 mg subcutaneous injection was estimated to be approximately 49% in healthy subjects.

Following the recommended intravenous induction dose regimen of TREMFYA 200 mg at Weeks 0, 4, and 8, mean ($\pm$ SD) peak serum guselkumab concentration at Week 8 was 68.3 ± 17.3 mcg/mL in subjects with ulcerative colitis.

Distribution

In subjects with plaque psoriasis, apparent volume of distribution was 13.5 L. In subjects with ulcerative colitis, apparent volume of distribution at steady-state was 10.1 L.

Elimination

Apparent clearance in subjects with plaque psoriasis was 0.516 L/day. Mean half-life of guselkumab was approximately 15 to 18 days in subjects with plaque psoriasis across trials.

The apparent clearance in subjects with ulcerative colitis was 0.531 L/day. Mean half-life of guselkumab was approximately 17 days in subjects with ulcerative colitis.

Metabolism

The exact pathway through which guselkumab is metabolized has not been characterized. As a human IgG monoclonal antibody, guselkumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Specific Populations

No apparent differences in clearance were observed in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly subjects. Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted. No specific trials have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of guselkumab.

Drug Interactions

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and conventional DMARDs such as methotrexate (MTX), azathioprine (AZA), and 6-mercaptopurine (6-MP), did not affect the clearance of guselkumab.

Cytochrome P450 Substrates

The effects of guselkumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), dextromethorphan (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in an exploratory study with 6 to 12 evaluable subjects with moderate-to-severe plaque psoriasis. Changes in AUC_{inf} of midazolam, S-warfarin, omeprazole, and caffeine after a single dose of guselkumab were not clinically relevant. For dextromethorphan, changes in AUC_{inf} after guselkumab were not clinically relevant in 9 out of 10 subjects; however, a 2.9-fold change in AUC_{inf} was observed in one individual [see *Drug Interactions* (7.1)].

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies

in the studies described below with the incidence of anti-drug antibodies in other studies, including those of guselkumab or of other guselkumab products.

Plaque Psoriasis

Up to Week 52, approximately 6% of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing antibodies. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subjects who experienced loss of efficacy after developing high antibody titers. Up to Week 156, approximately 9% of subjects treated with TREMFYA developed antidrug antibodies and of these subjects approximately 6% were classified as neutralizing antibodies. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions.

Psoriatic Arthritis

Up to Week 24, 2% (n=15) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 1 had antibodies that were classified as neutralizing antibodies. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics, efficacy and safety of guselkumab.

Ulcerative Colitis

Up to Week 56 in Studies UC1, UC2 and UC3, 11% (n=48) of subjects treated with TREMFYA at the recommended dosage developed antidrug antibodies. Of these subjects who tested positive for anti-guselkumab antibodies and were evaluable for neutralizing antibodies, 16% (n=6) had antibodies that were classified as neutralizing antibodies. Most of the subjects who were positive for antibodies to guselkumab had low titers. Two subjects with the highest antibody titers exhibited low trough levels of guselkumab. There was no identified clinically significant effect of antidrug antibodies on injection site reactions, or effectiveness of guselkumab, over the treatment duration of 56 weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TREMFYA.

No effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 25 mg/kg twice weekly (6 times the exposure (AUC) in humans administered 200 mg intravenously and 10 times the exposure (AUC) at the 200 mg subcutaneous dose).

No effects on fertility parameters were observed after female guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly (12 times the exposure (AUC) in humans administered 200 mg intravenously and 21 times the exposure (AUC) at the 200 mg subcutaneous dose).

14 CLINICAL STUDIES

14.1 Plaque Psoriasis

Four multicenter, randomized, double-blind trials (PsO1 [NCT02207231], PsO2 [NCT02207244], PsO3 [NCT02203032], and PsO4 [NCT02905331]) enrolled subjects 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had an Investigator's Global Assessment (IGA) score of ≥ 3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥ 12 , and a minimum affected body surface area (BSA) of 10%. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

Trials PsO1 and PsO2

In PsO1 and PsO2, 1443 subjects were randomized to either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter) administered with a prefilled syringe, placebo or U.S. licensed adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter).

Both trials assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an IGA score of 0 (“cleared”) or 1 (“minimal”);
- the proportion of subjects who achieved at least a 90% reduction from baseline in the PASI composite score (PASI 90).

Comparisons between TREMFYA and U.S. licensed adalimumab were secondary endpoints at the following time points:

- at Week 16 (PsO1 and PsO2), the proportions of subjects who achieved an IGA score of 0 or 1, a PASI 90, and a PASI 75 response;
- at Week 24 (PsO1 and PsO2), and at Week 48 (PsO1), the proportions of subjects achieving an IGA score of 0, an IGA score of 0 or 1, and a PASI 90 response.

Other evaluated outcomes included improvement in psoriasis symptoms assessed on the Psoriasis Symptoms and Signs Diary (PSSD) and improvements in psoriasis of the scalp at Week 16.

In both trials, subjects were predominantly men and white, with a mean age of 44 years and a mean weight of 90 kg. At baseline, subjects had a median affected BSA of approximately 21%, a median PASI score of 19, and 18% had a history of psoriatic arthritis. Approximately 24% of subjects had an IGA score of severe. In both trials, 23% had received prior biologic systemic therapy.

Clinical Response

Table 3 presents the efficacy results at Week 16 in PsO1 and PsO2.

Table 3: Efficacy Results at Week 16 in Adults with Plaque Psoriasis (NRI^a)

Endpoint	PsO1		PsO2	
	TREMFYA (N=329) n (%)	Placebo (N=174) n (%)	TREMFYA (N=496) n (%)	Placebo (N=248) n (%)
IGA response of 0/1 ^{b, c}	280 (85)	12 (7)	417 (84)	21 (8)
PASI 90 response ^b	241 (73)	5 (3)	347 (70)	6 (2)

^a NRI = Non-Responder Imputation

^b Co-Primary Endpoints

^c IGA response of 0 (cleared) or 1 (minimal)

Table 4 presents the results of an analysis of all the North America sites (i.e., U.S. and Canada), demonstrating superiority of TREMFYA to U.S. licensed adalimumab.

Table 4: Efficacy Results in Adults with Plaque Psoriasis (NRI^a)

Endpoint	PsO1		PsO2	
	TREMFYA (N=115) ^b n (%)	Adalimumab ^c (N=115) ^b n (%)	TREMFYA (N=160) ^b n (%)	Adalimumab ^c (N=81) ^b n (%)
IGA response of 0/1 (cleared or minimal)				
Week 16	97 (84)	70 (61)	119 (74)	50 (62)
Week 24	97 (84)	62 (54)	119 (74)	46 (57)
Week 48	91 (79)	62 (54)	NA	NA
IGA response of 0 (cleared)				
Week 24	61 (53)	27 (23)	76 (48)	23 (28)
Week 48	54 (47)	28 (24)	NA	NA
PASI 75 response				
Week 16	105 (91)	80 (70)	132 (83)	51 (63)
PASI 90 response				
Week 16	84 (73)	47 (41)	102 (64)	34 (42)
Week 24	92 (80)	51 (44)	113 (71)	41 (51)
Week 48	84 (73)	53 (46)	NA	NA

^a NRI = Non-Responder Imputation

^b Subjects from sites in the United States and Canada

^c U.S. licensed adalimumab

An improvement was seen in psoriasis involving the scalp in subjects randomized to TREMFYA compared to placebo at Week 16.

Examination of age, gender, race, body weight, and previous treatment with systemic or biologic agents did not identify differences in response to TREMFYA among these subgroups.

Maintenance and Durability of Response

To evaluate maintenance and durability of response (PsO2), subjects randomized to TREMFYA at Week 0 and who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with TREMFYA every 8 weeks or be withdrawn from therapy (i.e., receive placebo).

At Week 48, 89% of subjects who continued on TREMFYA maintained PASI 90 compared to 37% of subjects who were re-randomized to placebo and withdrawn from TREMFYA. For responders at Week 28 who were re-randomized to placebo and withdrawn from TREMFYA, the median time to loss of PASI 90 was approximately 15 weeks.

Patient Reported Outcomes

Greater improvements in symptoms of psoriasis (itch, pain, stinging, burning and skin tightness) at Week 16 in TREMFYA compared to placebo were observed in both trials based on the Psoriasis Symptoms and Signs Diary (PSSD). Greater proportions of subjects on TREMFYA compared to U.S. licensed adalimumab achieved a PSSD symptom score of 0 (symptom-free) at Week 24 in both trials.

Trial PsO3

PsO3 [NCT02203032] evaluated the efficacy of 24 weeks of treatment with TREMFYA in subjects (N=268) who had not achieved an adequate response, defined as IGA ≥ 2 at Week 16 after initial treatment with U.S. licensed ustekinumab (dosed 45 mg or 90 mg according to the subject's baseline weight at Week 0 and Week 4). These subjects were randomized to either continue with U.S. licensed ustekinumab treatment every 12 weeks or switch to TREMFYA 100 mg at Weeks 16, 20, and every 8 weeks thereafter. Baseline characteristics for randomized subjects were similar to those observed in PsO1 and PsO2.

In subjects with an inadequate response (IGA ≥ 2 at Week 16 to U.S. licensed ustekinumab), greater proportions of subjects on TREMFYA compared to U.S. licensed ustekinumab achieved an IGA score of 0 or 1 with a ≥ 2 grade improvement at Week 28 (31% vs. 14%, respectively; 12 weeks after randomization).

Trial PsO4

PsO4 [NCT02905331] evaluated the efficacy, safety, and pharmacokinetics of TREMFYA administered with the One-Press injector. In this study, 78 subjects were randomized to receive either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter) [N=62], or placebo [N=16]. Baseline characteristics for subjects were comparable to those observed in PsO1 and PsO2. The co-primary endpoints were the same as those for PsO1 and PsO2. Secondary endpoints included the proportion of subjects who achieved an IGA score of 0 at Week 16 and the proportion of subjects who achieved a PASI 100 response at Week 16.

A greater proportion of subjects in the guselkumab group achieved an IGA score of 0 or 1 or a PASI 90 response at Week 16 (81% and 76%, respectively) than in the placebo group (0% for both endpoints). The proportion of subjects who achieved an IGA score of 0 at Week 16 was higher in the guselkumab group compared to the placebo group (56% vs. 0%). The proportion of subjects who achieved a PASI 100 response at Week 16 was higher in the guselkumab group compared to the placebo group (50% vs. 0%).

14.2 Psoriatic Arthritis

The safety and efficacy of TREMFYA were assessed in 1120 subjects in 2 randomized, double-blind, placebo-controlled trials (PsA1 [NCT03162796] and PsA2 [NCT03158285]) in adult subjects with active psoriatic arthritis (PsA) (≥ 3 swollen joints, ≥ 3 tender joints, and a C-reactive protein (CRP) level of ≥ 0.3 mg/dL in PsA1 and ≥ 5 swollen joints, ≥ 5 tender joints, and a CRP level of ≥ 0.6 mg/dL in PsA2) who had inadequate response to standard therapies (e.g., conventional DMARDs [cDMARDs]), apremilast, or nonsteroidal anti-inflammatory drugs [NSAIDs]). Subjects in these trials had a diagnosis of PsA for at least 6 months based on the Classification criteria for Psoriatic Arthritis (CASPAR) and a median duration of PsA of 4 years at baseline.

In PsA1 approximately 31% of subjects had been previously treated with up to 2 anti-tumor necrosis factor alpha (anti-TNF α) agents whereas in PsA2 all subjects were biologic naïve. Approximately 58% of subjects from both trials had concomitant methotrexate (MTX) use. Subjects with different subtypes of PsA were enrolled in both trials, including polyarticular arthritis with the absence of rheumatoid nodules (40%), spondylitis with peripheral arthritis (30%), asymmetric peripheral arthritis (23%), distal interphalangeal involvement (7%) and arthritis mutilans (1%). At baseline, over 65% and 42% of the subjects had enthesitis and dactylitis, respectively and 79% had $\geq 3\%$ body surface area (BSA) psoriasis skin involvement.

PsA1 evaluated 381 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and every 8 weeks (q8w) thereafter, or TREMFYA 100 mg SC every 4 weeks (q4w). PsA2 evaluated 739 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and q8w thereafter, or TREMFYA 100 mg SC q4w. The primary endpoint in both trials was the percentage of subjects achieving an ACR20 response at Week 24.

Clinical Response

In both trials, subjects treated with TREMFYA 100 mg q8w demonstrated a greater clinical response including ACR20, compared to placebo at Week 24 (Tables 5 and 6). Similar responses were seen regardless of prior anti-TNF α exposure in PsA1, and in both trials similar responses were seen regardless of concomitant cDMARD use, previous treatment with cDMARDs, gender and body weight.

Table 5: Percent of Subjects with ACR Responses in PsA1

	Placebo (N=126)	TREMIFYA 100 mg q8w (N=127)	
	Response Rate	Response Rate	Difference from Placebo (95% CI)
ACR 20 response^a			
Week 16	25%	52%	27 (15, 38)
Week 24	22%	52%	30 (19, 41)
ACR 50 response^a			
Week 16	13%	23%	10 (1, 19)
Week 24	9%	30%	21 (12, 31)
ACR 70 response^a			
Week 16	6%	8%	2 (-4, 8)
Week 24	6%	12%	6 (-0.3, 13)

^a Subjects with missing data at a visit were imputed as non-responders at that visit. Subjects who met escape criteria (less than 5% improvement in both tender and swollen joint counts) at Week 16 were allowed to initiate or increase the dose of the permitted concomitant medication and remained on the randomized group. Subjects who initiated or increased the dose of non-biologic DMARD or oral corticosteroids over baseline, discontinued study/study medication or initiated protocol prohibited medications/therapies for PsA prior to a visit were considered non-responders at that visit.

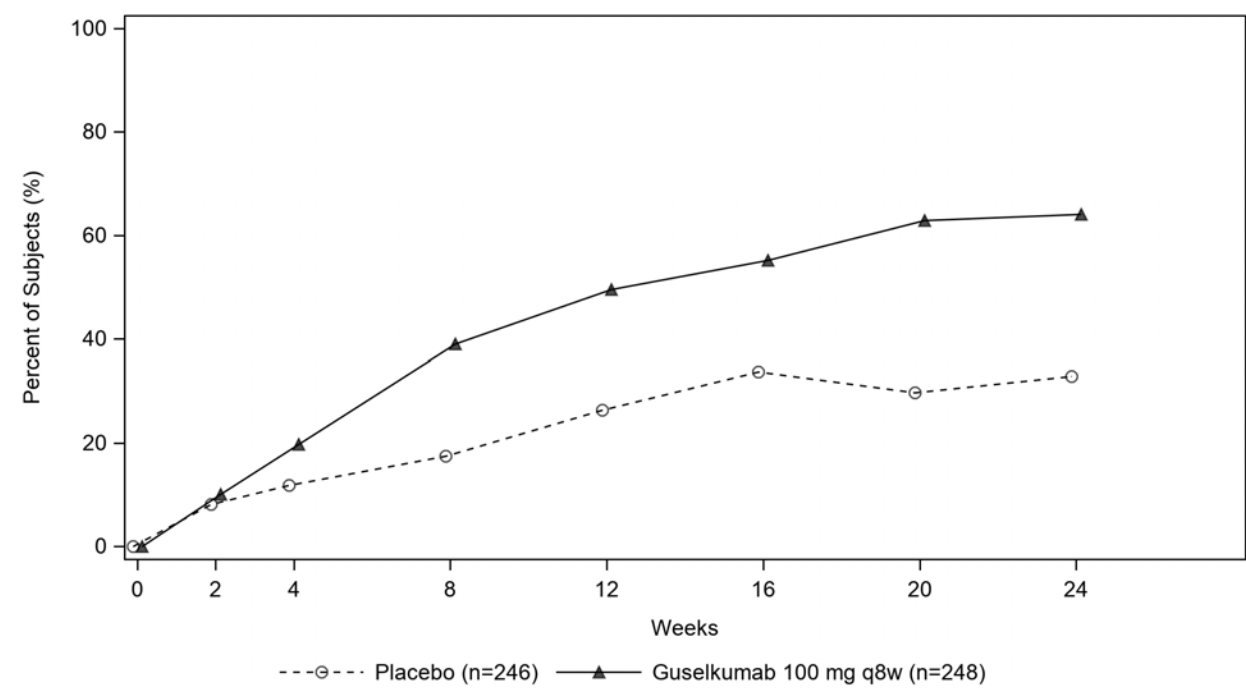
Table 6: Percent of Subjects with ACR Responses in PsA2

	Placebo (N=246)	TREMIFYA 100 mg q8w (N=248)	
	Response Rate	Response Rate	Difference from Placebo (95% CI)
ACR 20 response^a			
Week 16	34%	55%	22 (13, 30)
Week 24	33%	64%	31 (23, 40)
ACR 50 response^a			
Week 16	9%	29%	19 (13, 26)
Week 24	14%	32%	17 (10, 24)
ACR 70 response^a			
Week 16	1%	14%	13 (9, 17)
Week 24	4%	19%	15 (9, 20)

^a Subjects with missing data at a visit were imputed as non-responders at that visit. Subjects who met escape criteria (less than 5% improvement in both tender and swollen joint counts) at Week 16 were allowed to initiate or increase the dose of the permitted concomitant medication and remained on the randomized group. Subjects who initiated or increased the dose of non-biologic DMARD or oral corticosteroids over baseline, discontinued study/study medication or initiated protocol prohibited medications/therapies for PsA prior to a visit were considered non-responders at that visit.

The percentage of subjects achieving ACR20 response in PsA2 by visit is shown in Figure 1.

Figure 1: Subjects Achieving ACR 20 Response by Visit Through Week 24 in PsA2



The results of the components of the ACR response criteria are shown in Table 7.

Table 7: Mean change (SD^a) from Baseline in ACR Component Scores at Week 16 and 24 based on Observed Data

	PsA1		PsA2	
	Placebo (N=126)	TREMFYA 100 mg q8w (N=127)	Placebo N=246	TREMFYA 100 mg q8w (N=248)
No. of Swollen Joints				
Baseline	10.1 (7.1)	10.9 (9.3)	12.3 (6.9)	11.7 (6.8)
Mean change at Week 16	-4.2 (7.0)	-7.3 (7.0)	-5.8 (7.1)	-7.2 (6.0)
Mean change at Week 24	-5.1 (6.9)	-7.3 (8.0)	-6.4 (7.2)	-8.1 (6.1)
No. of Tender Joints				
Baseline	19.8 (14.4)	20.2 (14.5)	21.6 (13.1)	19.8 (11.9)
Mean change at Week 16	-4.5 (10.8)	-10.2 (10.4)	-6.8 (10.5)	-9.0 (9.4)
Mean change at Week 24	-6.8 (13.0)	-10.5 (12.0)	-7.3 (11.2)	-10.4 (9.5)
Patient's Assessment of Pain^b				
Baseline	5.8 (2.2)	6.0 (2.1)	6.3 (1.8)	6.3 (2.0)
Mean change at Week 16	-0.8 (2.3)	-1.7 (2.4)	-0.9 (2.3)	-2.2 (2.5)
Mean change at Week 24	-0.7 (2.4)	-2.2 (2.6)	-1.1 (2.4)	-2.5 (2.5)
Patient Global Assessment^b				
Baseline	6.1 (2.2)	6.5 (2.0)	6.5 (1.8)	6.5 (1.9)
Mean change at Week 16	-1.0 (2.3)	-2.0 (2.6)	-1.0 (2.3)	-2.3 (2.6)
Mean change at Week 24	-0.9 (2.5)	-2.5 (2.7)	-1.2 (2.6)	-2.5 (2.5)
Physician Global Assessment^b				
Baseline	6.3 (1.7)	6.2 (1.7)	6.7 (1.5)	6.6 (1.6)
Mean change at Week 16	-1.9 (2.2)	-2.9 (2.4)	-2.1 (2.2)	-3.5 (2.3)
Mean change at Week 24	-2.2 (2.3)	-3.5 (2.4)	-2.5 (2.3)	-3.8 (2.3)
Disability Index (HAQ-DI)^c				
Baseline	1.2 (0.7)	1.2 (0.6)	1.3 (0.6)	1.3 (0.6)
Mean change at Week 16	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.5)	-0.3 (0.5)
Mean change at Week 24	-0.1 (0.5)	-0.3 (0.6)	-0.2 (0.5)	-0.4 (0.5)
CRP (mg/dL)				
Baseline	1.4 (1.9)	1.6 (2.4)	2.1 (2.7)	2.0 (2.4)
Mean change at Week 16	-0.2 (1.5)	-0.6 (2.2)	-0.6 (2.5)	-1.0 (2.2)
Mean change at Week 24	-0.0 (2.8)	-0.7 (2.1)	-0.5 (2.5)	-1.1 (2.2)

^a SD= standard deviation

^b Assessment based on Visual Analog Scale (cm) with the left end indicating “no pain” (for patient’s assessment of pain), “very well” (for patient global assessment), or “no arthritis activity” (for physician global assessment) and the right end indicating “the worst possible pain” (for patient assessment of pain), “poor” (for patient global assessment), or “extremely active arthritis (for physician global assessment).

^c Disability Index of the Health Assessment Questionnaire; 0 = no difficulty to 3 = inability to perform, measures the patient’s ability to perform the following: dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living

Treatment with TREMFYA resulted in an improvement in the skin manifestations of psoriasis in subjects with PsA.

Treatment with TREMFYA resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis.

Physical Function

TREMFYA treated subjects in the TREMFYA 100 mg q8w group in both PsA1 and PsA2 showed greater mean improvement from baseline in physical function compared to subjects treated with placebo as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Weeks 16 and 24. In both studies, the proportion of HAQ-DI responders (≥ 0.35 improvement in HAQ-DI score) was greater in the TREMFYA q8w dose group compared to placebo at Weeks 16 and 24.

Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). At Week 24, subjects in the TREMFYA 100 mg q8w dose group in both PsA1 and PsA2 showed greater improvement from baseline in the SF-36 physical component summary (PCS) compared with placebo. There was not a statistically significant improvement observed in the SF-36 MCS. At Week 24, there was numerical improvement in the physical

functioning, role-physical, bodily-pain, general health, social-functioning and vitality domains but not in the role-emotional and mental health domains. Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Studies PsA1 and PsA2. Treatment with TREMFYA resulted in improvement in fatigue as measured by FACIT-F.

14.3 Ulcerative Colitis

Induction Trial: UC1

In the 12-week induction study (UC1; NCT04033445), 701 subjects with moderately to severely active ulcerative colitis were randomized 3:2 to receive either TREMFYA 200 mg or placebo by intravenous infusion at Week 0, Week 4, and Week 8. Disease activity was assessed by the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally reviewed endoscopy (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, friability, and/or erosions; an ES of 3 was defined by spontaneous bleeding and ulceration. Enrolled subjects with a mMS between 5 and 9 and an ES of 2 or 3 were classified as having moderately to severely active ulcerative colitis. Subjects with inadequate response, loss of response, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine), biologic therapy (TNF blockers, vedolizumab), and/or Janus kinase (JAK) inhibitors were enrolled.

At baseline in UC1, the median mMS was 7, 64% of subjects had severely active disease ($mMS \geq 7$), and 68% of subjects had an ES of 3. In UC1, 49% of subjects had previously failed (inadequate response, loss of response, or intolerance) treatment with at least one biologic therapy and/or JAK inhibitor, 48% were biologic and JAK inhibitor naïve, and 3% had previously received but not failed a biologic or JAK inhibitor. The median age was 39 years (ranging from 18 to 79 years); 43% were female; and 72% identified as White, 21% as Asian, 1% as Black or African American, <1% as American Indian or Alaskan Native, and <1% as multiple racial groups.

Enrolled subjects were permitted to use stable doses of oral aminosalicylates, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 72% of subjects were receiving aminosalicylates, 21% of subjects were receiving immunomodulators, and 43% of subjects were receiving corticosteroids. Concomitant biologic therapies or JAK inhibitors were not permitted.

In UC1, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included endoscopic improvement, clinical response, and histologic endoscopic mucosal improvement (see Table 8).

Table 8: Proportion of Subjects with Ulcerative Colitis Meeting Efficacy Endpoints at Week 12 in UC1

Endpoint	Placebo	TREMFYA 200 mg Intravenous Infusion ^a	Treatment Difference (95% CI)
Clinical remission^b			
Total Population	N=280 8%	N=421 23%	15% (10%, 20%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 4%	N=208 13%	
Without prior biologic or JAK inhibitor failure ^e	N=144 12%	N=213 32%	
Endoscopic improvement^f			
Total Population	N=280 11%	N=421 27%	16% (10%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 5%	N=208 15%	
Without prior biologic or JAK inhibitor failure ^e	N=144 17%	N=213 38%	
Clinical response^g			
Total Population	N=280 28%	N=421 62%	34% (27%, 41%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 20%	N=208 51%	
Without prior biologic or JAK inhibitor failure ^e	N=144 35%	N=213 71%	
Histologic endoscopic mucosal improvement (HEMI)^h			
Total Population	N=280 8%	N=421 24%	16% (11%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 4%	N=208 13%	
Without prior biologic or JAK inhibitor failure ^e	N=144 10%	N=213 33%	

^a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8

^b A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability

^c p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method (adjusted for stratification factors: biologic and/or JAK-inhibitor failure status and concomitant use of corticosteroids at baseline)

^d Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis

^e Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 7 subjects in the placebo group and 11 subjects in the TREMFYA group were previously exposed to, but did not fail, a biologic or JAK inhibitor

^f An endoscopy subscore of 0 or 1 with no friability

^g Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

^h An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Study UC1 was not designed to evaluate the relationship of histologic endoscopic mucosal improvement at Week 12 to disease progression and long-term outcomes.

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 4 in subjects treated with TREMFYA compared to placebo.

Endoscopic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. At Week 12 of UC1, a greater proportion of subjects treated with TREMFYA compared to placebo-treated subjects achieved endoscopic remission (15% vs 5%).

Fatigue Response

In UC1, subjects treated with TREMFYA experienced a clinically meaningful improvement in fatigue, assessed by the PROMIS-Fatigue Short form 7a, at Week 12, compared to placebo-treated subjects. The effect of TREMFYA to improve fatigue after 12 weeks of induction has not been established.

Maintenance Trial: UC2

The maintenance trial (UC2) evaluated 568 subjects who received one of two intravenous TREMFYA induction regimens, including the recommended 200 mg regimen, for 12 weeks in Studies UC1 or UC3 (induction dose-finding study) and demonstrated clinical response per mMS after 12 weeks. Subjects were re-randomized to receive a subcutaneous maintenance regimen of either TREMFYA 100 mg every 8 weeks, TREMFYA 200 mg every 4 weeks, or placebo for up to an additional 44 weeks.

In UC2, 42% of subjects had failed (inadequate response, loss of response, or intolerance) treatment with one or more biologics or JAK inhibitors.

The primary endpoint was clinical remission at Week 44 defined by mMS. Secondary endpoints included corticosteroid-free clinical remission, endoscopic improvement, histologic endoscopic mucosal improvement, all at Week 44 and maintenance of clinical remission at Week 44 in subjects who achieved clinical remission 12 weeks after intravenous TREMFYA induction treatment (see Table 9).

Table 9: Proportion of Subjects with Ulcerative Colitis Meeting Efficacy Endpoints at Week 44 in UC2

Endpoint	Placebo	TREMIFYA 100 mg Every 8 Weeks Subcutaneous Injection ^a	TREMIFYA 200 mg Every 4 Weeks Subcutaneous Injection ^b	Treatment Difference vs Placebo (95% CI)	
				TREMIFYA 100 mg	TREMIFYA 200 mg
Clinical remission ^c					
Total population ^d	N=190 19%	N=188 45%	N=190 50%	25% (16%, 34%) ^e	30% (21%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 59%		
Corticosteroid-free clinical remission ^h					
Total population ^d	N=190 18%	N=188 45%	N=190 49%	26% (17%, 34%) ^e	29% (20%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 7%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 57%		
Endoscopic improvement ⁱ					
Total population ^d	N=190 19%	N=188 49%	N=190 52%	30% (21%, 38%) ^e	31% (22%, 40%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 45%	N=88 42%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 52%	N=102 60%		
Histologic endoscopic mucosal improvement (HEMI) ^j					
Total population ^d	N=190 17%	N=188 44%	N=190 48%	26% (17%, 34%) ^e	30% (21%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 38%	N=88 39%		
Without prior biologic or JAK inhibitor failure ^g	N=115 23%	N=111 48%	N=102 56%		
Maintenance of Clinical Remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction					
Total population ^k	N=59 34%	N=66 61%	N=69 72%	26% (9%, 43%) ^l	38% (23%, 54%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=15 27%	N=20 60%	N=18 56%		
Without prior biologic or JAK inhibitor failure ^m	N=44 36%	N=46 61%	N=51 78%		

^a TREMFYA 100 mg as a subcutaneous injection every 8 weeks after the induction regimen^b TREMFYA 200 mg as a subcutaneous injection every 4 weeks after the induction regimen^c A stool frequency subscore of 0 or 1 and not increased from induction baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability^d Subjects who achieved clinical response 12 weeks following the intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3^e p<0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors^f Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis^g Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 7 subjects in the placebo group, 6 subjects in the TREMFYA 100 mg group, and 6 subjects in the TREMFYA 200mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor^h Not requiring any treatment with corticosteroids for at least 8 weeks prior to week 44 and also meeting the criteria for clinical remission at week 44ⁱ An endoscopy subscore of 0 or 1 with no friability

- ^j An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in $<5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)
- ^k Subjects who achieved clinical remission 12 weeks following intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3
- ^l $p < 0.01$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
- ^m Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 3 subjects in the placebo group, 3 subjects in the TREMFYA 100 mg group, and 3 subjects in the TREMFYA 200 mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor.

Study UC2 was not designed to evaluate the relationship of histologic endoscopic mucosal improvement at Week 44 to disease progression and long-term outcomes.

Endoscopic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. In UC2, greater proportions of subjects treated with TREMFYA 100 mg every 8 weeks or TREMFYA 200 mg every 4 weeks achieved endoscopic remission at Week 44 compared to placebo-treated subjects (35% and 34%, respectively, vs. 15%).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TREMFYA[®]/TREMFYA[®] PEN (guselkumab) injection is a clear and colorless to light yellow solution supplied as follows:

Subcutaneous Injection

- Carton of one 100 mg/mL single-dose One-Press patient-controlled injector (NDC: 57894-640-11)
- Carton of one 200 mg/2 mL single-dose prefilled pen (TREMFYA PEN) (NDC: 57894-651-02)
- Carton of one 100 mg/mL single-dose prefilled syringe with a 27G, half inch fixed needle assembled in a passive needle guard delivery system (NDC: 57894-640-01)
- Carton of one 200 mg/2 mL single-dose prefilled syringe with a 27G, half inch fixed needle assembled in a passive needle guard delivery system (NDC: 57894-651-22)

Intravenous Infusion

- Carton of one 200 mg/20 mL (10 mg/mL) single-dose vial (NDC: 57894-650-02)

16.2 Storage and Handling

TREMFYA is sterile and preservative-free. Discard any unused portion.

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F).
- Store in original carton until time of use.
- Protect from light until use.
- Do not freeze.
- Do not shake.
- Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (*Medication Guide and Instructions for Use*) before starting TREMFYA therapy, and each time the prescription is renewed, as there may be new information they need to know.

Hypersensitivity Reactions

Advise patients to discontinue TREMFYA and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [see *Warnings and Precautions* (5.1)].

Infections

Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection [see *Warnings and Precautions* (5.2)].

Immunizations

Advise patients treated with TREMFYA to avoid use of live vaccines [see *Warnings and Precautions* (5.4)].

Instruction on Injection Technique

Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique. Instruct patients who are self-administering to inject the full dose of TREMFYA/TREMFYA PEN [see *Medication Guide and Instructions for Use*].

Instruct patients or caregivers in the technique of proper needle and syringe disposal. Needles and syringes should be disposed of in a puncture-resistant container. Advise patients and caregivers not to reuse needles or syringes.

Remind patients if they forget to take their dose of TREMFYA/TREMFYA PEN to inject their dose as soon as they remember. They should then take their next dose at the appropriate scheduled time.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in patients exposed to TREMFYA during pregnancy [see *Use in Specific Populations* (8.1)].

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
US License No. 1864

For patent information: www.janssenpatents.com
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Medication Guide		
TREMFYA® (trem fye´ ah) (guselkumab) injection, for subcutaneous use	TREMFYA® (trem fye´ ah) PEN (guselkumab) injection, for subcutaneous use	TREMFYA® (trem fye´ ah) (guselkumab) injection, for intravenous use
What is the most important information I should know about TREMFYA? TREMFYA may cause serious side effects, including: • Serious allergic reactions. Stop using TREMFYA and get emergency medical help right away if you develop any of the following symptoms of a serious allergic reaction: ○ fainting, dizziness, feeling lightheaded (low blood pressure) ○ swelling of your face, eyelids, lips, mouth, tongue or throat ○ trouble breathing or throat tightness ○ chest tightness ○ skin rash, hives ○ itching • Infections. TREMFYA is a medicine that may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with TREMFYA and may treat you for TB before you begin treatment with TREMFYA if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with TREMFYA. Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including: ○ fever, sweats, or chills ○ cough ○ shortness of breath ○ blood in your phlegm (mucus) ○ muscle aches ○ warm, red, or painful skin or sores on your body different from your psoriasis ○ weight loss ○ diarrhea or stomach pain ○ burning when you urinate or urinating more often than normal See “What are the possible side effects of TREMFYA?” for more information about side effects.		
What is TREMFYA? TREMFYA is a prescription medicine used to treat adults: • with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet or UV light) • with active psoriatic arthritis (PsA) • with moderately to severely active ulcerative colitis It is not known if TREMFYA is safe and effective in children under 18 years of age.		
Do not use TREMFYA if you have had a serious allergic reaction to guselkumab or any of the other ingredients in TREMFYA. See the end of this Medication Guide for a complete list of ingredients in TREMFYA.		
Before using TREMFYA, tell your healthcare provider about all of your medical conditions, including if you: • have any of the conditions or symptoms listed in the section “What is the most important information I should know about TREMFYA?” • have an infection that does not go away or that keeps coming back. • have TB or have been in close contact with someone with TB. • have recently received or are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with TREMFYA. • are pregnant or plan to become pregnant. It is not known if TREMFYA can harm your unborn baby. Pregnancy Registry: If you become pregnant during treatment with TREMFYA, talk to your healthcare provider about registering in the pregnancy exposure registry for TREMFYA. You can enroll in this registry by visiting www.mothersbaby.org/ongoing-study/tremfya-guselkumab, by calling 1-877-311-8972, or emailing MotherToBaby@health.ucsd.edu. The purpose of this registry is to collect information about the safety of TREMFYA during pregnancy. • are breastfeeding or plan to breastfeed. It is not known if TREMFYA passes into your breast milk. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.		
How should I use TREMFYA/TREMFYA PEN? See the detailed “Instructions for Use” that comes with TREMFYA/TREMFYA PEN for information on how to prepare and inject a dose of TREMFYA, and how to properly throw away (dispose of) the used TREMFYA prefilled syringe, One-Press injector or prefilled pen (TREMFYA PEN). • Use TREMFYA exactly as your healthcare provider tells you to use it.		

- If you miss your TREMFYA dose, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. Call your healthcare provider if you are not sure what to do.
- If you inject more TREMFYA than prescribed, call your healthcare provider right away.
- Adults with plaque psoriasis or psoriatic arthritis will receive TREMFYA as an injection under the skin (subcutaneous injection).
- Adults with ulcerative colitis will receive their starter doses with TREMFYA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. After completing the starter doses, patients will receive TREMFYA as an injection under the skin (subcutaneous injection).

What are the possible side effects of TREMFYA?

TREMFYA may cause serious side effects including:

- See “What is the most important information I should know about TREMFYA?”

The most common side effects of TREMFYA include:

• respiratory tract infections	• headache	• injection site reactions
• joint pain (arthralgia)	• diarrhea	• stomach flu (gastroenteritis)
• fungal skin infections	• herpes simplex infections	• bronchitis

These are not all the possible side effects of TREMFYA. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TREMFYA?

- Store TREMFYA in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep TREMFYA in the original carton to protect it from light until time of use.
- TREMFYA is not made with natural rubber latex.
- Do not freeze TREMFYA.
- Do not shake TREMFYA.

Keep TREMFYA and all medicines out of the reach of children.

General information about the safe and effective use of TREMFYA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TREMFYA for a condition for which it was not prescribed. Do not give TREMFYA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TREMFYA that is written for health professionals.

What are the ingredients in TREMFYA?

Active ingredient: guselkumab

Inactive ingredients: Single-dose prefilled syringe, single-dose One-Press patient-controlled injector, single-dose prefilled pen for subcutaneous use: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection. Single-dose vial for intravenous infusion: EDTA disodium dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose and water for injection.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA, U.S. License Number 1864
 For patent information: www.janssenpatents.com
 © Johnson & Johnson and its affiliates 2017-2024
 For more information, call 1-800-526-7736 or go to www.tremfya.com.

This Medication Guide had been approved by the U.S. Food and Drug Administration.

Revised: 09/2024

INSTRUCTIONS FOR USE
TREMFYA® [trem fye' ah]
(guselkumab)
injection, for subcutaneous use
200mg/2mL Prefilled Syringe

This Instructions for Use contains information on how to inject TREMFYA.



SINGLE-DOSE

Important Information You Need to Know Before Injecting TREMFYA

TREMFYA comes in a single-dose prefilled syringe containing one 200 mg dose.

If your healthcare provider decides that you or a caregiver may be able to give your injections of TREMFYA at home, you should receive training on the correct way to prepare and inject TREMFYA before using the prefilled syringe.

Read this Instructions for Use before using your TREMFYA prefilled syringe and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Each TREMFYA prefilled syringe can only be used one time. Throw the used prefilled syringe away (see Step 4) after one dose, even if there is still medicine left in it. Do not reuse your TREMFYA prefilled syringe.

The TREMFYA prefilled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the device and lock into place.



Storage information

Store in refrigerator between **36°F to 46°F** (2°C to 8°C).

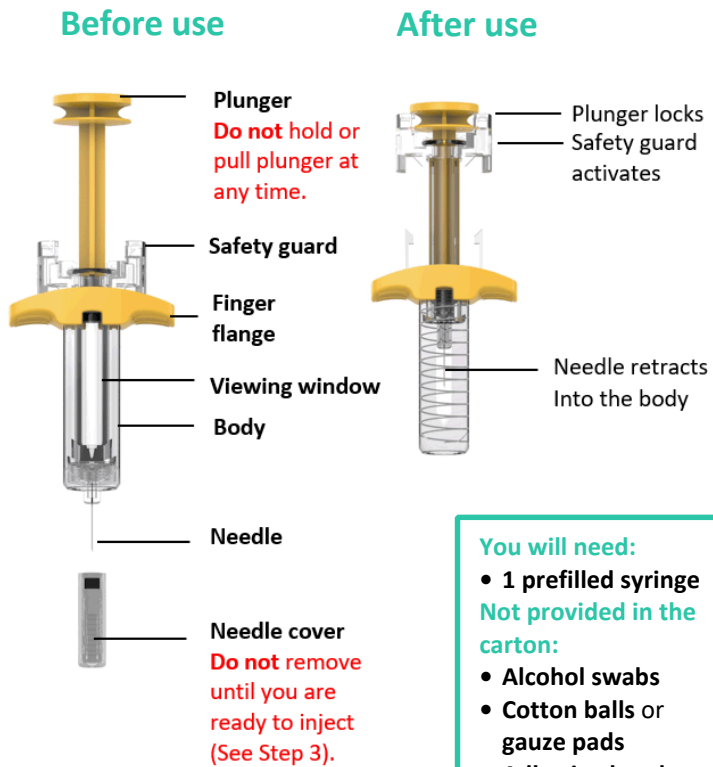
Do not freeze TREMFYA prefilled syringe.

Do not shake your TREMFYA prefilled syringe.

Keep TREMFYA prefilled syringe and all medicines out of reach of children.

Keep TREMFYA prefilled syringe in the original carton to protect from light and physical damage.

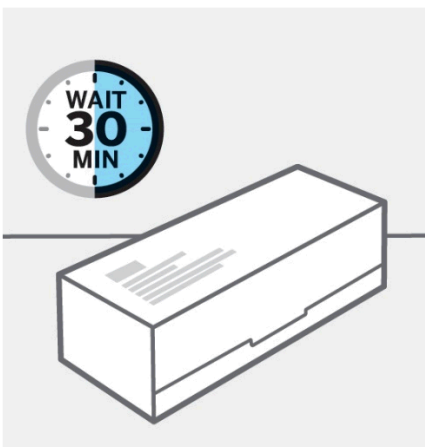
Prefilled syringe parts



You will need:

- 1 prefilled syringe
- Not provided in the carton:
- Alcohol swabs
- Cotton balls or gauze pads
- Adhesive bandages
- Sharps container (See Step 4)

1. Get ready



Allow TREMFYA to come to room temperature and inspect carton

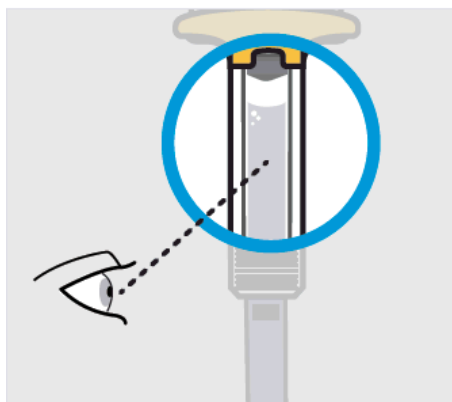
Remove the carton from the refrigerator and let the carton sit on a flat surface at room temperature for approximately **30 minutes** before use.

Do not warm the prefilled syringe any other way.

Check the expiration ('EXP') date.

Do not use your prefilled syringe if the expiration date has passed or if the seal on the carton is broken. Contact your healthcare provider or pharmacist for a new prefilled syringe.

2. Prepare to inject TREMFYA



Take the prefilled syringe out of the carton.

Inspect liquid to see that it is clear and colorless to slightly yellow

Check the liquid in the viewing window. It should be clear and colorless to slightly yellow and may contain tiny white or clear particles. You may also see air bubbles. This is normal.

Do not inject if the liquid is:

- cloudy or
- discolored or
- has large particles

Do not use the prefilled syringe if it is dropped. Call your healthcare provider or pharmacist for a new prefilled syringe.

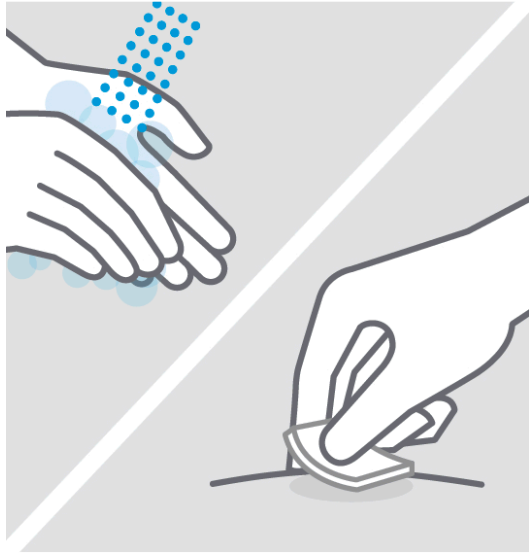


Choose injection site

Select a site from the following areas for your injection:

- Front of thighs
- Lower stomach area (lower abdomen), except for a 2-inch area right around your navel (belly-button)
- Back of upper arms (only if someone else is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.

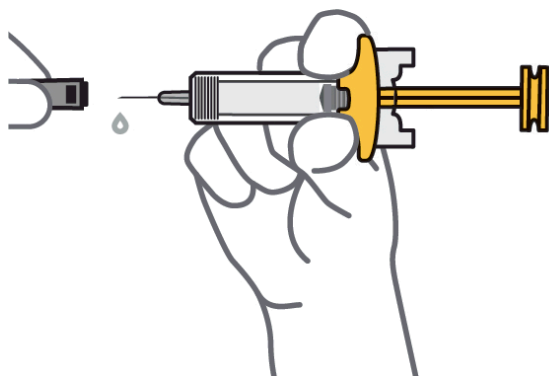
**Wash hands and clean injection site**

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan, or blow on the injection site after you have cleaned it.

3. Inject TREMFYA



Remove needle cover when you are ready to inject

Hold the prefilled syringe by the body and pull needle cover straight off. It is normal to see a few drops of liquid.

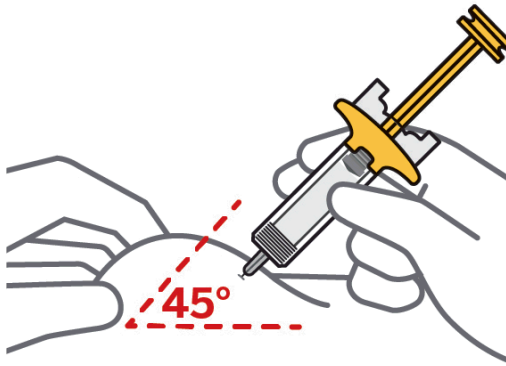
Inject TREMFYA within 5 minutes of removing the needle cover.

Do not put needle cover back on, as this may damage the needle or cause a needle stick injury.

Do not touch needle or let it touch any surface.

Do not use the prefilled syringe if it is dropped. Call your healthcare provider or pharmacist for a new prefilled syringe.

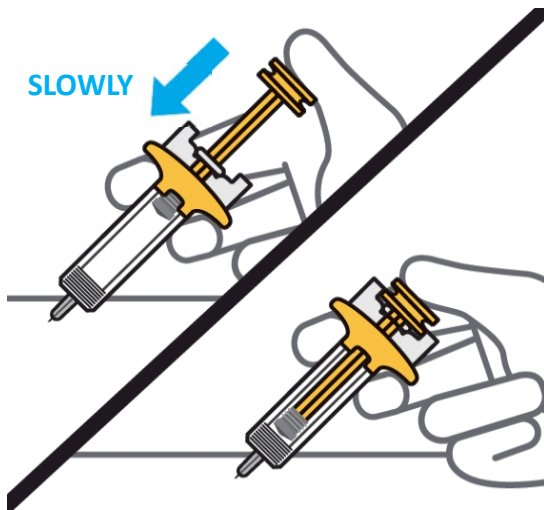
Do not hold or pull the plunger at any time.



Pinch injection site and insert needle at about a 45-degree angle

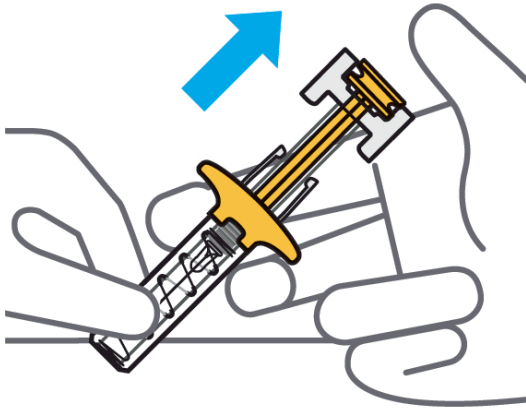
It is important to pinch enough skin to inject under the skin and not into muscle.

Insert needle with a quick dart-like motion.



Slowly press plunger all the way down until it stops to inject all of the liquid

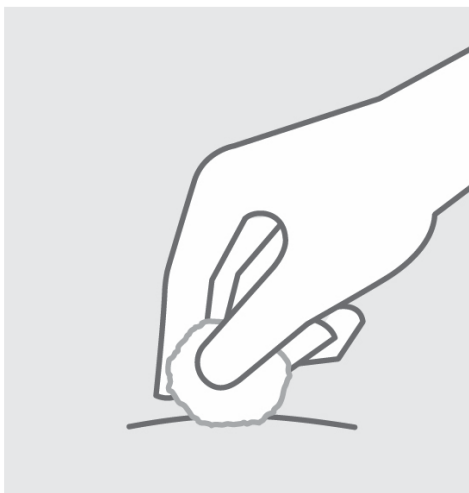
You will feel some resistance as you press the plunger, this is normal.



Release pressure from plunger to remove the needle from the skin

The needle will retract into the device and lock into place.

4. After your injection

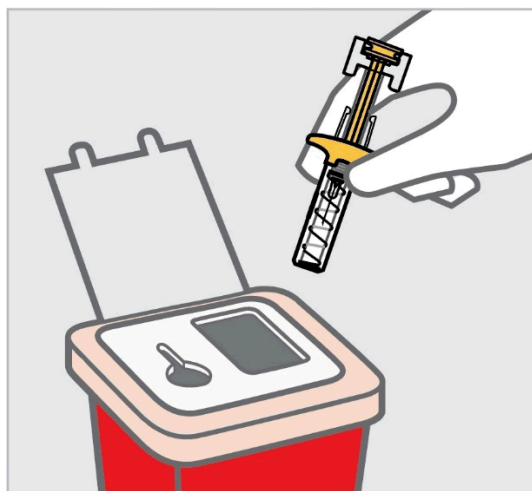


Check injection site

There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover the injection site with a bandage.



Dispose of your prefilled syringe

Put the used prefilled syringe in an FDA-cleared sharps disposal container right away after use.

Do not throw away (dispose of) your prefilled syringe in your household trash.

Do not recycle your used sharps disposal container.

For more information, see Disposing of TREMFYA prefilled syringe.

Disposing of TREMFYA prefilled syringe

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic
- can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal. You may also consult your pharmacist.



Need help?

Call your healthcare provider to talk about any questions you may have. For additional assistance or to share your feedback, call 800-526-7736.

Manufactured by:

Janssen Biotech, Inc.

Horsham, PA 19044, USA

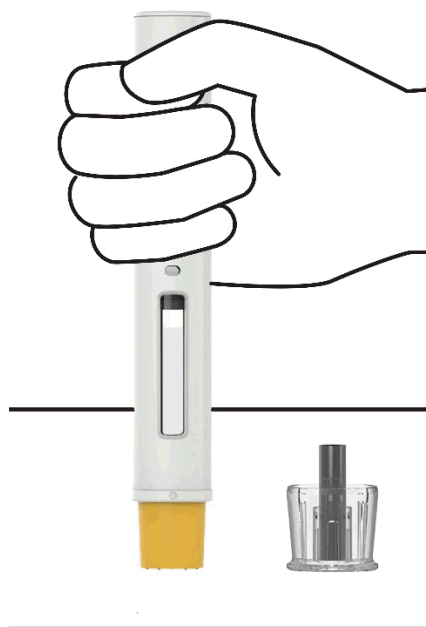
US License No. 1864

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Approved: September 2024

INSTRUCTIONS FOR USE
TREMFYA® PEN
[trem fye' ah Pen]
(guselkumab)
injection, for subcutaneous use
200mg/2mL Prefilled Pen

This Instructions for Use contains information on how to inject TREMFYA PEN.



SINGLE-DOSE

Important Information You Need to Know Before Injecting TREMFYA PEN

TREMFYA PEN comes in a single-dose Prefilled Pen containing one 200 mg dose.

If your healthcare provider decides that you or a caregiver may be able to give your injections of TREMFYA PEN at home, you should receive training on the correct way to prepare and inject TREMFYA PEN before using the Prefilled Pen.

Read this Instructions for Use before using your Prefilled Pen and each time you get a new Prefilled Pen. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Each TREMFYA PEN can only be used one time. Throw the used Prefilled Pen away (see Step 4) after one dose, even if there is still medicine left in it. Do not reuse your Prefilled Pen.



Storage information

Store in refrigerator between **36°F to 46°F** (2°C to 8°C).

Do not freeze your TREMFYA PEN.

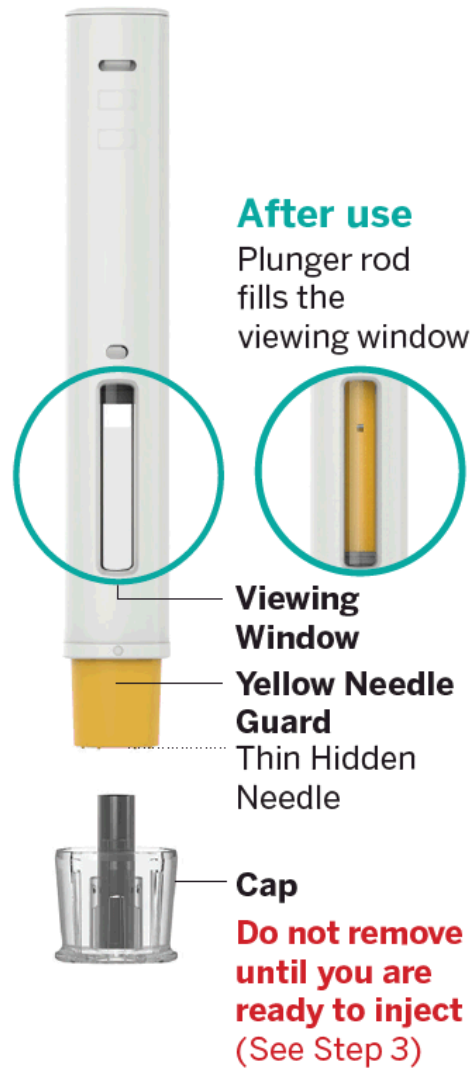
Do not shake your TREMFYA PEN.

Keep your TREMFYA PEN and all medicines out of reach of children.

Keep your TREMFYA PEN in the original carton to protect from light and physical damage.

TREMFYA PEN parts

Before use



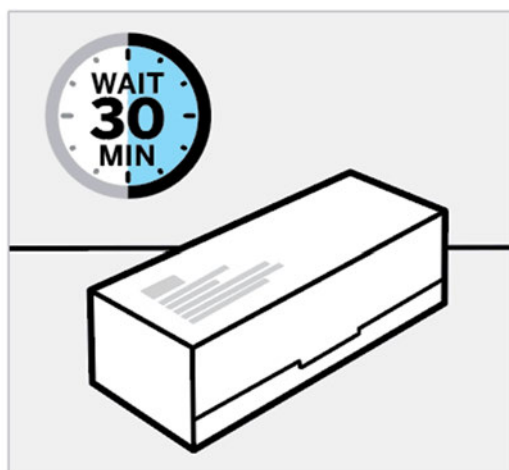
You will need:

- 1 Prefilled Pen

Not provided in the carton:

- Alcohol swabs
- Cotton balls or gauze pads
- Adhesive bandages
- Sharps container (See Step 4)

1. Get ready



Allow TREMFYA PEN to come to room temperature and inspect carton

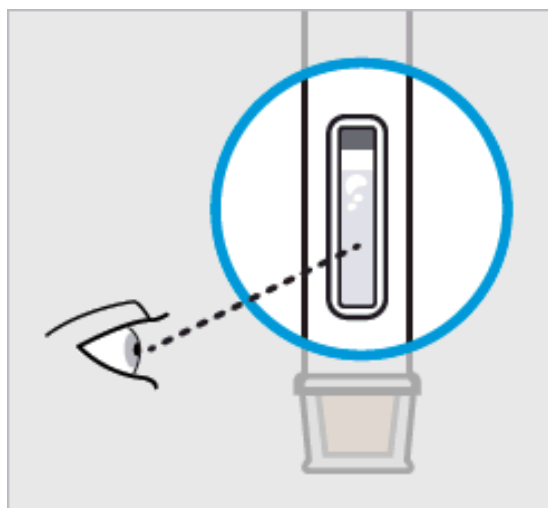
Remove the carton from the refrigerator and let the carton sit on a flat surface at room temperature for approximately **30 minutes** before use.

Do not warm the Prefilled Pen any other way.

Check the expiration ('EXP') date.

Do not use the Prefilled Pen if the expiration date has passed or if the seal on the carton is broken. Contact your healthcare provider or pharmacist for a new Prefilled Pen.

2. Prepare to inject TREMFYA PEN



Take your Prefilled Pen out of the carton.

Inspect liquid in window to see that it is clear and colorless to slightly yellow

Check the liquid in the viewing window. It should be clear and colorless to slightly yellow and may contain tiny white or clear particles. You may also see air bubbles. This is normal.

Do not inject if the liquid is:

- cloudy or
- discolored or
- has large particles

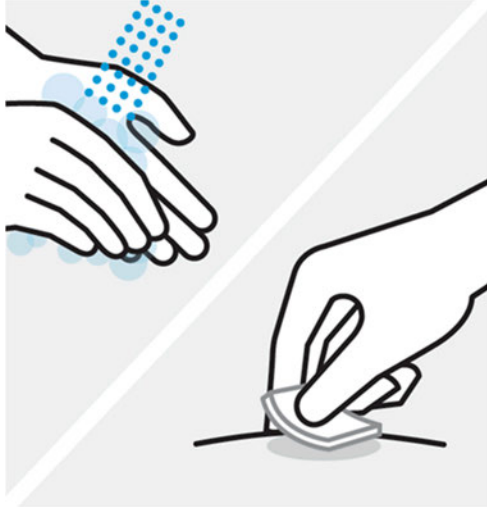
Call your healthcare provider or pharmacist for a new Prefilled Pen.

**Choose injection site**

Select from the following areas for your injection:

- Front of thighs
- Lower stomach area (lower abdomen), except for a 2-inch area right around your navel (belly-button)
- Back of upper arms (only if someone else is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.



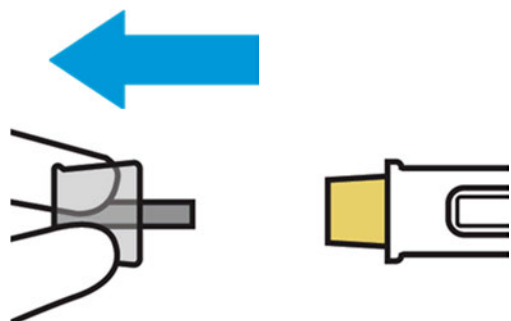
Wash hands and clean injection site

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan, or blow on the injection site after you have cleaned it.

3. Inject TREMFYA PEN



Remove cap when you are ready to inject

Do Not Touch Yellow Needle Guard!

This may start the injection and you will not receive the dose.

Pull the cap straight off. It is normal to see a few drops of liquid.

Inject TREMFYA PEN within 5 minutes of removing cap.

Do not put the cap back on as this may damage the needle.

Do not use your Prefilled Pen if it is dropped after removing the cap. Call your healthcare provider or pharmacist for a new Prefilled Pen.



Position the Prefilled Pen straight onto the injection site then push and hold the Prefilled Pen

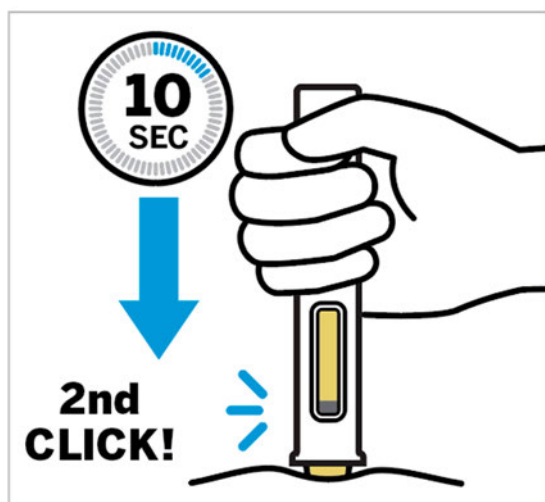
Do Not Lift The Prefilled Pen During Injection!

If you do, the yellow needle guard will lock and the full dose will not be delivered.

Position your Prefilled Pen straight onto the injection site with the yellow needle guard against the skin and the viewing window facing you.

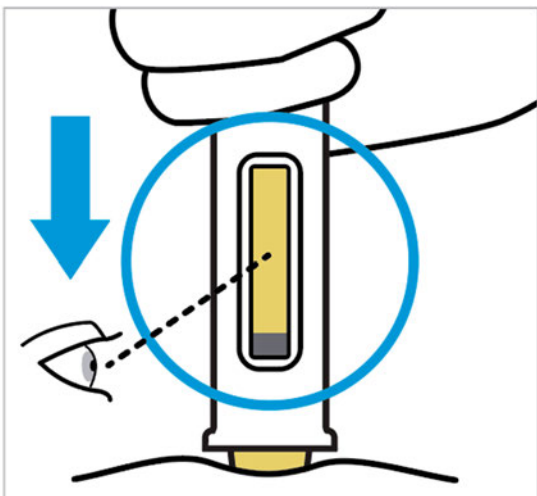
Press down on the Prefilled Pen and keep holding it down against the skin.

You will hear the first click.

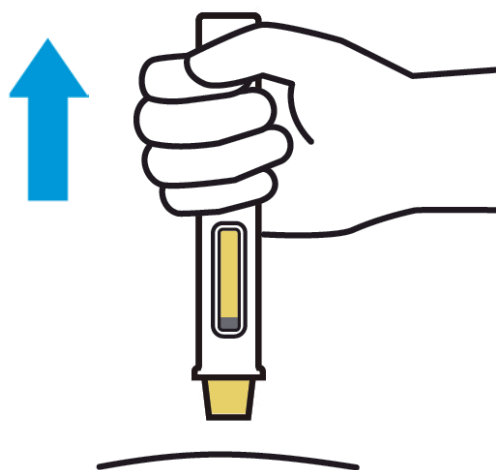


Keep holding your Prefilled Pen firmly against the skin for about 10 seconds to hear a second click

You are almost done.



Keep holding firmly against the skin and confirm your injection is complete
Your injection is complete when the plunger rod stops moving and fills the viewing window.



Lift straight up

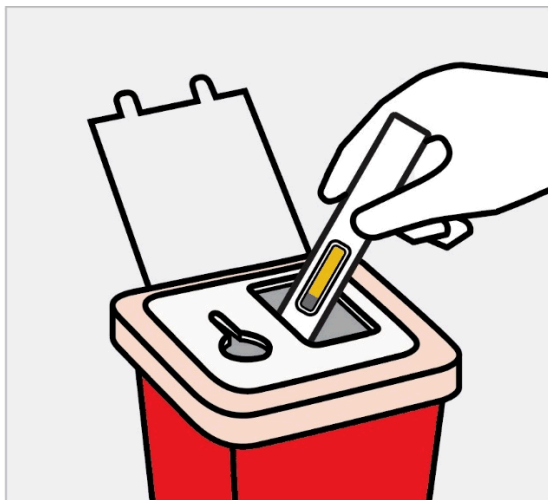
4. After your injection



Check injection site

There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site. If needed, cover the injection site with a bandage.



Dispose of your Prefilled Pen and cap

Put your used Prefilled Pen and cap in an FDA-cleared sharps disposal container right away after use.

Do not throw away (dispose of) your Prefilled Pen in your household trash.

Do not recycle your used sharps disposal container.

For more information, see Disposing of TREMFYA PEN.

Disposing of TREMFYA PEN

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of heavy-duty plastic
- can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal. You may also consult your pharmacist.



Need help?

Call your healthcare provider to talk about any questions you may have. For additional assistance or to share your feedback, call 800-526-7736.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
US License No. 1864

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Approved: September 2024

Instructions for Use

TREMFYA®

(trem fye ' ah)

(guselkumab)

Prefilled Syringe



SINGLE-DOSE

Important

TREMFYA comes as a single-dose prefilled syringe containing one 100 mg dose. Each TREMFYA prefilled syringe can only be used one time. Throw the used prefilled syringe away (See Step 3) after one dose, even if there is medicine left in it. Do not reuse your TREMFYA prefilled syringe.

If your healthcare provider decides that you or a caregiver may be able to give your injections of TREMFYA at home, you should receive training on the right way to prepare and inject TREMFYA using the prefilled syringe before attempting to inject. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider.

Read this Instructions for Use before using your TREMFYA prefilled syringe and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

The TREMFYA prefilled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the body of the device and lock into place.



Storage information

Store in refrigerator at **36° to 46°F** (2° to 8°C). **Do not** freeze TREMFYA prefilled syringe.

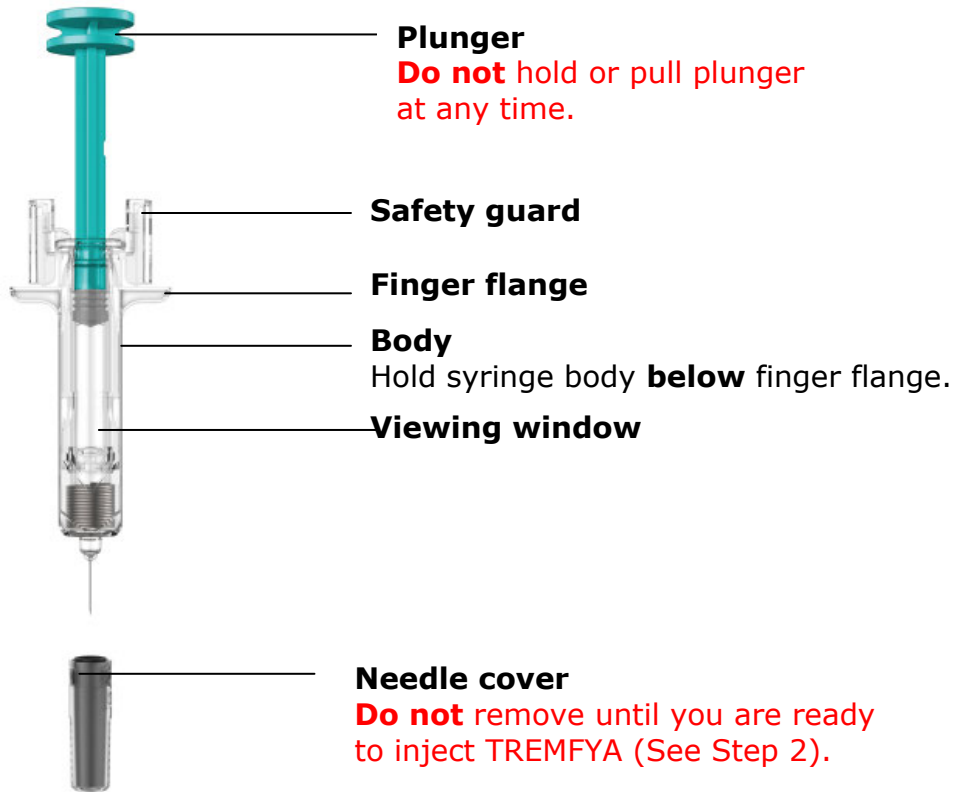
Keep TREMFYA prefilled syringe and all medicines out of reach of children.

Do not shake your TREMFYA prefilled syringe.

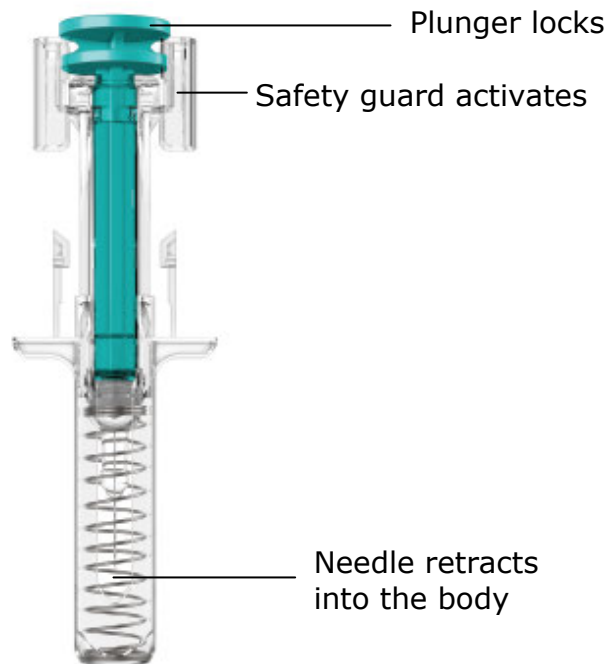
Keep TREMFYA prefilled syringe in the original carton to protect from light and physical damage.

Prefilled syringe parts

Before use



After use



You will need these supplies:

- **1 TREMFYA prefilled syringe**
- **Not provided in the TREMFYA prefilled syringe carton:**
- **1 Alcohol swab**
- **1 Cotton ball or gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container (See Step 3)**

1. Prepare for your injection



Inspect carton

Remove your TREMFYA prefilled syringe carton from the refrigerator.

Keep the prefilled syringe in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

Do not warm the prefilled syringe any other way.

Check the expiration date ('EXP') on the back panel of the carton.

Do not use your prefilled syringe if the expiration date has passed.

Do not inject TREMFYA if the perforations on the carton are broken. Call your healthcare provider or pharmacist for a refill.

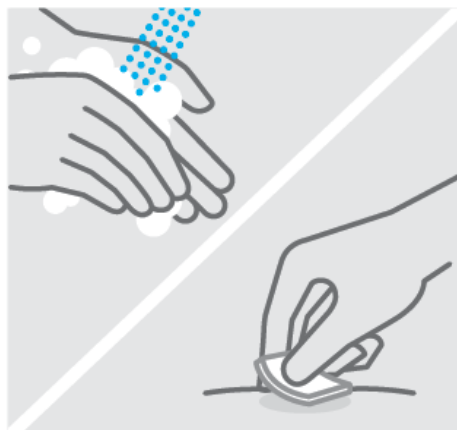


Choose injection site

Select from the following areas for your injection:

- **Front of thighs** (recommended)
- Lower stomach area (lower abdomen), except for a 2-inch area right around your navel (belly-button)
- Back of upper arms (only if someone else is giving you the injection)

Do not inject into skin that is tender, bruised, red, hard, thick, scaly or affected by psoriasis.

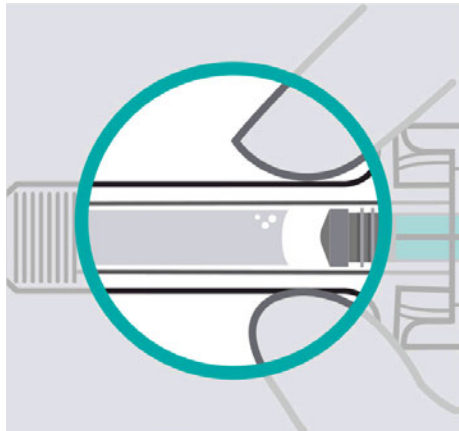


Clean injection site

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan, or blow on the injection site after you have cleaned it.



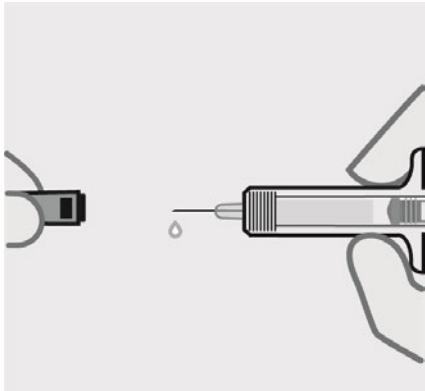
Inspect liquid

Take your TREMFYA prefilled syringe out of the carton.

Check the TREMFYA prefilled syringe liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is cloudy or discolored, or has large particles. Call your healthcare provider or pharmacist for a refill.

2. Inject TREMFYA using prefilled syringe



Remove needle cover

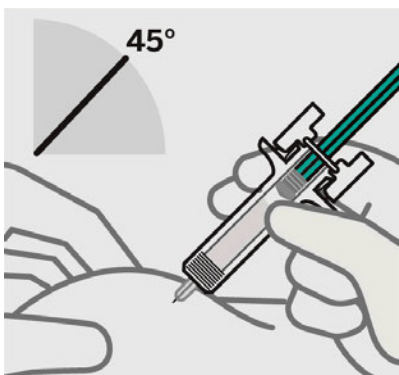
Hold your prefilled syringe by the body and pull needle cover straight off. It is normal to see a drop of liquid.

Inject TREMFYA within 5 minutes of removing the needle cover.

Do not put needle cover back on, as this may damage the needle or cause a needle stick injury.

Do not touch needle or let it touch any surface.

Do not use a TREMFYA prefilled syringe if it is dropped. Call your healthcare provider or pharmacist for a refill.



Position fingers and insert needle

Place your thumb, index and middle fingers **directly under the finger flange**, as shown.

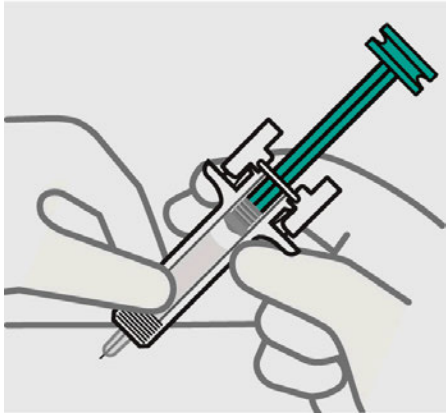
Do not touch plunger or area above finger flange as this may cause the needle safety device to activate.

Use your other hand to pinch skin at the injection site. Position syringe at about a 45 degree angle to the skin.

It is important to pinch enough skin to **inject under**

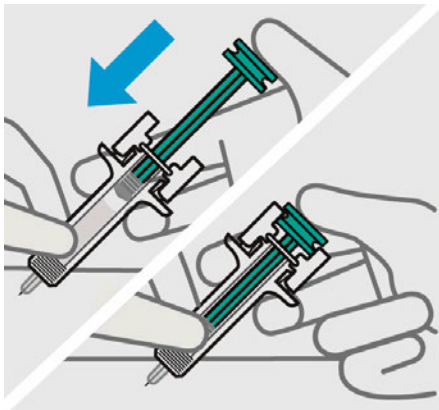
the skin and not into the muscle.

Insert needle with a quick, dart-like motion.



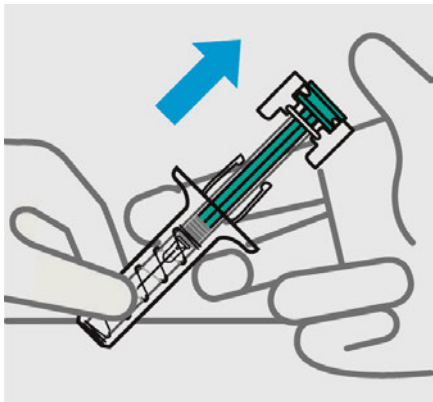
Release pinch and reposition hand

Use your free hand to grasp the body of the prefilled syringe.



Press plunger

Place thumb from the opposite hand on the plunger and press the plunger **all the way down until it stops**.



Release pressure from plunger

The safety guard will cover the needle and lock into place,

removing the needle from your skin.

3. After your injection



Dispose of your prefilled syringe

Put your used TREMFYA prefilled syringe in an FDA-cleared sharps disposal container right away after use.

Do not throw away (dispose of) your TREMFYA prefilled syringe in your household trash.

Do not recycle your used sharps disposal container.

For more information, see “How should I dispose of the used prefilled syringe?”



Check injection site

There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.



Need help?

Call your healthcare provider to talk about any questions you may have. For additional assistance or to share your feedback call 800-JANSSEN (800-526-7736).

How should I dispose of the used prefilled syringe?

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Janssen Biotech, Inc. Horsham, PA 19044

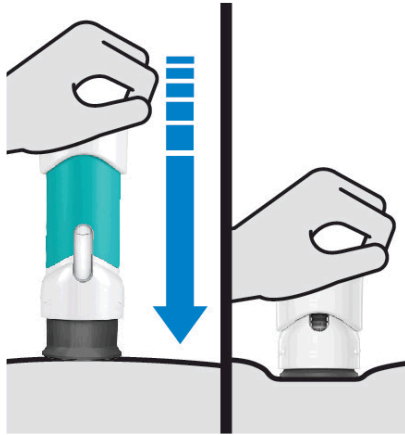
US License No. 1864

Approved: December 2017



INSTRUCTIONS FOR USE
TREMFYA® [trem fye' ah]
(guselkumab)
injection, for subcutaneous use
One-Press Patient-Controlled Injector

This "Instructions for Use" contains information on how to inject TREMFYA.



Important Information You Need to Know Before Injecting TREMFYA

TREMFYA comes in a single-dose One-Press injector containing one 100 mg dose.

During injection, push handle all the way down until teal body is not visible to inject the full dose.

DO NOT LIFT ONE-PRESS during injection. If you do, the One-Press will lock and you will not get the full dose.

Each One-Press injector can only be used one time. Throw away (See Step 3) after one dose, even if there is medicine left in it. Do not reuse your One-Press injector.

If your healthcare provider decides that you or a caregiver may be able to give your injections of TREMFYA at home, you should receive training on the right way to prepare and inject TREMFYA using the One-Press injector. Do not try to inject yourself until you have been trained by your healthcare provider.

Please read this Instructions for Use before using your One-Press injector and each time you get a new One-Press injector. There may be new information.

This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.



Storage information

Store in refrigerator at **36° to 46°F** (2° to 8°C).

Do not freeze your One-Press injector.

Do not shake your One-Press injector.

Keep your One-Press injector and all medicines out of reach of children.

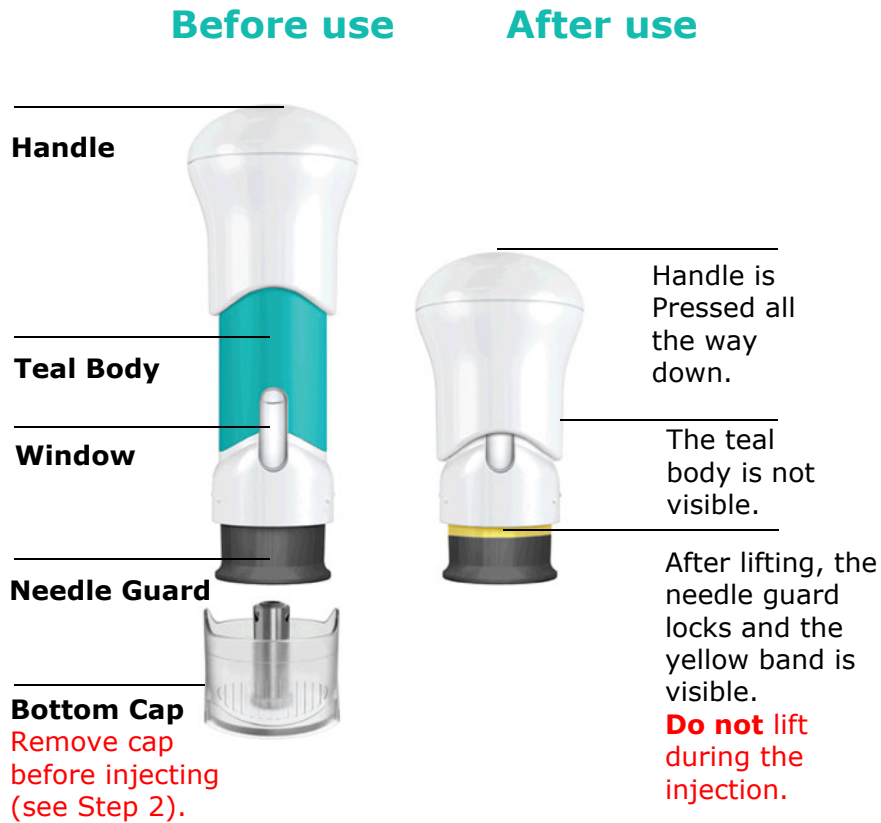
Keep your One-Press injector in the original carton to protect from light and physical damage.



Need help?

Call your healthcare provider to talk about any questions you may have. For additional assistance or to share your feedback call 800-JANSSEN (800-526-7736).

One-Press injector parts



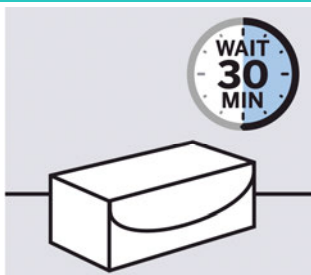
You will need:

- 1 One-Press injector

Not provided in the carton:

- 1 Alcohol swab
- 1 Cotton ball or gauze pad
- 1 Adhesive bandage
- 1 Sharps container (See Step 3)

1. Preparing to Inject TREMFYA

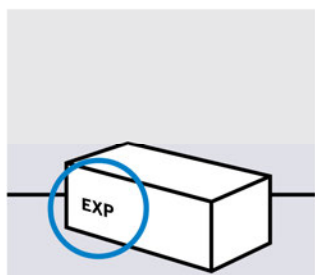


Inspect carton and allow TREMFYA to come to room temperature

Remove your One-Press injector carton from the refrigerator.

Keep your One-Press injector in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

Do not warm your One-Press injector any other way.



Check the expiration date ('EXP') on the carton

Do not use your One-Press injector if the expiration date has passed.

Do not inject TREMFYA if the seal on the carton is broken. Call your healthcare provider or pharmacist for a new One-Press injector.

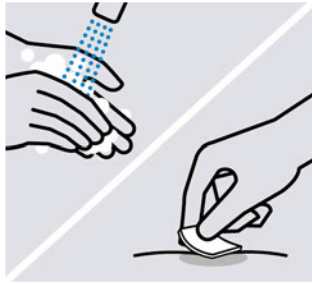


Choose injection site

Select from the following areas for your injection:

- **Front of thighs** (recommended)
- Lower stomach area (lower abdomen), except for a 2-inch area right around your navel (belly-button)
- Back of upper arms (only if someone else is giving you the injection)

Do not inject into skin that is tender, bruised, red, hard, thick, scaly, or affected by psoriasis.



Wash hands

Wash your hands well with soap and warm water.

Clean injection site

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan, or blow on the injection site after you have cleaned it.



Inspect liquid in window

Take your One-Press injector out of the carton.

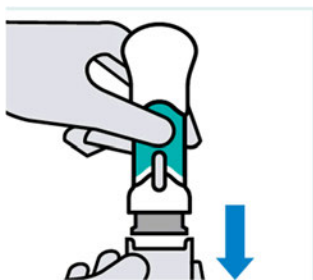
Check the liquid in the window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is:

- cloudy,
- discolored, or
- has large particles.

Call your healthcare provider or pharmacist for a new One-Press injector.

2. Injecting TREMFYA



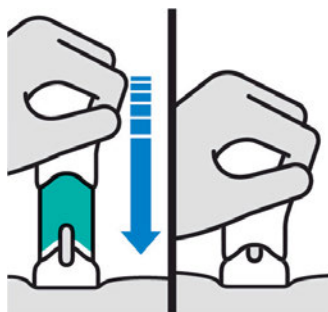
Pull off bottom cap

Keep hands away from the needle guard after the cap is removed. It is normal to see a few drops of liquid.

Inject TREMFYA within 5 minutes of removing the cap.

Do not put the cap back on. This could damage the needle.

Do not use a One-Press injector if it is dropped after removing the cap. Call your healthcare provider or pharmacist for a new One-Press injector.



Place straight on skin.

Push handle all the way down until teal body is not visible

DO NOT LIFT ONE-PRESS during injection!

If you do, the needle guard will lock, showing a yellow band, and you will not get the full dose.

You may hear a click when the injection begins. Keep pushing.

If you feel resistance, keep pushing. This is normal.

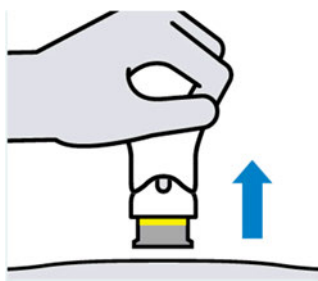
The medication injects as you push. Do this at a speed that is comfortable for you.



Confirm your injection is complete

Your injection is complete when:

- **The teal body is not visible.**
- You cannot press the handle down anymore.
- You may hear a click.



Lift straight up

The yellow band indicates that the needle guard is locked.

3. After your injection



Dispose of your One-Press injector

Put your used One-Press injector in a sharps disposal container right away after use.

Do not throw away (dispose of) your One-Press injector in your household trash.

Do not recycle your used sharps disposal container.

For more information, see “Disposing of TREMFYA One-Press injector”.



Check injection site

There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.

Disposing of TREMFYA One-Press injector

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

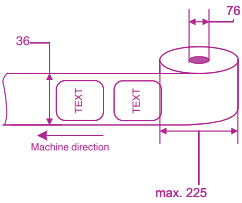
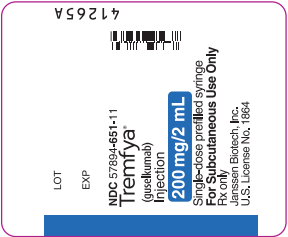
For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal. You may also consult your pharmacist.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

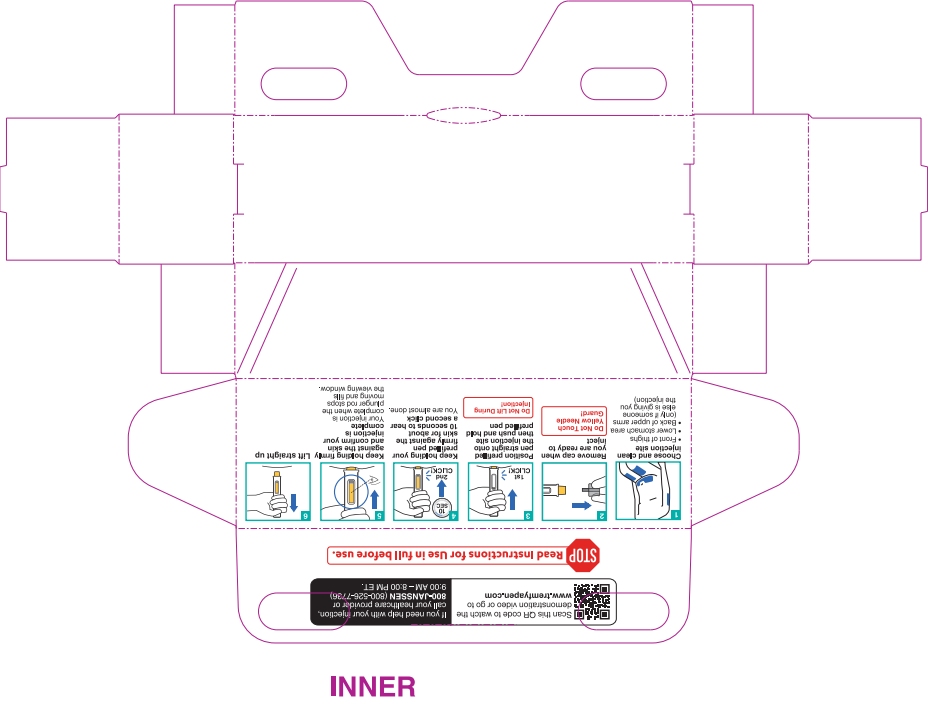
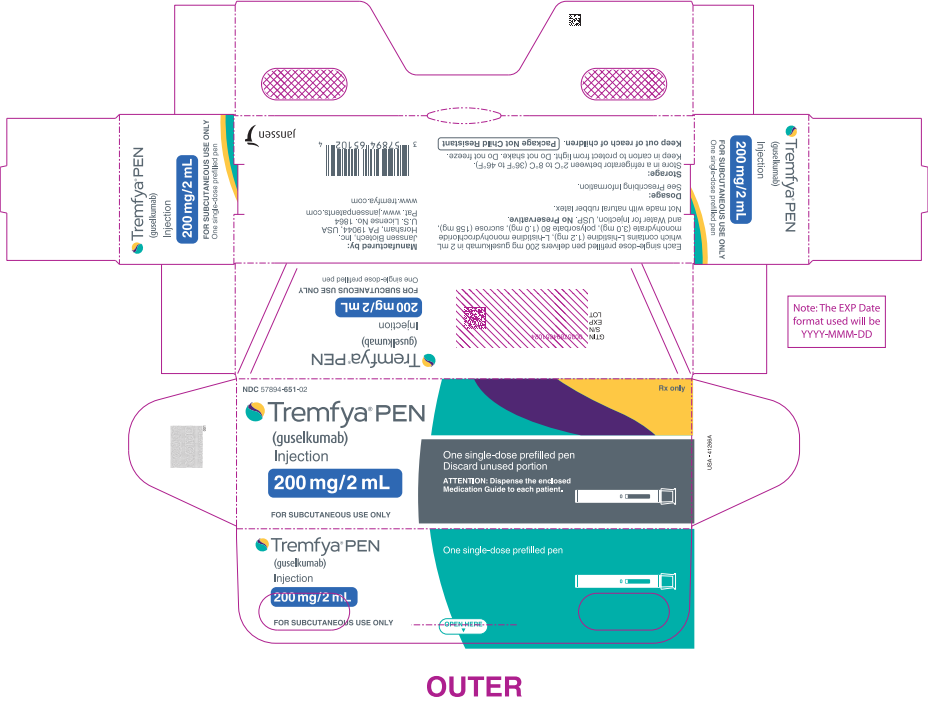
Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864
Revised: June 2023



Note: The EXP Date
format used will be
YYYY-MM



(b) (4)



(b) (4)

Note: The EXP Date
format used will be
YYYY-MM

NDC 57894-650-01

Tremfya 

(guselkumab)

Injection

200 mg/20 mL
(10 mg/mL)

Single-dose vial

Discard unused portion

Rx only

FOR INTRAVENOUS INFUSION ONLY

Storage: Store between 2°C to 8°C
(36°F to 46°F). Protect from light.
Do not shake. Do not freeze.

Dosage: See prescribing
information for dilution,
dosage, and administration.

Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License No. 1864



LOT

EXP

41254A

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA761061Orig1s021

MULTIDISCIPLINE REVIEW(s)

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761061/S-021
Priority or standard	Priority voucher redemption
Submit date(s)	3/11/2024
Received date(s)	3/11/2024
PDUFA goal date	9/11/2024
Division/office	Division of Gastroenterology
Review completion date	9/9/2024
Established/proper name	Guselkumab
(Proposed) proprietary name	TREMFYA
Pharmacologic class	IL-23 antagonist
Other product name(s)	CNTO1959
Applicant	Janssen Biotech, Inc.
Dosage form(s)/formulation(s)	Subcutaneous Injection • 100 mg/mL in a single-dose One-Press patient-controlled injector • 200 mg/2 mL in a single-dose prefilled pen • 100 mg/mL in a single-dose prefilled syringe • 200 mg/2 mL single-dose prefilled syringe Intravenous Injection • 200 mg/20 mL (10 mg/mL) solution in a single-dose vial
Applicant-proposed dosing regimen	<i>The recommended induction dosage is 200 mg administered by intravenous infusion over a period of at least one hour at Week 0, Week 4, and Week 8.</i> <i>The recommended maintenance dosage is 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.</i>
Applicant-proposed indication(s)/population(s)	Treatment of adult patients with moderately to severely active ulcerative colitis
SNOMED CT code for proposed indication disease term(s)¹	64766004 (Ulcerative colitis)
Regulatory action	Approval
Approved dosage (if applicable)	Induction The recommended induction dosage is 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8. Maintenance The recommended maintenance dosage is: • 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or • 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. Use the lowest effective recommended dosage to maintain therapeutic response.

BLA 761061/S-021
TREMIFYA (guselkumab)

Approved indication(s)/ population(s) (if applicable)	Treatment of adult patients with moderately to severely active ulcerative colitis
SNOMED CT code for approved indication disease term(s)¹	64766004 (Ulcerative colitis)

¹ For internal tracking purposes only.

Abbreviations: BLA, biologics license application; DG, Division of Gastroenterology; PDUFA, Prescription Drug User Fee Act;
SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADA	antidrug antibody
ADT	advanced therapy
AE	adverse event
AWC	adequate and well controlled
BLA	biologics license application
BQS	bioanalytical quality summary
CD	Crohn's disease
CDRH	Center for Devices and Radiological Health
CFI	comparative fit index
CI	confidence interval
C _{max}	maximum plasma concentration
CRP	C-reactive protein
CSR	clinical study report
CV	coefficient of variation
DPV	Division of Pharmacovigilance
eCDF	empirical cumulative distribution function
E-R	exposure-response
FAS	full analysis set
FDA	Food and Drug Administration
FVP	final vial product
GQ	grouped query
HEMI	histologic endoscopic mucosal improvement
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	intercurrent event
IL	interleukin
IQR	interquartile range
IS-1	Induction Study 1
IS-2	Induction Study 2
IV	intravenous
mMS	modified Mayo Score
MS	Maintenance Study
NAb	neutralizing antibody
NDA	new drug application
NOAEL	no observed adverse effect level
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PD	pharmacodynamic
PFS	prefilled syringe
PFS-U	prefilled syringe assembled with the UltraSafe Plus Needle Guard
PFS-Y	prefilled syringe assembled with YpsoMate autoinjector
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

BLA 761061/S-021
TREMFYA (guselkumab)

PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
PopPK	population pharmacokinetic
PREA	Pediatric Research Equity Act
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
Q4W	every 4 weeks
Q8W	every 8 weeks
RAS	randomized analysis set
RFAS	randomized full analysis set
RMSEA	root mean square error of approximation
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
sBLA	supplemental biologics license application
SC	subcutaneous
SEE	substantial evidence of effectiveness
SF	Short Form
SI	International System of Units
SRMR	standardized root mean squared residual
TBM	to-be-marketed
TEAE	treatment-emergent adverse event
UC	ulcerative colitis
USPI	United States Prescribing Information

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On March 11, 2024, supplemental biologics license application (sBLA) 761061/S-021 was submitted by Janssen Biotech, Inc., seeking the approval of guselkumab for the treatment of adults with moderately to severely active ulcerative colitis (UC). The application was submitted with an accompanying Rare Pediatric Disease Priority Voucher¹ and therefore was designated as a priority review. The sBLA was reviewed by the multidisciplinary review team, and each discipline recommended approval. The signatory authority concurs with the review team's recommendation.

In support of this sBLA, the Applicant submitted data from three studies conducted under a single protocol with a shared population (CNT01959UCO3001; QUASAR): Induction Study 1 (IS-1; phase 2b induction dose-ranging study), Induction Study 2 (IS-2; phase 3 induction study), and Maintenance Study (MS; phase 3 maintenance study).

Data from IS-2 and MS were submitted to support the primary evaluation of efficacy and the demonstration of substantial evidence of effectiveness. At Week I-12 of IS-2, statistically significant results were achieved on analyses comparing guselkumab 200 mg intravenous (IV) versus placebo for the primary endpoint of clinical remission and multiple ranked secondary endpoints. At Week M-44 of MS, statistically significant results were achieved on analyses of each guselkumab maintenance dosage group (i.e., guselkumab 100 mg subcutaneous [SC] at Week 16, and every 8 weeks [Q8W] thereafter, and guselkumab 200 mg SC at Week I-12, and every 4 weeks [Q4W] thereafter) versus placebo for the primary endpoint of clinical remission, as well as multiple ranked secondary endpoints.

FDA has typically relied upon data from two independent adequate and well-controlled (AWC) trials to establish effectiveness for drugs for the treatment of moderately to severely active UC. The results of the single, large, multicenter AWC trial conducted under the QUASAR program, including both induction (IS-2) and maintenance (MS) studies, were statistically persuasive and robust across prespecified primary and secondary endpoints that have been accepted to represent clinically meaningful aspects of UC that if left inadequately treated or untreated could contribute to significant morbidity or serious clinical sequelae. The strength of evidence provided by this single AWC trial is considered to be equivalent to what is generally expected from two AWC trials and is adequate to establish substantial evidence of effectiveness of guselkumab for the treatment of adult patients with moderately to severely active UC.

Data from IS-1, IS-2, and MS were submitted to support the primary evaluation of safety. The safety findings from these studies were generally similar to the established safety profile of

¹ Refer to Module 1.2 of BLA 761061/S-021 for full details of the Rare Pediatric Disease Priority Voucher redeemed in support of this application.

guselkumab for the previously approved indications (i.e., adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and adults with active psoriatic arthritis), although some adverse reactions observed in the prior programs were not observed in trials of adults with moderately to severely active UC (e.g., tinea infections, herpes simplex infections). The findings from IS-1, IS-2, and MS were also similar to the known safety profiles for approved therapeutic biologic products in the interleukin 23 (IL-23) antagonist class (e.g., risankizumab, mirikizumab). Of note, a comparable safety profile was observed for both guselkumab dosage regimens administered in MS (i.e., guselkumab 100 mg SC at Week 16, and Q8W thereafter, and guselkumab 200 mg subcutaneous SC at Week 12, and Q4W thereafter).

The data submitted in the application support that both recommended maintenance dosage regimens are safe and effective for the treatment of adults with moderately to severely active UC. To achieve long-term remission, some patients require dose escalation and/or changes in pharmacotherapy. Approval of both proposed maintenance dosage regimens provides patients and prescribers an option to adjust therapy with guselkumab, as medically appropriate. The risks of a therapy are generally greater with increased exposures, and although adequate to support approval, the available safety data are not sufficient to inform the potential risk for reactions that occur infrequently or only after prolonged exposure (e.g., malignancy). Accordingly, the review team recommends approval of both maintenance dosages, with instructions to use the lowest effective recommended dosage to maintain therapeutic response. Inclusion of these instructions allows healthcare providers flexibility and encourages reassessment of response during maintenance therapy to avoid the potential risks of long-term drug exposure to a higher dosage if patients are able to maintain therapeutic response with the lower dosage.

The overall-benefit risk assessment supports approval as described in the Benefit-Risk Framework. For detailed information supporting the basis for this approval, refer to the reviews included in this Interdisciplinary Assessment document and the Office of Product Quality Assessment III Review (dated September 5, 2024, located in the Panorama database), Office of Product Quality Office of Pharmaceutical Manufacturing Assessment Product Quality Microbiology/Facility Assessment Reviews (dated September 5, 2024, located in the Panorama database), and Division of Clinical Outcome Assessment (DCOA) review (dated September 3, 2024; DARRTS Reference ID: 5440631). Identified risks can be adequately communicated to patients and prescribers through product labeling and further monitored through studies to be completed to fulfill postmarketing requirements (PMRs) issued under 505(o)3 and routine pharmacovigilance post-approval. Additionally, as inadequately treated UC also causes significant morbidity and increased mortality in pediatric patients, PMRs will be issued under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of guselkumab in pediatric patients with moderately to severely active UC.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations.

As described above (Section [1.1](#)), data from IS-2 and MS were submitted to support the primary evaluation of efficacy and establish substantial evidence of effectiveness of guselkumab for the treatment of moderately to severely active UC in adults. The results of the single, large, multicenter AWC trial conducted under the QUASAR program, including both induction (IS-2) and maintenance (MS) studies, were statistically persuasive and robust across the prespecified primary endpoints, as well as multiple ranked secondary efficacy endpoints that have been accepted to represent clinically meaningful aspects of UC that if left inadequately treated or untreated could contribute to significant morbidity or serious clinical sequelae. The strength of evidence provided by this single AWC trial is considered to be equivalent to what is generally expected from two AWC trials and is adequate to establish substantial evidence of effectiveness of guselkumab for the treatment of adult patients with moderately to severely active UC.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Ulcerative colitis (UC) is a serious chronic, relapsing type of inflammatory bowel disease (IBD) affecting the colonic mucosa. The peak occurrence is between 20 and 40 years of age (Ungaro et al. 2017). UC may affect as many as 907,000 Americans; the annual incidence rate of UC in the United States is estimated to be 6.3 cases per 100,000 person-years, and the prevalence is estimated to be 312 cases per 100,000 persons (Lewis et al. 2023). - Patients with UC most commonly present with bloody diarrhea, rectal bleeding, tenesmus, urgency, abdominal pain, and passage of mucus in the stool. UC may be associated with systemic symptoms, including fatigue, fever, anorexia, nausea, weight loss, and dehydration. Patients may also experience symptoms secondary to complications of anemia and hypoalbuminemia (e.g., dyspnea, peripheral edema). - UC is also associated with extraintestinal manifestations that may affect a wide variety of organ systems (e.g., joints, skin, eyes, kidneys, hepatobiliary tract).	- UC is a serious chronic, relapsing inflammatory disorder of the colonic mucosa. - Patients with UC experience both intrainestinal and extraintestinal manifestations. - Inadequately treated UC may lead to significant morbidity and/or increased mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- The overall goal in the treatment and management of UC is induce and maintain lasting remission to reduce signs and symptoms of active disease, decrease the underlying mucosal inflammation, and prevent both short-term (e.g., severe bleeding, bowel perforation) and long-term complications (e.g., colon cancer). - The choice of therapy is guided by the disease severity, extent of disease, and presence of associated disease manifestations (e.g., extraintestinal complications, malabsorption). - Pharmacotherapy for UC includes 5-ASA products (e.g., mesalamine), corticosteroids, antibiotics, immunomodulators (e.g., azathioprine, 6-mercaptopurine, methotrexate), biologic therapies (e.g., tumor necrosis factor α [TNFα] blockers, integrin receptor antagonist, interleukin 23 [IL-23] antagonists), sphingosine-1-phosphate (S1P) receptor modulators, and Janus kinase (JAK) inhibitors. - Of these therapies, corticosteroids are not recommended for long-term use due to the toxicities associated with chronic steroid use. Additionally, while antibiotics, azathioprine, and methotrexate are widely used in clinical practice, they are not FDA approved for the treatment of UC. - There remains a need for novel therapies, as not all patients will respond or have a continued response to any given treatment. Patients may also have to discontinue effective therapies due to intolerance secondary to associated adverse reactions. - Guselkumab is a humanized monoclonal IgG1λ (lambda) antibody that selectively binds the p19 subunit of IL-23, proposed for the treatment of adults with moderately to severely active UC. Two other IL-23 antagonists (mirikizumab and risankizumab) and an IL-12/23 antagonists (ustekinumab) are currently approved for the treatment of adults with moderately to severely active UC.	- Guselkumab is the third biologic therapy within the class of IL-23 antagonists proposed for the treatment of moderately to severely active UC in adults. Available data from the class and associated class (i.e. IL-12/23 antagonists) support the suitability of IL-23 as a therapeutic target in UC. - Despite availability of therapies from several classes, some patients may not respond or lose response over time to the currently available therapies. Patients may also discontinue therapies due to intolerable adverse reactions. - Additional therapies are needed to treat adults with moderately to severely active UC.
Benefit	The efficacy of guselkumab for the treatment of adults with moderately to severely active UC was demonstrated in a single AWC trial which included a 12-week, randomized, double-blind, placebo-controlled induction study (Induction Study 2; IS-2) and	The robust results of efficacy analyses on clinically relevant endpoints from IS-2 and MS support the demonstration of substantial evidence of effectiveness of guselkumab for the treatment of adults with moderately to severely active UC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a 44-week, randomized, double-blind, placebo-controlled randomized withdrawal study (Maintenance Study; MS). - The results of efficacy analyses for the primary endpoint of clinical remission and multiple ranked secondary efficacy endpoints at Week I-12 and Week M-44 in IS-2 and MS, respectively, were statistically persuasive and robust ($p < 0.001$). Therefore, the data from IS-2 and MS provide the level of evidence generally expected from two adequate and well controlled (AWC) trials. - Both studies enrolled adults with moderately to severely active UC; defined as a baseline modified Mayo Score (mMS) of 5 to 9, including an endoscopic subscore (ES) of at least 2. Of the 701 adult subjects with moderately to severely active UC enrolled in IS-2, 51.6% had prior therapeutic biologic product or JAK inhibitor exposure. Of the 568 adult subjects with moderately to severely active UC enrolled in MS, 45.6% had prior therapeutic biologic product or JAK inhibitor exposure. - In IS-2, statistically significant results were achieved for analyses of the primary endpoint of clinical remission at Week I-12, as well as multiple ranked secondary endpoints (guselkumab 200 mg intravenous [IV] versus placebo). - In MS, statistically significant results were achieved for the analyses of the primary endpoint of clinical remission at Week M-44 for each maintenance regimen (i.e., guselkumab 100 mg SC every 8 weeks and guselkumab 200 mg SC every 4 weeks) compared to placebo. In addition, each maintenance dosage regimen demonstrated statistically significant results compared to placebo on clinically relevant multiplicity-controlled secondary endpoints at Week M-44, including: corticosteroid-free clinical remission, endoscopic improvement, histologic endoscopic mucosal improvement (HEMI), and maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction. - The proportion of subjects meeting the criteria for the primary and some secondary efficacy endpoints was nominally higher for subjects treated with the higher maintenance dosage regimen of guselkumab (i.e., 200 mg SC Q4W) compared to subjects treated with the 100 mg SC Q8W regimen in MS.	- Comparable treatment effects versus placebo were observed for both administered maintenance dosages in MS. - Availability of both maintenance dosages would be of benefit to patients and prescribers, as it would allow for adjustments to therapy, as medically appropriate. - As statistically significant results were achieved on analyses of the primary and ranked secondary endpoints on analyses of each dosage regimen compared to placebo, the review team recommends approval of both dosages with a recommendation to use the lowest effective recommended dosage to maintain therapeutic response. - Inclusion of these instructions allows providers flexibility and encourages reassessment of response during maintenance therapy. The availability of both dosages permits dose escalation in patients who do not experience adequate response or lose response over time, as well as the potential for dose reduction in patients who achieved therapeutic response with the higher dosage and are assessed by their healthcare provider to have the potential for continued response with the lower dosage. - Although, exposure-response data suggest higher guselkumab clearance in adults of higher body weight, the available data do not support a definitive association between this finding and lower efficacy in subjects with higher body weight. The currently approved prescribing information for guselkumab includes the following statement in Section 12.3 PHARMACOKINETICS: Special Populations, "Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	However, the study was not powered to directly compare these treatment groups, the observed differences were small, and each group performed superiorly when individually compared to placebo, with robust results. - Although exposure-response data support higher clearance of guselkumab in adults with a higher body weight, the results of efficacy analyses were comparable between adults of higher body weights between the dosage regimens administered in MS. - Fatigue is a clinically relevant symptom in adults with UC; however, fatigue may be impacted by multiple disease nonspecific factors. - In IS-2 and MS, fatigue was assessed with the Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue SF-7a instrument. The Applicant provided qualitative and quantitative data to support that the PROMIS-Fatigue SF-7a instrument is fit-for-purpose to assess fatigue in adults with moderately to severely active UC. - Results of the analysis of the Applicant's endpoint of "fatigue response" (defined as a ≥ 7-point improvement from induction baseline in PROMIS-Fatigue SF-7a) achieved statistically significant results versus placebo in IS-2. - Anchor-based analyses indicated there is no single threshold that adequately defines meaningful change in fatigue in adult subjects with UC. Although these analyses did not support the Applicant's proposed definition of "fatigue response," they did support that subjects treated with guselkumab experienced a clinically meaningful improvement in fatigue at Week I-12 of IS-2, compared to placebo-treated subjects. - As UC is a chronic condition, data to support the potential for continued benefit of therapies on fatigue beyond the induction period are important to inform the clinical relevance of short-term evaluations. - The results of the analysis of "fatigue response" were also statistically significant in MS; however, the interpretability of the results of this analysis is limited by the high number of placebo subjects who experienced an intercurrent event (ICE) in MS and the prespecified handling of ICEs in the efficacy analysis.	The review team agrees that this statement accurately describes the findings observed in MS. - The PROMIS-Fatigue SF-7a is fit-for-purpose instrument to assess fatigue in adults with moderately to severely active UC. - The Applicant reported statistically significant results for the analysis of "fatigue response" from IS-2 and MS. The proposed responder definition for "fatigue response" has not been adequately supported to represent clinically meaningful improvement to patients with UC. - Anchor-based analyses support that subjects treated with guselkumab in IS-2 experienced a clinically meaningful improvement in fatigue compared to placebo-treated subjects at Week I-12. - The results of the analyses of fatigue at Week M-44 were affected by the disproportionate occurrence of ICE between the placebo and guselkumab arms. As supplementary analyses did not support that strong evidence had been provided for the effect of guselkumab on fatigue at Week M-44, the data are not adequate to demonstrate the benefit of guselkumab on fatigue long-term. - Despite the above-mentioned limitations of the analyses of fatigue, the statistically significant results of the analysis of "fatigue response" and supportive anchor-based analyses from IS-2 and the favorable results for the analysis of "fatigue response" from MS are adequate to support descriptive inclusion of the treatment effect of guselkumab on fatigue at Week I-12 in IS-2 in the prescribing information. - The analysis of fatigue from MS at Week M-44 did not provide strong evidence of benefit, due to the impact of ICE on the interpretability of the results. The review team recommends that inclusion of the following statement in the PI, "The effect of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Because subjects experiencing an ICE could not be “fatigue responders,” the analysis for this endpoint effectively evaluated the effect on both the fatigue response and/or the occurrence of an ICE. The proportion of subjects experiencing an ICE was greater in the placebo arm (48.9%), as compared to either the guselkumab 100 mg SC arm (18.6%) or the guselkumab 200 mg SC arm (23.2%). (b) (4)	TREMIFYA to improve fatigue after 12 weeks of induction has not been established.”
Risk and risk management	- The primary evaluation of the safety of guselkumab in adults with moderately to severely active UC was based on data from the phase 2b induction dose-ranging study (IS-1), IS-2, and MS. - The primary induction safety database included subjects who received at least one dose of guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo in IS-1 or IS-2. - The primary maintenance safety database included subjects who received at least one dose of 100 mg SC Q8W, 200 mg SC Q4W, or placebo in the 44-week, placebo-controlled portion of MS. - The currently approved prescribing information for guselkumab includes contraindications for serious hypersensitivity reactions, as well as warnings and precautions for hypersensitivity reactions, infections, and tuberculosis. - The safety profile of guselkumab for the treatment of moderately to severely active UC was generally similar to the safety profile of the currently approved indications (i.e., adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and adults with active psoriatic arthritis), although some adverse reactions (ARs) observed in the prior programs were not observed in studies of adults with moderately to severely active UC (e.g., tinea infections, herpes simplex infections). - Within MS, the safety findings between both administered maintenance dosages were comparable. - The size of the safety database and duration of exposure, while adequate to support approval and inform the common ARs	- The observed safety findings support a favorable safety profile for guselkumab for the treatment of adults with moderately to severely active UC. - The dosage regimens proposed for the treatment of adults with moderately to severely active UC are higher than those previously approved, and the safety database was inadequate to fully assess the risks of guselkumab in the intended use population. - To further assess the risk and potential for dose-dependence of adverse events of special interest PMRs are needed under 505(o)3, including: - Completion of the ongoing long-term extension studies in adults with moderately to severely active UC to evaluate for risk of serious outcomes, including malignancy, over a 5 year period of exposure (b) (4) - The safety findings were comparable between the maintenance dosage regimens administered in MS.

BLA 761061/S-021
TREMIFYA (guselkumab)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	associated with guselkumab use, are inadequate to fully assess the risk, and potential dose-dependence, of some adverse events of special interests, including malignancy, as these events occur infrequently and may be more likely to occur after prolonged exposure. • There are insufficient data to inform women of guselkumab use during pregnancy. A pregnancy registry study is currently ongoing for the approved indication as postmarketing requirements (PMRs) under 505(o)3. • No data are available to inform the potential effects of guselkumab administration to a nursing mother on the breastfed infant.	However, as the risk of therapy may increase with increased exposure to the therapy, and uncertainty remains regarding the risk and potential dose-dependence of some adverse events (e.g., malignancy), patients and providers should be instructed to use the lowest effective recommended dosage to maintain therapeutic response.

Source: Generated by FDA review team

Abbreviations: AR, adverse reaction; AWC, adequate and well-controlled; ES, endoscopic subscore; FDA, Food and Drug Administration; HEMI, histologic endoscopic mucosal improvement; IBD, Inflammatory Bowel Disease; ICE, intercurrent event; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; JAK, Janus Kinase; mMS, modified Mayo Score; MS, Maintenance Study; PI, prescribing information; PMR, postmarketing requirement; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous; UC, ulcerative colitis

2.2. Conclusions Regarding Benefit-Risk

Moderately to severely active UC is a serious chronic condition which, when inadequately treated, can cause significant morbidity and increased mortality. Although multiple therapies have been approved to treat this condition, there is a need for the development of novel therapies for patients who have had an inadequate response, loss of response, or intolerance to available therapeutic options.

Through demonstration of statistically significant differences on the analyses of clinically relevant and informative endpoints assessing guselkumab treated subjects compared to subjects who received placebo in the IS-2 and MS components of the QUASAR program, the Applicant established the benefit of guselkumab for the treatment of adults with moderately to severely active UC. In IS-2, guselkumab; administered as three IV doses of 200 mg at Weeks 0, 4, and 8; was superior to placebo in inducing the primary endpoint of clinical remission, as defined by the modified Mayo Score at Week I-12. In MS, both the guselkumab 100 mg SC and the guselkumab 200 mg SC dosage regimens were superior compared to placebo on evaluation of the primary endpoint of clinical remission at Week M-44. Support for the demonstration of effectiveness was also provided by the robust results of the analyses of multiplicity-controlled clinically relevant secondary endpoints at Week I-12 (IS-2) and Week M-44 (MS).

FDA has typically relied upon data from two independent adequate and well-controlled (AWC) trials to establish effectiveness for drugs for the treatment of moderately to severely active UC. The results of the single, large, multicenter AWC trial conducted under the QUASAR program, including both induction (IS-2) and maintenance (MS) studies, were statistically persuasive and robust across the prespecified primary endpoints, as well as multiple ranked secondary efficacy endpoints that have been accepted to represent clinically meaningful aspects of UC that if left inadequately treated or untreated could contribute to significant morbidity or serious clinical sequelae. The strength of evidence provided by this single AWC trial is considered to be equivalent to what is generally expected from two AWC trials and is adequate to establish substantial evidence of effectiveness of guselkumab for the treatment of adult patients with moderately to severely active UC.

As discussed in Section [6.3.2](#), analyses of the guselkumab 100 mg SC dose and the guselkumab 200 mg SC maintenance dosages each demonstrated statistically significant results compared to placebo at Week M-44 for the primary endpoint of clinical remission and multiplicity controlled clinically relevant secondary endpoints. Although the study was not powered to directly compare efficacy between these two treatment arms, point estimates of the response rates for the endpoints of clinical remission, corticosteroid-free clinical remission, histologic endoscopic mucosal improvement, and maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction were nominally higher in the 200 mg SC Q4W treatment arm compared to the 100 mg SC Q8W treatment arm. While the 100 mg SC Q8W dosage is the lowest effective dosage, the 200 mg SC Q4W dosage may be appropriate in some patients for whom it is deemed appropriate by their health care provider and may provide an additional option for adjustment of care for patients who experience an inadequate response or loss of response to treatment with the 100 mg SC Q8W dosage regimen.

The available safety data from the 200 mg (IS-1 and IS-2) and the 400 mg (IS-1) IV induction dosage regimens and the 100 mg SC and 200 mg maintenance regimens (MS) were adequate to support the demonstration of an acceptable safety profile and approval of the proposed recommended dosage regimens. Of note, the safety findings were generally similar to the safety profiles for the currently approved indications (i.e., adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and adults with active psoriatic arthritis), although some adverse reactions observed in the prior programs were not observed in studies of adults with moderately to severely active UC (e.g., tinea infections, herpes simplex infections). The safety findings were also comparable for both maintenance dosage regimens assessed in subjects with UC in MS. However, the size of the safety database and duration of exposure are inadequate to sufficiently assess the risk, and potential dose-dependence, of some adverse events of special interests, including malignancy, as these events occur infrequently and may be more likely to occur after prolonged exposure to guselkumab; the risk of guselkumab use during pregnancy; or the risk to a breastfed infant of guselkumab administration to a lactating woman. The uncertainty regarding these risks will be further evaluated through postmarketing studies and monitored routine pharmacovigilance post-approval. See Section [24](#).

Overall, the data submitted in support of BLA 761061/S-021 are adequate to establish substantial evidence of effectiveness and a favorable benefit-risk assessment to support approval of guselkumab for the treatment of adult patients with moderately to severely active UC.

The review team recommends approval of the 200 mg IV Q4W induction dosage and both the 100 mg SC Q8W and 200 mg SC Q4W maintenance dosages of guselkumab for the treatment of adults with moderately to severely active UC, with a recommendation included to use the lowest effective dosage needed to maintain therapeutic response. This allows prescribers flexibility and encourages reassessment of response during maintenance therapy in order to avoid the potential risks of long-term drug exposure to a higher dosage if patients are able to maintain therapeutic response with the lower dosage.

II. Interdisciplinary Assessment

3. Introduction

Product Information

Guselkumab is a human monoclonal IgG1 λ (lambda) antibody that selectively binds the p19 subunit of interleukin (IL) 23. With the submission of this supplemental biologics license application (sBLA), the Applicant seeks to expand the approved indications to include the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

Guselkumab was first approved by the FDA in 2017, under the trade name TREMIFYA, for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. It was subsequently approved for adult patients with active psoriatic

arthritis in 2020. The recommended dosage regimen for both approved indications is 100 mg subcutaneous (SC) at Week 0, Week 4, and every 8 weeks (Q8W) thereafter.

At the time of submission of this sBLA, two dosage forms are currently approved, both via SC administration:

- 100 mg/mL solution in a single-dose prefilled syringe assembled with UltraSafe Plus Needle Guard (PFS-U) and
- a single-dose One-Press patient-controlled injector.

Current Submission

The Applicant submitted data from three studies conducted under a single protocol (CNT01959UCO3001; QUASAR): Induction Study 1 (IS-1; phase 2b induction dose-ranging study), Induction Study 2 (IS-2; phase 3 induction study), and Maintenance Study (MS; phase 3 maintenance study) to support approval of guselkumab for the treatment of adult patients with moderately to severely active UC.

The Applicant proposes to rely upon data from IS-2 and MS to support the primary evaluation of efficacy and establish substantial evidence of effectiveness. Data from IS-1, IS-2, and MS were submitted to support the primary evaluation of safety.

The Applicant's proposed recommended dosage regimens are:

Induction:

The recommended induction dosage of TREMIFYA is 200 mg administered by intravenous infusion over a period of at least one hour at Week 0, Week 4, and Week 8.

Maintenance:

The recommended maintenance dosage of TREMIFYA is 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and Q8W thereafter, may be used.

The primary endpoint for both IS-2 and MS is the proportion of subjects achieving clinical remission, at Week I-12 and M-44 respectively.

In this sBLA, three new dosage forms are proposed for adults with moderately to severely active UC.

Induction therapy (intravenous [IV]):

- final vial product with 200 mg/20 mL (10 mg/mL) solution in a single-dose vial

Maintenance therapy (SC):

- 200 mg/2 mL single-dose prefilled syringe (PFS-U)
- 200 mg/2 mL single-dose prefilled pen (prefilled syringe assembled with Ypsomate autoinjector [PFS-Y])

Available Therapies

The currently approved systemic therapies for the treatment of moderately to severely active UC are summarized in [Table 3](#).

Table 3. Summary of Biologic Therapies and Small Molecules Currently Approved for the Treatment of Adults With Moderately to Severely Active Ulcerative Colitis

Product(s) Name	Dosing/ Administration
Infliximab (Remicade) BLA 103772* Initial Approval: 1998 Year of Approval for UC: 2005	IV 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks
Adalimumab (Humira) BLA 125057* Initial Approval: 2002 Year of Approval for UC: 2012	SC Initial dose: (Day 1): 160 mg Second dose: Two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
Golimumab (Simponi) BLA 125289 Initial Approval and Year of Approval for UC: 2009	SC Initial dose 200 mg at Week 0, followed by 100 mg at Week 2, and then 100 mg every 4 weeks
Vedolizumab (Entyvio) BLA 125476 Initial Approval: 2014 Year of Approval for UC: 2023	IV or SC Week 0: 300 mg infused intravenously over approximately 30 minutes Week 2: 300 mg infused intravenously over approximately 30 minutes Week 6: Patients may remain on ENTYVIO intravenous therapy or switch to subcutaneous injection after receiving two ENTYVIO intravenous doses administered at Week 0 and Week 2 Intravenous Infusion: 300 mg infused over approximately 30 minutes and then every 8 weeks thereafter Subcutaneous Injection: 108 mg subcutaneously once every 2 weeks
Tofacitinib (Xeljanz/Xeljanz XR) NDA 203214/NDA 208246 Initial Approval: 2012 Year of Approval for UC: 2018	Tablet, Oral Solution Xeljanz: 10 mg Twice daily for at least 8 weeks for a maximum of 16 weeks, then 5 or 10 mg twice daily Xeljanz XR22 mg Once daily for at least 8 weeks for a maximum of 16 weeks, then 11 mg once daily

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Product(s) Name	Dosing/ Administration
Upadacitinib (Rinvoq) NDA 211675 Initial Approval: 2019 Year of Approval for UC:2022	Extended-Release Tablets Induction: 45 mg once a day for 8 weeks Maintenance: 30 mg or 15 mg once daily (30 mg QD for patients with refractory, severe, or extensive disease)
Ustekinumab (Stelara) BLA 761044 Initial Approval: 2009 Year of Approval for UC: 2016	SC or IV A single IV infusion using weight-based dosing Induction: Up to 55 kg (IV): 260 mg (2 vials), greater than 55 kg to 85 kg: 390 mg (3 vials), greater than 85 kg: 520 mg (4 vials) Maintenance (8 weeks after initial dose): 90 mg SC injection every 8 weeks
Ozanimod (Zeposia) NDA 209899 Initial Approval: 2020 Year of Approval for UC: 2021	Capsule Titration is required for treatment initiation Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily Maintenance dosage Day 8 and thereafter: 0.92 mg once daily
Etrasimod (Velsipity) NDA 216956 Initial Approval and Year of Approval for UC: 2023	Tablet 2 mg once daily

Source: Reviewer generated table.

* Additional therapeutic options approved for the treatment of adults with moderately to severely active UC include biosimilar products to Remicade (infliximab): Avsola (Infliximab-AXXQ) BLA 761086, Inflectra (Infliximab-DYYB) BLA 125544, Ixifi (Infliximab-QBTX) BLA 761072, and Renflexis (Infliximab-ABDA) BLA 761054 and biosimilar products to Humira (adalimumab): Abrilada (Adalimumab-AFZB) BLA 761118, Amjevita (Adalimumab-ATTO) BLA 761024, Cyltezo (Adalimumab-ADBIM) BLA 761058, Hadlima (Adalimumab-BWWD) BLA 761059 Hulio (Adalimumab-FKJP), BLA 761154, Hyrimoz (Adalimumab-ADAZ) BLA 761071, Idacio (Adalimumab-AACF) BLA 761255, and Yusimry (Adalimumab-AQVH) BLA 761216

Abbreviations: IV, intravenous; QD, once daily; SC, subcutaneous; XR, extended release

The review team identified the following key review issues that have a significant impact on approvability and/or labeling.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Establishing Substantial Evidence of Effectiveness

3.1.1.2. Selection of Maintenance Dose

3.1.2. Key Safety Review Issues

No key safety review issues were identified for this application.

3.2. Approach to the Clinical Review

Determination of Efficacy

Data from IS-2 and MS were submitted to support the primary determination of efficacy. The results of the single, large, multicenter AWC trial conducted under the QUASAR program, including both induction (IS-2) and maintenance (MS) studies, were statistically persuasive and robust across the prespecified primary endpoints, as well as multiple ranked secondary efficacy endpoints that have been accepted to represent clinically meaningful aspects of UC that if left inadequately treated or untreated could contribute to significant morbidity or serious clinical sequelae. The strength of evidence provided by this single AWC trial is considered to be equivalent to what is generally expected from two AWC trials and is adequate to establish substantial evidence of effectiveness of guselkumab for the treatment of adult patients with moderately to severely active UC. See Section [2.2](#).

Induction Period

The primary determination of short-term (induction period) efficacy was established on the basis of a single study (IS-2). The primary analysis was conducted at Week I-12, assessing the proportion of subjects that achieved clinical remission in each treatment arm.

Maintenance Period

Evaluation of efficacy over a longer duration of treatment (through 56 weeks, including 12 weeks of induction and 44 weeks of maintenance) was conducted and analyzed separately in MS. MS utilized a randomized withdrawal design, which enrolled subjects who achieved clinical response after 12 weeks of induction therapy with guselkumab 200 mg or 400 mg regimens or placebo in IS-1 (the phase 2 dose-finding study) or IS-2. The primary analysis assessed the proportion of subjects in clinical remission at Week M-44.

Supportive Evidence

The Applicant also submitted efficacy data from IS-1; however, the ability of IS-1 to contribute to the primary determination of efficacy was limited by key differences from IS-2 and MS in the study endpoints, multiplicity control procedure, methods for handling intercurrent events, and the inclusion of an interim analysis. See Section [6.2.3](#).

Determination of Safety

Induction Period

The safety of 12 weeks of treatment with guselkumab was evaluated in the pooled population composed of subjects who received guselkumab regimens of 200 mg IV or 400 mg IV or placebo in IS-1 and subjects who received guselkumab 200 mg IV or placebo in IS-2.

Maintenance Period

The primary analysis of safety for long-term treatment with guselkumab focused on the 44-week placebo-controlled treatment period after re-randomization in MS in the population of subjects who achieved clinical response following 12 weeks of induction therapy with guselkumab 200 mg IV, 400 mg IV, or placebo. In MS, these subjects received placebo or guselkumab regimens of either 100 mg SC Q8W or 200 mg SC Q4W.

Supportive Evidence

The Applicant also submitted safety data from guselkumab clinical development programs for other indications (i.e., Crohn's disease [CD], plaque psoriasis, and psoriatic arthritis) as supportive evidence of safety.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1 to 3 for each indication.

- (1) Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

TREMIFYA (guselkumab) injection is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

- (2) SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

- a. Adequate and well-controlled clinical investigation(s):

- i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
ii. ☒ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence
OR
c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)

- (3) Complete response, if applicable

- d. ☐ SEE was established
e. ☐ SEE was not established (*if checked, omit item 2*)

Table 4. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations for Guselkumab¹

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CNT01959UCO3001 (Induction Study 1)	Adults with moderately to severely active ulcerative colitis	Phase: 2b Control type: Placebo Randomization: Standard randomization (1:1:1 ratio) Blinding: Double-blind	<u>Drug:</u> TREMFYA (Guselkumab) <u>Dosage:</u> • Guselkumab 200 mg IV Q4W (N=101) • Guselkumab 400 mg IV Q4W (N=107) • Placebo IV Q4W (N=105) Number treated: 313 Duration (quantity and units): 12 weeks for subjects who were clinical responders at Week I-12 and 24 weeks for subjects who were clinical non-responders at Week I-12	<u>Primary:</u> Clinical response at Induction Week 12 (Week I-12) <u>Secondary:</u> • Clinical remission at Week I-12 • Symptomatic remission at Week I-12 • Endoscopic improvement at Week I-12 • Histologic endoscopic mucosal improvement at Week I-12 • Endoscopic remission at Week I-12	Planned: 150 subjects, up to a maximum of 390 subjects Actual: 313	Centers: 141 Countries: 27

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CNT01959UCO3001 (Induction 2)	Adults with moderately to severely active ulcerative colitis	Phase: 3 Control type: Placebo Randomization: Standard randomization (3:2 ratio) Blinding: Double-blind	Drug: TREMFYA (Guselkumab) Dosage: - Guselkumab 200 mg IV Q4W (N=421) - Placebo IV (N=280) Number treated: 701 Duration (quantity and units): 12 weeks for subjects who were clinical responders at Week I-12, and 24 weeks for subjects who were clinical non-responders at Week I-12	<u>Primary:</u> Clinical remission at Induction Week 12 (Week I-12) <u>Secondary:</u> - Symptomatic remission at Weeks I-2, I-4, and I-12 - Endoscopic improvement at Week I-12 - Clinical response at Week I-12 - IBDQ remission at Week I-12 - Histologic endoscopic mucosal improvement at Week I-12 - Fatigue response at Week I-12 - Endoscopic remission at Week I-12	Planned: 736 Actual: 701	Centers: 240 Countries: 32

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
CNT01959UCO3001 (Maintenance Study)	Adults with moderately to severely active ulcerative colitis	Phase: 3 Control type: Placebo Randomization: Standard randomization (1:1:1 ratio) Blinding: Double-blind	Drug: TREMFYA (Guselkumab) Dosage: - Guselkumab 100 mg SC Q8W (N=186) - Guselkumab 200 mg SC Q4W (N=190) - Placebo SC (N=192) Number treated: 568 Duration (quantity and units): 44 weeks	<u>Primary:</u> Clinical remission at Maintenance Week 44 (Week M-44) <u>Secondary:</u> - Endoscopic improvement at Week M-44 - Maintenance of clinical response at Week M-44 - Histologic endoscopic mucosal improvement at Week M-44 - Symptomatic remission at Week M-44 - Corticosteroid-free clinical remission at Week M-44 - Fatigue response at Week M-44 - Maintenance of clinical remission at Week M-44 in subjects who achieved clinical remission after 12 weeks of induction - Endoscopic remission at Week M-44	Planned: 484 Actual: 568	Centers: 254 Countries: 32

Source: Reviewer generated table, adapted from submitted clinical study reports and adsl.xpt.

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies

Abbreviations: IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; M-44, Maintenance Week 44; N, number of subjects; NCT, national clinical trial; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

4. Patient Experience Data

The Applicant's evaluations of efficacy for IS-2 and MS were based on data collected to inform the evaluation of the modified Mayo Score (mMS) a 3-component clinician-reported outcome instrument (score 0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally reviewed endoscopy (ES). The Applicant also included several other patient-reported outcome instruments in IS-2 and MS including: the Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Short Form (SF)-7a, the Inflammatory Bowel Disease Questionnaire, and the PROMIS-29 assessment.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		Section 6
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		Section 16.2.2
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (please specify) Patient survey	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	The Division of Gastroenterology regularly participates in public meetings, workshops, and scientific conferences that engage stakeholders within the IBD community including patients, advocates, physicians, and researchers.
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	

Abbreviations: IBD, inflammatory bowel disease

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Guselkumab is a fully human IgG1 λ (lambda) antibody that selectively binds the p19 subunit of IL-23. In in vitro studies, guselkumab showed binding to human and cynomolgus IL-23 with equilibrium dissociation constants of 3.3 and 1.9 pM, respectively. Guselkumab completely inhibited the activity of native guinea pig IL-23 with comparable reactivity to human and cynomolgus IL-23. Guselkumab inhibited IL-23-induced phosphorylation of Signal Transducer and Activator of Transcription (STAT) 3 in a dose-dependent manner in NKL cells. Guselkumab inhibited IL-23-induced cytokine production (IL-17A, IL-17F, and IL-22) in mouse splenocytes and human peripheral blood mononuclear cells. The in vitro results indicate that guselkumab inhibits the binding of IL-23 to the IL-23 receptor and subsequent signaling events. An in vivo study in mice showed that guselkumab significantly inhibited increases in serum IL-1 α and granulocyte colony stimulating factor induced by human IL-23 in C57BL/6 mice. Decreased monocyte chemoattractant protein-1 was also evident after guselkumab treatment in this study. Thus, guselkumab may be effective in reducing gastrointestinal inflammation in patients with inflammatory bowel disease (IBD), including UC, through its activity blocking the interaction between IL-23 and IL-23 receptors.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	IL-23 antagonist
Mechanism of action	Guselkumab is a human IgG1 lambda monoclonal antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Blocking IL-23 with guselkumab inhibits the release of proinflammatory cytokines and chemokines.
Active moieties	Guselkumab
QT prolongation	Not applicable
General Information	
Bioanalysis	Serum guselkumab concentrations were measured using an ECLIA on the MSD platform. This is the same method used to quantify guselkumab in clinical studies supporting prior approvals for the psoriasis and psoriatic arthritis indications. Addenda to the method were provided to support quantitation of guselkumab in subjects with UC. Method validation and in-study bioanalysis were found to be acceptable.
Healthy subjects versus patients	Observed mean [SD] C_{max} values following a single 200 mg IV dose were comparable between healthy subjects (58.8 [10.9] to 59.1 [10.6] µg/mL) in study CNTO1959EDI1001 and subjects with UC in IS-1 (60.9 [16.8] µg/mL) and IS-2 (62.6 [15.2] µg/mL). Population PK analysis suggests that guselkumab clearance may be higher in subjects with UC relative to healthy subjects. Baseline C-reactive protein (CRP) laboratory values and subjects' prior biologic failure status were identified by the Applicant as covariates affecting guselkumab clearance, with higher baseline CRP or prior biologic failure associated with higher guselkumab clearance. However, the reported differences in clearance were small and not supported as likely clinically relevant. Notably, other covariates, such as modified Mayo Score (mMS) and disease duration, did not have a statistically significant effect on guselkumab clearance.

Characteristic	Drug Information
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Following induction dosing with 200 mg IV at Weeks 0, 4, and 8 in subjects with UC, mean (SD) peak serum guselkumab concentration at Week 8 was 68.3 (17.3) µg/mL (pooled data from IS-1 and IS-2). Following maintenance dosing with 100 mg SC Q8W in subjects with UC, mean (SD) trough concentrations at steady state ranged from 1.26 (0.86) µg/mL to 1.66 (1.24) µg/mL. Following maintenance dosing with 200 mg SC Q4W in subjects with UC, mean (SD) trough concentrations at steady state ranged from 9.48 (4.96) µg/mL to 10.7 (6.0) µg/mL.
Range of effective dose(s) or exposure	In IS-1, two induction dosages of 200 mg IV and 400 mg IV administered at Weeks 0, 4, and 8 were evaluated. Both doses demonstrated statistically significant results versus placebo on the primary endpoint (clinical response at Week I-12), as well as numerous secondary endpoints versus placebo. In MS, clinical responders from IS-1 and IS-2 were randomized to one of two maintenance dosages: 100 mg SC Q8W or 200 mg SC Q4W. Each dosage demonstrated statistically significant results on the primary endpoint (clinical remission at Week M-44), as well as numerous secondary endpoints, versus placebo.
Maximally tolerated dose or exposure	A maximally tolerated dose was not identified in subjects with UC. The highest induction dosage of guselkumab evaluated in subjects with UC was 400 mg IV administered at Weeks 0, 4, and 8. The highest maintenance dosage evaluated was 200 mg SC Q4W. The highest dosages evaluated were well-tolerated.
Dose proportionality	Guselkumab exhibited linear PK in healthy subjects and subjects with psoriasis between doses of 10 mg and 300 mg. In IS-1, median serum concentrations were approximately dose proportional between IV doses of 200 and 400 mg at each visit through Week I-12. At Week I-12, serum trough concentrations increased 2-fold for a 2-fold increase in dose.
Accumulation	Following induction with 200 mg IV administered at Weeks 0, 4, and 8; peak serum concentrations did not appear to accumulate. From Week I-4 to Week I-12, median trough concentrations accumulated about 1.6-fold to 1.7-fold. With maintenance dosing with 200 mg SC Q4W, serum trough concentrations are similar to those achieved with 200 mg IV Q4W during induction therapy. With maintenance dosing with 100 mg SC Q8W, serum trough concentrations decline until steady state is reached.
Time to achieve steady state	After initiation of maintenance dosing with 100 mg SC Q8W at Week M-4 or 200 mg SC Q4W at Week M-0, steady state is achieved by Week M-12 or Week M-8, respectively.
Bridge between to-be-marketed and clinical trial/study formulations	In IS-1 and IS-2, the IV induction dose was prepared by transferring drug substance from the approved guselkumab 100 mg PFS-U device into an IV bag containing 100 mL dextrose. In MS, all doses were administered using the 1-mL PFS-U presentation. Three new drug products are proposed for guselkumab administration in adults with UC including 1) a 200 mg/2 mL PFS-U for SC injection, 2) a 200 mg/2 mL PFS-Y (AI) for SC injection, and 3) a 200 mg/20 mL (10 mg/mL) vial product for IV infusion. Two BE studies (CNT01959ED11001 and

Characteristic	Drug Information
	CNTO1959CRD1003) were conducted to bridge the proposed drug product presentations with the 1-mL PFS-U used in IS-1, IS-2, and MS. Data from the BE studies support BE of the 1-mL PFS-U used in these studies and the to-be-marketed presentations.
	Absorption
Bioavailability	For a typical patient, the estimated absolute bioavailability (95% CI) for a SC dose is 58.8% (55.0, 62.6). This is consistent with the reported absolute bioavailability of 49% following a single 100 mg SC dose administered to healthy subjects.
T _{max}	The observed median T _{max} following a SC dose in healthy subjects was five days (study CNTO1959CRD1003).
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	The estimated typical apparent volume of distribution at steady state is 10.1 L.
Plasma protein binding	Not applicable
Drug as substrate of transporters	Not applicable
	Elimination
Mass balance results	Not applicable
Clearance	The estimated typical apparent clearance at steady state is 0.531 L/day.
Half-life	The mean half-life in subjects with ulcerative colitis is approximately 17 days.
Metabolic pathway(s)	Not applicable
Primary excretion pathways (% dose)	Not applicable

Characteristic	Drug Information
	<i>Intrinsic Factors and Specific Populations</i>
Body weight	Body weight was identified as a statistically significant covariate impacting the clearance of guselkumab. Higher body weight was associated with higher clearance. However, no clinically relevant associations were identified based on subject body weight. No dosage adjustments based on body weight are recommended for induction or maintenance dosing.
Age	Age was identified as a statistically significant covariate impacting the clearance of guselkumab. Younger age was associated with higher clearance. Note that age replaced baseline-estimated eGFR in the covariate model as the two covariates were correlated, while monoclonal antibody disposition is typically not affected by renal function. The effect of age on clearance is not considered to be clinically relevant, and no dosage adjustments are recommended. Note that the impact of age was determined based on adult subjects with UC enrolled in IS-1, IS-2, and MS. Pediatric subjects were not enrolled and included in analyses of age on guselkumab clearance.
Renal impairment	No dedicated studies have been conducted to evaluate the impact of renal impairment on the PK of guselkumab. In the population PK analysis, eGFR (eGFR >90 mL/min [normal, N=597]; 60 to 90 mL/min [mild, N=245]; and 30 to 60 mL/min [moderate, N=17]) was identified as a significant covariate on guselkumab clearance but was replaced with age in the final model, as age and eGFR were correlated. Renal function did not have a significant effect on steady state guselkumab exposures.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment on the PK of guselkumab. In the population PK analysis, total bilirubin (median [range] =6 [3, 47] µmol/L) was not identified as a significant covariate affecting guselkumab clearance.
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	As a monoclonal antibody, guselkumab is not expected to have a direct effect on drug metabolizing enzymes. However, CYP450 enzyme expression may be increased after guselkumab treatment due to improvement in inflammation. Available evidence suggests no clinically relevant effect of IL-23 antagonists on exposure of probe CYP substrates. However, further information may be needed as no dedicated DDI studies have been conducted in subjects with UC.
Inhibition/induction of transporter systems	Not applicable
	<i>Immunogenicity (if Applicable)</i>
Bioanalysis	ADAs to guselkumab were detected using an ECLIA method on the MSD platform. A tiered approach was used consisting of a screening test, a verification test, and measurement of antibody titers. Neutralizing antibodies were detected using a non-cell-based ECLIA method. The drug tolerance of the NAb assay used for the China cohort is lower than the observed guselkumab serum trough concentrations and was considered unsuitable for NAb assessment for subjects in China. Accordingly, subjects from the China cohort were excluded from the NAb assessment. As both the number of subjects from this cohort and the incidence of ADA were small, it is unlikely that removal of these subjects would impact the interpretability of the NAb assessment or the resulting conclusions.

BLA 761061/S-021
TREMFYA (guselkumab)

Characteristic	Drug Information
Incidence	In IS-1, IS-2, and MS, the ADA incidence among subjects who received the proposed to-be-marketed induction and maintenance dosage regimens was 11% (48/435). Among ADA-positive subjects that were evaluable for neutralizing antibodies, the incidence of neutralizing antibodies was 16% (N=6).
Clinical impact	In general, there was no apparent impact of immunogenicity on the efficacy of guselkumab. Although immunogenicity did not impact PK in most patients, serum trough concentrations were reduced in some ADA-positive patients with higher titers. A higher proportion of ADA-positive subjects reported injection site reactions relative to ADA-negative subjects. However, the incidence of injection site reactions was low.

Source: Approved labeling for guselkumab (TREMFYA); Module 2.7.2, Summary of Clinical Pharmacology; Module 2.7.1, Summary of Biopharmaceutic Studies; Integrated Summary of Immunogenicity; Population PK and Exposure-Response Modeling Report; Clinical Study Reports for CNTO1959CRD1003, CNTO1959EDI1001, QUASAR IS-1, QUASAR IS-2, and QUASAR Maintenance Study; Original Clinical Pharmacology Review for BLA 761061 in DARRTS (date July 13, 2017; reference ID 4123785).

Abbreviations: ADA, antidrug antibody; AI, autoinjector; BE, bioequivalence; CD, Crohn's disease; C_{max}, maximum plasma concentration; CRP, C-reactive protein; DDI, drug-drug interaction; ECLIA, electrochemiluminescence immunoassay; eGFR, estimated glomerular filtration rate; EPC, established pharmacologic class; IS-1, QUASAR Induction Study 1; IS-2, QUASAR Induction Study 2; IV, intravenous; MS, Maintenance Study; MSD, Meso Scale Discovery; PFS-U, prefilled syringe assembled with UltraSafe Plus Needle Guard; PFS-Y, prefilled syringe assembled with YpsoMate autoinjector; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SD, standard deviation; UC, ulcerative colitis; Week I-12, Induction Week 12; Week M-#, maintenance week number

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

In IS-1, a phase 2b placebo-controlled, induction dose-finding study, two induction dosages of guselkumab were evaluated: 200 mg IV Q4W and 400 mg IV Q4W versus placebo. Based on the results from an interim analysis of the first 150 randomized subjects in IS-1, 200 mg IV Q4W was selected to be evaluated further in the phase 3 placebo-controlled induction study, IS-2. The Applicant's proposed recommended induction dosage regimen for treatment of patients with moderately to severely active UC is 200 mg IV Q4W (i.e., 200 mg administered at Weeks 0, 4, and 8).

In MS, induction clinical responders from IS-1 and IS-2 were randomized to 1 of 2 maintenance dosage regimens of guselkumab, 100 mg SC Q8W or 200 mg SC Q4W, or placebo. The Applicant's proposed recommended maintenance dosage regimens for the treatment of adults with moderately to severely active UC are 200 mg SC Q4W beginning at Week 12 and 100 mg SC Q8W beginning at Week 16.

6.1.1. Induction Dosing

The proposed recommended induction dosage regimen of 200 mg IV administered at Weeks 0, 4, and 8 is an appropriate induction dosage for the treatment of adult patients with moderately to severely active UC.

The rationale for selection of the 200 mg and 400 mg IV doses for evaluation in IS-1 was based on the results of a phase 2 study of guselkumab in subjects with CD, data from the development program for a related therapeutic biologic, and physiologic rationale supporting potential differences in PK between subjects with CD and UC.

In the study of guselkumab in subjects with CD, 3 induction dosages were assessed; 200 mg, 600 mg, or 1200 mg IV administered at Weeks 0, 4, and 8. Based on this phase 2 study, the 200 mg dosage was selected for confirmatory evaluation in phase 3 evaluations in subjects with CD. The Applicant noted that for ustekinumab, a dual antagonist of IL-23 and IL-12 (different mechanism of action from guselkumab which only targets IL-23) also developed by the Applicant, the same dosage regimen was found to be safe and efficacious, and is therefore approved, for the treatment of CD and the treatment of UC. Thus, providing support for the suitability of the data from the phase 2 study of guselkumab in subjects with CD to support the selection of the 200 mg IV dosage for evaluation in subjects with UC. However, the Applicant hypothesized that patients with UC may have a higher inflammatory burden and be at risk for increased intestinal permeability that may lead to increased drug clearance compared to patients with CD. Thus, a higher induction dosage of 400 mg IV was also selected for evaluation in subjects with UC in IS-1.

Efficacy results from IS-1 showed that both induction dosages of 200 mg and 400 mg demonstrated statistically significant greater efficacy over placebo on the primary endpoint of clinical response at Week I-12. In addition, both induction doses demonstrated greater efficacy than placebo on multiple secondary endpoints at Week I-12, including: clinical remission, symptomatic remission, endoscopic improvement, histologic endoscopic mucosal improvement (HEMI), and endoscopic remission.^{2,3} For additional details, refer to Section [6.2.3.4](#).

Dose-/Exposure-Response Relationships for Induction Efficacy

In IS-1, there was no apparent dose-response on the primary endpoint of clinical response at Week I-12. Both the 200 mg and 400 mg IV dosages achieved similar results with 61.4% and 60.7% of subjects achieving clinical response at Week I-12, respectively, relative to 27.6% of subjects randomized to placebo. Both induction doses also achieved similar results for most secondary endpoints, although a numerically higher proportion of subjects randomized to 400 mg IV achieved HEMI at Week I-12 (200 mg IV: 20.8%; 400 mg IV: 27.1%; placebo: 8.6%).

A lack of dose-response was further suggested by data on pharmacodynamic (PD) markers. Both induction doses yielded greater reductions relative to placebo at Week I-12 in C-reactive protein (CRP), fecal calprotectin, serum IL-22, serum IL-17A, and serum interferon-gamma (IFN γ). While these inflammatory markers have not been supported to be fit-for-purpose assessments for use in adult UC trials, they may be used in clinical practice as markers of underlying inflammation attributed to UC disease activity. Both the 200 mg and 400 mg IV dosages performed comparably across all PD markers assessed, and a dose-dependent response was not apparent.

Exposure-response analyses for induction efficacy were conducted based on data from randomized and treated subjects with UC from IS-1 and IS-2 with a mMS of 5 to 9 at baseline and who had evaluable data for both pharmacokinetics (PK) and selected efficacy endpoints (i.e., clinical remission, clinical response, endoscopic improvement, and HEMI). These efficacy endpoints at Week I-12 were evaluated in relation to population PK predicted C_{trough} at Week I-12. For additional details on exposure-response analyses for efficacy, see Section [14.5](#).

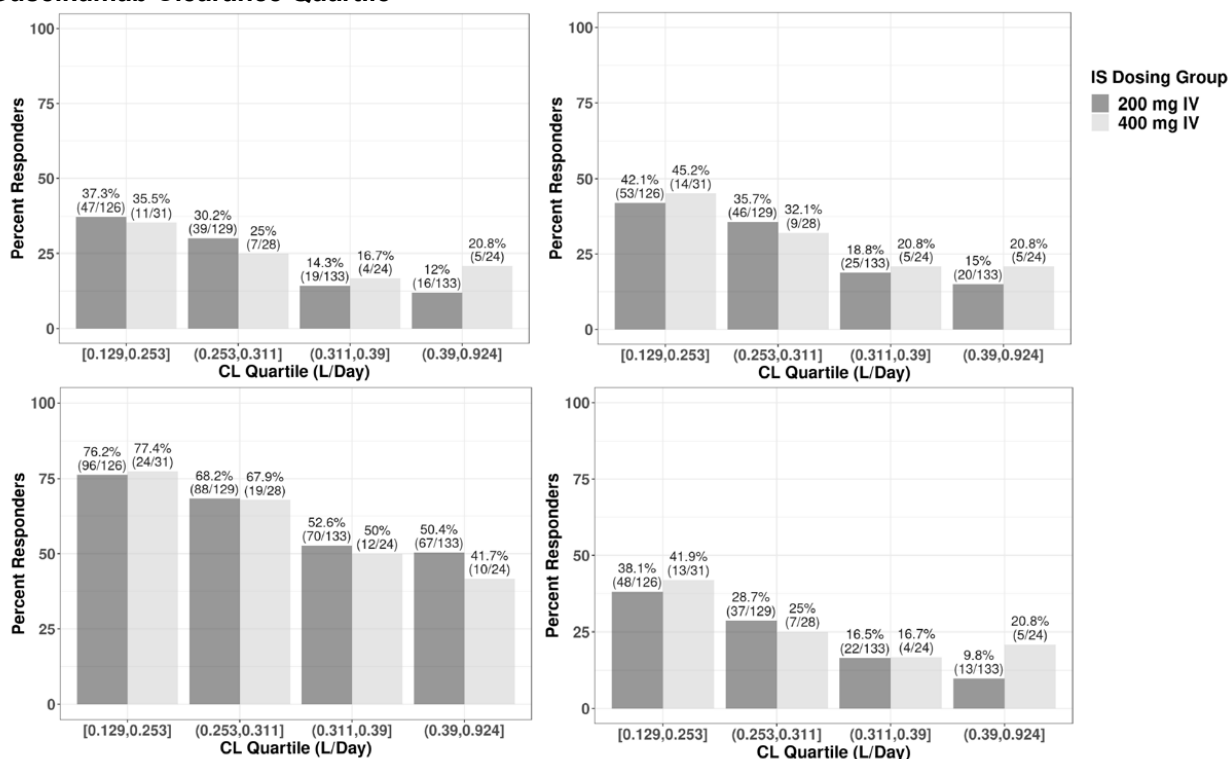
Initial exposure-response analyses suggested a positive exposure-response relationship between exposure and all efficacy endpoints (source: Figure 10, Summary of Clinical Pharmacology). However, this contrasts with the observed efficacy results in IS-1 where no dose-response was observed between the 200 mg and 400 mg IV dosages. It was thus hypothesized that disposition characteristics based on guselkumab clearance could be associated with the response to treatment, although the mechanisms by which clearance affects treatment response are unknown.

² Note that this endpoint was termed “endoscopic healing” in IS-1, IS-2, and MS by the Applicant. This endpoint was termed “endoscopic improvement” in this review document to maintain consistency with the terminology the Division recommends for this endpoint in UC trials.

³ This endpoint was termed “histologic endoscopic mucosal healing” in IS-1, IS-2, and MS by the Applicant. This endpoint was termed “histologic endoscopic mucosal improvement” (HEMI) in this review document to maintain consistency with the endpoints the Division recommends in UC trials.

Exposure-response analyses relating efficacy endpoints at Week I-12 by guselkumab clearance quartile are shown in [Figure 1](#). After accounting for guselkumab clearance, there was no apparent dose-response relationship for any efficacy endpoint, consistent with the observed lack of dose-response in IS-1. Results also indicate that lower rates of efficacy were observed for subjects with higher guselkumab clearance (e.g., patients with higher body weight or lower serum albumin). Despite this, a dosage greater than 200 mg IV is not expected to yield higher rates of efficacy. Thus, guselkumab clearance may be related to underlying disease and dosage increases may not improve efficacy, provided that adequate exposures have been achieved following administration of a lower dosage.

Figure 1. Exposure-Response Analysis Between Induction Efficacy Endpoints at Week I-12 and Guselkumab Clearance Quartile



Source: Figure 11, Summary of Clinical Pharmacology.

Top left, clinical remission; bottom left, clinical response; top right, endoscopic improvement; bottom right, histologic-endoscopic mucosal improvement

Abbreviations: CL, clearance; IS, Induction Study; IV, intravenous; Week I-12, Induction Week 12

Based on the analyses of efficacy data from the interim analysis of IS-1, the 200 mg IV dose was selected as the induction dosage for evaluation in IS-2. Efficacy results from IS-2 showed that subjects randomized to induction with 200 mg IV guselkumab demonstrated statistically significant greater efficacy over placebo on the primary endpoint of clinical remission at Week I-12 (22.6% versus 7.9%, respectively), as well as multiple ranked secondary endpoints at Week I-12, including: clinical response, symptomatic remission, endoscopic improvement, HEMI, and endoscopic remission. Refer to [Section 6.2](#) for additional details.

Overall, based on observed efficacy data from IS-1, IS-2, and exposure-response analyses for induction efficacy, the proposed induction dosage of 200 mg IV administered at Weeks 0, 4,

and 8 is an appropriate induction dosage for the treatment of adults with moderately to severely active UC.

6.1.2. Maintenance Dosing

The proposed recommended maintenance dosage regimens of 100 mg SC Q8W administered beginning at Week 16 and 200 mg SC Q4W administered beginning at Week 12 are both considered appropriate maintenance dosages for the treatment of adults with moderately to severely active UC.

The proposed maintenance dosage regimen of 100 mg SC Q8W was selected for evaluation in MS as it is the same dosage regimen currently approved for the treatment of adults with psoriasis and psoriatic arthritis. A dosage regimen of 200 mg SC Q4W was also selected for evaluation in MS to determine whether greater efficacy in adults with UC could be achieved through administration of a higher dosage. These regimens provide an approximate four-fold dose range for assessment of dose- and exposure-response relationships for maintenance treatment of UC.

Efficacy results from MS showed that each maintenance dosage regimen (i.e., 100 mg SC Q8W and 200 mg SC Q4W) demonstrated statistically significant greater efficacy over placebo on the primary endpoint of clinical remission at Week M-44. In addition, both maintenance regimens demonstrated greater efficacy over placebo on multiple ranked secondary endpoints at Week M-44, including corticosteroid-free clinical remission, endoscopic improvement, HEMI, and maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction. For additional details, refer to Section [6.2.2](#).

Dose-/Exposure-Response Relationships for Maintenance Efficacy

In MS, the 200 mg SC Q4W dosage regimen performed numerically better than the 100 mg SC Q8W dosage regimen on the primary endpoint of clinical remission at Week M-44, with 50.0% and 45.2% of patients achieving clinical remission, respectively, as compared with 18.9% of subjects randomized to placebo. The observed difference in proportions between the two guselkumab dosages is small and not likely to be clinically significant. Both maintenance dosage regimens also performed comparably on most secondary endpoints, although point estimates were higher for the 200 mg SC Q4W arm than the 100 mg SC Q8W arm, with the greatest difference seen on the results of the analysis of maintenance of clinical remission at Week M-44 in subjects who achieved clinical remission after 12 weeks of induction (100 mg SC Q8W: 60.6%; 200 mg SC Q4W: 72.5%; placebo: 33.9%). For the Week M-44 secondary endpoints of corticosteroid-free clinical remission, endoscopic improvement, and HEMI; response rates were also numerically higher among subjects randomized to 200 mg SC Q4W relative to those randomized to 100 mg SC Q8W; however, the differences between guselkumab treatment arms for these endpoints were small (< 5% difference). MS was not designed or powered to enable comparative evaluations between guselkumab treatment arms, and both dosage regimens established efficacy compared to placebo on the evaluation of clinically relevant endpoints.

Similar to IS-2, no apparent dose-dependent trend was observed on evaluations of exploratory PD markers assessed by the Applicant (i.e., CRP, fecal calprotectin) in MS. Among Week I-12 induction responders, reductions in CRP and fecal calprotectin were observed through Week M-

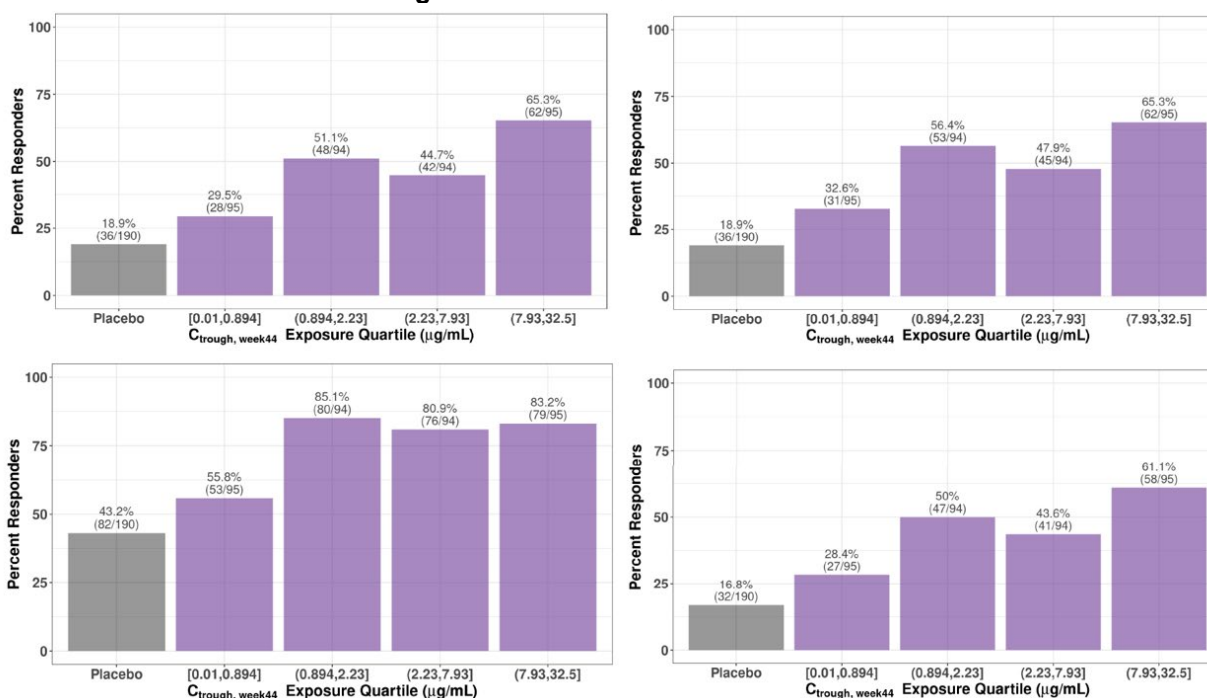
44 in subjects randomized to either dosage of guselkumab. In contrast, CRP and fecal calprotectin concentrations were found to increase during the treatment period for induction responders randomized to placebo in MS.

Exposure-response analyses for maintenance efficacy were conducted based on data from randomized and treated subjects with UC from MS with a mMS of 5 to 9 at induction baseline, and who had evaluable data for both PK and selected efficacy endpoints (i.e., clinical remission, clinical response, endoscopic improvement, and HEMI). These efficacy endpoints at Week M-44 were evaluated in relation to population PK predicted C_{trough} at Week M-44. Refer to Section [14.5](#) for additional details.

Exposure-response analyses suggested a positive relationship between trough concentrations at Week M-44 and all selected efficacy endpoints. While this may be consistent with observed results of analyses in MS for the endpoint of maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction, this contrasts with results for the primary endpoint of clinical remission and other secondary endpoints, which did not support the demonstration of apparent dose-response between the 100 mg SC Q8W and 200 mg SC Q4W dosages. Per the Applicant, as was observed in the exposure-response analyses to support induction therapy, serum guselkumab exposure remained statistically significant after analyses accounting for guselkumab clearance. Thus, exposure-response modeling based on guselkumab exposure was conducted. Exposure-response analyses relating efficacy endpoints at Week M-44 by guselkumab Week M-44 C_{trough} quartile are shown in [Figure 2](#).

Data from exposure-response analyses reveal a positive trend with trough concentrations at Week M-44. All exposure quartiles demonstrate efficacy over placebo, with an approximate plateau of effect (i.e., similar rates of efficacy) predicted for subjects with trough concentrations falling in quartiles two to four (Week M-44 trough concentration $>0.894 \mu\text{g/mL}$). For endpoints included in the E-R analyses (i.e., clinical remission and HEMI), the highest exposure quartile (Week M-44 trough concentration $>7.93 \mu\text{g/mL}$) appears to show the highest rate of efficacy relative to lower exposure quartiles.

Figure 2. Exposure-Response Analysis Between Maintenance Efficacy Endpoints at Week M-44 and Guselkumab Week M-44 Trough Concentration Quartile



Source: Figure 12, Summary of Clinical Pharmacology.

Top left, clinical remission; bottom left, clinical response; top right, endoscopic improvement; bottom right, histologic-endoscopic mucosal improvement

Note that clinical response is not considered to be a clinically relevant endpoint at long-term.

Abbreviations: $C_{\text{trough, week44}}$, guselkumab serum trough concentration at Week M-44; Week M-44, Maintenance Week 44

The observed median (interquartile range) serum trough concentrations at Week M-44 in MS were 1.10 (0.72, 1.84) $\mu\text{g/mL}$ for subjects randomized to 100 mg SC Q8W and 9.65 (6.62, 12.9) $\mu\text{g/mL}$ for subjects randomized to 200 mg SC Q4W. Based on the quartiles used for exposure-response efficacy analyses, at least 50% of subjects in the 100 mg SC Q8W arm fall in the second quartile of exposure (concentration between 0.894 and 2.23 $\mu\text{g/mL}$). Meanwhile, at least 75% of subjects in the 200 mg SC Q4W arm fall in the third and fourth exposure quartiles (concentration >2.23 $\mu\text{g/mL}$). The data thus suggest that similar rates of efficacy could be achieved with either the 100 mg SC Q8W or 200 mg SC Q4W dosage. Although E-R data suggest that higher rates of clinical remission and HEMI may be achieved with the 200 mg SC Q4W dosage compared to the 100 mg SC Q8W dosage, this is not consistent with the efficacy data from MS, which although the study was not designed or powered to characterize dose-response, only suggested a potential dose-response for the endpoint of maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction.

For discussion on the impact of body weight on guselkumab exposure, refer to Section 8.1.2. Observed guselkumab serum trough concentrations at Week M-44 by body weight quartile are shown in Table 44. Among subjects randomized to 200 mg SC Q4W, at least 75% of subjects in the highest body weight quartile (≥ 81.8 kg) are also expected to fall in the third and fourth exposure quartiles. However, among subjects randomized to 100 mg SC Q8W, most subjects in the highest body weight quartile (≥ 83.5 kg) are expected to fall in the lowest exposure quartile. Thus, for the 100 mg SC Q8W dosage, there is a possibility for reduced efficacy among subjects

with higher body weight. Nevertheless, observed maintenance efficacy rates were generally comparable across body weight quartiles with no trend of lower efficacy among subjects with higher body weight ([Table 45](#)). Accordingly, a recommendation for consideration of selection of the higher dosage for subjects of higher body weight is not warranted or supported by the available data. Of note, this finding was also observed in the development programs for the approved indications (i.e., psoriasis, psoriatic arthritis). The following statement is included in the current prescribing information in Section 12.3 PHARMACOKINETICS: Special Populations:

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

Overall, based on the results of efficacy analyses from MS and exposure-response analyses for maintenance efficacy, both proposed maintenance dosage regimens of 100 mg SC Q8W administered beginning at Week 16 and 200 mg SC Q4W administered beginning at Week 12 are considered appropriate maintenance regimens for the treatment of adults with moderately to severely active UC. The selection of the recommended maintenance dosage regimens is also discussed in Section [6.3.2](#).

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

The efficacy of guselkumab for the treatment of adults with moderately to severely active UC was evaluated in a single phase 3 induction study (Study CNTO1959UCO3001, IS-2) and a single phase 3 maintenance study (Study CNTO1959UCO3001, MS). Of note, MS included subjects who had completed IS-2. As such IS-2 and MS are considered to be a single AWC trial. Although two independent induction studies and one maintenance study are most commonly utilized to support a demonstration of substantial evidence of effectiveness (SEE) in development programs for therapies for the treatment of inflammatory bowel disease (e.g., CD and UC), the analyses of the primary and clinically relevant multiplicity controlled secondary endpoints from IS-2 and MS yielded statistically persuasive and robust results that are considered to provide the level of evidence generally expected from two independent AWC trials. See Section [6.3.1](#) for additional details.

6.2.1. Study CNTO1959UCO3001, Induction Study 2 (IS-2)

6.2.1.1. Design, IS-2

Study CNTO1959UCO3001, IS-2, is a randomized, double-blind, placebo-controlled study. Subjects were randomized in a 3:2 ratio to guselkumab 200 mg IV Q4W or placebo IV Q4W administered at Weeks I-0 (i.e., Induction Study Week 0), I-4, and I-8. The primary efficacy endpoint of clinical response; defined as a decrease from induction baseline in the mMS by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1; was evaluated at Week I-12. Study intervention after Week I-12 depended on subjects' clinical response status at Week I-12. The rules for study intervention after Week I-12 were as follows:

- Clinical responders at Week I-12 entered MS
- Subjects initially randomized to placebo who were not clinical responders at Week I-12 crossed over and received guselkumab 200 mg IV at Weeks I-12, I-16, and I-20
- Subjects initially randomized to guselkumab who were not clinical responders at Week I-12 received 3 doses of guselkumab 200 mg SC at Weeks I-12, I-16, and I-20
- Subjects not in clinical response at Week I-12 were re-evaluated at Week I-24. Clinical responders at Week I-24 entered MS while non-responders had a safety follow-up visit approximately 12 weeks after their last dose of study intervention.

6.2.1.2. Eligibility Criteria, IS-2

Key Inclusion Criteria:

- (1) Male or female, 18 years of age or older
- (2) Documented diagnosis (histological and either endoscopic or radiographic) of UC at least 3 months prior to screening
- (3) Moderately to severely active UC, defined as a baseline (Week I-0) mMS of 4 to 9, inclusive, using the Mayo endoscopy subscore obtained during the central review of the video endoscopy
- (4) Mayo rectal bleeding subscore ≥ 1 at baseline
- (5) Screening endoscopy with ≥ 2 on the endoscopy subscore of the Mayo score as obtained during the central review of the video endoscopy
- (6) Subject must:
 - a. Have failed a therapeutic biologic product or JAK inhibitor, i.e., have received treatment with one or more TNF α antagonists, vedolizumab, or tofacitinib at a dose approved for the treatment of UC, and have a documented history of failure to respond to or tolerate such treatment as defined in the study protocol OR,
 - b. Be naïve to a therapeutic biologic product or JAK inhibitor (i.e., TNF α antagonists, vedolizumab, and tofacitinib) or not have demonstrated a history of failure to respond to,

or tolerate, such a therapy and have a prior or current UC medication history that includes at least one of the following:

- i. Inadequate response to or failure to tolerate current treatment with oral corticosteroids or immunomodulators (6-mercaptopurine [6-MP] or azathioprine [AZA]); OR,
- ii. History of failure to respond to, or tolerate, at least one of the following therapies: oral or IV corticosteroids or immunomodulators (6-MP or AZA); OR,
- iii. History of corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC)

(7) Screening laboratory test results within the following parameters, and if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted during the approximately eight-week screening period:

- a. Hemoglobin ≥ 8.0 g/dL (International System of Units [SI]: ≥ 80.0 g/L)
- b. White blood cell count $\geq 3 \times 10^3$ cells/ μ L (SI: $\geq 3.0 \times 10^9$ cells/L)
- c. Neutrophils $\geq 1.5 \times 10^3$ cells/ μ L (SI: $\geq 1.5 \times 10^9$ cells/L)
- d. Platelets $\geq 100 \times 10^3$ cells/ μ L (SI: $\geq 100 \times 10^9$ cells/L)
- e. Serum creatinine ≤ 1.5 mg/dL (SI: ≤ 133 μ mol/L)
- f. Alanine aminotransferase and aspartate aminotransferase concentrations must be ≤ 2 times the upper limit of the normal range for the laboratory conducting the test.
- g. Direct (conjugated) bilirubin < 1.0 mg/dL

6.2.1.3. Statistical Analysis Plan, IS-2

Unless otherwise indicated, the presented statistical analyses were prespecified in the Applicant's statistical analysis plan (SAP).

Randomization

Randomization was stratified by prior therapeutic biologic product or JAK inhibitor failure status (i.e., subjects who had an inadequate response or failure to tolerate TNF α antagonists, vedolizumab, or tofacitinib) (Yes/No), region (Eastern Europe, Asia, or Rest of World), and concomitant use of corticosteroids at baseline (Yes/No).

Study Endpoints

Primary Endpoint

The primary endpoint was clinical remission at Week I-12, with clinical remission defined as having a stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability.

Secondary Endpoints

IS-2 included eight multiplicity-controlled secondary endpoints.

- Symptomatic remission at Week I-12, with symptomatic remission defined as a stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0
- Endoscopic improvement at Week I-12, with endoscopic improvement defined as an endoscopy subscore of 0 or 1 with no friability
- Clinical response at Week I-12, with clinical response defined as a decrease from induction baseline in the mMS by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. The mMS is the sum of the stool frequency, rectal bleeding, and endoscopy Mayo subscores.
- HEMI at Week I-12, with HEMI defined as achieving a combination of histologic improvement (i.e., neutrophil infiltration in $< 5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) and endoscopic improvement, defined as an endoscopy subscore of 0 or 1 with no friability
- Symptomatic remission at Week I-4
- Fatigue response at Week I-12, with fatigue response defined as a ≥ 7 -point improvement from induction baseline in PROMIS Fatigue SF-7a
- Symptomatic remission at Week I-2
- Endoscopic remission at Week I-12, with endoscopic remission defined as an endoscopy subscore of 0

See Section [16.1](#) for additional discussion on the scoring metrics.

Statistical Analysis

Analysis Population

The randomized analysis set (RAS), full analysis set (FAS), and safety analysis set (SAS) were the analysis populations key to this review. The RAS included all subjects who were randomized to the study. The FAS and SAS were identically defined and included all randomized subjects with a mMS of 5 to 9 who received at least 1 (partial or complete) dose of study intervention. The FAS was used for the primary efficacy analyses with subjects grouped according to their randomized study intervention.

Intercurrent Events

The following intercurrent events (ICEs) were defined in IS-2:

- (1) An ostomy or colectomy (partial or total)
- (2) Prohibited change in UC medication
- (3) Discontinuation of study intervention due to lack of efficacy or an adverse event (AE) of worsening of UC
- (4) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine
- (5) Discontinuation of study intervention due to reasons other than those in ICE 3 and 4

ICE categories 1-3 and 5 was handled with the composite strategy and subjects experiencing those ICE were considered non-responders. ICE category 4 was handled by the treatment policy strategy.

Efficacy Analysis (Primary Endpoint)

The primary endpoint (i.e., proportion of subjects in clinical remission) was evaluated by a Cochran-Mantel-Haenszel test stratified by therapeutic biologic and/or JAK inhibitor failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No). The adjusted treatment difference and corresponding 95% CI were reported using the stratified risk difference with Mantel-Haenszel weights with the same strata as defined above. The Wald-type CIs used the variance estimator described in [Kim and Won \(2013\)](#), whereas the [Sato \(1989\)](#) variance estimator is the default method for estimating the variance in SAS Proc Freq. However, in all analyses in all studies (i.e., IS-2 and MS), the two methods produced qualitatively similar CIs and the Applicant's method for calculating CIs appeared reasonable. Subjects missing any of the Mayo subscores used to define clinical remission were treated as non-responders (i.e., non-responder imputation).

Efficacy Analysis (Secondary Endpoints)

The statistical methodology for testing the major secondary endpoints was the same as the methodology for the primary endpoint.

Multiplicity Control

A fixed sequence testing procedure was used to control for multiplicity over the primary and major secondary endpoints at the two-sided 0.05 significance level. The endpoints were tested sequentially in the following order: clinical remission at Week I-12, symptomatic remission at Week I-12, endoscopic improvement at Week I-12, clinical response at Week I-12, HEMI at Week I-12, symptomatic remission at Week I-4, fatigue response at Week I-12, symptomatic remission at Week I-2, and endoscopic remission at Week I-12 ([Figure 13](#)).

Calculation of Mayo Subscores

Data on rectal bleeding and stool frequency were reported for the seven days prior to the targeted visit. For the prespecified primary analysis, the corresponding subscores were calculated by the

average of the most recent three consecutive days⁴ within this seven-day window. If three consecutive days were not available, then two consecutive days and the closest nonconsecutive day were selected. If two consecutive days were not available, then the three nonconsecutive days closest to the visit were selected. If three days within this seven-day window were not available, then the corresponding score was set to missing. The FDA preferred approach is to calculate the two subscores by averaging all daily values from the seven-day window excluding the day of bowel preparation and the day of endoscopy ([April 2022](#)). For the FDA preferred approach, a minimum of three consecutive days of completed diary entries or four non-consecutive days are necessary for the subscore to be considered non-missing. The Applicant performed an additional sensitivity analysis using this FDA preferred alternative calculation of the Mayo score. For the primary endpoint, the results based on the Sponsor's prespecified calculation and the FDA's preferred calculation of the Mayo subscores were qualitatively similar (Section [6.2.1.4](#)), and the choice of methods did not significantly impact conclusions.

6.2.1.4. Results of Analyses, IS-2

Subject Disposition

Subject disposition is summarized in [Table 7](#). A total of 1,005 subjects were screened, and 736 subjects were randomized. Among those 736 subjects, 702 subjects had a mMS of 5 to 9 and 34 had a mMS of 4. One of subjects with a mMS between 5 and 9 did not receive study intervention because of inadequate venous access for study intervention administration. Therefore, the Full Analysis Set included 701 subjects. Among the 701 subjects, 32 (4.6%) subjects (9 in the guselkumab 200 mg IV group and 23 in the placebo IV group) terminated study participation prior to Week I-12. Among the 701 subjects, 42 (6.0%) subjects (18 in the guselkumab 200 mg IV group and 24 subjects in the placebo IV group) discontinued study intervention prior to Week I-12. Overall, rates of discontinuation of study and treatment were slightly higher in the placebo group.

4 The following days are excluded from the average: 1) The day(s) medications were taken for constipation, diarrhea, or irregularity. 2) The day(s) of a procedure or preparation for procedure that could affect outcomes. 3) The 48 hours after the use of antimotility agents. 4) The 48 hours immediately following a colonoscopy.

Table 7. Subject Disposition, IS-2

Subject Disposition	Placebo IV Q4W n (%^a)	Guselkumab 200 mg IV Q4W n (%^a)	Total n (%^a)
Screened	-	-	1005
Randomized	296	440	736
Modified Mayo score			
Modified Mayo score =4	15	19	34
Modified Mayo score =5-9	281	421	702
FAS	280	421	701
Discontinued study before Week I-12	23 (8.2)	9 (2.1)	32 (4.6)
Reason for discontinuing study before Week I-12			
Death	2 (0.7)	0 (0)	2 (0.3)
Withdrawal by subject ^b	16 (5.7)	8 (1.9)	24 (3.4)
Other ^b	5 (1.8)	1 (0.2)	6 (0.9)
Discontinued treatment before Week I-12	24 (8.6)	18 (4.3)	42 (6.0)
Reason for discontinuing treatment before Week I-12			
Adverse event	1 (0.4)	6 (1.4)	7 (1.0)
Adverse event – worsening of UC	8 (2.9)	1 (0.2)	9 (1.3)
Death	1 (0.4)	1 (0.2)	2 (0.3)
Lack of efficacy	0	2 (0.5)	2 (0.3)
Physician decision	2 (0.7)	1 (0.2)	3 (0.4)
Pregnancy	0	1 (0.2)	1 (0.1)
Withdrawal by subject ^b	11 (3.9)	6 (1.4)	17 (2.4)
Other ^b	1 (0.4)	0	1 (0.1)

Source: Reviewer generated table using ADDISP.xpt, ADMAYO.xpt, and ADSL.xpt.

^a Percentages are based on the number of the subjects in the FAS.

^b One subject in the guselkumab 200 mg group withdrew from the study and one subject in the placebo group discontinued the study prior to Week I-12 for reasons related to the conflict in Ukraine.

Abbreviations: FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; Q4W, every 4 weeks; n, percentage of subjects in the FAS; UC, ulcerative colitis

Protocol Deviations

Study-specific major protocol deviations are summarized in [Table 8](#). Sixty-eight (9.7%) subjects in the FAS had major protocol deviations prior to Week I-12, with the most common protocol deviation being entering the study without satisfying the entry criteria (39/701 [5.6%]). Protocol deviations were not considered to have impacted the conclusions of the study.

Table 8. Major Protocol Deviations (FAS), IS-2

Parameter	Placebo IV Q4W	Guselkumab	Total
	N=280 n (%)	200 mg IV Q4W N=421 n (%)	N=701 n (%)
Subjects with ≥1 major protocol deviation	26 (9.3)	42 (10.0)	68 (9.7)
Entered but did not satisfy criteria	16 (5.7)	23 (5.5)	39 (5.6)
Received a disallowed concomitant treatment	3 (1.1)	1 (0.2)	4 (0.6)
Received wrong treatment or incorrect dose	0	1 (0.2)	1 (0.1)
Other ^a	9 (3.2)	20 (4.8)	29 (4.1)

Source: Clinical Study Report, Table 1 (page 72). Verified by reviewer.

^a One subject in the placebo group and one subject in the guselkumab 200 mg group had a significant protocol deviation related to COVID-19.

Abbreviations: FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment arm; n, percentage of subjects with given protocol deviation; Q4W, every 4 weeks

Demographic Characteristics

Baseline demographic characteristics of the FAS population are summarized in [Table 9](#). In the FAS population, the majority of subjects were male (56.9%) and White (72.5%). The median age was 39.0 years (range 18 to 79 years), and the most common region was Eastern Europe (42.2%). The baseline demographic characteristics were generally similar between the two treatment arms.

Table 9. Demographic and Baseline Characteristics (FAS), IS-2

Demographic Characteristics	Placebo IV Q4W N=280	Guselkumab 200 mg IV Q4W N=421	Total N=701
Age Group, n (%)			
<65 Year	266 (95.0)	394 (93.6)	660 (94.2)
≥65	14 (5.0)	27 (6.4)	41 (5.8)
Age, years			
Mean (SD)	39.8 (13.4)	41.0 (13.9)	40.5 (13.7)
Median	38.0	39.0	39.0
IQR	29.0, 48.0	30.0, 51.0	30.0, 50.0
Min, Max	18, 75	18, 79	18, 79
Sex, n (%)			
Female	119 (42.5)	183 (43.5)	302 (43.1)
Male	161 (57.5)	238 (56.5)	399 (56.9)
Race, n (%)			
American Indian or Alaska Native	0	1 (<1)	1 (<1)
Asian	62 (22.1)	88 (20.9)	150 (21.4)
Black or African American	3 (1.1)	4 (1.0)	7 (1.0)
Native Hawaiian or African American	0	2 (<1)	2 (<1)
White	205 (73.2)	303 (72.0)	508 (72.5) ^a
Multiple	10 (3.6)	22 (5.2)	32 (4.6)
Not Reported	0	1 (<1)	1 (<1)
Ethnicity, n (%)			
Hispanic or Latino	22 (7.9)	25 (5.9)	47 (6.7)
Not Hispanic or Latino	239 (85.4)	368 (87.4)	607 (86.6)
Not Reported	19 (6.8)	28 (6.7)	47 (6.7)
Region, n (%)			
Asia	58 (20.7)	84 (20.0)	142 (20.3)
Eastern Europe	117 (41.8)	179 (42.5)	296 (42.2)
Latin America	17 (6.1)	25 (5.9)	42 (6.0)
North America	13 (4.6)	22 (5.2)	35 (5.0)
Western Europe	45 (16.1)	67 (15.9)	112 (16.0)
Other ^b	30 (10.7)	44 (10.5)	74 (10.6)
Weight (kg)			
Mean (SD)	71.8 (17.0)	72.9 (16.7)	72.5 (16.8)
Median	70.0	71.3	70.6
IQR	58.8, 84.2	60.0, 83.7	59.2, 84.0
Min, Max	38, 122	40, 127	38, 127

Source: Clinical Study Report Table 2 (pages 78-79). Verified by reviewer using ADSL.xpt.

^a Percent of subjects who identified as White was 72.47% and is rounded to 72% in the label

^b Includes countries Australia, Israel, Jordan and New Zealand.

Abbreviations: FAS, full analysis set; IQR, interquartile range; IS, Induction Study 2; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q4W, every 4 weeks; SD, standard deviation

Other Baseline Characteristics

Baseline UC disease characteristics of the FAS population are summarized in [Table 10](#). In the FAS population, the median duration of disease was 5.3 years, and the median mMS was 7.0. The baseline disease characteristics were generally similar between the two treatment arms.

Table 10. Baseline UC Characteristics (FAS), IS-2

Baseline Characteristics	Placebo IV Q4W N=280	Guselkumab 200 mg IV Q4W N=421	Total N=701
Duration, years			
Mean (SD)	7.1 (6.5)	7.8 (7.7)	7.5 (7.3)
Median	5.2	5.5	5.3
IQR	2.4, 9.5	2.6, 10.6	2.5, 10.0
Min, Max	0, 41	0, 48	0, 48
Extent, n (%)			
Extensive	147 (52.5)	188 (44.7)	335 (47.8)
Limited to left side of colon	133 (47.5)	233 (55.3)	366 (52.2)
Total Mayo score			
Mean (SD)	9.2 (1.3)	9.1 (1.4)	9.1 (1.4)
Median	9.0	9.0	9.0
IQR	8.0, 10.0	8.0, 10.0	8.0, 10.0
Min, Max	6, 12	6, 12	6, 12
Modified Mayo score			
Mean (SD)	6.9 (1.1)	6.9 (1.1)	6.9 (1.1)
Median	7.0	7.0	7.0
IQR	6.0, 8.0	6.0, 8.0	6.0, 8.0
Min, Max	5, 9	5, 9	5, 9
Modified Mayo score, n (%)			
5-6	102 (36.4)	147 (34.9)	249 (35.5)
7-9	178 (63.6)	274 (65.1)	452 (64.5) ^a
Endoscopy score, n (%)			
2	100 (35.7)	125 (29.7)	225 (32.1)
3	180 (64.3)	296 (70.3)	476 (67.9)
Oral CS use ^b , n (%)			
No	160 (57.1)	239 (56.8)	399 (56.9)
Yes	120 (42.9)	182 (43.2)	302 (43.1)
Therapeutic biologics and JAK inhibitors category ^b , n (%)			
Experienced without failure	7 (2.5)	11 (2.6)	18 (2.6)
Failure	136 (48.6)	208 (49.4)	344 (49.1)
Naive	137 (48.9)	202 (48.0)	339 (48.4)

Source: Based on Clinical Study Report Table 3 (pages 81-82). Verified by reviewer using ADADT.xpt, ADBDC.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a Percentage of subjects with MMS 7-9 is 64.48% and is rounded to 64% in the label

^b Values are based on data captured in the eCRF and are not identical to the values used for stratification in the IWRS.

Abbreviations: CS, corticosteroid; eCRF, electronic case report form; FAS, full analysis set; IQR, interquartile range; IS-2, Induction Study 2; IWRS, Interactive Web Response System; mMS, modified Mayo Score; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q4W, every 4 weeks; SD, standard deviation; UC, ulcerative colitis

Concomitant Therapy and Medication History

Concomitant medication usage related to UC in the FAS population is summarized in [Table 11](#). In the FAS, 612/701 (87.3%) subjects were receiving 1 or more concomitant medications for UC. Concomitant medication usage was generally similar between the two treatment arms.

Table 11. Summary of Concomitant Medications for UC at Baseline (FAS), IS-2

Concomitant Medication	Placebo IV Q4W N=280 n (%)	Guselkumab 200 mg IV Q4W N=421 n (%)	Total N=701 n (%)
Subjects who received any of the following UC medications	247 (88.2)	365 (86.7)	612 (87.3)
Oral corticosteroid use	120 (42.9)	182 (43.2)	302 (43.1)
Corticosteroid use (excl. budesonide and beclomethasone dipropionate)	88 (31.4)	158 (37.5)	246 (35.1)
Budesonide	27 (9.6)	22 (5.2)	49 (7.0)
Beclomethasone dipropionate	6 (2.1)	2 (0.5)	8 (1.1)
Immunomodulatory drugs	54 (19.3)	92 (21.9)	146 (20.8)
6-mercaptopurine	5 (1.8)	11 (2.6)	16 (2.3)
Azathioprine	44 (15.7)	78 (18.5)	122 (17.4)
Methotrexate	5 (1.8)	3 (0.7)	8 (1.1)
Oral aminosaliculates	204 (72.9)	304 (72.2)	508 (72.5) ^a

Source: Based on Clinical Study Report Table 4 (pages 84), Verified by reviewer using ADMEDRVW.xpt, ADSL.xpt.

^a Percent of subjects who used oral aminosaliculates 72.47% and is rounded to 72% in the label

Abbreviations: FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks; UC ulcerative colitis

Treatment Compliance

Treatment compliance with investigational product administration (IP) was generally high. At each of the scheduled visits, over 90% of subjects in the FAS received all scheduled doses of IP (i.e., doses at Week 0, Week 4, and Week 8) ([Table 12](#)).

Table 12. Exposure to Scheduled Study Intervention- IP Administration (FAS), IS-2

Study Week	Placebo IV Q4W N=280 n (%)	Guselkumab 200 mg IV Q4W N=421 n (%)	Total N=701 n (%)
Subjects receiving a scheduled study intervention			
Week I-0	280 (100)	421 (100)	701 (100)
Week I-4	265 (94.6)	408 (96.9)	673 (96.0)
Week I-8	253 (90.4)	401 (95.2)	654 (93.3)

Source: Clinical Study Report Table TSIX501 (page 1108). Verified by reviewer using ADEX.xpt.

Abbreviations: FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks

Efficacy Results – Primary Endpoint

The percentage of subjects achieving clinical remission was larger in the guselkumab group (22.6%), as compared to the placebo group (7.9%) ([Table 13](#)). The adjusted difference (95% CI) in remission rates between the 2 treatment groups was 14.9% (9.9%, 19.9%). The prespecified test of the null hypothesis (e.g., equal remission rates) was statistically significant with a p-value of <0.001, indicating that there was a difference in the remission rates between the 2 arms.

Table 13. Clinical Remission at Week I-12 (FAS), IS-2

Parameter	Placebo IV Q4W N=280	Guselkumab 200 mg IV Q4W N=421
Number (%) of subjects achieving clinical remission at Week I-12	22 (7.9%)	95 (22.6%)
95% CI ^a	(4.7%, 11.0%)	(18.6%, 26.6%)
Adjusted treatment difference (95% CI) ^b	14.9% (9.9%, 19.9%)	
p-Value ^c	<0.001	

Source: Clinical Study Report Table 5 (page 92). Verified by reviewer using ADEFF.xpt.

^a The 95% CIs of the percentages for each treatment group were based on the normal approximation.

^b The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor failure status and concomitant use of corticosteroids.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; MH, Mantel-Haenszel; N, number of subjects in treatment group; Q4W, every 4 weeks

For the clinical remission endpoint, 53/701 (7.6%) subjects experienced ICE 1-3 or 5 and were classified as non-responders (20/421 [4.8%] subjects in the guselkumab 200 mg IV group and 33/280 [11.8%] subjects in the placebo IV group; [Table 68](#)). Of note, only 20/721 (2.7%) subjects experienced only ICE 5 (i.e., treatment discontinuation for reasons other than lack of efficacy, AE, COVID-19, or the conflict in Ukraine). Therefore, most of the experienced intercurrent events were likely due to an unfavorable outcome and the use of non-responder imputation to handle these ICE is considered appropriate. After accounting for the ICE strategies, 9/701 (1.3%) subjects had a missing mMS at Week I-12 (3/421 [0.7%] subjects in the guselkumab 200 mg IV group and 6/280 [2.1%] subjects placebo IV group).

To evaluate the robustness of the results to the methods for handling missing data, the Applicant performed a tipping point analysis. No tipping point was found. Under the most extreme scenario (i.e., all 3 guselkumab 200 mg IV subjects were non-responders and all 6 placebo IV subjects were responders), the results remained statistically significant ($p < 0.001$). A second sensitivity analysis, using the FDA preferred method for calculating the mMS, resulted in 25 and 96 subjects respectively in the placebo and guselkumab 200 mg IV groups with clinical remission and produced similar results (treatment difference = 14.1%, 95% CI = 8.9% to 19.2%, p -value < 0.001). The Applicant indicated that only 18 subjects (10/421 [2.4%] in the guselkumab 200 mg IV group and 8/280 [2.9%] in the placebo group) had source data that could not be verified due COVID-19 or the conflict in Ukraine, and that a sensitivity analysis excluding those subjects produced similar results ($p < 0.001$).

The primary analysis was repeated in subgroups defined by demographic characteristics ([Figure 21](#)) and baseline UC characteristics ([Figure 22](#)). In key subgroups analyzed, the proportion of subjects achieving clinical remission at Week I-12 tended to favor guselkumab relative to placebo. However, among subjects with prior therapeutic biologic and/or JAK inhibitor therapy failure, 26/208 (12.5%) and 5/136 (3.7%) in the guselkumab 200 mg IV group and placebo IV group, respectively, achieved clinical remission, and the adjusted difference (95% CI) in remission rates was only 8.8% (3.3%, 14.3%). In addition to evaluating subgroups within the FAS, an additional analysis evaluated the subgroup of subjects with a mMS of 4. The response rates in the guselkumab 200 mg IV group and placebo IV group were respectively 3/15 (20.0%) and 11/19 (57.9%), and the adjusted difference (95% CI) in remission rates was 36.7% (10.3%, 63.1%).

Efficacy Results – Secondary Endpoints

Results for the secondary endpoints are summarized in [Table 14](#). The response rates for each of the endpoints was higher in the guselkumab 200 mg IV group, as compared to the placebo group. Based on the prespecified multiple testing procedure, six of the key secondary endpoints were statistically significant (i.e., symptomatic remission at Week I-12, endoscopic improvement at Week I-12, symptomatic remission at Week I-4, HEMI at Week I-12, fatigue response at Week I-12). The key secondary endpoints of symptomatic remission at Week I-2 and endoscopic remission at Week I-12 were not statistically significant; although, the results for endoscopic remission at Week I-12 were nominally significant. Results of analyses of these endpoints by prior use of therapeutic biologic products and/or JAK inhibitors are presented in [Table 69](#).

Table 14. Efficacy Results for Secondary Endpoints (FAS), IS-2

Secondary Endpoints	Placebo IV Q4W N=280 n (%)	Guselkumab 200 mg IV Q4W N=421 n (%)	Adjusted Treatment Difference ^a	p-Value ^b
Symptomatic remission at Week I-12	58 (20.7%)	210 (49.9%)	29.4% (22.8,36.0)	<0.001
Endoscopic improvement at Week I-12	31 (11.1%)	113 (26.8%)	16.0% (10.5,21.4)	<0.001
Clinical response at Week I-12	78 (27.9%)	259 (61.5%)	33.8% (26.9,40.7)	<0.001
Symptomatic remission at Week I-4	36 (12.9%)	95 (22.6%)	9.9% (4.4,15.4)	<0.001
Histologic endoscopic mucosal improvement at Week I-12	21 (7.5%)	99 (23.5%)	16.2% (11.1,21.2)	<0.001
Fatigue response at Week I-12	60 (21.4%)	173 (41.1%)	19.8% (13.1,26.4)	<0.001
Symptomatic remission at Week I-2	26 (9.3%)	51 (12.1%)	3.0% (-1.5,7.5)	0.21
Endoscopic remission at Week I-12	14 (5.0%)	63 (15.0%)	10.1% (5.9,14.3)	<0.001

Source: Clinical Study Report Table 6 (page 95). Verified by reviewer using ADEFF.xpt, ADHIST1.xpt, ADIBDQ1.xpt, ADPROMS1.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^b The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor failure status and concomitant use of corticosteroids

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; MH, Mantel-Haenszel; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks

The review team performed additional supplementary analyses for the fatigue endpoint to address several concerns with the methodology utilized in the Applicant's analyses. First, the prespecified analysis used the raw score conversion table to calculate the PROMIS-Fatigue SF-7a score, whereas the FDA preferred scoring method uses the response pattern scoring approach. Second, as discussed in Section [16.4](#), there may not be a single clinically meaningful threshold for the binary definition of "fatigue response," and the appropriate threshold may depend on baseline symptom severity. To address these first two concerns, the review team repeated the primary analysis for fatigue response using the response pattern scoring approach and a range of thresholds ([Table 77](#)) to define response, in addition to evaluating the PROMIS-Fatigue SF-7a score as a continuous outcome ([Table 71](#)). Results from all analyses remained nominally statistically significant with p-values below 0.001. Third, there was a concern with using non-responder imputation to handle ICE, as the occurrence of an ICE and the lack of a fatigue response may not be strongly correlated since fatigue is a more distal UC symptom (as compared to symptoms like diarrhea that are clearly mechanistically attributable to colonic mucosal inflammation). It is unclear whether ICE such as prohibited changes in UC medication are

related to negative fatigue outcomes, and a non-negligible proportion of subjects experiencing ICE could still qualify as fatigue responders.

Experiencing an ICE (e.g., prohibited changes in UC medication) was considered more likely to reflect poor outcomes for symptoms such as rectal bleeding and stool frequency, or lack of histologic improvement. Therefore, supplementary analyses were performed to evaluate if the results for the fatigue endpoint were heavily influenced by using the composite strategy (i.e., non-responder imputation) for handling ICE 1-3 and 5. In the guselkumab 200 mg IV and placebo groups, 21/421 (5.0%) and 33/280 (11.8%) subjects experienced 1 of these ICE.

Although a larger percentage of subjects experienced an ICE in the placebo group and were imputed as non-responders, the difference in ICE rates (i.e., 11.8% to 5.0% = 6.8%) was not thought to be the key factor in guselkumab's observed effect on the fatigue endpoint and the corresponding adjusted treatment difference of 19.8%. Of note, a likely conservative analysis omitting subjects with these ICE resulted in 60/247 (24.3%) subjects in the placebo group and 173/400 (43.2%) subjects in the guselkumab 200 mg IV having a fatigue response, with a corresponding adjusted treatment difference (95% CI) of 19.0% (11.9%, 26.1%). Finally, repeating the primary analysis using an extreme imputation procedure for subjects with one of these ICE (i.e., all guselkumab subjects were non-responders and all placebo subjects were responders) still produced a nominally significant p-value of 0.032. Considered collectively, these analyses provided strong evidence of the effect of treatment with guselkumab on fatigue at Week I-12 compared to placebo.

Finally, the review team evaluated the mean change from baseline in the stool frequency and rectal bleeding subscores over time. [Table 72](#) shows that for both subscores, the change from baseline was larger (i.e., more negative) in the 200 mg guselkumab group, as compared to the placebo group, starting at Week I-2.

6.2.2. Study CNTO1959UCO3001, Maintenance Study (MS)

6.2.2.1. Design, MS

Study CNTO1959UCO3001, MS, is a randomized, double-blind, placebo-controlled withdrawal study. The study population included clinical responders from IS-1 and IS-2. The following two populations were randomized in a 1:1:1 ratio to guselkumab 200 mg SC Q4W, guselkumab 100 mg SC Q8W, or placebo SC.

- Subjects who were randomized to guselkumab in the induction studies and were clinical responders at Week I-12
- Subjects who were randomized to placebo in the induction studies, were not clinical responders at Week I-12, crossed-over to guselkumab, and were clinical responders at Week I-24

Additionally, the following two populations were included in MS, but did not undergo randomization.

- Subjects who were randomized to placebo in the induction studies and were clinical responders at Week I-12
- Subjects who were randomized to guselkumab in the induction studies, were not clinical responders at Week I-12, remained on guselkumab from Week I-12 to Week I-24, and were clinical responders at Week I-24

Primary efficacy endpoints were evaluated at Week M-44. Subjects receiving oral corticosteroids on entry into MS began tapering their daily dose of corticosteroids at Week M-0. During MS, subjects in clinical flare between Week M-4 and Week M-32 (inclusive) underwent an endoscopy to evaluate for loss of clinical response (evaluated by mMS). Randomized subjects who met predefined criteria for loss of clinical response (i.e., no longer satisfied the definition of clinical response) were eligible to receive a single-blinded dose adjustment to guselkumab 200 mg SC Q4W. Subjects randomized to guselkumab 200 mg SC Q4W received a sham dose adjustment (i.e., stayed at the same dose).

6.2.2.2. Eligibility Criteria, MS

The randomized population for MS were clinical responders to IV guselkumab from IS-1 or IS-2 who were randomized to receive guselkumab 200 mg SC Q4W, guselkumab 100 mg SC Q8W, or placebo SC. These included guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24. The eligibility criteria for IS-1 and IS-2 were the same (refer to Section [6.2.1.2](#)).

6.2.2.3. Statistical Analysis Plan, MS

Unless otherwise indicated, the presented statistical analyses were prespecified in the SAP.

Randomization

Randomization was stratified by clinical remission status at maintenance baseline (Yes/No), concomitant use of corticosteroids at maintenance baseline (Yes/No), and initial induction treatment (guselkumab 400 mg IV, guselkumab 200 mg IV, and placebo IV to guselkumab 200 mg IV).

Study Endpoints

Definitions for endpoints (e.g., clinical remission) also used in IS-2 were provided in Section [6.2.1.3](#) and will not be repeated here.

Primary Endpoint

The primary endpoint was clinical remission at Week M-44.

Secondary Endpoints

MS included eight multiplicity-controlled secondary endpoints.

- Symptomatic remission at Week M-44
- Endoscopic improvement at Week M-44
- Corticosteroid-free (i.e., not requiring any treatment with corticosteroids for at least eight weeks prior) clinical remission at Week M-44
- Clinical response at Week M-44
- HEMI at Week M-44
- Fatigue Response at Week M-44
- Clinical remission at Week M-44 among the subjects who had achieved clinical remission at maintenance baseline (i.e., maintenance of clinical remission at M-44 in subjects who achieved clinical remission after 12 weeks of induction)
- Endoscopic remission at Week M-44

Statistical Analysis

Analysis Population

The RAS, randomized full analysis set (RFAS), and randomized safety analysis set were the analysis populations key to this review. The RAS included all subjects who were randomized in this study. The RFAS and the randomized safety analysis set are identically defined and included all subjects with a mMS of 5 to 9 who were randomized and received at least 1 (partial or complete) dose of study intervention in MS. The RFAS was used for the primary efficacy analyses with subjects grouped according to their randomized study intervention.

ICE

The following ICEs were defined for this study:

- (1) An ostomy or colectomy (partial or total)
- (2) Meeting the criteria for a dose adjustment
- (3) Prohibited change in UC medication
- (4) Discontinuation of study intervention due to lack of efficacy or an AE of worsening of UC
- (5) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine
- (6) Discontinuation of study intervention due to reasons other than those in ICEs 4 and 5

ICE categories 1-4 and 6 were handled with the composite strategy and subjects experiencing those ICE were considered non-responders. ICE category 5 was handled by the treatment policy strategy.

Efficacy Analysis (Primary Endpoint)

The primary endpoint (i.e., proportion of subjects in clinical remission) was evaluated by a Cochran-Mantel-Haenszel test stratified by remission status at maintenance baseline (Yes/No)

and induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover to guselkumab 200 mg). The adjusted treatment difference and corresponding 95% confidence interval were reported using the stratified risk difference with Mantel-Haenszel weights with the same strata as defined above. See Section 6.2.1.3 for a discussion on the variance estimator used for the Wald-type confidence interval. Subjects missing any of the Mayo subscores used to define clinical remission will be treated as non-responders (i.e., non-responder imputation).

Efficacy Analysis (Secondary Endpoints)

The statistical methodology for testing the major secondary endpoints was the same as the methodology for the primary endpoint.

Multiplicity Control

A fixed sequence testing procedure (Figure 14) was used to control for multiplicity over the primary and major secondary endpoints for both dose groups at the 2-sided 0.05 significance level. The first 4 hypotheses will be sequentially tested in the following order: clinical remission (200 mg), endoscopic improvement (200 mg), clinical remission (100 mg), and endoscopic improvement (100 mg). The remaining secondary endpoints were then be tested in the following order, alternating between the 200 and 100 mg groups: clinical response, HEMI, symptomatic remission, corticosteroid-free clinical remission, fatigue response, maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction, and endoscopic remission.

Calculation of Mayo Subscores

The calculation of the Mayo subscores was the same as the calculation used for IS-2. See Section 6.2.1.3 for additional discussion.

6.2.2.4. Results of Analyses, MS

Subject Disposition

Subject disposition is summarized in Table 15. A total of 846 subjects who completed IS-1 or IS-2 enrolled in MS and 599 subjects were randomized. Among those 599 subjects, 568 subjects had a mMS of 5 to 9 and were included in the RFAS. Among the 568 subjects, 32 (5.3%) subjects (10 in the guselkumab 100 mg SC group, 13 in the guselkumab 200 mg SC group, and 9 in the placebo group) discontinued the study early. Among the 568 subjects, 68 (11.4%) subjects (20 in the guselkumab 100 mg SC group, 22 in the guselkumab 200 mg SC group, and 26 in the placebo group) discontinued study intervention prior to the last scheduled dose at Week M-40. An additional placebo subject prematurely discontinued treatment but that subject's treatment status was missing at the time of the database lock due to the conflict in Ukraine. Of note, subjects who experienced a loss of clinical response were eligible for a single blinded dose adjustment and, therefore, could be continued on treatment. Finally, among the 568 subjects, 1 subject in the guselkumab 200 mg SC group was unblinded prior to Week M-44 due to a treatment-emergent adverse event (TEAE).

Table 15. Subject Disposition, MS

Subject Disposition	Placebo SC n (%^a)	Guselkumab 100 mg SC Q8W n (%^a)	Guselkumab 200 mg SC Q4W n (%^a)	Total n (%^a)
Enrolled	-	-	-	846
Randomized	201	199	199	599
Modified Mayo score				
Modified Mayo score =4	11	11	9	31
Modified Mayo score =5-9	190	188	190	568
RFAS	190	188	190	568
Discontinued study	9 (4.5)	10 (5)	13 (6.5)	32 (5.3)
Reason for discontinuing study				
Lost to follow-up	1 (0.5)	1 (0.5)	0	2 (0.3)
Withdrawal by subject	7 (3.5)	9 (4.5)	10 (5.0)	26 (4.3)
Other	1 (0.5)	0	3 (1.5)	4 (0.7)
Discontinued treatment	26 ^b (12.9)	20 (10.1)	22 (11.1)	68 (11.4)
Reason for discontinuing treatment				
Adverse event	4 (2.0)	4 (2.0)	2 (1.0)	10 (1.7)
Adverse event – worsening of UC	8 (4.0)	3 (1.5)	8 (4.0)	19 (3.2)
Lack of efficacy	5 (2.5)	3 (1.5)	1 (0.5)	9 (1.5)
Lost to follow-up	0	1 (0.5)	1 (0.5)	2 (0.3)
Physician decision	0	4 (2.0)	1 (0.5)	5 (0.8)
Withdrawal by subject	8 (4.0)	4 (2.0)	7 (3.5)	19 (3.2)
Other	1 (0.5)	1 (0.5)	2 (1.0)	4 (0.7)

Source: Reviewer generated table using ADDISP.xpt, ADMAYO.xpt, and ADSL.xpt.

^a Percentages are based on the number of the subjects in the RFAS.

^b Does not include one subject who was missing treatment disposition status due to the conflict in Ukraine.

Abbreviations: MS, Maintenance Study; n, number of subjects in the RFAS; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; UC, ulcerative colitis

Protocol Deviations

Study-specific major protocol deviations are summarized in [Table 16](#). Forty-four (7.7%) subjects in the FAS population had major protocol deviations, with the most common protocol deviation category being other (e.g., procedure not performed, labs not collected). Protocol deviations were not considered to have impacted the conclusions of the study.

Table 16. Major Protocol Deviations (RFAS), MS

	Placebo SC N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Total N=568 n (%)
Protocol Deviation				
Subjects with ≥1 significant protocol deviation	16 (8.4)	16 (8.5)	12 (6.3)	44 (7.7)
Developed withdrawal criteria but not withdrawn	1 (0.5)	0	0	1 (0.2)
Entered but did not satisfy criteria	0	1 (0.5)	0	1 (0.2)
Received a disallowed concomitant treatment	0	1 (0.5)	0	1 (0.2)
Received wrong treatment or incorrect dose	0	3 (1.6)	2 (1.1)	5 (0.9)
Other ^a	15 (7.9)	11 (5.9)	10 (5.3)	36 (6.3)

Source: Based on Clinical Study Report, Table 2 (page 63). Verified by reviewer.

^a One subject in the guselkumab 100 mg SC Q8W group and one subject in the guselkumab 200 mg SC Q4W had a major protocol deviation related to COVID-19; Eight subjects in the placebo SC group, two subjects in the guselkumab 100 mg SC Q8W group and three subjects in the guselkumab 200 mg SC Q4W had a major protocol deviation related to the conflict in Ukraine.

Abbreviations: MS, Maintenance Study; N, number of subjects in treatment group; n, percentage of subjects with given protocol deviation; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous

Demographic Characteristics

Baseline demographic characteristics of the RFAS population are summarized in [Table 17](#). In the RFAS population, the majority of subjects were male (54.8%) and White (73.2%). The median age was 39.0 years (range 18 to 79 years), and the most common region was Eastern Europe (45.8%). The baseline demographic characteristics were generally similar between the two treatment arms.

Table 17. Demographic and Induction Baseline Characteristics (RFAS), MS

Characteristics	Placebo SC Q4W N=190	Guselkumab 100 mg SC Q8W N=188	Guselkumab 200 mg SC Q4W N=190	Total N=568
Age group, n (%)				
<65 Year	178 (93.7)	176 (93.6)	179 (94.2)	533 (93.8)
≥65	12 (6.3)	12 (6.4)	11 (5.8)	35 (6.2)
Age, years				
Mean (SD)	41.2 (13.6)	40.3 (13.0)	40.6 (14.7)	40.7 (13.7)
Median	39.5	39.0	39.0	39.0
IQR	31.0, 49.0	32.0, 47.0	28.0, 53.0	30.0, 49.0
Min, Max	18, 76	18, 79	18, 75	18, 79
Sex, n (%)				
Female	81 (42.6)	86 (45.7)	90 (47.4)	257 (45.2)
Male	109 (57.4)	102 (54.3)	100 (52.6)	311 (54.8)
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	34 (17.9)	38 (20.2)	44 (23.2)	116 (20.4)
Black or African American	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)
Native Hawaiian or African American	1 (<1)	0	0	1 (<1)
White	142 (74.7)	139 (73.9)	135 (71.1)	416 (73.2)
Not Reported	10 (5.3)	9 (4.8)	9 (4.7)	28 (4.9)
Multiple	1 (<1)	0	0	1 (<1)
Ethnicity, n (%)				
Hispanic or Latino	7 (3.7)	10 (5.3)	11 (5.8)	28 (4.9)
Not Hispanic or Latino	173 (91.1)	163 (86.7)	168 (88.4)	504 (88.7)
Not Reported	10 (5.3)	15 (8.0)	11 (5.8)	36 (6.3)
Region, n (%)				
Asia	30 (15.8)	36 (19.1)	42 (22.1)	108 (19.0)
Eastern Europe	102 (53.7)	85 (45.2)	88 (46.3)	275 (48.4)
Latin America	7 (3.7)	8 (4.3)	10 (5.3)	25 (4.4)
North America	9 (4.7)	9 (4.8)	11 (5.8)	29 (5.1)
Western Europe	31 (16.3)	35 (18.6)	25 (13.2)	91 (16.0)
Other ^a	11 (5.8)	15 (8.0)	14 (7.4)	40 (7.0)
Weight (kg)				
Mean (SD)	73.6 (17.0)	70.7 (16.8)	70.9 (16.6)	71.7 (16.8)
Median	72.0	68.8	69.2	70.0
IQR	61.3, 83.8	58.2, 83.5	57.5, 81.8	59.0, 83.0
Min, Max	43, 126	40, 116	44, 122	40, 126
Induction study, n (%)				
IS-1 placebo -> guselkumab	17 (8.9)	15 (8.0)	17 (8.9)	49 (8.6)
IS-1 guselkumab 200 mg	23 (12.1)	19 (10.1)	18 (9.5)	60 (10.6)
IS-1 guselkumab 400 mg	21 (11.1)	22 (11.7)	22 (11.6)	65 (11.4)
IS-2 placebo -> guselkumab	40 (21.1)	40 (21.3)	40 (21.1)	120 (21.1)
IS-2 guselkumab 200 mg	89 (46.8)	92 (48.9)	93 (48.9)	274 (48.2)

Source: Clinical Study Report Table 4 (pages 69-71). Verified by reviewer using ADSL.xpt.

^a Includes countries Australia, Israel, Jordan and New Zealand.

Abbreviations: IQR, interquartile range; IS-1, Induction Study 1; IS-2, Induction Study 2; MS, Maintenance Study; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; SD, standard deviation

Other Baseline Characteristics

UC disease characteristics at maintenance baseline in the RFAS population are summarized in [Table 18](#). In the RFAS population, the median mMS was 2.0, and 194/568 subjects (34%) had experienced clinical remission. The disease characteristics at maintenance baseline were generally similar between the two treatment arms.

Table 18. UC Characteristics (RFAS), MS

Characteristics	Placebo SC Q4W N=190	Guselkumab 100 mg SC Q8W N=188	Guselkumab 200 mg SC Q4W N=190	Total N=568
Mayo score at maintenance BL				
Mean (SD)	3.3 (2.0)	3.2 (1.9)	3.2 (1.9)	3.2 (1.9)
Median	3.0	3.0	3.0	3.0
IQR	2.0, 5.0	2.0, 5.0	2.0, 5.0	2.0, 5.0
Min, Max	0, 8	0, 7	0, 8	0, 8
Modified Mayo score at maintenance BL				
Mean (SD)	2.5 (1.6)	2.6 (1.5)	2.5 (1.5)	2.5 (1.5)
Median	2.0	2.0	3.0	2.0
IQR	1.0, 4.0	1.0, 4.0	1.0, 4.0	1.0, 4.0
Min, Max	0, 6	0, 6	0, 6	0, 6
Clinical remission at maintenance BL, n (%)				
No	131 (68.9)	122 (64.9)	121 (63.7)	374 (65.8)
Yes	59 (31.1)	66 (35.1)	69 (36.3)	194 (34.2)
Therapeutic biologics and JAK inhibitors category, n (%)				
Experienced without failure	7 (3.7)	6 (3.2)	6 (3.2)	19 (3.3)
Failure	75 (39.5)	77 (41.0)	88 (46.3)	240 (42.3)
Naive	108 (56.8)	105 (55.9)	96 (50.5)	309 (54.4)

Source: Based on Clinical Study Report Table 5 (pages 74-76). Verified by reviewer using ADBDC.xpt, ADSL.xpt.

Abbreviations: BL, baseline; CRP, C-reactive protein; IQR, interquartile range; MS, Maintenance Study; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; SD, standard deviation; UC, ulcerative colitis

Concomitant Therapy and Medication History

Concomitant UC medications were to be maintained at a stable dose throughout IS-1 or IS-2. Concomitant UC medications from Week I-0 in the RFAS population are summarized in [Table 19](#). In the RFAS, 498/568 (87.7%) subjects were receiving 1 or more concomitant medications for UC. Concomitant medication usage was generally similar between the two treatment arms.

Table 19. Summary of Concomitant Medications for UC at Induction Baseline (RFAS), MS

	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Total N=568 n (%)
Concomitant Medications				
Subjects who received any of the following UC medications	168 (88.4)	164 (87.2)	166 (87.4)	498 (87.7)
Oral corticosteroid use	77 (40.5)	74 (39.4)	76 (40.0)	227 (40.0)
Corticosteroid use (excl. budesonide and beclomethasone dipropionate)	63 (33.2)	58 (30.9)	71 (37.4)	192 (33.8)
Budesonide	12 (6.3)	16 (8.5)	4 (2.1)	32 (5.6)
Beclomethasone dipropionate	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Immunomodulatory drugs	43 (22.6)	41 (21.8)	42 (22.1)	126 (22.2)
6-mercaptopurine/azathioprine	42 (22.1)	39 (20.7)	41 (21.6)	122 (21.5)
Methotrexate	1 (0.5)	2 (1.1)	1 (0.5)	4 (0.7)
Oral aminosalicylates	145 (76.3)	146 (77.7)	147 (77.4)	438 (77.1)

Source: Based on Clinical Study Report Table 6 (pages 78). Verified by reviewer using ADMEDRVW.xpt, ADSL.xpt.

Abbreviations: MS, Maintenance Study; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; UC, ulcerative colitis

Dose Adjustment

During MS, subjects in the RFAS who met criteria for loss of clinical response were eligible to receive a single blinded dose adjustment. A total of 118 (20.8%) subjects (19/188 [10.1%] in the guselkumab 100 mg SC group, 30/190 [15.8%] in the guselkumab 200 mg SC group, and 69/190 [36.3%] in the placebo group) received a dose adjustment. Among these 118 subjects, 29 subjects discontinued the study prior to Week M-40 (i.e., the final dose of IP). Of note, a larger percentage of subjects in the placebo group received a dose adjustment, as compared to either guselkumab group.

Treatment Compliance

Treatment compliance with IP administration was generally high. Over 85% of subjects in the RFAS received all doses of the IP through the final scheduled dose at Week M-40 ([Table 20](#)).

Table 20. Exposure to Scheduled Study Intervention- IP Administration (RFAS), MS

Study Week	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Total N=568 n (%)
Subjects receiving a scheduled study intervention				
Week M-0	190 (100)	188 (100)	190 (100)	568 (100)
Week M-4	188 (98.9)	184 (97.9)	189 (99.5)	561 (98.8)
Week M-8	189 (99.5)	185 (98.4)	188 (98.9)	562 (98.9)
Week M-12	186 (97.9)	180 (95.7)	187 (98.4)	553 (97.4)
Week M-16	181 (95.3)	180 (95.7)	183 (96.3)	544 (95.8)
Week M-20	177 (93.2)	177 (94.1)	183 (96.3)	537 (94.5)
Week M-24	173 (91.1)	176 (93.6)	178 (93.7)	527 (92.8)
Week M-28	169 (88.9)	170 (90.4)	175 (92.1)	514 (90.5)
Week M-32	167 (87.9)	168 (89.4)	172 (90.5)	507 (89.3)
Week M-36	165 (86.8)	169 (89.9)	171 (90.0)	505 (88.9)
Week M-40	162 (85.3)	168 (89.4)	167 (87.9)	497 (87.5)

Source: Generated by reviewer using ADEX.xpt.

Abbreviations: MS, Maintenance Study; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; UC, ulcerative colitis

Efficacy Results – Primary Endpoint

The percentage of subjects achieving the primary endpoint of clinical remission was larger in the 100 mg guselkumab group (45.2%) and 200 mg guselkumab group (50.0%), as compared to the placebo group (18.9%) (Table 21). The adjusted difference (95% CI) in remission rates between the 100 mg guselkumab group and the placebo group was 25.2% (16.4%, 33.9%), and between the 200 mg guselkumab group and the placebo group was 29.5% (20.9%, 38.1%). The prespecified test of the null hypothesis (e.g., equal remission rates) was statistically significant for both comparisons with p-values <0.001, indicating that there were differences in the remission rates between the guselkumab groups and the placebo group.

Table 21. Clinical Remission at Week M-44 (RFAS), MS

Parameter	Placebo SC Q4W N=190	Guselkumab 100 mg SC Q8W N=188	Guselkumab 200 mg SC Q4W N=190
Number (%) of subjects achieving clinical remission at Week I-44	36 (18.9%)	85 (45.2%)	95 (50.0%)
95% CI ^a	(13.4%, 24.5%)	(38.1%, 52.3%)	(42.9%, 57.1%)
Adjusted treatment difference (95% CI) ^b		25.2% (16.4%, 33.9%)	29.5% (20.9%, 38.1%)
p-Value ^c		<0.001	<0.001

Source: Clinical Study Report Table 7 (page 85). Verified by reviewer using ADEFF.xpt.

^a The 95% CIs of the percentages for each treatment group were based on the normal approximation.

^b The treatment difference was based on the common risk difference stratified by clinical remission status at maintenance baseline and induction treatment using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; N, number of subjects in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous

For the clinical remission endpoint, 172/578 (30.2%) subjects experienced ICE 1, 2, 3, 4, or 6 and were classified as non-responders (35/188 [18.6%] in the guselkumab 100 mg group, 44/190 [23.2%] in the guselkumab 200 mg group, and 93/190 [48.9%] in the placebo group; [Table 73](#)). These ICEs tended to reflect a lack of treatment efficacy. The majority of subjects experiencing these ICEs experienced a dose adjustment due to loss of clinical response (112/172 [68.6%]; [Table 73](#)), and only a small percentage of these subjects (24/172 [14.0%]) experienced only ICE 6 (i.e., treatment discontinuation not related to efficacy, AE of worsening UC, COVID-19, or the conflict in Ukraine), which may not necessarily be related to lack of efficacy. After accounting for the ICE strategies, 2/568 (0.4%) subjects had a missing mMS at Week M-44 (1/190 [0.5%] subject in the guselkumab 200 mg SC group and 1/190 [0.5%] subject in the placebo group).

To test the robustness of the results to the methods for handling missing data, the Applicant performed a tipping point analysis. No tipping point was found. Under the most extreme scenario (i.e., the guselkumab 200 mg subject was a non-responder and the placebo subject was a responder), all results remained statistically significant ($p < 0.001$). A second sensitivity analysis ([Table 74](#)) used the FDA preferred method for calculating the mMS and produced qualitatively similar results with p -values < 0.001 . A third sensitivity analysis ([Table 74](#)) intended to evaluate efficacy among subjects receiving the proposed to-be-marketed (TBM) dose excluded the 65 subjects who received guselkumab 400 mg IV Q4W during the induction study. This analysis produced qualitatively similar results with p -values < 0.001 and indicates that the inclusion of subjects who received induction doses other than the proposed TBM induction dose in the efficacy analyses did not substantially affect the results of efficacy analyses at Week M-44. Finally, the Applicant indicated that 10 subjects (2/188 [1.1%] in the guselkumab 100 mg group, 4/190 [2.1%] in the guselkumab 200 mg group and 4/190 [2.91%] in the placebo group) had source data that could not be verified due to COVID-19 and the conflict in Ukraine and that a sensitivity analysis excluding those subjects also produced similar results (p -values < 0.001).

The primary analysis was repeated in subgroups defined by demographic characteristics ([Figure 23](#) and [Figure 24](#)) and UC characteristics ([Figure 25](#) and [Figure 26](#)). In all key subgroups analyzed, the proportion of subjects in clinical remission at Week I-12 favored guselkumab relative to placebo. Moreover, the treatment effect (i.e., adjusted treatment difference) varied little across subgroups. However, when evaluating guselkumab 100 mg SC Q8W, the adjusted treatment difference (95% CI) decreased from 36.8% (20.5%, 53.0%) to 8.4% (-9.5%, 26.2%) as the weight increased from the lowest to highest quartiles providing suggestive evidence that the lower dose (i.e., 100 mg SC Q8W) may be less effective in subjects with higher weights. A similar trend was not observed when evaluating guselkumab 200 mg SC Q4W. Of note the currently approved prescribing information for guselkumab includes the following statement in Section 12.3 PHARMACOKINETICS: Special Populations, “Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.” The review team agrees that this statement accurately describes the findings observed in MS.

Efficacy Results – Secondary Endpoints

Results for the secondary endpoints are summarized in [Table 22](#). The response rates for each of the endpoints was higher in the guselkumab 100 mg and guselkumab 200 mg groups, as compared to the placebo group. Based on the prespecified multiple testing procedure, all

comparisons were statistically significant. Results by prior therapeutic biologic and JAK inhibitor failure status are presented in [Table 75](#). Results for corticosteroid-free clinical remission at Week M-44 among subjects using corticosteroids at induction baseline are presented in [Table 76](#).

Table 22. Efficacy Results for Secondary Endpoints (RFAS), MS

Secondary Endpoints	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)
Symptomatic remission at Week M-44	71 (37.4%)	132 (70.2%)	131 (68.9%)
Adjusted tx dif (95% CI) ^a		31.9% (22.5,41.2) ^b	30.5% (21.2,39.9) ^b
Endoscopic improvement at Week M-44	36 (18.9%)	93 (49.5%)	98 (51.6%)
Adjusted tx dif (95% CI) ^a		29.5% (20.7,38.3) ^b	31.1% (22.5,39.8) ^b
Corticosteroid-free clinical remission at Week M-44	35 (18.4%)	85 (45.2%)	93 (48.9%)
Adjusted tx dif (95% CI) ^a		25.7% (17.0,34.5) ^b	29.0% (20.5,37.6) ^b
Clinical response at Week M-44	82 (43.2%)	146 (77.7%)	142 (74.7%)
Adjusted tx dif (95% CI) ^a		33.6% (24.5,42.7) ^b	30.7% (21.5,40.0) ^b
Histologic endoscopic mucosal improvement at Week M-44	32 (16.8%)	82 (43.6%)	91 (47.9%)
Adjusted tx dif (95% CI) ^a		25.7% (17.1,34.3) ^b	29.6% (21.1,38.0) ^b
Fatigue response at Week M-44	56 (29.5%)	95 (50.5%)	82 (43.2%)
Adjusted tx dif (95% CI) ^a		20.1% (10.7,29.5) ^b	12.6% (3.3,21.9) ^c
Maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction	20 (33.9%) ^d	40 (60.6%) ^d	50 (72.5%) ^d
Adjusted tx dif (95% CI) ^a		25.9% (9.2,42.5) ^c	38.4% (22.7,54.1) ^b
Endoscopic remission at Week M-44	29 (15.3%)	65 (34.6%)	64 (33.7%)
Adjusted tx dif (95% CI) ^a		18.5% (10.2,26.8) ^b	16.8% (9.0,24.7) ^b

Source: Clinical Study Report Table 8 (page 89). Verified by reviewer using ADEFF.xpt, ADHISTI.xpt, ADIBDQI.xpt, ADPROMSI.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by induction dose treatment and, for all endpoints except maintenance of clinical remission, clinical remission status at maintenance baseline using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

^b p-value<0.001

^c p-value<0.01

^d percentage based on the number of subjects in clinical remission at baseline

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; N, number of subjects in treatment group; n, number of subjects meeting criteria; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; tx dif, treatment difference

As discussed in the above review of the IS-2 results, there is a concern with using non-responder imputation to handle ICE for the fatigue endpoint as the occurrence of an ICE and the lack of a fatigue response may not be strongly correlated. This was a significant concern for the results of this analysis from MS as a high percentage (30.3%) of subjects in the MS experienced an ICE prior to Week M-44. [Table 23](#) shows a larger percentage of subjects in the placebo group (48.9%) experienced an ICE, as compared to either the guselkumab 100 mg SC (18.6%) or the guselkumab 200 mg SC (23.2%) groups.

Table 23. Efficacy Results for Fatigue Endpoint (RFAS), MS

	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)
Fatigue Endpoint			
Fatigue responders	56 (29.5%)	95 (50.5%)	82 (43.2%)
Fatigue non-responders	134 (70.5%)	93 (49.5%)	108 (56.8%)
ICE	93 (48.9%)	35 (18.6%)	44 (23.2%)
<7-point change in PROMIS-Fatigue score ^a	41 (21.6%)	58 (30.9%)	64 (33.7%)

Source: Reviewer generated using ADPRMSI.xpt.

^a Includes subjects with missing data after accounting for ICE.

Abbreviations: ICE, intercurrent events; MS, Maintenance Study; N, number of subjects in treatment group; n, number of subjects meeting criteria; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous

Therefore, the lower response rate in the placebo group is, in part, a consequence of the comparatively larger number of subjects experiencing an ICE and who, by definition, could not be fatigue responders. Given that the primary analysis for this endpoint effectively evaluated the effect on both the fatigue response and/or the occurrence of an ICE, additional supplementary analyses were performed to determine if the data provided strong evidence to demonstrate that guselkumab had an effect on fatigue itself at Week M-44. See Section 16.3.2 for detailed results from these analyses. Of note, options for supplementary analyses and evaluating the fatigue status of subjects experiencing ICE were limited because there was only a single assessment (i.e., at Week M-28) using the PROMIS-Fatigue SF-7a between Week M-0 and Week M-44. Notably, the first set of supplementary analyses used alternative methods to handle ICE (i.e., treatment policy strategy, omitting subjects with ICE), and these analyses did not produce nominally significant results. The second set of supplementary analyses were tipping point analyses that allowed the probability of fatigue response to vary among individuals who experienced ICE. These analyses suggested that there were plausible scenarios that would not have resulted in statistically significant results had subjects who experienced an ICE continued on their assigned treatments and been assessed at Week M-44. Based on these results, the review team concluded that the data from the MS did not provide strong evidence supporting the effect of guselkumab on fatigue at Week M-44. However, these results did provide supportive evidence of the potential for a continued effect on fatigue following induction, and therefore, contributed to the review team's decision to include descriptive results of the effect of guselkumab on fatigue at Week I-12 in the prescribing information. As discussed in Section 1.2.1, as UC is a chronic condition, data to support the potential for continued benefit of therapies on fatigue beyond the induction period are important to inform the clinical relevance of short-term evaluations and the suitability of including a description of these assessments in labeling.

6.2.3. Study CNTO1959UCO3001, Induction Study 1 (IS-1)

Although the primary evidence for efficacy is based on analyses of data generated from IS-2 and MS, efficacy results generated from IS-1 are considered to be supportive evidence. A brief description of the design, analysis, and results for IS-1 will be presented in the following sections. Of note, the elements of the design and analysis are generally similar to those elements in IS-2. The key differences with IS-2 are inclusion of the additional dosage group (i.e.,

guselkumab 400 mg IV Q4W) and the choice of the primary efficacy endpoint (i.e., clinical response).

6.2.3.1. Design, IS-1

IS-1 was a phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study. Subjects were randomized in a 1:1:1 ratio to guselkumab 200 mg IV Q4W, guselkumab 400 mg IV Q4W, or placebo IV Q4W. The primary efficacy endpoint was evaluated at Week I-12. Study intervention after Week I-12 depended on the subjects' clinical response (i.e., a decrease from induction baseline in the mMS by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1) status at Week I-12, with the rules similar to those used in IS-2.

6.2.3.2. Eligibility Criteria, IS-1

The eligibility criteria were generally similar to the criteria used for IS-2. See Section [6.2.1.2](#)

6.2.3.3. Statistical Analysis Plan, IS-1

The statistical analysis plan was generally similar to the plan used for IS-2. Key differences, discussed below, include the study endpoints, multiplicity control procedure, methods for handling intercurrent events, and the inclusion of an interim analysis.

Study Endpoints

The primary endpoint was clinical response at Week I-12 and the secondary endpoints included:

- Clinical remission at Week I-12
- Symptomatic remission at Week I-12
- Endoscopic improvement at Week I-12
- HEMI at Week I-12
- Endoscopic remission at Week I-12

Multiplicity Control

A step-up Hochberg multiple testing procedure was used to control the family-wise Type-I error rate for testing the primary endpoints of the two treatment doses. There was no multiplicity control procedure for the secondary endpoints.

Intercurrent Events

The ICEs for IS-1 are similar to the ICEs for IS-2. The methods (i.e., composite strategy) for handling the first three ICEs in IS-1 are similar to the methods used for IS-2. However, in IS-1, a hypothetical strategy⁵ is used to handle ICE (i.e., discontinuation due to COVID-19 related

⁵ No subject had ICE as the reason for treatment discontinuation, so the hypothetical strategy did not need to be implemented.

reasons excluding COVID-19 infection) and a treatment policy strategy is used to handle ICE five (i.e., discontinuation of study intervention due to COVID-19 infection or for reasons other than lack of efficacy, AE of worsening UC, or other COVID-19 related reasons).

Interim Analysis

IS-1 included an interim analysis that occurred after 150 randomized subjects completed the Week I-12 visit or terminated study participation prior to Week I-12. The purpose of the interim analysis was to select a dose to be carried forward into IS-2. However, the protocol also indicates that CNTO1959UCO3001 could have been terminated early for futility based on interim analysis results.

6.2.3.4. Results of Analyses, IS-1

Only key results from IS-1 are included in this review.

Subject Disposition

Subject disposition is summarized in [Table 24](#). A total of 483 subjects were screened and 328 subjects were randomized. Among those 328 subjects, 314 subjects had a mMS of 5 to 9, and 14 had a mMS of 4. One subject with a mMS between 5 and 9 in the placebo IV group did not receive study intervention because of a newly diagnosed COVID-19 infection. Therefore, the FAS included 313 subjects. Among the 313 subjects, 5 (1.6%) subjects (2 in the guselkumab 200 mg IV group, 1 in the guselkumab 400 mg IV group and 2 in the placebo IV group) terminated study participation prior to Week I-12. Among the 313 subjects, 9 (2.9%) subjects (3 in the guselkumab 200 mg IV group, 1 in the guselkumab 400 mg IV group and 5 subjects in the placebo IV group) discontinued study intervention prior to Week I-12. Overall, rates of study and treatment discontinuation were low.

Table 24. Subject Disposition, IS-1

Subject Disposition	Placebo IV Q4W n (%^a)	Guselkumab 200 mg IV Q4W n (%^a)	Guselkumab 400 mg IV Q4W n (%^a)	Total n (%^a)
Screened	-	-	-	483
Randomized	109	108	111	328
Modified Mayo score				
Modified Mayo score =4	3	7	4	14
Modified Mayo score =5-9	106	101	107	314
FAS	105	101	107	313
Discontinued study before Week I-12	2 (1.9)	2 (2)	1 (0.9)	5 (1.6)
Reason for discontinuing study before Week I-12				
Withdrawal by subject	1 (1)	1 (1)	1 (0.9)	3 (1)
Other	1 (1)	1 ^b (1)	0 (0)	2 (0.6)
Discontinued treatment before Week I-12	5 (4.8)	3 (3)	1 (0.9)	9 (2.9)
Reason for discontinuing treatment before Week I-12				
Adverse event – worsening of UC	2 (1.9)	1 (1)	0 (0)	3 (1)
Lack of efficacy	2 (1.9)	0 (0)	0 (0)	2 (0.6)
Withdrawal by subject	1 (1)	1 (1)	1 (0.9)	3 (1)
Other	0 (0)	1 (1)	0 (0)	1 (0.3)

Source: Reviewer generated table using ADDISP.xpt, ADMAYO.xpt, and ADSL.xpt.

^a Percentages are based on the number of the subjects in the FAS.

^b One subject in the placebo group discontinued from the study for reasons related to COVID-19.

Abbreviations: FAS, full analysis set; IS-1, Induction Study 1; IV, intravenous; n, number of subjects in the FAS; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis

Demographic Characteristics

Baseline demographic characteristics of the FAS population are summarized in [Table 25](#). In the FAS population, the majority of subjects were male (59.1%) and White (71.6%). The median age was 39.0 years (range 18 to 84 years), and the most common region was Eastern Europe (48.9%). The baseline demographic characteristics were generally similar across the three treatment arms.

Table 25. Demographic and Baseline Characteristics (FAS), IS-1

Characteristic	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107	Total N=313
Age Group, n (%)				
<65 Year	98 (93.3)	94 (93.1)	101 (94.4)	293 (93.6)
≥65	7 (6.7)	7 (6.9)	6 (5.6)	20 (6.4)
Age, years				
Mean (SD)	41.2 (15.1)	43.3 (14.3)	40.4 (13.8)	41.6 (14.4)
Median	39.0	42.0	39.0	39.0
IQR	29.0, 53.0	33.0, 54.0	30.0, 49.0	30.0, 53.0
Min, Max	18, 84	18, 79	18, 76	18, 84
Sex, n (%)				
Female	39 (37.1)	41 (40.6)	48 (44.9)	128 (40.9)
Male	66 (62.9)	60 (59.4)	59 (55.1)	185 (59.1)

Characteristic	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107	Total N=313
Race, n (%)				
American Indian or Alaska Native	0	0	0	0
Asian	24 (22.9)	23 (22.8)	27 (25.2)	74 (23.6)
Black or African American	1 (1.0)	1 (1.0)	1 (<1)	3 (1.0)
Native Hawaiian or African American	0	0	0	0
White	77 (73.3)	73 (72.3)	74 (69.2)	224 (71.6)
Not Reported	3 (2.9)	3 (3.0)	5 (4.7)	11 (3.5)
Multiple	0	1 (1.0)	0	1 (<1)
Ethnicity, n (%)				
Hispanic or Latino	4 (3.8)	5 (5.0)	4 (3.7)	13 (4.2)
Not Hispanic or Latino	97 (92.4)	92 (91.1)	98 (91.6)	287 (91.7)
Not Reported	4 (3.8)	4 (4.0)	5 (4.7)	13 (4.2)
Region, n (%)				
Asia	24 (22.9)	22 (21.8)	25 (23.4)	71 (22.7)
Eastern Europe	50 (47.6)	52 (51.5)	51 (47.7)	153 (48.9)
Latin America	0	2 (2.0)	2 (1.9)	4 (1.3)
North America	6 (5.7)	3 (3.0)	7 (6.5)	16 (5.1)
Western Europe	23 (21.9)	20 (19.8)	18 (16.8)	61 (19.5)
Other ^a	2 (1.9)	2 (2.0)	4 (3.7)	8 (2.6)
Weight (kg)				
Mean (SD)	68.8 (16.3)	70.3 (16.5)	71.7 (18.6)	70.3 (17.2)
Median	69.3	68.6	70.3	69.9
IQR	54.2, 77.1	55.8, 82.0	59.2, 83.1	55.8, 80.0
Min, Max	43, 108	36, 112	42, 148	36, 148

Source: Clinical Study Report Table 2 (pages 70-71). Verified by reviewer using ADSL.xpt.

^a Includes countries Australia, Israel, and New Zealand.

Abbreviations: FAS, full analysis set; IQR, interquartile range; IS-1, Induction Study 1; IV, intravenous; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation

Other Baseline Characteristics

Baseline UC disease characteristics of the FAS population are summarized in [Table 26](#). In the FAS population, the median duration of disease was 7.5 years, and the median mMS was 9.2. The baseline disease characteristics were generally similar across the three treatment arms.

Table 26. Baseline UC Characteristics (FAS), IS-1

Baseline Characteristics	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107	Total N=313
Duration, years				
Mean (SD)	7.7 (7.2)	7.0 (6.0)	7.9 (7.1)	7.5 (6.8)
Median	5.8	5.1	6.6	5.8
IQR	2.5, 10.7	2.6, 10.5	2.8, 10.3	2.6, 10.5
Min, Max	0, 43	0, 36	0, 40	0, 43
Extent, n (%)				
Extensive	46 (43.8)	48 (47.5)	59 (55.1)	153 (48.9)
Limited to Left Side of Colon	59 (56.2)	53 (52.5)	48 (44.9)	160 (51.1)

	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107	Total N=313
Baseline Characteristics				
Mayo score				
Mean (SD)	9.0 (1.3)	9.2 (1.3)	9.3 (1.3)	9.2 (1.3)
Median	9.0	9.0	9.0	9.0
IQR	8.0, 10.0	8.0, 10.0	8.0, 10.0	8.0, 10.0
Min, Max	6, 12	7, 12	6, 12	6, 12
Modified Mayo score				
Mean (SD)	6.9 (1.1)	7.0 (1.1)	7.0 (1.0)	7.0 (1.0)
Median	7.0	7.0	7.0	7.0
IQR	6.0, 8.0	6.0, 8.0	6.0, 8.0	6.0, 8.0
Min, Max	5, 9	5, 9	5, 9	5, 9
Modified Mayo score, n (%)				
5-6	36 (34.3)	30 (29.7)	29 (27.1)	95 (30.4)
7-9	69 (65.7)	71 (70.3)	78 (72.9)	218 (69.6)
Endoscopy score, n (%)				
2	30 (28.6)	35 (34.7)	29 (27.1)	94 (30.0)
3	75 (71.4)	66 (65.3)	78 (72.9)	219 (70.0)
Oral CS use ^a , n (%)				
No	65 (61.9)	60 (59.4)	63 (58.9)	188 (60.1)
Yes	40 (38.1)	41 (40.6)	44 (41.1)	125 (39.9)
Therapeutic biologics and JAK inhibitors category ^a , n (%)				
Experienced without failure	3 (2.9)	3 (3.0)	5 (4.7)	11 (3.5)
Failure	51 (48.6)	46 (45.5)	51 (47.7)	148 (47.3)
naïve	51 (48.6)	52 (51.5)	51 (47.7)	154 (49.2)

Source: Based on Clinical Study Report Table 3 (pages 73-74). Verified by reviewer using ADADT.xpt, ADBDC.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a Values are based on data captured in the eCRF and are not identical to the values used for stratification in the IWRS. Abbreviations: CS, corticosteroid; FAS, full analysis set; IQR, interquartile range; IS-1, Induction Study 1; IV, intravenous; Q4W, every 4 weeks; N, number of subjects in treatment group; n, percentage of subjects within given characteristic; Q8W, every 8 weeks; SD, standard deviation; UC, ulcerative colitis

Efficacy Results – Primary Endpoint

The percentage of subjects achieving clinical response was larger in the guselkumab 200 mg group (61.4%) and the guselkumab 400 mg group (60.7%), as compared to the placebo group (27.6%) ([Table 27](#)). The adjusted difference (95% CI) in response rates between the guselkumab 200 mg and placebo groups was 33.6% (20.9%, 46.3%), and between the guselkumab 400 mg and placebo groups was 33.1% (20.8%, 45.4%). The prespecified tests of the null hypothesis (e.g., equal response rates) were statistically significant for both comparisons with p-values <0.001, indicating that there were differences in the response rates between the guselkumab groups and the placebo group.

Table 27. Clinical Response at Week I-12 (FAS), IS-1

Parameter	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107
Number (%) of subjects achieving clinical response at Week I-12	29 (27.6%)	62 (61.4%)	65 (60.7%)
95% CI ^a	(19.1%, 36.2%)	(51.9%, 70.9%)	(51.5%, 70.0%)
Adjusted treatment difference (95% CI) ^b		33.6% (20.9%, 46.3%)	33.1% (20.8%, 45.4%)
p-Value ^c		<0.001	<0.001

Source: Clinical Study Report Table 5 (page 83). Verified by reviewer using ADEFF.xpt.

^a The 95% CIs of the percentages for each treatment group were based on the normal approximation.

^b The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-1, Induction Study 1; IV, intravenous; MH, Mantel-Haenszel; N, number of subjects in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks

Efficacy Results – Secondary Endpoints

The results for the secondary endpoint of clinical remission are presented in [Table 28](#). The percentage of subjects achieving clinical remission was larger in the guselkumab 200 mg group (25.7%) and the guselkumab 400 mg group (25.2%), as compared to the placebo group (9.5%). The adjusted difference (95% CI) in response rates between the guselkumab 200 mg and placebo groups was 16.3% (6.3%, 26.3%), and between the guselkumab 400 mg and placebo groups was 15.7% (6.0%, 25.4%). The prespecified tests of the null hypothesis (e.g., equal response rates) were nominally significant for both comparisons with p-values of 0.002, supporting that there were differences in the response rates between the guselkumab groups and the placebo group. These tests were not controlled for multiplicity.

Table 28. Clinical Remission at Week I-12 (FAS), IS-1

Parameter	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107
Number (%) of subjects achieving clinical remission at Week I-12	10 (9.5%)	26 (25.7%)	27 (25.2%)
95% CI ^a	(3.9%, 15.1%)	(17.2%, 34.3%)	(17.0%, 33.5%)
Adjusted treatment difference (95% CI) ^b		16.3% (6.3%, 26.3%)	15.7% (6.0%, 25.4%)
p-Value ^c		0.002	0.002

Source: Clinical Study Report Table 6 (page 86). Verified by reviewer using ADEFF.xpt.

^a The 95% CIs of the percentages for each treatment group were based on the normal approximation.

^b The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-1, Induction Study 1; IV, intravenous; MH, Mantel-Haenszel; N, number of subjects in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks

For the clinical remission endpoint, 11/313 (3.5%) subjects experienced ICE 1 through 3 or 5 (3/101 [3.0%] subjects in the guselkumab 200 mg IV group, 2/107 [1.9%] subjects in the guselkumab 400 mg IV group and 6/105 [5.7%] subjects in the placebo IV group). After accounting for the ICE strategies, 3/313 (1.0%) subjects had a missing mMS at Week I-12 (1/101 [1.0%] subject in the guselkumab 200 mg IV group, 1/107 [1.0%] subject in the guselkumab

400 mg IV group and 1/105 [1.0%] subject placebo IV group). A sensitivity analysis, using the FDA preferred method for calculating the mMS, resulted in 9, 25, and 27 subjects, respectively, in the placebo, guselkumab 200 mg IV, and guselkumab 400 mg IV groups with clinical remission and produced similar results (treatment difference for 200 mg comparison =16.2%, 95% CI = [6.4%, 26.0%], p-value=0.002; treatment difference for 400 mg comparison =16.7%, 95% CI = [7.1%, 26.2%], p-value=0.001). The clinical remission endpoint was evaluated in subgroups defined by demographic characteristics ([Figure 23](#) and [Figure 24](#)) and baseline UC characteristics ([Figure 25](#) and [Figure 26](#)). In key subgroups analyzed, the proportion of subjects achieving clinical remission at Week I-12 tended to favor guselkumab relative to placebo.

Results for other secondary endpoints are summarized in [Table 29](#). The response rates for each of the endpoints was higher in the guselkumab 200 mg IV and guselkumab 400 mg IV groups, as compared to the placebo group. As there was no multiple testing procedure to control the Type I error rate for the secondary endpoints, results for the secondary endpoints are not considered statistically significant. However, the results for all endpoints other than endoscopic remission in the guselkumab 400 mg IV group were nominally significant.

Table 29. Efficacy Results for Secondary Endpoints (FAS), IS-1

Secondary Endpoints	Placebo IV Q4W N=105	Guselkumab 200 mg IV Q4W N=101	Guselkumab 400 mg IV Q4W N=107
Symptomatic remission at Week I-12	21 (20.0%)	50 (49.5%)	51 (47.7%)
Adjusted treatment difference (95% CI) ^a		29.4% (17.2%,41.6%)	27.7% (15.7%,39.7%)
p-Value ^b		<0.001	<0.001
Endoscopic Improvement at Week I-12	13 (12.4%)	31 (30.7%)	33 (30.8%)
Adjusted treatment difference (95% CI) ^a		18.3% (7.5%,29.0%)	18.5% (7.9%,29.0%)
p-Value ^b		0.001	<0.001
Histologic endoscopic Mucosal Improvement at Week I-12	9 (8.6%)	21 (20.8%)	29 (27.1%)
Adjusted treatment difference (95% CI) ^a		12.1% (2.8%,21.4%)	18.5% (8.7%,28.4%)
p-Value ^b		0.014	<0.001
Endoscopic Remission at Week I-12	7 (6.7%)	18 (17.8%)	15 (14.0%)
Adjusted treatment difference (95% CI) ^a		11.3% (2.6%,20.0%)	7.3% (-0.5%,15.2%)
p-Value ^b		0.013	0.076

Source: Clinical Study Report Table 7 (page 87), Table 8 (page 88), Table 9 (page 89), and Table 10 (page 90). Verified by reviewer using ADEFF.xpt, ADHIST1.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^b The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-1, Induction Study 1; IV, intravenous; MH, Mantel-Haenszel; N, number of subjects in treatment group; Q4W, every 4 weeks; Q8W, every 8 weeks

6.2.4. Suitability of Efficacy Assessments for Inclusion in the Prescribing Information

The following summary includes discussion of the review team's assessment of the suitability of inclusion of the Applicant's proposed efficacy assessments within the prescribing information. For additional details of the labeling review of this application, see [Section 23](#).

Overall Population and Specification of Subgroups by Prior Treatment History

In Section 14 of the prescribing information, the Applicant proposed to include results for the efficacy assessments included in tabular format for the following subgroups: 1) total population, 2) biologic and JAK inhibitor naïve, and 3) prior biologic and/or JAK inhibitor failure. Although these categories have been displayed in prescribing information for other approved products, the approach to the treatment of adults with moderately to severely active UC is evolving, and many patients are now treated with therapeutic biologic products or JAK inhibitors as first line of treatment. As use of these products has become more widespread, patients may transition from treatment for reasons other than developing “failure” to treatment. Inclusion of the efficacy data from subjects treated with, but not considered to have failed, these products provide relevant and important information for patients and providers. Accordingly, the review team determined that it was appropriate to include data generated from the entire primary efficacy population based on the following groups/subgroups: 1) total population, 2) subjects without prior biologic and/or JAK inhibitor failure (i.e., subjects that are biologic and/or JAK inhibitor naïve, and subjects with biologic and/or JAK inhibitor exposure but did not meet criteria for failure), and 3) subjects with prior biologic and/or JAK inhibitor failure. See Section [16.1](#).

Review Team Assessment and Considerations- Specific Endpoints

Clinical Remission

The Applicant assessed clinical remission (defined as a stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability) as the primary endpoint for IS-2 and MS at Week I-12 and Week M-44, respectively. The Applicant’s selection of clinical remission as the primary endpoint for IS-2 and MS is consistent with the recommended approach provided in the guidance for industry *Ulcerative Colitis: Developing Drugs for Treatment* ([April 2022](#)). Additionally, the reported results for the analyses of this endpoint were statistically persuasive ($p < 0.001$) ([Table 14](#) and [Table 22](#)) and robust to sensitivity analyses to evaluate potential impacts of ICE and the method used by the Applicant to calculate the mMS (Section [6.2.1.4](#) and Section [6.2.2.4](#)). The review team agrees with inclusion of the results of these analyses in tabular format in the prescribing information.

Corticosteroid-Free Remission at Week M-44

Corticosteroid-free remission was defined by the Applicant as meeting criteria for clinical remission at Week 44 without requiring any treatment with corticosteroids for at least the prior eight weeks. This definition is aligned with FDA recommendations. As corticosteroids are associated with many adverse events (e.g., hypertension, obesity, gastritis, impaired wound healing) and their long-term use is discouraged, achieving remission without requiring corticosteroids is meaningful to patients and providers. Both guselkumab treatment arms (i.e., guselkumab 100 mg SC Q8W and guselkumab 200 mg SC Q4W) achieved statistically significant results versus placebo for this endpoint at Week M-44 (See [Table 20](#)). The review team recommends inclusion of the results of these analyses in tabular format in the prescribing information.

Endoscopic Assessments

The Applicant assessed two endpoints based solely on endoscopic assessments within the multiple testing procedure: 1) endoscopic improvement (defined as an endoscopy subscore of 0 or 1 with no friability) and 2) endoscopic remission (defined as an endoscopy subscore = 0). These definitions are aligned with FDA recommendations. The results for the analyses of endoscopic improvement were statistically significant for both IS-2 and MS. Statistically significant results were also achieved for the endpoint of endoscopic remission in MS. The results of the analysis of endoscopic remission in IS-2 were nominally significant; however, this endpoint was unable to be assessed in the multiple testing procedure as the results of the preceding analysis in the hierarchy (i.e., symptomatic remission at Week I-2) were not statistically significant (See [Table 14](#) and [Table 22](#)).

The assessment of gross inflammation that can be visualized on endoscopy is a clinically relevant outcome of interest. Patients who achieve either endoscopic improvement or endoscopic remission have been shown to have better outcomes than those with continued active inflammation ([Leung et al. 2017](#); [Turner et al. 2021](#)). Of the endpoints assessed by the Applicant, endoscopic remission is a more stringent definition, and data suggest that patients who achieve ES of 0 have better long-term outcomes compared to those who have minimal but residual disease activity (as assessed by ES of 1)) ([Barreiro-de Acosta et al. 2016](#)). Although both endpoints (i.e., endoscopic improvement and endoscopic remission) are considered clinically meaningful and will be included in labeling, the endpoint of endoscopic remission was nominally, but not statistically, significant in IS-2. Accordingly, the results of endoscopic improvement will be presented in tabular format, and the results of endoscopic remission will be presented descriptively. This approach is also consistent with other products that have been approved for the treatment of moderately to severely active UC.

Clinical Response

The Applicant defined clinical response as a decrease from induction baseline in the mMS by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. In IS-2, a greater proportion of subjects in the guselkumab 200 mg IV arm compared to the placebo group achieved this endpoint at Week I-12, and results were statistically significant ([Table 14](#)).

The Applicant's definition of clinical response and proposed inclusion of the results for this analysis at Week I-12 in tabular format are acceptable. Although long-term clinical remission remains the overall goal of therapy for UC, in many patients it may take longer than the relatively short induction period to achieve remission. The objective assessment of improvement in disease activity at the end of induction through the endpoint of clinical response is meaningful, as it is informative to patients and providers to guide continued treatment decisions.

However, the review team does not recommend inclusion of the analysis of this endpoint at Week-44 in the prescribing information. Clinically, for a therapy to be considered successful, patients should achieve clinical remission by the end of the maintenance period. While the results of analyses of clinical remission are meaningful at this timepoint, the results of analyses of clinical response are not.

Histologic Endoscopic Mucosal Improvement (HEMI)

“Histologic endoscopic mucosal improvement” (HEMI) was defined by the Applicant as achieving a combination of histologic improvement (i.e., neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) and endoscopic improvement, defined as an endoscopy subscore of 0 or 1 with no friability. In IS-2 and MS, statistically significant results for the guselkumab arms were achieved compared to placebo arms at Week I-12 and Week M-44 ([Table 14](#) and [Table 22](#), respectively).

Histologic resolution of mucosal inflammation in subjects who achieved endoscopic remission in UC is a clinically meaningful endpoint; published data support that the achievement of improvement in endoscopic and histologic findings after induction therapy was subsequently reported to be associated with lower disease activity (by Mayo and partial Mayo score) at the end of maintenance therapy than either histologic or endoscopic improvement alone ([Li et al. 2020](#)). In addition, early achievement of improvement in neutrophilic inflammation (consistent with a Geboes score of <3.1) has also been associated as a positive predictor of response to biologic therapy (with response defined as the achievement of endoscopic improvement by Week 52) ([Narula et al. 2022](#)). Although there remains uncertainty as to the optimal instrument to quantify histologic activity and response to treatment, the Geboes score is widely accepted and understood in clinical practice and has been utilized in several other UC development programs. Additionally, sufficient support for the use of the Geboes score in patients with UC is available in published literature ([Mosli et al. 2017](#)).

Therefore, the statistically significant results of the analyses of the clinically relevant endpoint of HEMI will be included in tabular format in the prescribing information. As endoscopic improvement is expected to occur prior to histologic resolution of mucosal inflammation clinically, the Applicant’s terminology used in definition of HEMI was reordered to specify the criteria used to define endoscopic improvement (i.e., an endoscopy subscore of 0 or 1 with no friability) and list those criteria prior to the criteria for histologic improvement (i.e., neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system).

Finally, as neither IS-2 nor MS were designed to evaluate the relationship of HEMI (at Week I-12 and M-44, respectively) to disease progression and long-term outcomes, statements will be added to the PI to qualify the potential interpretation of the endpoint analyses.

Maintenance of Clinical Remission at Week 44 in Subjects Who Achieved Clinical Remission after 12 Weeks of Induction

To assess maintenance of clinical remission, the Applicant compared the proportion of patients who achieved clinical remission after 12 weeks of induction therapy and remained in remission at Week M-44 across treatment arms. This also represents a clinically important concept, as the goal of treatment is to achieve and maintain a state of disease inactivity (remission). Both guselkumab treatment arms (i.e., guselkumab 100 mg SC Q8W and guselkumab 200 mg SC Q4W) achieved statistically significant results versus placebo for this endpoint at Week M-44

(See [Table 20](#)). Therefore, the review team agrees with inclusion of this endpoint in labeling in tabular format.

(b) (4) **Rectal Bleeding Subscores, and Stool Frequency Subscores**

(b) (4)

However, early assessments of both rectal bleeding and stool frequency are informative to patients and providers to better characterize the anticipated onset of improvement in the relevant symptoms of UC. (b) (4)

(b) (4)

Fatigue Response

Qualitative data support that fatigue is an important symptom experienced by adults with UC. (b) (4)

(b) (4)

(b) (5) A greater proportion of subjects in the guselkumab 200 mg IV arm achieved this endpoint at Week I-12, compared to placebo, and these results were statistically significant. (b) (4)

(b) (4)

Week 24 Responders

Subjects who did not achieve “clinical response” at Week 12 in IS-1 and IS-2 were eligible to continue an additional 12 weeks of induction therapy with guselkumab 200 mg SC at Week 12, 16, and 20. See Sections [6.2.1.1](#) and [6.2.3.1](#). This subset of subjects was not included in the primary efficacy population, and the data generated from this cohort were not collected as part of a randomized, controlled evaluation. As such, the Applicant’s analyses of Week 24 Responders do not provide interpretable data to inform treatment effect and are not recommended for inclusion in labeling.

6.3. Key Efficacy Review Issues

6.3.1. Establishing Substantial Evidence of Effectiveness

Issue

FDA has typically relied upon data from two independent AWC trials to establish effectiveness for drugs for the treatment of moderately to severely active UC. The Applicant submitted data from a single AWC trial, which included a 12-week induction study (IS-2) and a 44-week maintenance study (MS), to provide SEE for guselkumab for the treatment of adult patients with moderately to severely active UC.

Background

Efficacy results from two phase 3 studies were submitted to support the primary evaluation of efficacy for this sBLA. These two phase 3 studies were IS-2 (12-week, phase 3, Induction Study) and MS (44-week, MS). However, as subjects enrolled in IS-2 were subsequently eligible to enroll into the MS, these studies are considered to represent a single AWC trial.

Assessment

IS-2 and MS provide strong evidence to support the efficacy of guselkumab for the treatment of adults with moderately to severely active UC. The primary and ranked secondary endpoints prespecified for evaluation in IS-2 and MS have been accepted to represent clinically meaningful aspects of UC, which if left inadequately treated or untreated could contribute to significant morbidity or serious clinical sequelae. IS-2 achieved statistically significant results for the primary and most secondary endpoints (see Section [6.2.2.4](#)). The results of analyses of efficacy endpoints in MS achieved statistically significant results for both dosage regimens (i.e., 100 mg SC Q8W and 200 mg SC Q4W) for the primary and all secondary endpoints (see Section [6.2.2.4](#)). Moreover, the statistical tests for the primary endpoint and multiple secondary endpoints in each study achieved p-values <0.001. Of note, when prespecified, the probability of a single study achieving a p-value <0.00125 provides the same level of evidence against the null hypothesis as two independent studies each achieving a p-value <0.05. Therefore, based on the studies' success on their primary and multiple secondary endpoints with all reporting highly significant p-values, IS-2 and MS provide highly persuasive evidence for treatment efficacy.

Conclusion

Because subjects enrolled in IS-2 were eligible to subsequently enroll into MS, the two studies are considered to represent a single AWC trial. However, as noted above, the efficacy results for the primary and multiple ranked secondary efficacy endpoints in both studies were statistically persuasive ($p < 0.001$) and robust. Therefore, these data provided the level of evidence that is generally expected from two adequate and well controlled trials and are adequate to establish SEE of guselkumab for the treatment of adult patients with moderately to severely active UC.

6.3.2. Selection of Maintenance Dose

Issue

Determination of the recommended maintenance dosage regimens for the treatment of adults with moderately to severely active UC.

Background

The Applicant's proposed recommended dosage regimens for maintenance are as follows.

Induction:

The recommended induction dosage of TREMFYA is 200 mg administered by intravenous infusion over a period of at least one hour at Week 0, Week 4, and Week 8.

Maintenance:

The recommended maintenance dosage of TREMFYA is 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and Q8W thereafter, may be used.

To evaluate the suitability of the Applicant's proposed recommended dosage regimens for maintenance, the review team assessed results of the efficacy analyses conducted at Week M-44 from MS. This study was a randomized withdrawal study where subjects who achieved clinical response after 12 weeks of induction in IS-1 or IS-2 were randomized to receive placebo, guselkumab 100 mg SC Q8W beginning at Week I-16 (Week M-4), or guselkumab 200 mg SC at Week I-12 (Week M-0). See Section [6.2.2.1](#) for additional details.

Both dosage regimens demonstrated statistically significant efficacy results compared to placebo at Week M-44 for the primary endpoint, as well as for all ranked secondary endpoints (i.e., symptomatic remission, endoscopic improvement, corticosteroid-free clinical remission, clinical response, HEMI, fatigue response, maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction, and endoscopic remission). See Section [6.2.2.3](#).

To further evaluate the suitability of the Applicant's proposed recommended maintenance dosage regimens, the review team evaluated the submitted exposure-response analyses and conducted additional subgroup analyses.

Assessment

Exposure-Response

In the overall population, exposure-response analyses revealed a positive trend between guselkumab serum trough concentrations at Week M-44 and endpoints of clinical remission, clinical response, endoscopic improvement, and HEMI (selected by the Applicant for evaluation). For endpoints of clinical remission and HEMI, the highest rate of efficacy was observed in the highest exposure quartile. Comparison of observed serum trough concentrations from MS to quartiles used for exposure-response efficacy analyses indicated that most subjects randomized to 100 mg SC Q8W would generally fall within the second exposure quartile, while most subjects randomized to 200 mg SC Q4W would fall within the third and fourth exposure quartiles. Accordingly, the E-R analyses suggest that patients treated with 200 mg SC Q4W may achieve higher rates of clinical remission and HEMI based on the distribution of subject exposure favoring higher quartiles for that dosage regimen (i.e., third and fourth quartile) and the

association between increased exposure quartile and greater relative efficacy observed for those endpoints. However, all exposure quartiles demonstrated efficacy over placebo for the Week M-44 endpoints evaluated (i.e., clinical remission, clinical response, endoscopic improvement, and HEMI), with an approximate plateau of effect (i.e., similar rates of efficacy) predicted for subjects with trough concentrations falling in quartiles two through four. As such, these data support that similar efficacy could be achieved regardless of whether patients receive 100 mg SC Q8W or 200 mg SC Q4W, as most subjects administered either regimen achieved exposures at or above the second quartile.

Based on observed serum trough concentrations by body weight quartile, there is potential for comparatively lower efficacy for subjects with higher body weight who receive the 100 mg SC Q8W dosage. Among subjects randomized to 200 mg SC Q4W, at least 75% of subjects in the highest body weight quartile (≥ 81.8 kg) are expected to fall in the third and fourth exposure quartiles. Among subjects randomized to 100 mg SC Q8W, most subjects in the highest body weight quartile (≥ 83.5 kg) are expected to fall in the lowest exposure quartile, thus achieving exposures below the approximate plateau of effect predicted for subjects with UC (i.e., trough concentrations falling in quartiles two through four).

Dose-Response

Both dosage regimens achieved statistically significant results compared to placebo for the primary and ranked secondary endpoints in MS (Section [6.2.2](#)). Point estimates of the response rates were slightly higher in the 200 mg SC Q4W treatment arm as compared to the 100 mg SC Q8W treatment arm for the following key clinically relevant endpoints: clinical remission (50.0% versus 45.2%), HEMI (47.9% versus 43.6%), maintenance of clinical remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction (72.5% versus 60.6%), and corticosteroid-free remission (48.9% versus 45.2%). Although the slightly higher response rates in the 200 mg SC Q4W arm may suggest that the higher dose may achieve slightly better efficacy, the study was not powered to directly compare the efficacy in the two treatment arms and the ability to make formal comparisons of efficacy between the two treatment groups is limited. Of note, for the remaining ranked secondary endpoints, the response rate was slightly higher in the 200 mg SC Q4W treatment arm as compared to the 100 mg SC Q8W treatment arm for endoscopic improvement (51.6% versus 49.5%) and slightly lower in the 200 mg SC Q4W treatment arm as compared to the 100 mg SC Q8W treatment arm for symptomatic response (68.9% versus 70.2%), clinical response (74.7% versus 77.7%), fatigue response (43.2% versus 50.5%), and endoscopic remission (33.7% versus 34.6%).

The analysis of the primary endpoint of clinical remission was repeated in subgroups defined by demographics and baseline disease characteristics. For both dose groups, the estimates of efficacy (i.e., difference in response rates between treated and placebo subjects) were relatively constant across subgroups, and the estimate in each subgroup was generally similar to the estimate of in the overall population. Therefore, there was no clear dose-response identified in any subgroup of subjects.

In the 100 mg SC Q8W treatment arm, the estimated treatment effect showed a slight decrease as weight increased ([Figure 23](#)), whereas this trend was not apparent in the 200 mg SC Q4W treatment arm. This observation is consistent with the results from the exposure-response

analysis which demonstrated that most subjects in the highest body weight quartile are expected to fall in the lowest exposure quartile (i.e., achieve exposures below the approximate plateau of effect) and provides suggestive evidence for the potential for reduced efficacy of the 100 mg SC Q8W dose in individuals of higher body weights. However, the available data do not support a definitive association between increased body weight and decreased efficacy. Of note, increased clearance and volume of distribution of guselkumab were also observed with higher body weights in the development programs for the approved indications (i.e., psoriasis, psoriatic arthritis). The following statement is included in the current prescribing information in Section 12.3 PHARMACOKINETICS: Special Populations:

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

Conclusion

The data submitted in the application support that both maintenance dosage regimens are effective for the treatment of adults with moderately to severely active UC compared to placebo with no clear dose-response observed on analyses of the overall population or identified subgroups of interest. Although the exposure-response analyses suggest the potential for decreased efficacy as a result of decreased relative exposures in subjects of higher body weight administered the 100 mg Q8W dosage regimen, a definitive association was not identified. The review team agrees that the current language in the prescribing information accurately describes the results of assessments conducted in subjects with UC.

UC is a chronic disease that requires life-long medical management. About 20-30% of patients experience inadequate or nonresponse to available medical therapies, and about 25-45% of subjects who initially achieve clinical response may subsequently develop secondary loss of response ([Roda et al. 2016](#); [Rubin et al. 2019](#)). To achieve long-term remission, some subjects require adjustments and/or changes in pharmacotherapy. The availability of both proposed maintenance dosage regimens provides patients and prescribers an option to adjust therapy with guselkumab, as medically appropriate.

However, the risks of a therapy are generally greater with increased exposures, and, although adequate to support approval, the available safety data are not sufficient to inform the potential risk for reactions that occur infrequently or only after prolonged exposure (e.g., malignancy). As a result of the remaining uncertainty regarding these risks, the review team recommends approval of both maintenance dosages, with instructions to use the lowest effective dosage to maintain therapeutic response. Inclusion of these instructions allows prescribers flexibility and encourages reassessment of response during maintenance therapy in order to avoid the potential risks of long-term drug exposure to a higher dosage if patients are able to maintain therapeutic response with the lower dosage.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Adverse findings related to guselkumab use in nonclinical studies were limited to reproductive toxicity studies. There were no significant adverse findings in the general toxicology studies.

Nonclinical safety of guselkumab was previously evaluated in safety pharmacology studies and repeat-dose subcutaneous and intravenous toxicity studies conducted in cynomolgus monkeys for durations of up to 24 weeks. No adverse findings were observed in monkeys following repeated dosing for up to 24 weeks at dose levels up to 50 mg/kg/week.

Reproductive toxicology studies were conducted in cynomolgus monkeys and guinea pigs. In the enhanced pre- and post-natal development (ePPND) study, neonatal monkey deaths occurred in the offspring of 1 of 16 control monkeys, 3 of 14 in low dose (10 mg/kg/week SC) and 3 of 14 high dose monkeys (50 mg/kg/week SC). Two SC fertility studies were conducted in young sexually mature male guinea pigs. In the first male guinea pig fertility study, an increase in early resorptions per litter and the percentage of post-implantation loss was noted at the 100 mg/kg twice weekly dose. In the second male guinea pig fertility study, there were no treatment related effects noted at the 100 mg/kg twice weekly dose. The results of the second male guinea pig fertility study do not negate the results of the first male guinea pig fertility study.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The risks of guselkumab have been well characterized during development for the currently approved indications of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and adults with active psoriatic arthritis. The current prescribing information for guselkumab includes a contraindication related to hypersensitivity to guselkumab or any excipients in guselkumab. In addition, warnings and precautions related to hypersensitivity reactions, infections, and tuberculosis are also included in the current prescribing information.

There are established class-related risks of IL-23 antagonist and related therapeutic biologic products (IL-12/23 antagonists). In consideration of the known safety profile of IL-23 antagonists and related therapeutic biologic products (IL-12/23 antagonist), as well as the established safety profile of guselkumab in other indications, respiratory tract infections, abdominal pain, leukopenia, anemia, and injection site reactions were identified as potential class-related adverse reactions (ARs) by the review team.

In addition to the evaluation of safety data using the individual preferred terms (PTs), grouped queries were conducted to assess these potential class-related ARs associated with guselkumab exposure. See Section [7.6.1.6](#) and Section [7.6.2.6](#) for PTs included in the grouped queries, results of the conducted analyses, and clinical interpretation of results.

Furthermore, hepatotoxicity is included in the Warnings & Precautions for IL-23 antagonists currently approved for UC (i.e., mirikizumab, risankizumab) and CD (i.e., risankizumab). Additionally, the risk of elevated liver enzymes is included in guselkumab prescribing information for the psoriasis indication, although these elevations are described as mild to moderate in severity. A review of data submitted as supportive evidence of safety (i.e., safety data from the guselkumab CD clinical development program) was completed to further assess this potential risk. See Section [7.6.3](#).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

A high-level summary of available postmarketing data from July 13, 2017 (initial approval date for guselkumab for plaque psoriasis) through July 12, 2023, was included in this submission. According to the Applicant's summary, the estimated cumulative global exposure from July 13, 2017, to June 30, 2023, is 407,104 person-years, and no new adverse drug reactions were identified based on these data. Based on this report, device malfunction/use errors and drug-induced liver injury were identified for additional evaluation by the review team.

7.3.1. Drug-Device Combination Product

A Post-Marketing Adverse Event Report for the 100 mg/1 mL drug product presentations (i.e., 100 mg/mL in a single-dose prefilled syringe [1 mL PFS-U] or single-dose One-Press patient-controlled injector (1 mL PFS-S)) was included with the 90-Day Safety Update (SDN 1234; Submitted 6/6/24). The report focused on device-related AEs including device malfunction and use errors and included a cumulative review of Global Medical Safety global safety database from July 13, 2017 (approval of adults with plaque psoriasis) through January 31, 2024.

Per this report, 9,763 events potentially indicative of device malfunction or use errors for the One-Press Patient-controlled Injector (pre-filled pen), 1,720 events potentially indicative of device malfunction or use errors for UltraSafe (pre-filled syringe), and 706 events potentially indicative of device malfunction or use errors for unspecified product (either pre-filled pen or pre-filled syringe) were identified.

Of these cases, four cases reported a fatal outcome. The cases were reviewed and deemed by the Applicant as unrelated to device issues. Causes of death included pancreatic carcinoma; metastatic prostate cancer with renal failure; cerebral hemorrhage; and acute generalized exanthematous pustulosis with pneumothorax and urosepsis. The review team agrees with the Applicant's assessment that the fatalities were unrelated to the noted device issues.

A review of commonly reported Medical Dictionary for Regulatory Activities (MedDRA) PTs potentially indicative of device malfunction or use errors was also completed by the Applicant, and details of this review were submitted in the 90-day Safety Update. The majority of the events in this report for all currently approved product presentations were classified as nonserious. Most serious AEs were deemed by the Applicant as associated with underlying conditions that were managed using guselkumab and not assessed to be device related. The review team agreed with the Applicant's assessment.

7.3.2. Hepatotoxicity

Hepatotoxicity, including potential drug-induced liver injury (DILI), was identified as a potential class-related AR. The Division of Pharmacovigilance (DPV) was consulted to evaluate reports of liver injury reported with guselkumab injection, as well as all AEs with guselkumab injection to identify reports of AEs with the potential for serious outcomes or serious labeled events with an increase in severity that are not described in the Applicant's proposed labeling for this sBLA. DPV-I reviewed multiple data sources to identify safety signals for guselkumab including FAERS reports, the medical literature, and the Applicant's periodic safety reports. This review did not identify any new or worsening safety signals warranting a change in labeling for guselkumab at this time. See DPV consult memo uploaded by Suraj Rajasimhan dated June 28, 2024, for full details (DARRTS Reference ID: 5405761).

In addition to the evaluation of postmarket data by DPV, a potential signal for DILI was identified during review of the supportive safety information submitted by the Applicant from their development program for guselkumab for the treatment of moderately to severely active CD. See Section [7.6.3](#) for additional discussion of these data and details of the July 18, 2024, consultation review by Paul Hayashi, MD of the Division of Hepatology and Nutrition's DILI Team on (DARRTS Reference ID: 5416230).

7.3.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by other disciplines based on review of post-market data.

7.4. FDA Approach to the Safety Review

To support the safety of guselkumab for the treatment of adults with moderately to severely active UC the Applicant provided safety data from induction and maintenance periods of the QUASAR program. Data generated from the induction studies, IS-1 and IS-2, were used to support the primary evaluation of safety for induction therapy with guselkumab 200 mg IV at Week I-0, Week I-4, and Week I-8. Data from MS were submitted to support the primary evaluation of safety for maintenance therapy with 100 mg SC at Week 16, and then Q8W thereafter, or 200 mg SC at Week 12, and then Q4W thereafter.

Pooled data from IS-1 and IS-2 were used to assess AEs that occurred during the induction period (Week I-0 to Week I-12), and data from MS were used to assess AEs that occurred from Week M-0 to Week M-44. The Applicant performed safety analyses on the safety analyses set, which included all subjects who received at least one dose of any study drug, and safety data were analyzed according to the treatment received. Adverse events and severe adverse events (SAEs) were collected from the time of obtaining an informed consent and at each visit until the end of the study. TEAEs were defined as those that initially developed or worsened in severity compared to baseline during the treatment period. All TEAEs were coded and classified according to the specified Medical Dictionary for Regulatory Activities version at the time of analysis by primary system organ class, high-level term, and preferred term (PT).

Prespecified adverse events of special interest included malignancies and active tuberculosis. The Applicant identified the following AEs as “Other Adverse Events of Interest”: opportunistic infections, anaphylactic reactions, serum sickness, major adverse cardiovascular event, venous thromboembolism, and hepatic disorders.⁶

Independent review and analysis of safety data from the individual studies was conducted. To promote the identification of less common potential safety signals using a larger sample size, the safety analysis of induction dosing was based on pooled data from IS-1 and IS-2. IS-1 and IS-2 enrolled comparable subject populations and evaluated a common dosage regimen (i.e., 200 mg IV at Week 0, Week 4, and Week 8). As no notable differences were identified on review of the safety data from the individual studies, except where noted, the pooled analyses are included below in the safety review.

All safety assessments and conclusions are those of the review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

7.5. Adequacy of the Clinical Safety Database

While the premarket safety database contains limited data to sufficiently assess the potential for rare events and those of long latency, the safety database was considered adequate to characterize the common adverse events and provide a safety assessment to support evaluation of the proposed indication to treat adult patients with moderately to severely active UC and recommended dosage regimens of guselkumab 200 mg IV at Week I-0, Week I-4, and Week I-8, followed by either 100 mg SC at Week I-16, and Q8W thereafter, or 200 mg SC at Week I-12, and Q4W thereafter.

Subjects enrolled in IS-1 were randomized to receive guselkumab 400 mg IV, 200 mg IV, or placebo. Subjects enrolled into IS-2 were randomized to receive guselkumab 200 mg IV or placebo. Placebo subjects who did not achieve clinical response at Week I-12 were eligible to receive 12 weeks of guselkumab induction therapy. Subjects enrolled in IS-1 and IS-2 who achieved clinical response after 12 weeks of induction therapy (i.e., subjects randomized to guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo [including subjects who achieved clinical response on placebo at Week I-12 and placebo non-responders who received guselkumab 200 mg IV from Week I-12 to I-24 who achieved clinical response at Week I-24]) were eligible to enroll into MS and were randomized to receive guselkumab 100 mg SC Q8W, 200 mg SC Q4W, or placebo.

The primary induction safety database includes subjects randomized into IS-1 and IS-2 who received guselkumab 200 mg IV, guselkumab 400 mg IV, or placebo from baseline through Week I-12. The primary maintenance safety database includes subjects who achieved clinical

⁶ Clinically important hepatic disorders are defined as hepatic disorder AEs reported as SAEs or AEs leading to discontinuation of study intervention. Hepatic disorder AEs are defined as the narrow terms in the MedDRA SMQ of “Drug Related Hepatic Disorders - Comprehensive Search.”

response after 12 weeks of induction therapy who were randomized into MS to receive 100 mg SC Q8W, 200 mg SC Q4W, or placebo.

The primary safety database for induction included pooled data from 107 subjects exposed to guselkumab 400 mg IV, 522 subjects exposed to guselkumab 200 mg IV, and 385 subjects exposed to placebo in IS-1 or IS-2. The primary safety database for maintenance included 190 subjects exposed to guselkumab 200 mg SC Q4W, 186 subjects exposed to guselkumab 100mg SC Q8W, and 192 subjects exposed to placebo in MS.

[Table 30](#) and [Table 31](#), respectively, summarize the exposure periods for the induction and maintenance safety population(s).

Table 30. Duration of Exposure, Safety Population, IS-1 and IS-2 (Pooled)^a

Parameter	Guselkumab 200 mg IV Q4W N=522	Guselkumab 400 mg IV Q4W N=107	Placebo IV Q4W N=385
Duration of treatment, weeks			
Mean (SD)	7.8 (1.7)	8 (1)	7 (2.7)
Median (Q1, Q3)	8.1 (8, 8.3)	8.1 (8, 8.1)	8.1 (7.7, 8.1)
Min, Max	0.1, 10.3	0.1, 9.1	0.1, 9.1
Patients treated, by duration, n (%)			
<4 weeks	14 (2.7)	1 (0.9)	17 (4.4)
≥4 weeks	345 (66.1)	66 (61.2)	137 (35.6)
≥8 weeks	298 (57.1)	54 (50.5)	106 (27.5)

Source: adex.xpt and adsl.xpt; Software: R.

^a Duration of the placebo-controlled active treatment period is 12 weeks.

Abbreviations: IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment arm; n, percentage of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, every four weeks; SD, standard deviation

Table 31. Duration of Exposure, Safety Population, MSA

Parameter	Guselkumab 100 mg SC Q8W N=186	Guselkumab 200 mg SC Q4W N=190	Placebo SC Q4W N=192
Duration of treatment, weeks			
Mean (SD)	36.2 (10.3)	34.9 (11.2)	29.2 (13.3)
Median (Q1, Q3)	40.1 (39.6, 40.5)	40.1 (38.9, 40.4)	39 (16.3, 40.1)
Min, max	3.3, 45	0.1, 42.1	0.1, 42.1
Patients treated, by duration, n (%)			
<4 weeks	2 (1.1)	2 (1.1)	4 (2.1)
≥4 weeks	184 (98.9)	188 (98.9)	128 (66.7)
≥16 weeks	167 (89.8)	167 (87.9)	149 (77.6)
≥40 weeks	120 (64.5)	118 (62.1)	76 (39.6)

Source: adex.xpt and adsl.xpt; Software: R.

^a Duration of the active treatment period is 44 weeks

Abbreviations: MS, Maintenance Study; N, number of subjects in treatment arm; n, percentage of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous; SD, standard deviation

Note, in IS-1 and IS-2, 298/522 (57.1%) of subjects in the guselkumab 200 mg group, 54/107 (50.5%) subjects in the guselkumab 400 mg group, and 106/385 (27.5%) of subjects in the placebo group that were included in the primary induction safety population had a duration of exposure ≥8 weeks, indicating a completed induction dosing regimen. In MS, 120/186 (64.5%)

of subjects in the guselkumab 100 mg group, 118/190 (62.1%) of subjects in the guselkumab 200 mg group, and 76/192 (39.6%) of subjects in the placebo group that were included in the primary maintenance safety database had a total duration of exposure ≥ 40 weeks, indicating completion of all planned maintenance dosing. Given the duration of exposures in the studies, the safety database is deemed sufficient to characterize the safety of guselkumab in adults with moderately to severely active UC when used through 12 weeks of induction therapy and through 44 weeks of maintenance therapy (i.e., a total of 56 week of exposure).

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, IS-1 and IS-2

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, IS-1 and IS-2

[Table 32](#) provides an overview of TEAEs reported in the primary induction safety database (i.e., subjects enrolled in studies IS-1 and IS-2).

Table 32. Overview of Adverse Events, Safety Population, IS-1 and IS-2 (Pooled)

Event Category	Guselkumab 200 mg IV Q4W N=522 n (%)	Guselkumab 400 mg IV Q4W N=107 n (%)	Placebo IV Q4W N=385 n (%)
SAE	13 (2.5)	3 (2.8)	26 (6.8)
AE leading to permanent discontinuation of study drug	8 (1.5)	0	14 (3.6)
AE leading to interruption of study drug	9 (1.7)	0	4 (1.0)
Any AE ^a	253 (48.5)	53 (49.5)	197 (51.2)
Severe and worse	14 (2.7)	4 (3.7)	25 (6.5)
Moderate	77 (14.8)	22 (20.6)	70 (18.2)
Mild	162 (31.0)	27 (25.2)	102 (26.5)

Source: adae.xpt; Software: R.

^a Severity as assessed by the investigator

Treatment-emergent adverse event defined as any AE occurring at or after the initial administration of study intervention

Abbreviations: AE, adverse event; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; Q4W, every four weeks; SAE, serious adverse event

The overall incidence of TEAEs by category was similar across the treatment groups. A greater proportion of placebo subjects reported SAEs, SAEs with fatal outcome, and AEs leading to study drug discontinuation compared to subjects who received guselkumab 200 mg IV or 400 mg IV. The majority of TEAEs were mild or moderate in severity.

7.6.1.2. Deaths, Pooled Analyses, IS-1 and IS-2

Of subjects included in the primary induction safety database, there were three deaths reported in IS-2. One death was reported in the guselkumab 200 mg IV group, and two deaths were reported in the placebo group. No deaths were reported in IS-1.

The death that occurred in the subject treated with guselkumab 200 mg IV was reviewed and adjudicated as likely due to pre-existing cardiovascular risk factors and likely unrelated to guselkumab exposure.

Subject ID (b) (6): 57-year-old Asian female with a medical history of UC, diabetes mellitus, hyperlipidemia, and chronic tobacco use who experienced a fatal acute myocardial infarction on Day 7⁷ of Study IS-2. The subject was randomized to receive guselkumab 200 mg IV Q4W IV. On Study Day 6, the subject experienced chest pain, and she was hospitalized for symptoms on Study Day 7. An electrocardiogram was completed, which was suggestive of an acute inferior and posterior myocardial infarction. An emergency coronary angiography was performed which revealed significant coronary artery disease. A subsequent interventional procedure was completed, including stent placement of the left main-left anterior descending artery. The subject became hypotensive (blood pressure 80/51 mm Hg) and bradycardic (heart rate 40 beats/min). Despite resuscitative efforts, the subject passed away on Study Day 7. The cause of death was acute myocardial infarction. An autopsy was not performed. The investigator considered the event of acute myocardial infarction to be severe in intensity and not related to study intervention.

Two deaths were reported in subjects in the placebo group (Subject ID (b) (6) passed away from “natural causes;” Subject ID (b) (6) passed away from “cardiac arrest”).

The review team agrees with the assessing investigator’s evaluations and conclusions that the reported fatalities were unrelated to guselkumab administration.

7.6.1.3. Serious Adverse Events, Pooled Analyses, IS-1 and IS-2

As noted above, the proportion of SAEs was greater in the placebo group, 26/385 (6.8%) subjects, compared to either the guselkumab 200 mg IV group, 13/522 (2.5%) subjects, or the guselkumab 400 mg IV group, 3/107 (2.8%) subjects. [Table 33](#) provides a summary of SAEs reported in at least one subject who received guselkumab and in a greater proportion of subjects in either guselkumab treatment arm compared to placebo in IS-1 and IS-2.

⁷ Study day of death is defined as date of death minus date of first dose of study treatment plus 1.

Table 33. Serious Adverse Events Reported in More Than at Least One Guselkumab Subject and Greater in Either Treatment Arm Versus Placebo, Safety Population, IS-1 and IS-2 (Pooled)

System Organ Class Preferred Term	Guselkumab 200 mg IV Q4W N=522 n (%)	Guselkumab 400 mg IV Q4W N=107 n (%)	Placebo IV Q4W N=385 n (%)
Blood and lymphatic system disorders			
Anemia	2 (0.4)	1 (0.9)	1 (0.3)
Cardiac disorders			
Acute myocardial infarction	1 (0.2)	0	0
Myocardial infarction	1 (0.2)	0	0
Atrial fibrillation	0	1 (0.9)	0
Gastrointestinal disorders			
Intestinal perforation	1 (0.2)	0	0
Mucosal prolapse syndrome	1 (0.2)	0	0
Infections and infestations			
Clostridium difficile infection	2 (0.4)	0	0
Staphylococcal sepsis	1 (0.2)	0	0

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention. Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; SOC, system organ class; Q4W, every four weeks.

The most frequently reported SAEs were anemia and clostridium difficile (0.4% each). Interpretation of these results is limited, given the small number of SAEs reported in each treatment arm.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Pooled Analyses, IS-1 and IS-2

A higher proportion of placebo subjects, 13/385 (3.6%) subjects, reported AEs leading to treatment discontinuation compared to subjects randomized to guselkumab 200 mg IV, 8/522 (1.5%) subjects. No subjects randomized to guselkumab 400 mg IV reported AEs leading to treatment discontinuation. The most commonly reported AE leading to discontinuation of study intervention was “colitis ulcerative,” occurring in 11/385 (2.9%) of subjects in the placebo group compared to 3/522 (0.6%) in the guselkumab 200 mg group. AEs leading to treatment discontinuation reported in at least one subject who received guselkumab and in a greater proportion of subjects than placebo are shown in [Table 34](#). Of note, all these AEs occurred in one subject in the guselkumab 200 mg IV Q4W group and no subjects in the placebo group. Interpretation of these results is limited, given small number of events reported per treatment arm.

Table 34. Subjects With Adverse Events Leading to Treatment Discontinuation Reported in More Than One Subject and Greater in Either Treatment Arm Versus Placebo, Safety Population, IS-1 and IS-2 (Pooled)

System Organ Class Preferred Term	Guselkumab 200 mg IV Q4W N=522 n (%)	Placebo IV Q4W N=385 n (%)
Cardiac disorders		
Myocardial infarction	1 (0.2)	0
Gastrointestinal disorders		
Diarrhea	1 (0.2)	0
General disorders and administration site conditions		
Chest discomfort	1 (0.2)	0
Chills	1 (0.2)	0
Infections and infestations		
Staphylococcal sepsis	1 (0.2)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1 (0.2)	0

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention. Abbreviations: IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; SOC, system organ class; Q4W, every four weeks

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, IS-1 and IS-2

[Table 35](#) shows the overall distribution of TEAEs and TEAEs that occurred in $\geq 2\%$ of subjects treated with either guselkumab 200 mg IV or 400 mg IV and at a higher rate than placebo.

Table 35. Treatment-Emergent Adverse Events Occurring at $\geq 2\%$ Frequency and at a Higher Rate Than Placebo, Safety Population, IS-1 and IS-2 (Pooled)

Preferred Term	Guselkumab 200 mg IV Q4W N=522 n (%)	Guselkumab 400 mg IV Q4W N=107 n (%)	Placebo IV Q4W N=385 n (%)
Any AE	253 (48.5)	53 (49.5)	197 (51.2)
Respiratory tract infections ^a	46 (8.8)	6 (5.6)	28 (7.3)

Source: adae.xpt; Software: R.

^a Respiratory tract infections includes PTs: COVID-19, influenza, nasopharyngitis, respiratory tract infection, upper respiratory tract infection, and viral respiratory tract infection

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention.

Analysis is subject level (i.e., each subject is counted once regardless of the number of reported events).

Coded as MedDRA preferred terms

Abbreviations: AE, adverse event; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, percentage of subjects with at least one adverse event; Q4W, every 4 weeks

Overall, the proportion of subjects with at least one TEAE was greater in the placebo group (197/385 [51.2%] subjects) compared to the guselkumab 200 mg IV (253/522 [48.5%] subjects) and 400 mg IV (53/107 [49.5%] subjects) groups. In the combined IS-1 and IS-2 up to Week I-12, respiratory tract infections occurred in 8.8% of subjects in the guselkumab 200 mg IV Q4W group and 7.3% of subjects in the placebo group. The review team recommends inclusion of this

analysis in Section 6, ADVERSE REACTIONS, of the United States Prescribing Information (USPI).

7.6.1.6. FDA Grouped Queries, Pooled Analyses, IS-1 and IS-2.

In consideration of the known safety profile of IL-23 antagonists and related therapeutic biologic products (IL-12/23 inhibitors), as well as the established safety profile of guselkumab in other indications, the following grouped queries (GQ) were conducted.

- Respiratory tract infections (COVID-19, influenza, nasopharyngitis, respiratory tract infection, upper respiratory tract infection, and viral respiratory tract infection)
- Leukopenia (leukopenia, lymphopenia, lymphocyte count decreased, lymphocyte percentage decreased, monocytopenia, neutropenia, neutrophil count decreased, white blood cell count decreased)
- Anemia (anemia, hematocrit decreased, iron deficiency anemia, hemoglobin decreased)
- Abdominal pain (abdominal pain, abdominal pain upper)

Results of analyses for these grouped queries are shown in [Table 36](#).

Table 36. Grouped Queries, IS-1 and IS-2 (Pooled)

	Guselkumab 200 mg IV Q4W N=522 n (%)	Guselkumab 400 mg IV Q4W N=107 n (%)	Placebo IV Q4W N=385 n (%)
Preferred Term			
Respiratory tract infections	46 (8.8)	6 (5.6)	28 (7.3)
Leukopenia	18 (3.4)	5 (4.7)	17 (4.4)
Anemia	41 (7.9)	9 (8.4)	42 (10.9)
Abdominal pain	12 (2.3)	3 (2.8)	10 (2.6)

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention.

Analysis is subject level (i.e., each subject is counted once regardless of the number of reported events).

Coded as MedDRA preferred terms

Abbreviations: IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment group; n, percentage of subjects with given adverse event; Q4W, every 4 weeks

Of the conducted GQ, only respiratory tract infections were reported in a higher proportion of subjects randomized to guselkumab 200 mg versus placebo (8.8% and 7.3%, respectively). As “respiratory tract infections” occurred at rate of $\geq 2\%$, and higher than placebo in subjects with UC.

7.6.1.7. Laboratory Findings, Pooled Analyses, IS-1 and IS-2

Review of the results for chemistry and hematology values that occurred at $\geq$ level 2 criteria⁸ by treatment arm revealed that, in general, the proportion of subjects with abnormal values were similar between the proposed TBM dose (guselkumab 200 mg IV) and placebo. Additionally,

⁸ Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.

there were no notable dose-dependent changes in laboratory values between guselkumab induction treatment groups (i.e., guselkumab 200 mg IV or 400 mg IV).

7.6.1.8. Vital Signs, Pooled Analyses, IS-1 and IS-2

In IS-1 and IS-2, vital signs were obtained at screening, baseline, every four weeks until Week I-24 (or until the early termination visit, if applicable), and at the safety follow-up visit. No significant abnormalities in vital signs were observed in treatment or placebo arms in IS-1 or IS-2, and no clinically meaningful trends or changes were identified upon review of vital signs when comparing guselkumab 200 mg IV or 400 mg IV to placebo-treated subjects.

7.6.2. Safety Results, MS

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, MS

[Table 37](#) provides an overview of TEAEs reported in MS.

Table 37. Overview of Adverse Events, Safety Population, MS

	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)
Event Category			
SAE	5 (2.7)	12 (6.3)	1 (0.5)
AE leading to permanent discontinuation of study drug	7 (3.8)	5 (2.6)	13 (6.8)
AE leading to interruption of study drug	4 (2.2)	2 (1.1)	2 (1.0)
Any AE ^a	120 (64.5)	133 (70.0)	131 (68.2)
Severe and worse	10 (5.4)	6 (3.2)	5 (2.6)
Moderate	49 (26.3)	54 (28.4)	69 (35.9)
Mild	61 (32.8)	73 (38.4)	57 (29.7)

Source: adae.xpt; Software: R.

^a Severity as assessed by the investigator

Treatment-emergent adverse event defined as any AE occurring at or after the initial administration of study intervention

Abbreviations: AE, adverse event; MS, Maintenance Study; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; Q4W, every four weeks; Q8W, every eight weeks; SAE, serious adverse event; SC, subcutaneous

The proportion of any AEs reported was similar or lower in the guselkumab treatment groups versus placebo (120/186 [64.5%] subjects in the guselkumab 100 mg SC group, 133/190 [70%] subjects in the guselkumab 200 mg SC group, and 131/192 [68.2%] subjects in the placebo group). SAEs occurred more frequently in both guselkumab groups (5/186 [2.7%] subjects in the 100 mg IV group and 12/190 [6.3%] subjects in the 200 mg IV group) versus placebo (1/192 [0.5%]). The rate of AEs leading to permanent discontinuation of the study drug was lower in both guselkumab groups versus placebo (7/186 [3.8%] subjects in the 100 mg IV group, 5/190 [2.6%] subjects in the 200 mg IV group, and 13/192 [6.8%] subjects in the placebo group). While the proportion of subjects that reported AEs leading to study drug interruption was slightly higher in the 200 mg group versus the 100 mg and placebo groups (4/186 [2.2%] subjects in the 100 mg IV group, 2/190 [1.1%] subjects in the 200 mg IV group, and 2/192 [1.0%] subjects in

the placebo group), the total number of subjects that reported AEs leading to study interruption was small. The majority of AEs were mild or moderate in severity.

7.6.2.2. Deaths, MS

No deaths were reported from baseline through Week M-44 in MS.

7.6.2.3. Serious Adverse Events, MS

A greater proportion of subjects treated with guselkumab reported SAEs compared to placebo (5/186 [2.7%] subjects in the guselkumab 100 mg SC group, 12/190 [6.3%] subjects in the guselkumab 200 mg SC group, and 1/192 [0.5%] subjects in the placebo group). SAEs reported in at least one guselkumab subject and greater in either guselkumab treatment arm versus placebo are shown in [Table 38](#).

Table 38. Serious Adverse Events Reported in at Least One Guselkumab Subject and Greater in Either Treatment Arm Versus Placebo, Safety Population, MS

System Organ Class Preferred Term	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)
Cardiac disorders			
Atrial fibrillation	0	1 (0.5)	0
Eye disorders			
Cataract	0	1 (0.5)	0
Gastrointestinal disorders			
Abdominal pain	0	1 (0.5)	0
Umbilical hernia	1 (0.5)	0	0
Infections and infestations			
Bacterial infection	0	1 (0.5)	0
Complicated appendicitis	0	1 (0.5)	0
Abscess limb	1 (0.5)	0	0
Injury, poisoning, and procedural complications			
Incarcerated incisional hernia	0	1 (0.5)	0
Incisional hernia	0	1 (0.5)	0
Postoperative respiratory failure	0	1 (0.5)	0
Rib fracture	0	1 (0.5)	0
Musculoskeletal and connective tissue disorders			
Osteoarthritis	0	1 (0.5)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
Adenocarcinoma	0	1 (0.5)	0
Fibroadenoma of breast	0	1 (0.5)	0
Nervous system disorders			
Guillain-Barre syndrome	0	1 (0.5)	0
Haemorrhagic stroke	0	1 (0.5)	0
Syncope	1 (0.5)	0	0
Psychiatric disorders			
Anxiety	0	2 (1.1)	0
Acute psychosis	1 (0.5)	0	0
Reproductive system and breast disorders			
Gynecomastia	0	1 (0.5)	0

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Abbreviations: AE, adverse event; MS, Maintenance Study; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous

Anxiety was the most frequently reported SAE and the only SAE that occurred in more than one guselkumab-treated subject (2/107 [1.1%] of subjects in the guselkumab 200 mg SC group). Given the small number of events reported in each treatment arm, interpretation of these results is limited.

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, MS

Subjects with AEs leading to treatment discontinuation are shown in [Table 39](#).

Table 39. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, MS

System Organ Class Preferred Term	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)
Any AE leading to discontinuation	7 (3.8)	5 (2.6)	13 (6.8)
Gastrointestinal disorders			
Rectal stenosis	1 (0.5)	0	0
Colitis ulcerative	3 (1.6)	3 (1.6)	9 (4.7)
Infections and infestations			
Pneumonia	0	0	1 (0.5)
Injury, poisoning, and procedural complications			
Maternal exposure during pregnancy	1 (0.5)	0	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)			
Adenocarcinoma	0	1 (0.5)	0
Basal cell carcinoma	0	0	1 (0.5)
Breast cancer	0	0	2 (1.0)
Nervous system disorders			
Haemorrhagic stroke	0	1 (0.5)	0
Syncope	1 (0.5)	0	0
Skin and subcutaneous tissue disorders			
Pruritus	1 (0.5)	0	0

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention.
Duration is 40 weeks.

Abbreviations: AE, adverse event; MS, Maintenance Study; N, number of subjects in treatment arm; n, percentage of subjects with adverse event; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous; SOC, system organ class

Fewer subjects in the guselkumab groups reported an AE leading to treatment discontinuation compared to placebo; 7/186 (3.8%) and 5/190 (2.6%) of subjects in the guselkumab 100 mg and 200 mg groups, respectively, versus 13/192 (6.8%) of subjects in the placebo group. All AEs in the guselkumab groups that led to treatment discontinuation and that occurred more frequently than in the placebo group occurred at a rate <1%. Given the small number of reported events, interpretation of the results is limited.

7.6.2.5. Treatment-Emergent Adverse Events, MS

[Table 40](#) summarizes the common TEAEs that were reported at a frequency of $\geq 3\%$ of subjects in either guselkumab group and at a rate greater than the placebo during MS.

Table 40. Subjects With Treatment-Emergent Adverse Events Occurring at $\geq 3\%$ Frequency, and Higher Than Placebo, Safety Population, MS

	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)
Preferred Term			
Any AE	120 (64.5)	133 (70)	131 (68.2)
Injection site reactions ^a	2 (1.1)	17 (8.9)	2 (1)
Arthralgia	8 (4.3)	15 (7.9)	13 (6.8)
Upper respiratory tract infection	6 (3.2)	13 (6.8)	8 (4.2)

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention. Analysis is subject level (i.e., each subject is counted once regardless of the number of reported events).

Coded as MedDRA preferred terms

^a Injection site reactions includes PTs: administration site pain, injection site hematoma, injection site hemorrhage, injection site hypersensitivity, injection site erythema, injection site pain, injection site pruritus, injection site rash, injection site reaction, and injection site urticaria.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, Maintenance Study; N, number of patients in treatment arm; n, percentage of subjects with at least one event; Q4W, every four weeks; Q8W, every eight weeks; SC, subcutaneous

A greater proportion of subjects in the placebo group reported TEAEs compared to the guselkumab 100 mg SC group, whereas TEAEs were reported at similar rates between the guselkumab 200 mg SC group and placebo group. Arthralgia and upper respiratory tract infection are included as adverse reactions in the currently approved prescribing information for guselkumab. The review team recommends inclusion of the PTs listed in [Table 40](#) in the ADVERSE REACTIONS section of the prescribing information, as they occurred in $\geq 3\%$ of subjects treated with the proposed recommended maintenance dosage regimens (i.e., guselkumab 100 mg SC Q8W or 200 mg SC Q4W) and at a rate greater than the placebo.

See Section [7.6.2.6](#) for grouped query results conducted in support of the evaluation of “injection site reactions.”

7.6.2.6. FDA Grouped Queries, MS

In consideration of the known safety profile of IL-23 antagonists and related therapeutic biologic products (IL-12/23 antagonists), as well as the established safety profile of guselkumab in other indications, the following grouped queries (GQ) were conducted.

- Injection site reaction (administration site pain, injection site erythema, injection site hematoma, injection site hemorrhage, injection site hypersensitivity, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site urticaria)
- Respiratory tract infections (COVID-19, influenza, nasopharyngitis, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection)
- Leukopenia (leukopenia, lymphocyte count decreased, lymphopenia, neutropenia, neutrophil count decreased, white blood cell count decreased)
- Anemia (anemia, hemoglobin decreased, iron deficiency anemia)
- Abdominal pain (abdominal pain, abdominal pain upper, abdominal pain lower)

TEAEs based on these grouped queries for MS are shown in [Table 41](#).

Table 41. Grouped Queries, MS

	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)
Grouped Query			
Injection site reactions	2 (1.1)	17 (8.9)	2 (1)
Respiratory tract infections	42 (22.6)	41 (21.6)	49 (25.5)
Leukopenia	10 (5.4)	9 (4.7)	7 (3.6)
Abdominal pain	10 (5.4)	7 (3.7)	5 (2.6)
Anemia	6 (3.2)	7 (3.7)	6 (3.1)

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as any AE occurring at or after the initial administration of study intervention.

Analysis is subject level (i.e., each subject is counted once regardless of the number of reported events).

Coded as MedDRA preferred terms

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MS, Maintenance Study; N, number of subjects in treatment group; n, percentage of subjects with given adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

Injection Site Reactions

A risk for injection site reactions has been associated with subcutaneous administration of guselkumab therapy for the currently approved indications. Of note, GQ results in subjects with UC indicate a higher proportion of subjects randomized to guselkumab 200 mg SC treatment arm compared to placebo reported TEAEs concerning for injection site reactions. It is important to note that during MS the 200 mg guselkumab dosage was administered as two 100 mg injections. As the distribution of guselkumab administration over two injection sites may have contributed to increased ARs, it is unclear whether the incidence of injection site reactions when the dosage is administered in a single injection will be similar to that observed during MS. This potential risk will be included in Section 6, ADVERSE REACTIONS, of the prescribing information. See Section [7.6.2.5](#).

Respiratory Tract Infections

The review team notes that risk of infections and upper respiratory tract infections are included in the Warnings and Precautions and Adverse Reactions sections of the currently approved UPSI for guselkumab, respectively. The GQ results did not reveal a potential imbalance between treatment and placebo arms. However, a review of individual PTs does indicate a potential increased risk of upper respiratory tract infections that may be associated with guselkumab exposure in patients with UC. See Section [7.6.2.5](#).

Leukopenia and Anemia

As with review of induction data from IS-1 and IS-2, interpretation of the results of GQs for “leukopenia” and “anemia” is limited by the small number of TEAEs reported for the PT include in each GQ. Additionally, review of available laboratory data did not reveal observable trends in the results of hematology assessments (including white blood cell count and hemoglobin) across treatment arms. See Section [7.6.2.7](#).

Abdominal Pain

While a higher proportion of subjects randomized to guselkumab arms (i.e., 100 mg SC and 200 mg SC) compared to placebo arm reported TEAEs concerning for “abdominal pain,” the number of TEAEs reported is small, and interpretability of available data are limited.

7.6.2.7. Laboratory Findings, MS

Review of the chemistry and hematology values that occurred at $\geq$ level 2 criteria⁹ by treatment arm revealed that, in general, the proportion of subjects with abnormal values were similar between the proposed recommended maintenance dosage regimens (i.e., guselkumab 200 mg SC Q4W or 100 g SC Q8W) and placebo. Additionally, there were no notable changes in laboratory values between guselkumab treatment groups suggestive of a dose-dependent effect.

7.6.2.8. Vital-Sign Analyses, MS

In MS, vital signs were obtained at screening, baseline, every four weeks until Week M-44 (or until the early termination visit, if applicable), and at the safety follow-up visit. No significant abnormalities in vital signs were observed in treatment or placebo arms in MS, and no clinically meaningful trends or changes were identified upon review of vital signs when comparing guselkumab 100 mg SC or 200 mg SC to placebo-treated subjects.

7.6.2.9. 90-Day Safety Update, MS

After the Week M-44 assessment, enrolled subjects were eligible to continue into the long-term extension portion of MS. Subjects continued to receive their assigned treatment (e.g., placebo,

⁹ Threshold level 2 as defined by the Standard Safety Tables & Figures Integrated Guide.

guselkumab 100 mg SC Q8W, guselkumab 200 mg SC Q8W) and were monitored at pre-specified timepoints as delineated in the study protocol.

A 90-day safety update report for MS, which included safety data after Week M-44 visit with a data cutoff of January 31, 2024, was submitted during the review cycle. Per the Applicant, the 90-day safety update included additional safety data from 587.8 total subject years. This update also included a safety assessment for device-related issues. See Section [7.3.1](#).

No deaths were reported for subjects in the long-term extension. Ulcerative colitis was the most common AE leading to discontinuation of study intervention. The frequency of SAEs per 100 subject-years after Week M-44 through the data cut off point was consistent with or lower than the frequency of SAEs reported between Week M-0 and Week M-44. The most commonly reported SAE in both periods was ulcerative colitis. Serious infections were reported in 8 subjects exposed to guselkumab. Notably, risk of infections is included in the Warnings & Precautions of the currently approved USPI, and none were cases of active TB or opportunistic infections. Malignancy (reported in 2 guselkumab-treated subjects; prostate cancer reported in a subject with history of prostate adenocarcinoma prior to study enrollment; basal cell carcinoma reported in a subject treated with guselkumab 200 mg IV at Week 0, 4, and 8, then rerandomized to placebo during maintenance), MACE (reported in 2 guselkumab-treated subjects; one subject reported acute coronary syndrome, and subsequent cardiac evaluation was negative; one subject with history of prior MI reported thrombotic cerebral infarction), and VTE (one SAE of pulmonary embolism in a subject who underwent pancreaticoduodenectomy and jejunostomy due to concern for suspected duodenal tumor; one nonserious AE of pulmonary embolism in subject with history of PE prior to study enrollment) were infrequently reported, and review of the submitted narratives did not support probable relation to guselkumab administration. No cases of anaphylaxis, serum sickness, or clinically important hepatic disorders were reported in the update.

No new or worsening safety signals associated with guselkumab exposure in adults with moderately to severely active UC were identified based on review of the 90-Day Safety Update.

7.6.3. Additional Supportive Evidence of Safety

Safety data from guselkumab clinical development programs in adults with CD, psoriasis, and psoriatic arthritis were submitted as supportive evidence of safety. See Section [7.4](#). Review of these data prompted the review team to pursue additional expert evaluations of the potential for guselkumab to cause hepatotoxicity, including DILI.

Hepatotoxicity

As described in Section [7.2](#), hepatotoxicity is included in the Warnings & Precautions for IL-23 antagonists currently approved for the treatment of adults with moderately to severely active UC (i.e., mirikizumab, risankizumab) and CD (i.e., risankizumab). Additionally, although described as mild to moderate, the risk for elevated liver enzymes is currently included in the guselkumab prescribing information based on data generated to support the psoriasis indication. As CD represents a related indication to UC, a case level review of safety data from the CD clinical

development program¹⁰ (also submitted as supportive evidence of safety for BLA 761061/S-021) was completed to assess this potential risk. Of note, one subject (Subject (b) (6)) exposed to guselkumab 1200 mg IV induction dose in the Study CNT01959CRD3001 (GALAXI 1; phase 2 study) was found to meet Hy's law criteria. Additional analyses (e.g., eDISH, enzyme shift tables) could not be completed as limited safety data from the CD program were included in this sBLA submission (i.e., S-021). See memo uploaded by Paul Hayashi, MD of the Division of Hepatology and Nutrition's DILI Team on July 18, 2024 (DARRTS Reference ID: 5416230).

The consultants noted; however, that this subject was exposed to a 1200 mg IV dose, which is six times higher than proposed induction dosage for adults with moderately to severely active UC (i.e., 200 mg IV). Additionally, review of data submitted to support the primary evaluation of safety of guselkumab in adults with moderately to severely active UC did not reveal a potential risk for hepatotoxicity associated with the proposed dosing regimen (i.e., 200 mg IV at Week 0, Week 4, and Week 8, and 100 mg SC at Week 16, and every 8 weeks thereafter, or 200 mg SC at Week 12, and every 4 weeks thereafter). See Sections [7.6.1](#) and [7.6.2](#). Therefore, the available data do not support a potential risk of hepatotoxicity in adults with moderately to severely active UC, and no labeling changes are warranted at this time.

The primary review team agrees with the assessment of the DILI Team. To obtain additional data to further evaluate this potential signal in patients with UC, a PMR under 505(o)3 to evaluate long-term safety outcomes of interest, including hepatotoxicity, in patients with IBD exposed to guselkumab will be issued at the time of approval for adults with moderately to severely active UC. See Section [24](#).

7.7. Key Safety Review Issues

No key safety review issues were identified during review of the application.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Overall, no alternative dosage regimens are recommended based on intrinsic factors for guselkumab in the treatment of UC.

¹⁰ Note, BLA 761071/S-024 for guselkumab in adults with moderately to severely active CD was submitted during the review cycle for S-021 (guselkumab in adults with moderately to severely active UC) and is currently under review with the Division (PDUFA Goal Date: December 20, 2024).

No dose adjustments based on intrinsic factors are recommended for guselkumab in the treatment of plaque psoriasis or psoriatic arthritis. With respect to intrinsic factors, the current approved labeling for guselkumab (TREMIFYA) describes the following.

- No apparent differences in clearance observed in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.
- Clearance and volume of distribution of guselkumab increases as body weight increases. However, observed clinical trial data indicate that dose adjustment for body weight is not warranted.
- No specific trials have been conducted to determine the effect of renal or hepatic impairment on the PK of guselkumab.
 - No dose adjustments or restrictions are recommended based on renal or hepatic impairment.

Population PK analysis was performed using pooled data from subjects with UC in IS-1, IS-2, and MS to identify intrinsic factors impacting the PK of guselkumab. For additional details, refer to Section [14.5](#). In the popPK analyses, covariates including body weight, baseline serum albumin, baseline CRP, age, sex, and biologic failure status at induction baseline were determined to have a statistically significant impact on the clearance of guselkumab.

Specifically, higher guselkumab clearance (lower exposure) was associated with the following:

- Higher body weight
- Lower baseline serum albumin levels
- Younger age
- Male sex
- Prior biologic failure status

Note that the estimated glomerular filtration rate (eGFR) was originally identified as a significant covariate affecting guselkumab clearance in place of age. In the final covariate model, eGFR was replaced with age, as both age and eGFR are correlated ($r = -0.4$). Age was also selected over eGFR as monoclonal antibody disposition is not typically affected by renal function.

The final population PK model was used to simulate exposure metrics for guselkumab. For statistically significant covariates impacting guselkumab clearance, the magnitude of change is shown in [Table 42](#). The magnitude of change caused by continuous covariates was expressed as a percent change from the median value when the covariate factor varied from the 5th to the 95th percentile of the population. For all continuous covariates, the magnitude of change in guselkumab clearance was within 25% when considering values from the 5th to 95th percentiles of the dataset. The greatest effects were observed for covariates of body weight and serum albumin levels, where up to a 23% change is predicted. Although a statistically significant impact of age was observed, the effect of age on clearance is relatively small and not considered to be clinically relevant. For binary covariates of sex and biologic failure status, higher guselkumab clearance was observed in females relative to males, and in subjects with prior biologic failure as compared to subjects who had not failed a prior biologic. For both covariates, the impact on clearance was about 11% and not considered to be clinically relevant.

Table 42. Estimated Magnitude of Change in Guselkumab Clearance for Statistically Significant Intrinsic Factors

Covariate	Median (5th, 95th)^a or Reference Value (%)^b	Magnitude of Change in CL^c
Body Weight (kg)	70.5 (48.1, 102)	–18.3% to +22.5%
Serum Albumin (g/L)	43 (36, 49)	+23.1% to –14.2%
Baseline CRP (mg/L)	4.28 (0.41, 37.4)	–8.2% to +8.2%
Age (years)	39 (21, 66)	+4.69% to –3.83%
Sex	Male (58.1%)	–11.1%
Biologic Failure Status	No prior biologic failure (51.6%)	+10.8%

Source: Table 6 and Section 3.2.1.1, Summary of Clinical Pharmacology; Tables 2 and 3, Population PK and E-R Report.

^a The median (5th, 95th) values are derived from the final dataset involving a total of 859 subjects with UC enrolled in IS-1, IS-2, and MS.

^b The percentage refers to the percent of the final dataset (N=859) represented by the reference value.

^c For continuous covariates, the magnitude of change is expressed as a range, i.e., percent change from the median value when the covariate factor varied from the 5th to the 95th percentile. For binary covariates (i.e., sex and biologic failure status), magnitude of change is expressed relative to the listed reference value.

Abbreviations: 5th, 5th percentile; 95th, 95th percentile; CL, clearance; CRP, C-reactive protein; IS-1, Induction Study 1; IS2, Induction Study 2; MS, Maintenance Study

8.1.1. Serum Albumin

No alternative dosage regimens are recommended based on serum albumin.

Patients with ongoing UC disease activity may have high protein turnover, which can lead to faster clearance of both albumin and monoclonal antibodies such as guselkumab. As shown in [Table 42](#), across the 5th to 95th percentile values for serum albumin at induction baseline, the predicted change in guselkumab clearance is up to 23%, with higher clearance and lower exposure predicted for patients with lower serum albumin levels. The population represented in IS-1, IS-2, and MS did not include many patients with hypoalbuminemia, as at least 95% of patients had serum albumin levels of 36 g/L or greater.

Guselkumab exposure was simulated for subjects with albumin levels below the population median (<43 g/L, N=376) relative to subjects with albumin levels greater than or equal to the population median (≥43 g/L, N=483). During induction, the geometric mean ratio (90% CI) for C_{trough} at Week I-12 and C_{avg} from Weeks 0-12 for subjects with lower serum albumin compared to subjects with higher serum albumin was 0.781 (0.736, 0.829) and 0.896 (0.871, 0.922), respectively (data derived from Figure 8, Summary of Clinical Pharmacology). During maintenance, the geometric mean ratio (90% CI) for C_{trough} at Week M-44 and C_{avg} from Weeks M40-44 for subjects with lower serum albumin compared to subjects with higher serum albumin was 0.836 (0.790, 0.885) and 0.890 (0.851, 0.931), respectively (data derived from Figure 9, Summary of Clinical Pharmacology).

Overall, patients with lower serum albumin levels are predicted to have 16% to 22% lower C_{trough} and 10% to 11% lower average concentrations relative to patients with higher serum albumin levels. These differences in exposure are not considered to be clinically relevant.

8.1.2. Body Weight

No alternative dosage regimens based on body weight are recommended.

Induction

Guselkumab concentrations at Week I-12 by baseline body weight quartile among subjects who received guselkumab induction with 200 mg IV in IS-1 and IS-2 are shown in [Table 43](#). In general, median serum guselkumab concentrations tended to decrease with increasing body weight quartile. For subjects in the lowest weight quartiles (body weight ≤ 55.8 kg or < 60.0 kg), median guselkumab concentrations at Week I-12 were about 1.3- to 1.5-fold greater relative to that among subjects in the highest weight quartiles (body weight > 82.0 kg or ≥ 83.7 kg).

Table 43. Median (CV%) and IQR Guselkumab Week I-12 Trough Concentrations ($\mu\text{g/mL}$) by Baseline Body Weight Quartile for Subjects on 200 mg IV Guselkumab, IS-1 and IS-2

Study Parameter	Body Weight Quartile			
	≤ 55.8 (N=24)	> 55.8 to ≤ 68.6 (N=20)	> 68.6 to ≤ 82.0 (N=21)	> 82.0 (N=20)
IS-1				
Median (CV%)	14.2 (58.0%)	9.1 (35.2%)	7.6 (63.6%)	10.7 (35.6%)
IQR	(5.66, 21.2)	(6.17, 10.4)	(5.04, 15.0)	(7.58, 13.1)
	< 60.0 (N=82)	≥ 60.0 to < 71.3 (N=86)	≥ 71.3 to < 83.7 (N=86)	≥ 83.7 (N=82)
IS-2				
Median (CV%)	11.2 (47.1%)	10.8 (41.5%)	8.51 (55.6%)	7.24 (52.4%)
IQR	(7.52, 15.3)	(7.51, 14.6)	(5.76, 12.4)	(4.96, 10.9)

Source: Reviewer-generated table derived from Tables TPKCONC303AA and TPKCONC303BA, CSR Addendum for IS-1; and Table TPKCONC504, CSR for IS-2.

Only includes subjects with modified Mayo score of 5 to 9 at induction baseline.

All weights are shown in units of kg.

Note: Concentrations below the lowest quantifiable concentration (< 0.01 $\mu\text{g/mL}$) were treated as 0 in calculating the summary statistics.

Abbreviations: CV, coefficient of variation; IQR, interquartile range; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of subjects in body weight quartile

Based on exposure-response analysis for induction efficacy ([Figure 1](#)), lower efficacy was observed for patients with higher guselkumab clearance. However, there was no apparent exposure-response relationship after accounting for individual clearance. Therefore, although higher body weight patients have higher guselkumab clearance and lower exposure, a dosage higher than the proposed 200 mg Q4W is not expected to yield higher rates of efficacy. An alternative induction dosage regimen is not recommended based on body weight.

Maintenance

Guselkumab concentrations at Week M-44 by baseline body weight quartile for subjects in the 200 mg SC Q4W arm and in the 100 mg SC Q8W arm are shown in [Table 44](#). In general, median serum guselkumab concentrations tended to decrease with increasing body weight quartile. Among subjects who received 200 mg SC Q4W, those in the lowest weight quartile (body weight < 57.5 kg) had median guselkumab concentrations at Week M-44 that were about 1.5-fold greater relative to that among subjects in the highest weight quartile (body weight ≥ 81.8 kg). Among subjects who received 100 mg SC Q8W, those in the lowest weight quartile (body

weight <58.2 kg) had median guselkumab concentrations at Week M-44 that were about 2.4-fold greater relative to that among subjects in the highest weight quartile (body weight ≥83.5 kg).

Table 44. Median (CV%) and IQR Guselkumab Week M-44 Trough Concentrations (µg/mL) by Baseline Body Weight Quartile and Dosage, MS

Dosage Parameter	Body Weight Quartiles			
	<57.5 (N=42)	≥57.5 to <69.5 (N=32)	≥69.5 to <81.8 (N=35)	≥81.8 (N=43)
200 mg SC Q4W				
Median (CV%)	11.6 (56.5%)	11.6 (38.5%)	7.77 (53.6%)	7.82 (45.2%)
IQR	(8.29, 17.1)	(8.44, 14.5)	(5.44, 12.1)	(5.00, 9.75)
	<58.2 (N=31)	≥58.2 to <68.8 (N=34)	≥68.8 to <83.5 (N=38)	≥83.5 (N=35)
100 mg SC Q8W				
Median (CV%)	1.84 (47.7%)	1.23 (54.9%)	1.00 (66.1%)	0.77 (84.7%)
IQR	(1.19, 2.77)	(0.77, 1.62)	(0.58, 1.84)	(0.54, 1.10)

Source: Reviewer-generated table derived from Tables TPKCONC603A and TPKCONC603B, CSR for Maintenance Study.

Only includes subjects with modified Mayo score of 5 to 9 at induction baseline.

All weights are shown in units of kg.

Note: For 200 mg SC Q4W, data includes subjects who received a sham dose adjustment. For 100 mg SC Q8W, data after dose adjustment were excluded for subjects who received an increased dose at the time of dose adjustment.

Note: Concentrations below the lowest quantifiable concentration (<0.01 µg/mL) were treated as 0 in calculating the summary statistics.

Abbreviations: CV, coefficient of variation; IQR, interquartile range; MS, Maintenance Study; N, number of subjects in body weight quartile; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

Based on the exposure-response analysis for maintenance efficacy ([Figure 2](#)), subjects in the 200 mg Q4W arm generally fall in the 3rd and 4th exposure quartiles (Week M-44 trough concentration >2.23 µg/mL). This includes subjects in the highest body weight quartile (≥81.8 kg), where at least 75% of subjects fall in the 3rd or 4th exposure quartiles. Subjects in the 100 mg Q8W arm generally fall in the 2nd quartile of exposure (Week M-44 trough concentration between 0.894 and 2.23 µg/mL). Subjects with Week M-44 trough concentrations in the 2nd exposure quartile demonstrated comparable efficacy to subjects with Week M-44 trough concentrations in higher exposure quartiles (based on endpoints of clinical remission, clinical response, endoscopic improvement, and HEMI). However, most subjects with the highest body weight (≥83.5 kg) are expected to fall in the lowest exposure quartile (Week M-44 trough concentration <0.894 µg/mL). Subjects with Week M-44 trough concentrations in the lowest exposure quartile had the lowest rates of efficacy relative to higher exposure quartiles. Although, subjects in the lowest exposure quartile still generally demonstrated greater rates of efficacy relative to placebo. Thus, for the 100 mg Q8W dosage, there is a possibility for reduced efficacy among subjects with higher body weight.

To determine whether there were differences in Week M-44 clinical outcomes by body weight among subjects randomized to guselkumab maintenance, rates of efficacy by baseline body weight quartile and maintenance dosage were evaluated for the endpoints of clinical remission, clinical response, endoscopic improvement, and HEMI ([Table 45](#)).

Among subjects who were randomized to receive 200 mg SC Q4W, a trend of lower efficacy with higher body weight was not observed for any of the endpoints evaluated. Relative to subjects with lower body weights, subjects in the highest body weight quartile (>83.0 kg) had the numerically greatest response rates for endpoints of clinical remission, clinical response, endoscopic improvement, and HEMI.

Among subjects randomized to 100 mg SC Q8W, a trend of lower efficacy with higher body weight was not observed for endpoints of clinical response, endoscopic improvement, and HEMI. For these endpoints, subjects in the highest body weight quartile performed comparably (clinical response, endoscopic improvement), or numerically better (HEMI) relative to subjects in the lowest body weight quartile. For the endpoint of clinical remission, a body weight-based trend is apparent such that a lower proportion of subjects with higher body weight achieved clinical remission at Week M-44. Nevertheless, the difference in proportions achieving clinical remission between the lowest and highest body weight quartiles is 8.3%. Thus, the difference in proportions may not be clinically significant.

Table 45. Week M-44 Efficacy Endpoints (N, %) by Baseline Body Weight Quartile Among Subjects on Guselkumab, MS

Dosage Endpoint	Body Weight Quartile			
	≤59.0	>59.0 and ≤70.0	>70.0 and ≤83.0	>83.0
100 mg SC Q8W	N=54	N=45	N=41	N=48
Clinical Remission	27 (50.0%)	20 (44.4%)	18 (43.9%)	20 (41.7%)
Clinical Response	42 (77.8%)	33 (73.3%)	34 (82.9%)	37 (77.1%)
Endoscopic Improvement	29 (53.7%)	21 (46.7%)	19 (46.3%)	24 (50.0%)
Histologic endoscopic Mucosal Improvement	22 (40.7%)	20 (44.4%)	17 (41.5%)	23 (47.9%)
200 mg SC Q4W	N=53	N=47	N=46	N=44
Clinical Remission	26 (49.1%)	25 (53.2%)	16 (34.8%)	28 (63.6%)
Clinical Response	42 (79.2%)	31 (66.0%)	30 (65.2%)	39 (88.6%)
Endoscopic Improvement	26 (49.1%)	26 (55.3%)	17 (37.0%)	29 (65.9%)
Histologic endoscopic Mucosal Improvement	25 (47.2%)	23 (48.9%)	16 (34.8%)	27 (61.4%)

Source: Reviewer-generated table based on Tables TEFKEY615A-D, CSR for Maintenance Study.

Only includes subjects with modified Mayo score of 5 to 9 at induction baseline. The body weight quartiles are based on subjects in the randomized full analysis set, which includes subjects who were randomized and treated in the Maintenance Study.

All weights are shown in units of kg.

Abbreviations: MS, Maintenance Study; N, number of subjects in body weight quartile; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

Overall, maintenance efficacy rates were comparable across body weight quartiles. A trend of lower efficacy among subjects with higher body weight was not observed for most endpoints at both evaluated maintenance dosages of 100 mg Q8W or 200 mg Q4W. Lower efficacy with higher body weight was observed for Week M-44 clinical remission among subjects randomized to 100 mg Q8W, but this trend was not observed among subjects randomized to 200 mg Q4W. In addition, when comparing between the two dosages within each weight quartile, the 200 mg Q4W dosage did not consistently improve the observed efficacy rates.

The data indicate that no alternative dosage regimens are needed based on body weight. Likewise, the data do not support recommend use of 200 mg Q4W over 100 mg Q8W for higher body weight patients.

8.1.3. Renal Impairment

No alternative dosage regimens based on renal impairment are recommended.

In the population PK covariate model, baseline-estimated eGFR was identified as a significant covariate affecting guselkumab clearance. In the final model, eGFR was replaced with age due to

the correlation between age and eGFR ($r = -0.4$) and because monoclonal antibody disposition is not typically affected by eGFR. The effect of age on guselkumab clearance is relatively small and not considered to be clinically relevant ([Table 42](#)).

The final dataset used for population PK analysis included 597 (69.5%) subjects with normal renal function (eGFR >90 mL/min), 245 (28.5%) subjects with mild renal impairment (eGFR =60 to 90 mL/min), and 17 (2.0%) subjects with moderate renal impairment (eGFR =30 to 60 mL/min) (data derived from Table 3, Population PK and Exposure-Response Report).

To determine the clinical relevance of renal impairment on guselkumab exposure, exposure metrics were simulated for subjects with mild and moderate renal impairment and compared to those among subjects with normal renal function. Geometric mean ratios and 90% CIs for guselkumab exposure metrics during induction and maintenance for subjects with renal impairment relative to subjects with normal renal function are shown in [Table 46](#).

Geometric mean ratio point estimates for subjects with mild renal impairment were ≤ 1.20 for both trough and average concentration during induction and maintenance. A larger impact of moderate renal impairment was predicted with geometric mean ratio point estimates ≤ 1.36 across all exposure metrics. For moderate renal impairment, the CIs are wide, likely due to the low sample size of subjects with moderate renal impairment.

Table 46. Comparison of Simulated Guselkumab Exposure for Subjects With Renal Impairment Relative to Subjects With Normal Renal Function

Study Week	Mild Renal Impairment (N=245)	Moderate Renal Impairment (N=17)
Week 12 C _{trough}	1.20 (1.12, 1.28)	1.32 (1.08, 1.61)
Week 0-12 C _{avg}	1.11 (1.07, 1.14)	1.20 (1.10, 1.32)
Week 44 C _{trough}	1.18 (1.11, 1.26)	1.36 (1.13, 1.64)
Week 40-44 C _{avg}	1.14 (1.09, 1.20)	1.30 (1.12, 1.51)

Source: Figures 4-5 and Attachment 17, Population PK and Exposure-Response Report.

Mild renal impairment: eGFR of 60 to 90 mL/min

Moderate renal impairment: eGFR of 30 to 60 mL/min

Values are shown as geometric mean ratios (90% CI) for subjects with renal impairment relative to subjects with normal renal function (eGFR >90 mL/min, N=597).

Study weeks include Week 0 of Induction Study (Week I-0) through Week 44 of Maintenance Study (Week M-44).

Abbreviations: C_{avg}, average serum concentration; CI, confidence interval; C_{trough}, serum trough concentration; eGFR, estimated glomerular filtration rate; N, number of subjects in specified group

Overall, the impact of renal impairment on guselkumab exposure is not considered to be clinically relevant. Dosage adjustments based on renal impairment are not recommended.

8.2. Extrinsic Factors

8.2.1. Drug-Drug Interactions

As a monoclonal antibody, guselkumab is not expected to have a direct effect on drug-metabolizing enzymes. However, guselkumab may affect the PK of other drugs as a result of improvement in inflammation as CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , interferon) during chronic inflammation. CYP enzyme

expression may be increased after reducing inflammatory burden, leading to increased metabolism and decreased exposure of CYP substrates.

The current approved labeling for guselkumab (TREMIFYA) recommends that upon initiation of guselkumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed. This recommendation was based on results from an exploratory drug-drug interaction study conducted in 6 to 12 evaluable subjects with moderate-to-severe plaque psoriasis (study CNTO1959PSO1003), which evaluated CYP substrate exposure following treatment with a single 200 mg SC dose of guselkumab. Based on study CNTO1959PSO1003, it was determined that there is a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19, and CYP1A2 as the changes in the area under the concentration-time curve (AUC_{inf}) were not considered clinically relevant (i.e., upper bound of the 90% CI for AUC_{inf} geometric mean ratio <2.0-fold) for midazolam, S-warfarin, omeprazole, and caffeine, respectively. The interaction potential could not be ruled out for drugs metabolized by CYP2D6 although results were highly variable due to the limited number of subjects in the study. For dextromethorphan (CYP2D6), changes in AUC_{inf} were not clinically relevant in 9 out of 10 subjects. However, a 2.9-fold change in AUC_{inf} was observed in one individual.¹¹

In the present submission (i.e., S-021), the Applicant has proposed to remove from the labeling recommendations monitoring therapeutic effect or drug concentration and considering dosage adjustment in patients who are receiving concomitant CYP450 substrates. The Applicant proposes that the potential of guselkumab treatment to cause clinically relevant drug-drug interactions with CYP substrate drugs is low. To support this proposal, the Applicant provided data from a nonclinical study and clinical drug-drug interaction (DDI) studies of guselkumab and ustekinumab. Ustekinumab is a monoclonal antibody targeting IL-23 and IL-12 that is approved for treatment of adult patients with moderately to severely active UC and moderately to severely active Crohn's disease. In contrast, guselkumab only targets IL-23.

The Applicant conducted an in vitro study to evaluate the impact of cytokines IL-23 and IL-12 at concentrations of 10 ng/mL on CYP450 enzymes in primary cultures of cryopreserved human hepatocytes. Results indicate that IL-23 and/or IL-12 at levels of 10 ng/mL did not alter human CYP450 enzyme activities, including CYPs 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. The results of this study are described in the current approved labeling for ustekinumab (Stelara). As described in the ustekinumab labeling, the clinical relevance of in vitro data has not been established.

¹¹ For additional details on study CNTO1959PSO1003, refer to the Clinical Pharmacology review dated July 13, 2017 (DARRTS reference ID: 4123785).

The Applicant also provided results from two clinical DDI studies:

- Study CNTO1959PSO1003: an open-label study evaluating the effect of a single SC dose of 200 mg guselkumab on the PK of a cocktail of representative CYP substrates in subjects with moderate to severe plaque psoriasis (results described above).
- Study CNTO1975CRD1003: an open-label study evaluating the effects of ustekinumab on the PK of a cocktail of representative CYP substrates in subjects with active CD and healthy subjects.
 - Ustekinumab was administered as a single IV infusion of 260 to 520 mg based on body weight on Day 8 followed by a 90 mg SC dose about 8 weeks after the initial IV dose (Day 64).
 - CYP substrates include caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A). The probe cocktail was administered on Days 1 (prior to ustekinumab treatment), 22 (2 weeks after IV induction ustekinumab administration), and 113 (7 weeks after the first maintenance SC ustekinumab administration).
 - Healthy subjects were matched to subjects with CD based on sex, age (± 10 years), and weight ($\pm 30\%$), and only received a single dose of probe cocktail on Day 1.

Note that a full review of study CNTO1975CRD1003 is currently being conducted under BLA 761044/S-014 (review ongoing) and results will only be briefly summarized in this review. Data provided here are only included as supportive evidence. Geometric mean ratios and associated 90% CIs for the maximum plasma concentration and AUC_{inf} for each of the probe CYP substrate drugs on Days 22 and 113 relative to Day 1 are shown in [Table 47](#). For all CYP substrates, AUC_{inf} geometric mean ratios on Days 22 and 113 relative to Day 1 were close to a value of 1, while the upper bound of the 90% CIs were all <1.5 -fold. The data suggest that ustekinumab treatment in subjects with Crohn's disease did not result in clinically relevant changes in the exposure of probe CYP substrates.

Table 47. Geometric Mean Ratios [90% CIs] for C_{max} and AUC_{inf} of CYP Probe Substrates After Ustekinumab Administration Relative to Before Ustekinumab Administration in Patients With Crohn's Disease

CYP Probe	GMR for C_{max} [90% CI] (%)		GMR for AUC_{inf} [90% CI] (%)	
	Day 22/Day 1	Day 113/Day 1	Day 22/Day 1	Day 113/Day 1
Midazolam	100.95 [87.64; 116.27]	88.61 [76.93; 102.07]	106.98 [96.16; 119.01]	89.92 [80.83; 100.04]
S-warfarin	96.49 [86.27; 107.91]	103.87 [92.87; 116.17]	106.60 [95.28; 119.27]	102.30 [91.43; 114.47]
Omeprazole	72.65 [56.82; 92.89]	100.68 [78.74; 128.73]	95.75 [77.41; 118.44]	116.16 [93.91; 143.68]
Dextromethorphan	90.41 [72.56; 112.66]	101.63 [81.56; 126.64]	92.26 [70.55; 120.65]	107.60 [82.28; 140.70]
Caffeine	99.56 [89.22; 111.11]	108.40 [97.14; 120.98]	102.54 [93.01; 113.06]	111.06 [100.73; 122.45]

Source: UC/Mod5.3.2.2/CNTO1275CRD1003/Tab13, Tab14, Tab16, Tab17, Tab19, Tab20, Tab21, Tab22, Tab25, and Tab26

Source: Table 3, Technical Report on Assessment of Guselkumab Disease-drug-drug Interaction Potential in Patients with Inflammatory Bowel Disease.

Data derived from study CNTO1275CRD1003, CSR submitted to BLA 761044

Abbreviations: AUC_{inf} , area under the serum concentration-time curve from time 0 to infinity; C_{max} , maximum serum concentration; CI, confidence interval; CYP, cytochrome P450; GMR, geometric mean ratio

A summary of DDI studies and label recommendations for IL-23 antagonists approved and proposed for IBD indications is shown in [Table 48](#). Although a dedicated DDI study with guselkumab has been conducted, study CNTO1959PSO1003 was conducted in a different patient population (i.e., plaque psoriasis) following administration of a single dose. It is unclear whether improvement in inflammation occurred following a single dose.

Dedicated DDI studies have been conducted with other inhibitors of IL-23 approved for IBD indications, including mirikizumab and risankizumab (both target IL-23 p19 - the same mechanism of action as guselkumab), and ustekinumab (IL-12/23 antagonist that targets p40 – a different mechanism of action than guselkumab). A summary of DDI results and label recommendations for other IL-23 antagonists is shown in [Table 48](#). The available data do not indicate that IL-23 antagonists have a clinically relevant effect on the exposure of probe CYP substrates.

Table 48. Summary of DDI Results and Label Recommendations for IL-23 antagonists Approved and Proposed for IBD Indications

Drug	IBD Indication	Cytokine Target	DDI Study Dosage	DDI Study Population, Results and Label Recommendations
Guselkumab	UC (proposed)	IL-23 p19	200 mg SC single dose	Population: Plaque psoriasis subjects No clinically relevant changes in exposure to caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), or midazolam (CYP3A). Interaction potential cannot be ruled out for dextromethorphan (CYP2D6). Consider monitoring for therapeutic effect or drug concentration of concomitant CYP450 substrates and consider dosage adjustment as needed.
Mirikizumab	UC	IL-23 p19	250 mg SC Q4W	Population: Plaque psoriasis subjects No changes in exposure to caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), or midazolam (CYP3A). No recommendations in Section 7.
Risankizumab	CD, UC	IL-23 p19	150 mg SC Q4W or 1800 mg IV Q4W	Population: Plaque psoriasis (150 mg SC Q4W) and CD (1800 mg IV Q4W) No clinically significant changes in exposure to caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), metoprolol (CYP2D6), or midazolam (CYP3A). No recommendations in Section 7.
Ustekinumab ^a	UC and CD	IL-12/23 p40	260 to 520 mg IV then 90 mg SC at Week 8 ^b	Population: CD subjects No clinically relevant changes in exposure apparent for caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), or midazolam (CYP3A). Consider monitoring for therapeutic effect or drug concentration of concomitant CYP450 substrates and consider dosage adjustment as needed.

Source: Approved labeling for guselkumab (TREMFA); approved labeling for mirikizumab (Omvoh); approved labeling for risankizumab (Skyrizi); Technical Report for Assessing Guselkumab Disease Drug-Drug Interaction Potential in Patients with IBD submitted to BLA 761061/S-021.

^a DDI study results for ustekinumab are not described in the current approved labeling. Labeling indicates that “No in vivo drug interaction studies have been conducted with STELARA.” DDI study results were not available at the time that DDI label recommendations were made.

^b The recommended dosage of ustekinumab is a single IV infusion using weight-based dosing followed by 90 mg SC 8 weeks after the initial IV dose. Weight-based IV dosing is as follows: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg.

Abbreviations: CD, Crohn’s disease; DDI, drug-drug interaction; IL, interleukin; IV, intravenous; p19, p19 subunit; p40, p40 subunit; Q4W, every 4 weeks; SC, subcutaneous; UC, ulcerative colitis

Although in general the evidence suggests that there is no clinically relevant effect of IL-23 or IL-12/23 inhibitors on exposure of probe CYP substrates, there remains a knowledge gap to fully inform the labeling. First, no dedicated DDI studies have been conducted in the target patient population of patients with UC. Second, DDI evaluation following administration of multiple doses of guselkumab have not been conducted. In addition, DDIs have not been evaluated following administration of the proposed induction dose of guselkumab for UC (i.e., 200 mg IV

Q4W), the highest dosage of guselkumab proposed. Lastly, although the in vivo data is derived from other monoclonal antibodies with the same or related mechanism of action as guselkumab, it is not clear that guselkumab would modulate the same pro-inflammatory cytokines to the same extent.

Overall, there is insufficient information to support removal of specific DDI management strategies from labeling. As such, the review team recommends retaining DDI management strategies in labeling (i.e., consider monitoring for therapeutic effect or drug concentration of concomitant CYP450 substrates, particularly those with a narrow therapeutic index, and consider dosage adjustment as needed). A dedicated DDI study of guselkumab in patients with UC has not been conducted. This is acceptable based on the following:

- Little evidence of clinically significant DDI potential for guselkumab following a single 200 mg SC dose in study CNTO1959PSO1003
- No evidence of DDI potential from other IL-23 antagonists approved for IBD indications
- The potential reversal of CYP suppression under inflammation by guselkumab treatment, if any, is not expected to lead to a significant increase in systemic exposure to CYP substrates, but rather a decrease in systemic exposure
- Although there is a potential concern for drugs with a narrow therapeutic index, monitoring of therapeutic effect, AEs, or drug concentration for such drugs is generally done regardless

Per the current approved labeling for guselkumab, population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids and conventional DMARDs such as methotrexate, did not affect the clearance of guselkumab. Based on population PK analysis, baseline use of immunomodulators including methotrexate, azathioprine, and 6-mercaptopurine, was not a statistically significant covariate on guselkumab clearance. For additional details, refer to Section [14.5](#).

8.3. Plans for Pediatric Drug Development

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable. BLA 761061/S-021 triggers PREA because guselkumab as proposed for the treatment of adults with moderately to severely active UC represents a new indication, route of administration, and dosing regimen. The following PREA postmarketing requirements (PMRs) will be issued at the time of application approval.

PMR 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 TREMIFYA (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

PMR 4696-2: Conduct a long-term extension study to evaluate the long-term safety of TREMIFYA (guselkumab) in pediatric 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 part of postmarketing requirement 4696-1.

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

The Applicant submitted an initial pediatric study plan (iPSP) under IND 140330, and agreement was reached on July 23, 2021 (DARRTS Reference ID: 4859011). The Applicant subsequently amended the agreed iPSP, and agreement with the amended iPSP was reached on July 12, 2023 (DARRTS Reference ID: 5206899). PMR 4696-5 is consistent with the assessment specified in the agreed amended iPSP. Although the study described in PMR 4696-6 was not specified in the agreed amended iPSP, the Applicant acknowledged the importance of long-term data to support evaluation of the safety of guselkumab in pediatric patients and agreed to conduct the proposed study during review of BLA 761061/S-021.

As outlined in the amended agreed iPSP and requested in the application submission, the Applicant is seeking a waiver of studies in pediatric patients less than 2 years of age with moderately to severely active UC on the basis that these studies are highly impracticable because the number of patients in that age group is so small. The review team agrees that the requested waiver is appropriate.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Pregnancy

See Section 7.1 for review of reproductive and fertility nonclinical studies conducted in support of this sBLA. Review of available human data of guselkumab exposure during pregnancy from clinical trials and the Applicant's pharmacovigilance database are insufficient to establish a risk of spontaneous abortion, congenital anomaly, or maternal or fetal adverse reactions. Guselkumab is an IL-23 monoclonal antibody that is expected to have similar placental transfer as endogenous IL-23.

Therefore, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under Subsection 8.1 Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta.

In comparison to other IL-23 antagonists approved by the Agency in the past for treatment of IBD, the Division of Pediatric and Maternal Health did not propose to include a Fetal/Neonatal Adverse Reactions subheading under Clinical Considerations in Section 8.1, recommending withholding live virus immunizations. The rationale to not include this recommendation was based on recent discussion with expert panelists at an FDA Public workshop held on July 11-12, 2024, titled *Evaluating Immunosuppressive Effects of in Utero Exposure to Drugs and Biologic Products*. See review memo uploaded by Tamara Johnson on July 20, 2024 under BLA 761061/S-021 (DARRTS Reference ID: 5420612) for full details and rationale.

Upon initial approval for plaque psoriasis, the Applicant was issued two PMRs for pregnancy-related studies with guselkumab. One study is a pregnancy registry (PMR 3225-2) and the other a database study (PMR 3225-3). With the approval in the UC population, two new pregnancy study PMRs (PMR 4696-4 and 4696-5) will be issued to compare the maternal, fetal, and infant outcomes of women with inflammatory bowel disease exposed to guselkumab during pregnancy and to assess adverse pregnancy in women exposed to guselkumab regardless of indication.

PMR 4696-4 requires a registry for prospective collection of detailed clinical information about pregnancy exposures and outcomes, and PMR 4696-5 requires 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. The Applicant will update the protocols for the ongoing PMR studies to include women exposed to guselkumab containing products with inflammatory bowel disease during pregnancy.

PMR 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 protocol(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.

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

PMR 4696-4: 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.

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

Lactation

There are limited pharmacovigilance cases of guselkumab use during lactation, with one report of thrush in an infant following exposure to guselkumab via breast milk and no published data on guselkumab use during lactation. Ulcerative colitis affects females of reproductive potential, and there are no data available to inform women regarding guselkumab use during lactation.

The calculation of the estimated daily infant dose from clinically observed PK measurements and any safety outcomes from breastfed infants (including local gastrointestinal effects) are valuable to inform patients and providers of the potential risks of guselkumab use in lactating women on the breastfed infant. Therefore, with approval of BLA 761061/S-021, a PMR for a clinical lactation study will be issued (PMR 4696-6).

PMR 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.

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

Further, similar to the Agency's approach to labeling for other monoclonal antibodies, labeling will include information under 8.2 that notes: "Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and the extent of systemic exposure to guselkumab in the breastfed infant are unknown."

Females and Males of Reproductive Potential

There are no available human data on the effects of guselkumab on male or female fertility. Animal fertility studies do not indicate any adverse effects. See Section 7.1. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, the review team recommends omitting Subsection 8.3 from labeling.

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team has assessed BLA 761061/S-021 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this sBLA from product quality, facility, microbiology, and sterility assurance perspectives.

TREMIFYA (guselkumab) injection is currently approved as a 100 mg/1 mL (100 mg/mL) solution for subcutaneous injection in a single-dose 1 mL pre-filled syringe (PFS) assembled with an UltraSafe Plus device (1 mL PFS-U) and One-Press auto-injector (1 mL PFS-S). BLA 761061/S-021 seeks approval of TREMIFYA presented as a 200 mg/2 mL (100 mg/mL) solution in a single-dose PFS assembled with an UltraSafe Plus device (2 mL PFS-U) and YpsoMate auto-injector (2 mL PFS-Y). The drug product formulation for the 2 mL PFS-U and 2 mL PFS-Y is the same as the formulation currently approved for 1 mL PFS-U and 1 mL PFS-S. The 2 mL PFS-U and 2 mL PFS-Y shall be stored up to 24 months from the date of unassembled 2 mL PFS manufacture at $5 \pm 3^\circ\text{C}$, protected from light.

BLA 761061/S-021 also seeks approval of a new 200 mg/20 mL (10 mg/mL) solution for intravenous (IV) injection in a single-dose final vial product (200 mg FVP).

(b) (4)
(b) (4)
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(b) (4). The 200 mg FVP shall be stored up to 24 months at $5 \pm 3^\circ\text{C}$, protected from light.

(b) (4)
Select OPQ-focused review issues are summarized below. See the Office of Product Quality Assessment III Review (dated September 5, 2024, located in the Panorama database) and the Office of Product Quality Office of Pharmaceutical Manufacturing Assessment Product Quality Microbiology/Facility Assessment Reviews (dated September 5, 2024, located in the Panorama database) for full details.

Immunogenicity Assays

Previously, an ECLIA with a drug tolerance level of 6 µg/mL was used to detect ADA for the indication of plaque psoriasis and psoriatic arthritis. Another ECLIA-based method with a drug tolerance level of 834.56 ng/mL was used to detect neutralizing antibodies (NAb). See Section 5.2. In support of this sBLA, the initial methods used to evaluate ADA and NAb were revised to include a solid phase extraction followed by acid dissociation step for improve drug tolerance levels (1,000 µg/mL and up to 63.07 µg, respectively).

Validation Report (b) (4) generated for the (b) (4) 9 neutralizing antibody (NAb) immunoassay validated at (b) (4) shows a reported drug tolerance of <1.0 ug/mL of drug in the presence of 2 ug/mL and 1 ug/mL NAb positive control. These data suggest that the presence of drug at the time of clinical immunogenicity sample collection during the China Cohort studies (mean steady state Ctrough during maintenance among all subjects ≥ 1.4 ug/mL, as reported above) can interfere with NAb assay performance. Therefore, NAb results for the China cohort were deemed inadequate to support the immunogenicity assessment. See Section 14.4.

Microbiology

Office of Pharmaceutical Manufacturing Assessment (OPMA) completed the product quality microbiology assessment, and recommended approval with issuance of the following post-marketing commitment, as agreed by the Applicant.

PMC 4695-1: Perform a supplemental low endotoxin recovery (LER) study to examine the effects of hold time at 15-25°C on endotoxin recovery using 3 batches of 20 mg/mL guselkumab FVP spiked with RSE or CSE and stored at 20-25°C to verify that the longest duration for the DP manufacturing process has no impact on endotoxin recovery.

Final Report Submission: 02/2025

9.1. Device or Combination Product Considerations

CDRH completed a review of the proposed drug product presentations for IV and SC administration for guselkumab induction and maintenance therapy, respectively. The available data was deemed adequate, and the review team recommends approval of the proposed drug product presentations. See CDRH review memo to support ICCR #00979891, by Jillian Socea and Shruti Mistry dated July 29, 2024, in Panorama for full details.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

IS-1, IS-2, and MS were performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, the International Council for Harmonisation guidelines for good clinical practice, and all applicable laws, rules, and regulations.

Refer to Section [22](#) and Section [25](#) of this review for details on clinical site inspections and review of financial disclosures, respectively.

11. Advisory Committee Summary

An advisory committee was not held for this application as outside expertise was not necessary to inform the team's assessment, and there were no controversial issues that would benefit from advisory committee discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

Key regulatory interactions for the clinical development of guselkumab intended to support the proposed indication of treatment of moderately to severely active ulcerative colitis (UC) in adults are described in [Table 49](#).

Table 49. Key Regulatory Interactions for the Clinical Development of Guselkumab

Date	Activity	Description
January 24, 2019	Type B, pre-IND meeting	FDA provided advice related to: - Overall study design, dose selection, endpoints, and statistical analysis - Adequacy of overall clinical development program
May 4, 2019	Type C Meeting, IND 105004	FDA Division of Dermatology and Dentistry/OII/CDER, provided advice regarding development plans for two new 2 mL presentations (i.e., 2 mL PFS-U and 2 mL PFS-Y)
June 12, 2019	IND 140330 submitted	IND submission received containing protocol CTO1959UCO3001(QUASAR).
July 17, 2019	SMP letter	The Agency provided additional recommendations for QUASAR including: - Enrollment criteria - Central endoscopy assessments to be used for the primary endpoint - Histopathology data to be collected using alternative grading scales
November 19, 2020	SAP submitted for IS-1	
May 7, 2021	SAP submitted for IS-2 and MS	SAPs incorporated advice from the FDA received on April 9, 2021, including diary-based calculation of weekly Mayo RBS and SFS
September 21, 2021	Revised SAP submitted for IS-1	Sponsor response to FDA advice received June 10, 2021, recommending revision to inclusion criterion to enroll patients with a mMS of 4 to 9 but the primary analysis population will only include subjects with a mMS of 5 to 9
August 10, 2022	Sponsor Response to Device Information Request	Sponsor supplied information requested by FDA regarding the proposed combination product being the same as the previously utilized combination product configurations for both the 1 mL PFS-U and 2 mL PFS-Y

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Date	Activity	Description
April 5, 2023	Type B, pre-sBLA meeting	Pre-sBLA Meeting Minutes issued following videoconference with the Sponsor to discuss the content, analyses, and data display formats for the following: • Summary of Clinical Efficacy • Integrated Summary of Efficacy • Summary of Clinical Safety • Integrated Summary of Safety • Case Narrative Summary and Case Report Form • Summary of Clinical Pharmacology data sets and programs • CMC data package
July 12, 2023	Amended Agreed iPSP letter	Amended Agreed iPSP Letter included: • Partial waiver for <2 years of age • Deferral request for 2 to <18 years of age • Plan for a study evaluating the PK, safety, and efficacy of guselkumab in children with moderately to severely active UC aged 2 to <18 years of age
December 1, 2023	Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Reviewer Voucher	The Applicant submitted Notification of Intent to submit an application with a Rare Pediatric Disease Priority Review Voucher to support the utility of guselkumab for treatment of adult patients with moderately to severely active UC
March 11, 2024	BLA 761061/S-021 submitted	Receipt of submission intended to: • Include the treatment of adult patients with moderately to severely active UC as an indication • Introduce three new product presentations: – 200 mg FVP for IV induction administration – 200 mg/2 mL PFS assembled with the UltraSafe Plus Needle Guard (2 mL PFS-U) – 200 mg/2 mL PFS assembled with the YpsoMate Autoinjector (2 mL PFS-Y)

Source: Reviewer generated.

Abbreviations: CMC, chemistry, manufacturing, and controls; FVP, final vial product; IND, investigational new drug; iPSP, initial pediatric study plans; IS-1 Induction Study 1; IS-2, Induction Study 2; mMS, modified Mayo Score; OII, Office of Immunology and Inflammation; PFS, prefilled syringe; PFS-U, prefilled syringe assembled with UltraSafe Plus Needle Guard; PFS-Y, prefilled syringe assembled with YpsoMate autoinjector; PK, pharmacokinetic; RBS, rectal bleeding; SAP, statistical analysis plan; sBLA, supplemental biologics license application; SFS, stool frequency; SMP, study may proceed; UC, ulcerative colitis

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Pharmacology/Toxicology studies were previously submitted and reviewed under the original BLA 761061 (submitted in support of guselkumab for the treatment of adults with psoriasis). The following is a summary review.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody (mAb) directed against the p19 subunit of interleukin (IL) 23. Binding of guselkumab to the p19 subunit of IL-23 disrupts the interaction of IL-23 with the IL-23 receptor, inhibiting the signaling and cytokine cascade. Guselkumab is currently approved for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy and adults with active psoriatic arthritis. In the current supplemental biologics license application (sBLA) submission, the Applicant is seeking approval of guselkumab for the treatment of adult patients with moderately to severely active UC. The maximum proposed human dose (MPHD) for guselkumab for adults with UC is 200 mg (3.3 mg/kg for a 60 kg individual) administered intravenous (IV) every 4 weeks (Q4W) for 3 doses and 200 mg subcutaneous (SC) Q4W thereafter.

Guselkumab was shown to not have activity against mouse or rat IL-23, partial activity against dog IL-23, and high affinity to guinea pig and non-human primates. Thus, cynomolgus monkeys and guinea pigs were selected as the pharmacologically relevant species for use in nonclinical studies with guselkumab.

Five-week SC and IV and 24-week SC toxicology studies were conducted in cynomolgus monkeys treated once weekly at doses of 10 or 50 mg/kg SC for 5 or 24 weeks or IV at a dose of 50 mg/kg for 5 weeks. No target organs were identified. The no observed adverse effect level (NOAEL) was 50 mg/kg/week for 5-week IV and 24-week SC studies. The maximum plasma concentration (C_{max}) and the area under the concentration-time curve (AUC)_{inf} were 993 μ g/mL and 5412 μ g*day/mL after 24 weeks, respectively.

In an enhanced pre- and post-natal development (ePPND) study, pregnant cynomolgus monkeys (0, 10, and 50 mg/kg groups) were administered SC doses of guselkumab from the beginning of organogenesis to parturition. Neonatal monkey deaths occurred in 1/16 control group, 3/14 low dose group and 3/14 in the high dose group. There were no other treatment related effects. Serum guselkumab levels gradually decreased over time but were still quantifiable up to 91 days in most maternal and infant animals. Concentrations in milk samples were below the lowest quantifiable concentration. One of 40 maternal animals and 1/24 infants in the guselkumab treated groups had antidrug antibodies (ADAs).

In a SC fertility study in young sexually mature female guinea pigs, no guselkumab-related changes were seen at doses up to 100 mg/kg twice weekly. Two SC fertility studies were conducted in young sexually mature male guinea pigs. In the first male guinea pig fertility study,

an increase in early resorptions per litter and percentage of post implantation loss was noted at 100 mg/kg twice weekly dose. No guselkumab-related changes in any of the evaluated fertility, early embryonic development and implantation parameters were observed at the lower dose of 25 mg/kg twice weekly. In the second male guinea pig fertility study, there were no treatment related effects noted at the 100 mg/kg twice weekly dose. The results of the second male guinea pig fertility study do not negate the results of the first male guinea pig fertility study. Therefore, the NOAEL for fertility, early embryonic development and implantation parameters is the lower dose of 25 mg/kg twice weekly for male guinea pigs.

No genetic toxicology or carcinogenicity studies have been conducted with guselkumab. A previously submitted carcinogenicity risk assessment with analysis of published literature regarding potential biological effects of IL-23 inhibition does not support a causal mechanistic/target-related link between IL-23 inhibition and increased cancer risk. No nonclinical studies to address the carcinogenic potential of guselkumab are recommended.

No approvability issues have been identified for guselkumab for the treatment of adults with moderately to severely active UC from a pharmacology/toxicology perspective.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Study Title: Interim Summary Report (Up to Six Months at Shelf-Life and Accelerated Conditions) of Guselkumab (CNT01959, JNJ-54160366) Induction and Maintenance Doses Final Drug Product Long Term Leachable Risk Assessment Associated with Final Container Closure Systems (TV-TEC-255113).

The proposed dosage regimen for guselkumab for adults with moderately to severely active UC is 200 mg IV Q4W at Weeks 0, 4, and 8, followed by a maintenance dosage regimen of either 100 mg SC at Week 16, and every 8 weeks (Q8W) thereafter, or 200 mg SC at Week 12, and Q4W thereafter. The maximum dose volume is 20 mL of the final vial product (FVP) and 2 mL of the prefilled syringe (PFS). The analytical evaluation threshold is (b) (4)/20 mL = 0.25 µg/mL. The Applicant's analytical methods have a limit of detection of (b) (4)/mL which is below the analytical evaluation threshold and is adequate.

Three batches of FVP and 3 batches of PFS were being stored at shelf life (5±3°C for up to 24 months) and accelerated conditions (25°C/60% RH for up to 6 months). The samples were analyzed up to 6 months at shelf-life and accelerated conditions and are to be analyzed at 12, 18, and 24 months at shelf life for volatile organic leachables, semi-volatile organic leachables, non-volatile organic leachables, and inorganic leachables.

Controlled extractable studies of the (b) (4) stoppers were previously conducted. No nitrosamines were detected above the limit of (b) (4) of stopper material. Among the extractables, the following were above the safety concern threshold (SCT) of (b) (4) (Table 50).

The lowest oral available NOAEL value of 5 mg/kg/day based on liver effects in the F0 generation from a two-generation study in mice ([Tyl et al. 2008](#)).

F1=12 (Extrapolation mouse to human)
F2=10 (variability between individuals)
F3=5 (4 months for F0)
F4=1 (Chronic liver inflammation)
F5=1 (NOAEL available)
F6=100 (<1% oral bioavailability in mice)
 $5 \times 50 / (12 \times 10 \times 5 \times 1 \times 1 \times 100) = 4.2 \mu\text{g/day}$

The maximum daily exposure of Bisphenol A (BPA) is 46 $\mu\text{g}/\text{dose}$. Three doses over 8 weeks are proposed, therefore, $46 \times 3 / 56 \text{ days} = 2.5 \mu\text{g/day}$. Since the maximum daily exposure is below the PDE, there are no safety concerns from the pharmacology/toxicology perspective.

The Applicant has submitted a risk assessment of potential elemental impurities as per International Council for Harmonisation Q3D (See page 8 of study report TV-TEC-255113).

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Clinical studies supporting clinical pharmacology information of guselkumab in patients with UC are summarized in [Table 52](#).

Table 52. Clinical Studies Supporting Use of Guselkumab in Patients With UC

Study	Design	Drug Product and Formulation^a	Dose and Regimen^b
CRD1003	Phase 1 BE study in healthy subjects comparing 2 mL PFS-U, 2 mL PFS-Y (AI), and 1 mL PFS-U for SC dosing	1 mL PFS-U, 2 mL PFS-U, 2 mL PFS-Y (AI) 100 mg/mL sterile liquid	Single SC dose of 200 mg
EDI1001	Phase 1 BE study in healthy subjects comparing vial product and PFS for IV dosing	1 mL PFS-U 100 mg/mL sterile liquid 200 mg vial product 10 mg/mL liquid	Single IV dose of 200 mg ^c
IS-1	Phase 2b induction dose-ranging study in subjects with UC	1 mL PFS-U 100 mg/mL sterile liquid	200 or 400 mg IV at Weeks 0, 4, and 8 ^c Clinical non-responders at Week I-12 received 200 mg SC at Weeks 12, 16, and 20
IS-2	Phase 3 induction study in subjects with UC	1 mL PFS 100 mg/mL sterile liquid	200 mg IV at Weeks 0, 4, and 8 ^c Clinical non-responders at Week I-12 received 200 mg SC at Weeks I-12, I-16, and I-20
MS	Phase 3 maintenance study in subjects with UC Note, subjects that met criteria for “clinical response” in IS-1 and IS-2 were eligible for enrollment	1 mL PFS 100 mg/mL sterile liquid	200 mg SC Q4W or 100 mg SC Q8W

Source: Tabular Listing of Clinical Studies, Summary of Biopharmaceutical Studies.

^a The proposed to-be-marketed drug products are a 200 mg/2 mL PFS, a 200 mg/2 mL AI, and a 200 mg/20 mL (10 mg/mL) vial product. Guselkumab is currently available as a 100 mg/mL solution in a 1 mL PFS.

^b Only guselkumab dosage regimens are shown. Placebo controls were also included in all parts of study UCO3001.

^c (b) (4).
Abbreviations: AI, autoinjector (also referred to as PFS-Y); BE, bioequivalence; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; MS, Maintenance Study; PFS, prefilled syringe; PFS-U, prefilled syringe assembled with UltraSafe Plus Needle Guard; PFS-Y, prefilled syringe assembled with Ypsomate autoinjector; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis

14.2.1. Study CRD1003

Title

“An open-label, randomized, parallel-group study to assess the pharmacokinetic bioequivalence of subcutaneously administered guselkumab delivered by 3 different devices in healthy participants”

Study Design

Briefly, Study CRD1003 was a randomized, open-label, 2-part, parallel group, adaptive design study conducted in healthy adult subjects aged between 18 and 60 years, inclusive, with body

weight between 50 and 90 kg, inclusive. All subjects received a single 200 mg SC dose of guselkumab, administered as 1 x 2 mL prefilled syringe assembled with UltraSafe Plus Needle Guard (PFS-U), 1 x 2 mL prefilled syringe assembled with YpsoMate autoinjector (PFS-Y) (autoinjector), or 2 x 1 mL PFS-U.

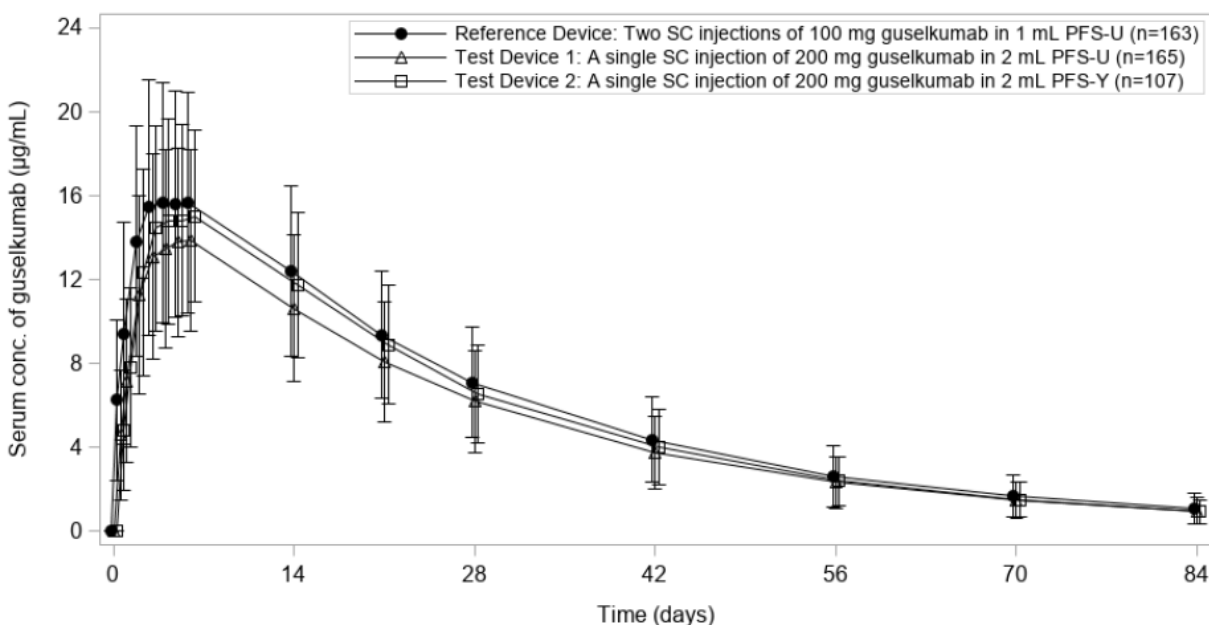
In Part 1, 42 subjects were planned to be randomized to each of the 3 device groups (i.e., N=126). Pharmacokinetic (PK) analysis results from Part 1 determined the groups needed and sample size adjustments in Part 2 to ensure that the sample sizes were adequate to demonstrate bioequivalence.

Overall, a total of 440 healthy subjects were randomized. Out of 440 subjects, 4 were not treated due to early termination prior to dosing. The PK analysis set included 164 subjects randomized to 1 mL PFS-U, 165 subjects randomized to 2 mL PFS-U, and 107 subjects randomized to 2 mL PFS-Y.

PK Results

Concentration-time profiles and PK parameters by drug product presentation are shown in [Figure 3](#) and [Table 53](#), respectively. The mean concentration-time profiles following SC injection across the three drug products were similar. Slightly lower peak concentrations were observed following injection with 1 x 2 mL PFS-U relative to the other drug products. Peak concentrations were achieved at about 5 days post-dose (i.e., by Day 6). Concentrations declined in an apparent mono-exponential manner. The mean (SD) half-life across products ranged from 19.1 (4.0) to 20.1 (4.8) days.

Figure 3. Mean (SD) Serum Guselkumab Concentration-Time Profiles Following a Single 200 mg SC Dose in the Linear Scale



Source: Figure 3, CSR for CRD1003.

Abbreviations: conc, concentration; PFS-U, prefilled syringe assembled with UltraSafe Plus Needle Guard; PFS-Y, prefilled syringe assembled with YpsoMate autoinjector; SC, subcutaneous; SD, standard deviation

Table 53. Summary of Guselkumab PK Parameters by Drug Product Presentation

Pharmacokinetic Parameter (mean [SD], t _{max} : median [range])	Reference Device 2x100 mg/mL PFS-U	Test Device 1 1x200 mg/2 mL PFS-U	Test Device 2 1x200 mg/2 mL PFS-Y
n	155 ^a	163 ^b	106 ^c
C _{max} (µg/mL)	16.7 (5.21)	14.8 (4.62)	15.9 (4.48)
t _{max} (day)	5.00 (1.98 – 14.99)	5.00 (2.00 – 14.04)	5.00 (2.00 – 14.01)
AUC _{0-85d} (µg.day/mL)	493 (169)	428 (150)	463 (148)
AUC _{last} (µg.day/mL)	493 (169)	428 (150)	463 (148)
AUC _{inf} (µg.day/mL)	526 (192)	459 (170)	491 (164)
t _{1/2} (day)	19.6 (4.2)	20.1 (4.8)	19.1 (4.0)
CL/F (L/day)	0.442 (0.202)	0.521 (0.296)	0.455 (0.159)
V _z /F (L)	11.9 (4.29)	14.1 (5.67)	12.1 (3.48)

^a n=154 for AUC_{0-85d} and AUC_{last}, n=153 for AUC_{inf}, CL/F, and V_z/F, n=160 for t_{1/2}
^b n=160 for AUC_{0-85d} and AUC_{last}, n=161 for AUC_{inf}, CL/F, and V_z/F
^c n=105 for AUC_{0-85d} and AUC_{last}, AUC_{inf}, t_{1/2}, CL/F, and V_z/F

Source: Table 10, CSR for CRD1003.

Abbreviations: AUC_{0-85d}, area under the plasma concentration-time curve from time 0 to day 85; AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the last measurable time point; C, clearance; C_{max}, maximum plasma concentration; PFS-U, prefilled syringe assembled with UltraSafe Plus Needle Guard; PFS-Y, prefilled syringe assembled with Ypsomate autoinjector; PK, pharmacokinetic; SD, standard deviation; T_{1/2}, half-life; t_{max}, time to maximum concentration; V_z, volume of distribution

Two different statistical methods were used for the bioequivalence assessment to preserve control of the Type I error:

- Two one-sided tests (TOST) procedure: estimated sample sizes in Part 1 and Part 2 were used to prespecify weights for Part 1 and Part 2, and a weighted sum of test statistics was used for bioequivalence testing
- Calculation of the geometric mean ratios and 90% repeated CIs for C_{max} and AUC_{inf} of 1 x 2 mL PFS-U and 1 x 2 mL PFS-Y relative to 2 x 1 mL PFS-U

Statistical evaluation of bioequivalence using the TOST procedure is shown in [Table 54](#). Inferences using the repeated CI method are shown in [Table 55](#). Based on the prespecified criteria, bioequivalence was demonstrated between 2 mL PFS-Y and 1 mL PFS-U in Part 1, Part 2, and in the combined test. In Part 1, bioequivalence was not demonstrated for 2 mL PFS-U relative to 1 mL PFS-U, with exposure approximately 12 to 13% lower when a 200 mg SC dose was administered as 1 x 2 mL PFS-U relative to 2 x 1 mL PFS-U. Bioequivalence was demonstrated between 2 mL PFS-U and 1 mL PFS-U in Part 2 and in the combined test, although point estimates for the C_{max} and AUC_{inf} geometric mean ratios remained similar to those determined in Part 1.

The reviewer's statistical analysis, conducted via calculation of geometric mean ratios and associated 90% CIs for all combined data from Part 1 and Part 2, corroborates the Applicant's conclusions that bioequivalence criteria were met between 1 mL PFS-U and 2 mL PFS-U; and between 1 mL PFS-U and 2 mL PFS-Y.

Table 54. Statistical Evaluation of Bioequivalence Using the Two One-Sided Tests Procedure

Device	PK Parameter	Part 1 ^c	Part 2 ^d	Combined ^e
Test Device 1 (2mL PFS-U) $t_{1-\alpha,df}=1.650$	AUC _{inf}	$T_{AUC, 1L} = 1.10$	$T_{AUC, 2L} = 1.79$	$T^*_{AUC, L} = 2.10$
		$T_{AUC, 1U} = -4.51$	$T_{AUC, 2U} = -7.66$	$T^*_{AUC, U} = -8.87$
	C _{max}	$T_{Cmax, 1L} = 1.19$	$T_{Cmax, 2L} = 2.19$	$T^*_{Cmax, L} = 2.49$
		$T_{Cmax, 1U} = -4.57$	$T_{Cmax, 2U} = -8.12$	$T^*_{Cmax, U} = -9.29$
Test Device 2 (2mL PFS-Y) $t_{1-\alpha,df}=1.651$	AUC _{inf}	$T_{AUC, 1L} = 1.88$	$T_{AUC, 2L} = 4.29$	$T^*_{AUC, L} = 4.61$
		$T_{AUC, 1U} = -4.50$	$T_{AUC, 2U} = -4.29$	$T^*_{AUC, U} = -6.06$
	C _{max}	$T_{Cmax, 1L} = 2.55$	$T_{Cmax, 2L} = 4.06$	$T^*_{Cmax, L} = 4.79$
		$T_{Cmax, 1U} = -3.95$	$T_{Cmax, 2U} = -5.14$	$T^*_{Cmax, U} = -6.47$

a: Brannath, W., König, F., & Bauer, P. (2006). Estimation in flexible two stage designs. *Statistics in Medicine*, 25(19), 3366-3381.

b: Berger, R. L., & Hsu, J. C. (1996). Bioequivalence trials, intersection-union tests and equivalence confidence sets. *Statistical Science*, 11(4), 283-319.

c: LS mean estimated using ANCOVA model with factor of Study Device (Test, Reference) and covariate of Body Weight.

d: LS mean estimated using ANCOVA model with factors of Study Device (Test, Reference) and Study Site (US, Germany), and covariate Body Weight.

e: Weighted test with pre-specified weight.

Source: Table 11, CSR for CRD1003.

Abbreviations: ANCOVA, analysis of covariance; AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; T, test statistic; $t_{1-\alpha,df}$, critical value based on the degrees of freedom of combined test statistics

Table 55. Statistical Evaluation of Bioequivalence Using the Confidence Interval Procedure

BE Test	PK Parameter	Part 1	Part 2	Combined
Test 1/ Reference	AUC _{inf}	87.32 (76.48, 99.69)	87.05 (80.51, 94.12)	87.15 (81.93, 93.58)
	C _{max}	87.74 (77.13, 99.82)	87.96 (81.90, 94.47)	87.88 (82.24, 93.91)
Test 2/ Reference	AUC _{inf}	91.25 (81.21, 102.52)	99.99 (91.75, 108.98)	96.34 (89.71, 103.46)
	C _{max}	95.31 (85.03, 106.84)	97.41 (89.90, 105.56)	96.56 (90.24, 103.32)

c: Lehmacher, W., & Wassmer, G. (1999). Adaptive sample size calculations in group sequential trials. *Biometrics*, 55(4), 1286-1290.

Source: Table 12, CSR for CRD1003.

Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration

Immunogenicity Results

Serum immunogenicity samples were collected pre-dose on Day 1, and post-dose at Days 29, 57, and 85. The immunogenicity incidence in each treatment group was 7/162 (4.3%) among subjects who received 2 x 1 mL PFS-U, 5/164 (3.0%) among subjects who received 1 x 2 mL PFS-U, and 7/106 (6.6%) among subjects who received 1 x 2 mL PFS-Y. The overall incidence was 4.4% (19/432).

14.2.2. Study EDI1001

Title

“An open-label, randomized, parallel-group study to assess the bioequivalence of the intravenous formulation of guselkumab using prefilled syringes assembled in an UltraSafe Plus Passive

Needle Guard and intravenous formulation of guselkumab using final vial product in healthy participants”

Study Design

Study EDI1001 was a randomized, open-label, parallel group study conducted in healthy subjects aged between 18 and 60 years, inclusive, with body weight between 50 and 90 kg, inclusive. All subjects received a single 200 mg IV dose of guselkumab, administered using the formulation contained in the 100 mg/1 mL PFS-U, or the formulation contained in the 10 mg/mL final vial product.

The contents of two 1 mL PFS-U products were transferred to an IV bag containing 100 mL dextrose for infusion. The contents of the final vial product were transferred to an IV bag containing 250 mL 0.9% normal saline for infusion. IV infusions were administered over a duration of 60±10 minutes.

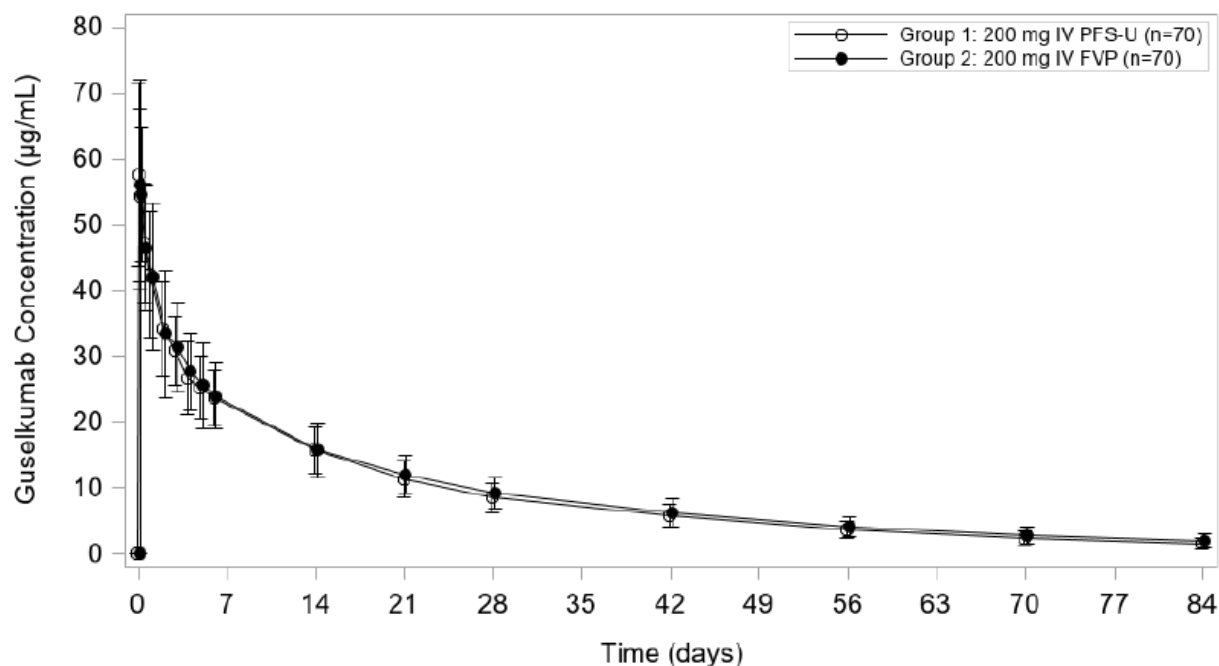
Overall, a total of 140 healthy subjects were randomized, with 70 subjects in each treatment group. All randomized subjects were included in the PK analysis set.

PK Results

Concentration-time profiles and PK parameters by drug product presentation are shown in [Figure 4](#) and [Table 56](#), respectively. Statistical evaluation of bioequivalence is shown in [Table 57](#). There was no apparent difference by drug product in the concentration-time profile following IV infusion. Peak concentrations were achieved about 30 minutes after the end of the infusion, corresponding to the first PK sample collected post-dose. Concentrations declined bi-exponentially through Day 85 and serum concentrations were still quantifiable at this time point. The mean (SD) half-life was 22.0 (5.8) to 23.8 (5.7) days.

Geometric mean ratios and associated 90% CIs for C_{max} , AUC_{0-85d} , and AUC_{inf} fell entirely within 80.00% to 125.00%, indicating bioequivalence between PFS-U and the proposed final vial product. The reviewer’s analysis corroborates the Applicant’s conclusions that bioequivalence criteria were met between PFS-U and the final vial product for IV administration.

Figure 4. Mean (SD) Serum Guselkumab Concentration-Time Profiles Following a Single 200 mg IV Dose in the Linear Scale



Source: Figure 3, CSR for EDI1001.

Abbreviations: FVP, final vial product; IV, intravenous; PFS-U, prefilled syringe assembled with UltraSafe Plus Passive Needle Guard; SD, standard deviation

Table 56. Summary of Guselkumab PK Parameters by Drug Product Presentation

Pharmacokinetic Parameter (mean [SD], t_{max} : median [range])	Group 1: 200 mg IV PFS-U	Group 2: 200 mg IV FVP
n	69 ^a	69 ^b
C_{max} , µg/mL	59.1 (10.6)	58.8 (10.9)
t_{max} , day	0.0625 (0.0592 - 5.0033)	0.0625 (0.0592 - 0.1688)
AUC_{0-85d} , µg.day/mL	748 (158)	780 (178)
AUC_{last} , µg.day/mL	743 (162)	780 (178)
AUC_{inf} , µg.day/mL	796 (184)	855 (223)
$T_{1/2}$, day	22.0 (5.8)	23.8 (5.7)
CL, L/day	0.264 (0.0606)	0.249 (0.0651)
V_z , L	8.07 (1.66)	8.26 (1.60)

^a n=68 for AUC_{0-85d} and n=66 for AUC_{inf} , CL and V_z .

^b n=68 for AUC_{inf} , CL and V_z .

Source: Table 8, CSR for EDI1001.

Abbreviations: AUC_{0-85d} , area under the plasma concentration-time curve from time 0 to day 85; AUC_{inf} , area under the plasma concentration-time curve from time 0 to infinity; AUC_{last} , area under the plasma concentration-time curve from time 0 to the last measurable time point; CL, clearance; C_{max} , maximum plasma concentration; IV, intravenous; FVP, final vial product; PFS-U, prefilled syringe assembled with UltraSafe Plus Passive Needle Guard; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; t_{max} , time to maximum concentration; V_z , volume of distribution

Table 57. Statistical Comparison of Guselkumab C_{max} and AUC Across IV Formulations

Parameter	Geometric Mean		Geometric Mean Ratio, %	90% CI, %	CV, %
	Group 1: 200 mg IV PFS-U (reference)	Group 2: 200 mg IV FVP (test)			
n	69 ^a	69 ^b			
C _{max} , µg/mL	57.9	57.8	99.77	94.36 - 105.50	20.0
AUC _{0-85d} , µg.day/mL	732	761	104.03	97.85 - 110.59	21.9
AUC _∞ , µg.day/mL	776	829	106.76	99.70 - 114.32	24.3

^a n=68 for AUC_{0-85d} and n=66 for AUC_∞.

^b n=68 for AUC_∞.

Source: TABPK07, CSR for EDI1001.

Abbreviations: AUC_{0-85d}, area under the plasma concentration-time curve from time 0 to day 85; AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; IV, intravenous; FVP, final vial product; PFS-U, prefilled syringe assembled with UltraSafe Plus Passive Needle Guard

Immunogenicity Results

Serum immunogenicity samples were collected pre-dose on Day 1, and post-dose at Days 29, 57, and 85. Out of 70 subjects in each treatment group, 1/70 1.4% subject in both the PFS-U and final vial product groups were positive for ADAs to guselkumab. The overall incidence was 1.4% (2/140).

14.2.3. Study CNTO1959UCO3001 (QUASAR)

Study CNTO1959UCO3001 (QUASAR) consisted of three randomized, double-blind, placebo-controlled, parallel-group studies conducted under a single protocol and included the following:

- Induction Study 1: phase 2b induction dose-ranging study
- Induction Study 2: phase 3 induction study
- Maintenance Study (MS): phase 3 maintenance study

For full study design details of the QUASAR study, refer to Section [6.2](#).

14.2.3.1. Induction Study 1

For details on the Induction Study 1 (IS-1) study design and subject disposition, refer to Section [6.2.3](#).

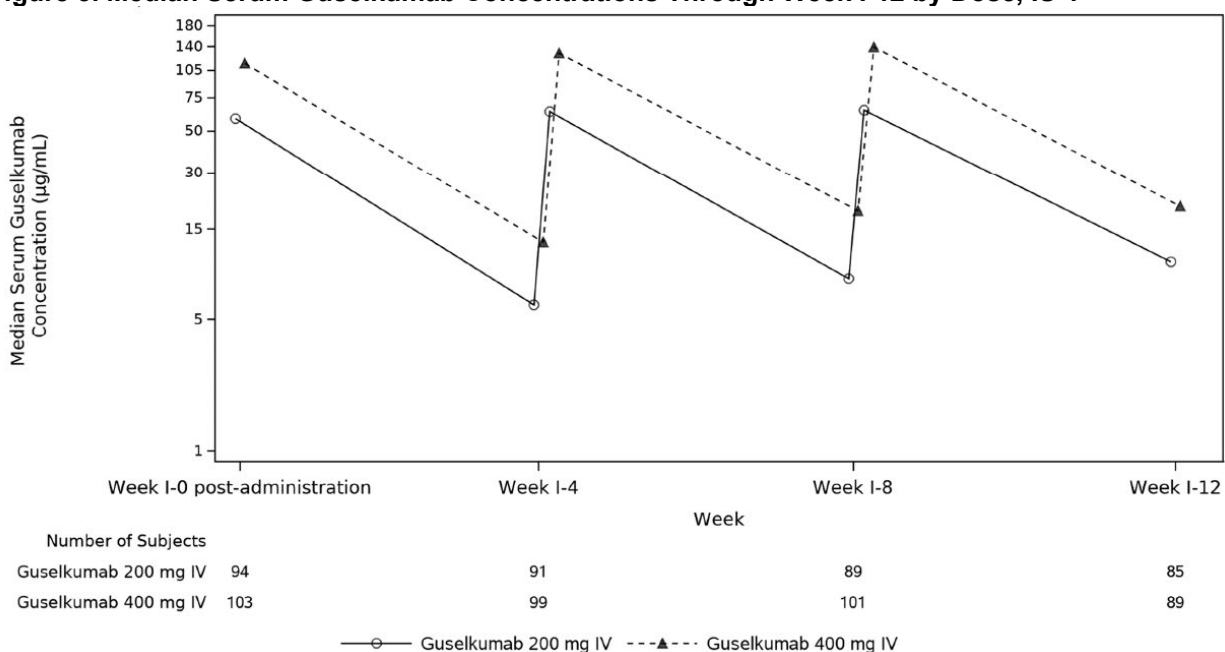
Guselkumab was supplied as a 100 mg/mL sterile liquid in a single-dose PFS assembled in an PFS-U. PFS-U supported both IV preparations and SC administrations. IV doses were prepared by transferring the contents of the 100 mg PFS devices into an IV bag containing 100 mL dextrose for infusion. IV doses were administered over a period of no less than 1 hour, and not more than two hours. SC doses of 200 mg were administered as 2 injections of 100 mg guselkumab, with each injection administered at a different location of the body (i.e., upper arm, abdomen, or thigh).

PK Results

Median concentration-time profiles following IV administration of 200 mg or 400 mg guselkumab at Weeks 0, 4, and 8 are shown in [Figure 5](#). Median serum concentrations were approximately dose proportional at each visit through Week I-12. At Week I-12, the median (coefficient of variation [CV]%) guselkumab trough concentrations were 10.1 µg/mL (55.5%) and 20.0 µg/mL (50.3%) for the 200 mg IV and 400 mg IV groups, respectively.

Peak serum concentrations measured 1 hour after IV administration did not appear to accumulate from Week I-0 to Week I-8. From Weeks I-0 to I-8, median (CV%) concentrations ranged from 58.4 µg/mL (27.6%) to 64.6 µg/mL (30.4%) for the 200 mg IV dose, and from 113.9 µg/mL (23.4%) to 139.7 µg/mL (30.8%) for the 400 mg IV dose. From Weeks I-4 to I-12, median serum trough concentrations accumulated 1.7-fold and 1.5-fold for the 200 mg and 400 mg doses, respectively (data derived from Table TPKCONC301AA, clinical study report [CSR] for IS-1).

Figure 5. Median Serum Guselkumab Concentrations Through Week I-12 by Dose, IS-1



Source: Figure 3, Summary of Clinical Pharmacology.

Note: Only includes subjects with modified Mayo score of 5 to 9 at induction baseline

Note: Concentrations below the lowest quantifiable concentration (i.e., <0.01 mcg/mL) were treated as 0 in calculating summary statistics.

Note: Serum guselkumab concentrations that fell outside the range of mean ± 3 SD for a given visit were excluded for pre- and post-infusion concentrations through the IV induction visits.

Abbreviation: IS-1, Induction Study 1; IV, intravenous; SD, standard deviation; Week I-#, induction week number

Guselkumab concentrations at Week I-12 by baseline body weight quartile is shown in [Table 58](#). In general, median serum guselkumab concentrations tended to decrease with increasing body weight quartile. For subjects in the lowest weight quartile (body weight ≤ 55.8 kg), median guselkumab concentrations at Week I-12 were about 1.3-fold greater relative to that among subjects in the highest weight quartile (body weight > 82.0 kg) for both the 200 and 400 mg dose groups.

Table 58. Median (CV%) Guselkumab Week I-12 Trough Concentrations (µg/mL) by Baseline Body Weight Quartile

IV Dose	N	≤55.8	N	>55.8 to ≤68.6	N	>68.6 to ≤82.0	N	>82.0
200 mg	24	14.2 (58.0%)	20	9.1 (35.2%)	21	7.6 (63.6%)	20	10.7 (35.6%)
400 mg	24	21.0 (47.4%)	22	26.5 (39.1%)	21	17.1 (48.7%)	22	15.7 (47.3%)

Source: Reviewer-generated table derived from Tables TPKCONC303AA and TPKCONC303BA, CSR Addendum for IS-1.

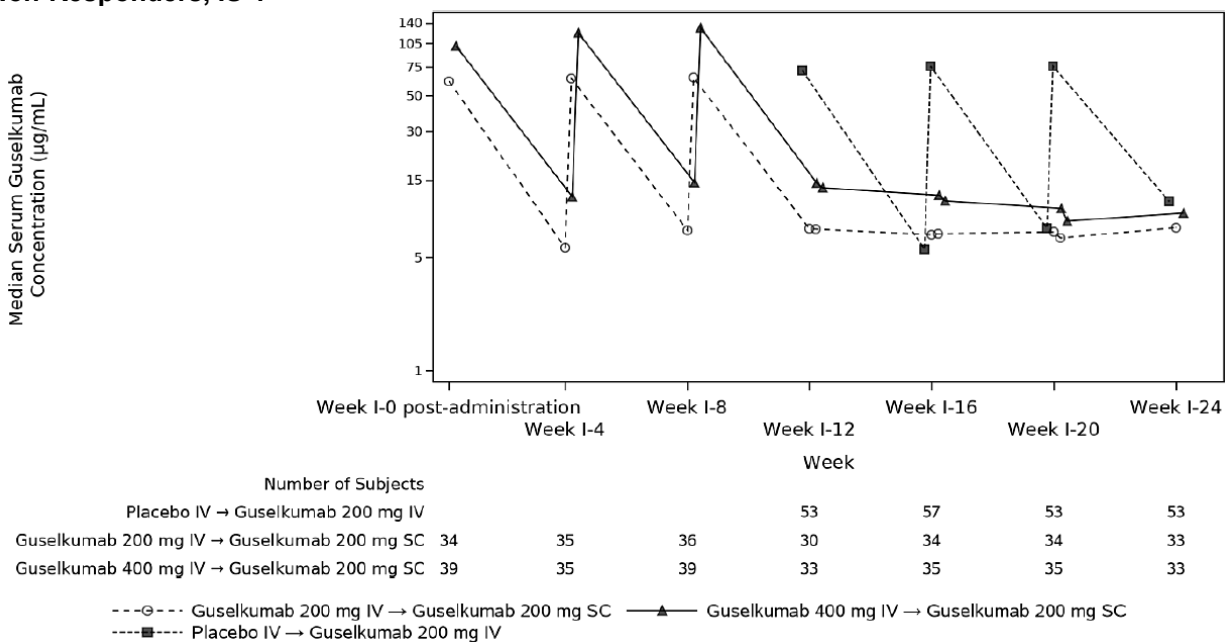
All weights are shown in units of kg.

Abbreviations: CV, coefficient of variation; IV, intravenous; N, number of subjects in treatment group

Subjects initially randomized to placebo who did not achieve clinical response at Week I-12 received 200 mg IV guselkumab at Weeks I-12, I-16, and I-20. In these subjects, the median (CV%) guselkumab serum trough concentration at Week 24 was 11.2 µg/mL (68.4%) (N=53), which was similar to the observed Week I-12 serum trough concentrations among subjects initially randomized to guselkumab.

Median serum guselkumab concentration-time profiles among clinical non-responders following IV administration of 200 mg IV or 400 mg IV guselkumab at Weeks I-0, I-4, and I-8, and SC administration of 200 mg at Weeks I-12, I-16, and I-20 are shown in [Figure 6](#). Median (CV%) serum guselkumab concentrations at Week I-24 were 7.7 µg/mL (55.4%) and 9.5 µg/mL (60.0%) for subjects initially randomized to receive 200 mg IV guselkumab (N=33) and 400 mg IV guselkumab (N=33), respectively.

Figure 6. Median Serum Guselkumab Concentrations Through Week I-24 Among Clinical Non-Responders, IS-1



Source: Figure GPKCONC302A, CSR Addendum for IS-1.

Note: Only includes subjects with modified Mayo score of 5 to 9 at induction baseline

Note: Concentrations below the lowest quantifiable concentration (i.e., <0.01 mcg/mL) were treated as 0 in calculating summary statistics.

Note: Includes subjects in the PK analysis set who were not in clinical response at Week I-12 and received guselkumab from Week I-12.

Abbreviation: IS-1, Induction Study 1; IV, intravenous; SC, subcutaneous, SD, standard deviation; Week I-#, induction week number

Among the guselkumab treatment groups, median serum guselkumab concentrations at Week I-12 tended to be lower for subjects who were not in clinical response at Week I-12 relative to

subjects who achieved clinical response. Among subjects randomized to 200 mg IV guselkumab, the median (CV%) Week I-12 serum guselkumab concentrations were 7.6 µg/mL (66.9%) for subjects who did not achieve clinical response (N=30) and 11.0 µg/mL (49.5%) for subjects who did achieve clinical response (N=55). Similarly, among subjects randomized to 400 mg guselkumab, the median (CV%) Week I-12 serum guselkumab concentrations were 14.5 µg/mL (57.8%) for subjects who did not achieve clinical response (N=33) and 24.4 µg/mL (43.2%) for subjects who did achieve clinical response (N=56).

14.2.3.2. Induction Study 2

For details on the Induction Study 2 (IS-2) study design and subject disposition, refer to Section [6.2](#).

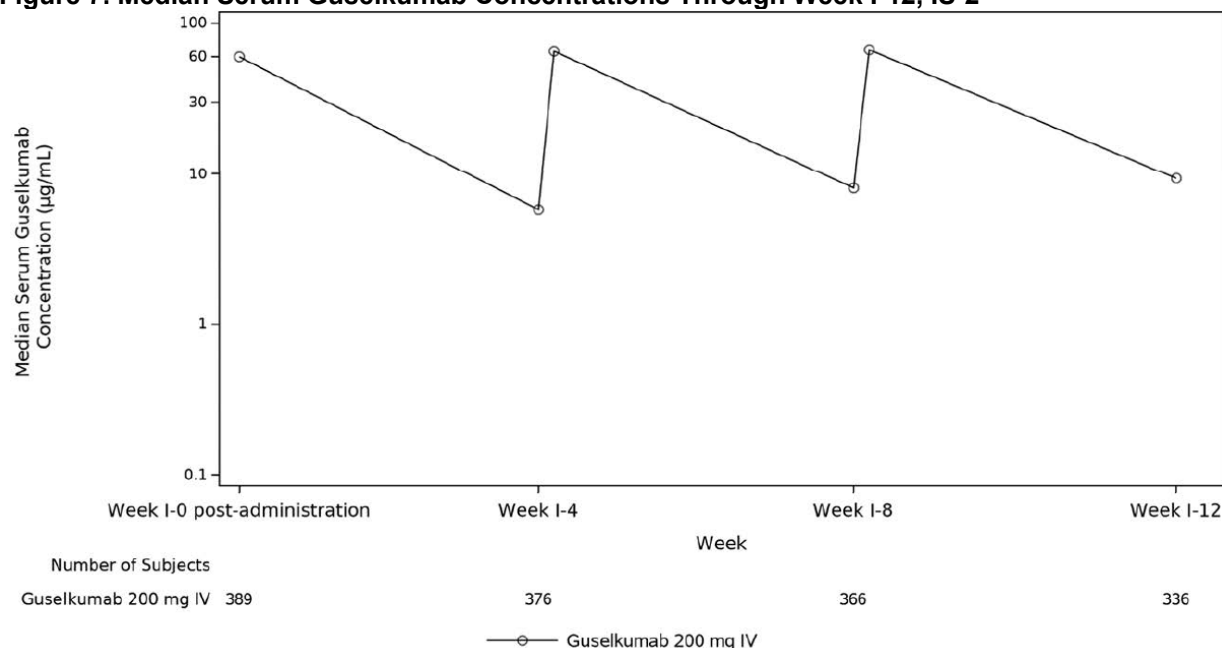
Guselkumab was supplied as a 100 mg/mL sterile liquid in a single-dose PFS-U. PFS-U supported both IV preparations and SC administrations. IV doses were prepared by transferring the contents of the 100 mg PFS devices into an IV bag containing 100 mL dextrose for infusion. IV doses were administered over a period of no less than 1 hour, and not more than 2 hours. SC doses of 200 mg were administered as 2 injections of 100 mg guselkumab, with each injection administered at a different location of the body (i.e., upper arm, abdomen, or thigh).

PK Results

Median concentration-time profiles following IV administration of 200 mg IV guselkumab at Weeks 0, 4, and 8 are shown in [Figure 7](#). At Week I-12, the median (CV%) guselkumab trough concentration was 9.4 µg/mL (50.8%). This value is similar to that observed among subjects randomized to receive 200 mg IV guselkumab in IS-1 (median [CV%] =10.1 µg/mL [55.5%]).

Peak serum concentrations measured 1 hour after IV administration did not appear to accumulate from Week I-0 to Week I-8. From Weeks I-0 to I-8, median (CV%) concentrations ranged from 60.1 µg/mL (24.3%) to 66.6 µg/mL (24.2%). From Weeks I-4 to I-12, median serum trough concentrations accumulated by about 1.6-fold (data derived from Table TPKCONC501A, CSR for IS-2).

Figure 7. Median Serum Guselkumab Concentrations Through Week I-12, IS-2



Source: Figure 5, Summary of Clinical Pharmacology.

Note: Only includes subjects with modified Mayo score of 5-9 at induction baseline

Note: Concentrations below the lowest quantifiable concentration (i.e., <0.01 mcg/mL) were treated as 0 in calculating summary statistics.

Note: Serum guselkumab concentrations that fell outside the range of mean $\pm$ 3SD for a given visit were excluded for pre- and post-infusion concentrations through the IV induction visits.

Abbreviation: IS-2, Induction Study 2; IV, intravenous; SD, standard deviation; Week I-#, induction week number

Guselkumab concentrations at Week I-12 by baseline body weight quartile is shown in [Table 59](#). In general, median serum guselkumab concentrations tended to decrease with increasing body weight quartile. For subjects in the lowest weight quartile (body weight <60.0 kg), median guselkumab concentrations at Week I-12 were about 1.5-fold greater relative to that among subjects in the highest weight quartile (body weight $\geq$ 83.7 kg).

Table 59. Median (CV%) Guselkumab Week I-12 Trough Concentrations (µg/mL) by Baseline Body Weight Quartile

IV Dose	Body Weight Quartile			
	<60.0 (N=82)	$\geq$ 60.0 to <71.3 (N=86)	$\geq$ 71.3 to <83.7 (N=86)	$\geq$ 83.7 (N=82)
200 mg	11.2 (47.1%)	10.8 (41.5%)	8.51 (55.6%)	7.24 (52.4%)

Source: Reviewer-generated table derived from Table TPKCONC504, CSR for IS-2.

All weights are shown in units of kg.

Abbreviations: CV, coefficient of variation; IV, intravenous; N, number of subjects in body weight quartile

Subjects initially randomized to placebo who did not achieve clinical response at Week I-12 received 200 mg IV guselkumab at Weeks I-12, I-16, and I-20. In these subjects, the median (CV%) guselkumab serum trough concentration at Week 24 was 10.0 µg/mL (48.2%) (N=112), which was similar to the observed Week I-12 serum trough concentrations among subjects initially randomized to guselkumab.

Subjects initially randomized to guselkumab who did not achieve clinical response at Week I-12 received 200 mg SC guselkumab at Weeks I-12, I-16, and I-20. The median (CV%) serum guselkumab concentration at Week I-24 was 6.92 µg/mL (56.7%) (N=91).

Among the guselkumab treatment groups, median serum guselkumab concentrations at Week I-12 tended to be lower for subjects who were not in clinical response at Week I-12 relative to subjects who achieved clinical response. Among subjects randomized to 200 mg guselkumab, the median (CV%) Week I-12 serum guselkumab concentrations were 7.5 µg/mL (53.9%) for subjects who did not achieve clinical response (N=106) and 10.5 µg/mL (47.2%) for subjects who did achieve clinical response (N=228).

14.2.3.3. Maintenance Study

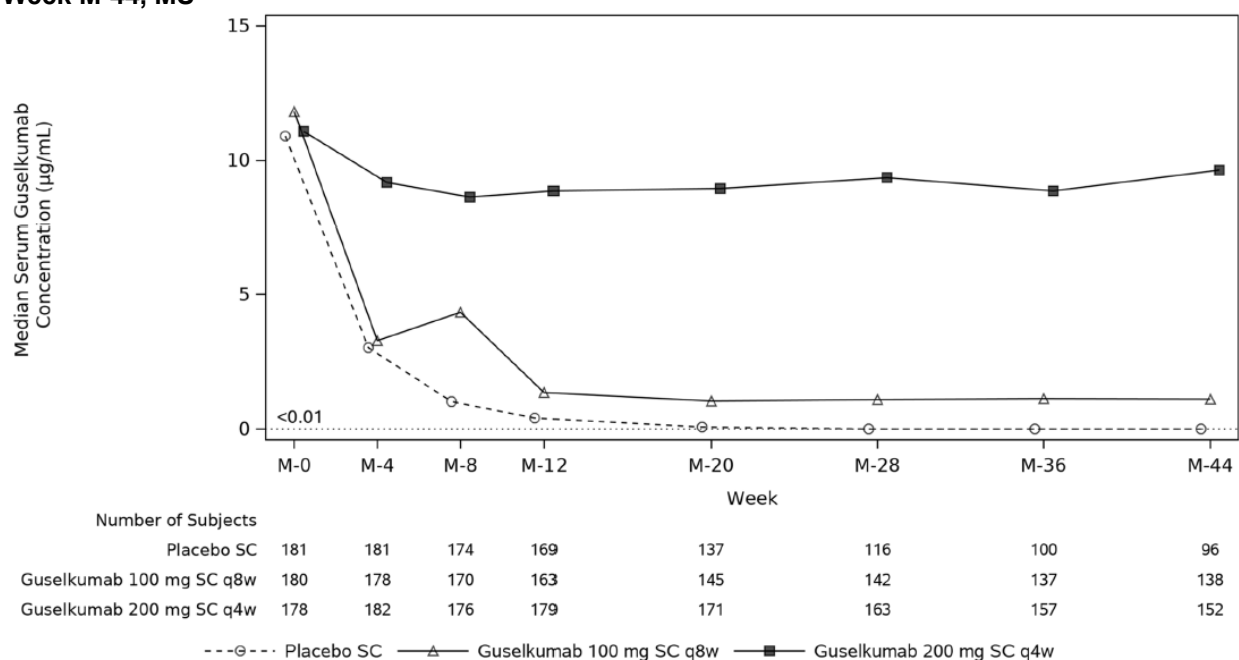
For details on study design and subject disposition in the MS, refer to Section [6.2.2](#).

Guselkumab was supplied as a 100 mg/mL sterile liquid in a single-dose PFS-U. SC doses of 200 mg SC were administered as 2 injections of 100 mg SC guselkumab. Subjects randomized to the 100 mg SC arm received 1 injection of 100 mg SC guselkumab and 1 injection of placebo to maintain the blind. As subjects received multiple SC injections at each visit, each injection was administered at a different location of the body (i.e., upper arm, abdomen, or thigh).

PK Results

Median concentration-time profiles among randomized subjects following SC administration of 200 mg SC Q4W guselkumab, 100 mg SC Q8W guselkumab, or placebo are shown in [Figure 8](#). Subjects who were randomized to receive 200 mg SC Q4W guselkumab achieved steady state concentrations by Week I-8, with median (CV%) steady state trough concentrations ranging from 8.63 µg/mL (47.8%) to 9.65 µg/mL (56.7%). Subjects who were randomized to receive 100 mg SC Q8W achieved steady state concentrations by Week I-12, with median (CV%) steady state trough concentrations ranging from 1.04 µg/mL (68.2%) to 1.35 µg/mL (74.5%). At Week M-44, subjects receiving 200 mg SC Q4W had trough concentrations approximately 9-fold greater relative to subjects receiving 100 mg SC Q8W, with median (CV%) concentrations of 9.65 µg/mL (56.7%) and 1.10 µg/mL (66.7%), respectively. Serum guselkumab concentrations declined among subjects randomized to placebo, with median concentrations falling below the lower limit of quantitation (0.01 µg/mL) by Week M-28.

Figure 8. Median Serum Guselkumab Concentrations Among Randomized Subjects Through Week M-44, MS



Source: Figure 7, Summary of Clinical Pharmacology.

Note: Only includes subjects with modified Mayo score of 5 to 9 at induction baseline

Note: Data after dose adjustment were excluded for subjects who received an increased dose at the time of dose adjustment

Note: Concentrations below the lowest quantifiable concentration (i.e., <0.01 mcg/mL) were treated as 0 in calculating summary statistics.

Note: Subjects randomized to 200 mg Q4W received doses beginning at Week M-0. Subjects randomized to 100 mg Q8W received doses beginning at Week M-4.

Abbreviations: MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; Week M-#, maintenance week number

Guselkumab concentrations at Week M-44 by baseline body weight quartile for subjects in the 200 mg SC Q4W arm and in the 100 mg SC Q8W arm are shown in [Table 60](#). In general, median serum guselkumab concentrations tended to decrease with increasing body weight quartile. Among subjects who received 200 mg SC Q4W, those in the lowest weight quartile (body weight <57.5 kg) had median guselkumab concentrations at Week M-44 that were about 1.5-fold greater relative to that among subjects in the highest weight quartile (body weight ≥81.8 kg). Among subjects who received 100 mg SC Q8W, those in the lowest weight quartile (body weight <58.2 kg) had median guselkumab concentrations at Week M-44 that were about 2.4-fold greater relative to that among subjects in the highest weight quartile (body weight ≥83.5 kg).

Table 60. Guselkumab Week M-44 Trough Concentrations (µg/mL) by Baseline Body Weight Quartile and Dosage, MS

Dosage	Body Weight Quartile			
	<57.5 (N=42)	≥57.5 to <69.5 (N=32)	≥69.5 to <81.8 (N=35)	≥81.8 (N=43)
200 mg SC Q4W				
Median (CV%)	11.6 (56.5%)	11.6 (38.5%)	7.77 (53.6%)	7.82 (45.2%)
IQR	(8.29, 17.1)	(8.44, 14.5)	(5.44, 12.1)	(5.00, 9.75)
	<58.2 (N=31)	≥58.2 to <68.8 (N=34)	≥68.8 to <83.5 (N=38)	≥83.5 (N=35)
100 mg SC Q8W				
Median (CV%)	1.84 (47.7%)	1.23 (54.9%)	1.00 (66.1%)	0.77 (84.7%)
IQR	(1.19, 2.77)	(0.77, 1.62)	(0.58, 1.84)	(0.54, 1.10)

Source: Reviewer-generated table derived from Tables TPKCONC603A and TPKCONC603B, CSR for the Maintenance Study. All weights are shown in units of kg.

Note: For 200 mg SC Q4W, data includes subjects who received a sham dose adjustment. For 100 mg SC Q8W, data after dose adjustment were excluded for subjects who received an increased dose at the time of dose adjustment.

Note: Concentrations below the lowest quantifiable concentration (<0.01 µg/mL) were treated as 0 in calculating the summary statistics.

Abbreviations: CV, coefficient of variation; IQR, interquartile range; MS, Maintenance Study; N, number of subjects in body weight quartile; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

In IS-1 and IS-2, subjects initially randomized to guselkumab who did not achieve clinical response by Week I-12 were given 200 mg SC guselkumab at Weeks I-12, I-16, and I-20. Clinical responders at Week I-24 were then transitioned to the MS, where all subjects received 200 mg SC Q4W. In these subjects, steady state was reached by Week M-0. Median (CV%) steady state trough concentrations ranged from 6.97 µg/mL (57.8%) to 8.64 µg/mL (52.9%) throughout the maintenance treatment period (N=87 to 118). The observed steady state trough concentrations were comparable to lower relative to those observed in Week I-12 clinical responders randomized to 200 mg SC Q4W (median [CV%] ranged from 8.63 µg/mL [47.8%] to 9.65 µg/mL [56.7%]).

A dose adjustment was permitted in randomized subjects who met the criteria for loss of clinical response. Among subjects randomized to receive 100 mg SC Q8W, median trough concentrations were generally lower among subjects who received a dose adjustment relative to subjects who did not receive a dose adjustment. At Week M-12, the timepoint at which most subjects received a dose adjustment, the median (CV%) guselkumab concentration was 0.70 µg/mL (83.8%) among subjects who received a dose adjustment (N=14), and 1.41 µg/mL (72.4%) among subjects who did not receive a dose adjustment (N=149). This trend was not observed among subjects who were randomized to 200 mg SC Q4W. Median (CV%) guselkumab concentrations from Week M-12 to M-44 ranged from 8.38 µg/mL (58.2%) to 9.68 µg/mL (52.7%) among subjects who received a sham dose adjustment (N=15 to 29), and 8.68 µg/mL (52.5%) to 9.68 µg/mL (56.6%) among subjects who did not receive a dose adjustment (N=137 to 150).

Note that there was no trend of higher body weight among subjects who received a dose adjustment. Among subjects with a modified Mayo Score (mMS) of 5 to 9 at induction baseline, the median (range) body weight at baseline for subjects in the 100 mg SC Q8W group who received a dose adjustment (N=19) was 70 (46.8, 116) kg. The median (range) body weight at baseline for subjects in the 200 mg SC Q4W group who received a sham dose adjustment (N=30) was 67.1 (48.9, 112) kg (data derived from reviewer's analysis of adsl.xpt dataset). These weight distributions are similar to those observed for all randomized induction responders. Median

(range) body weight values were 68.8 (40.0, 116) kg and 69.3 (44.4, 122) kg for subjects in the 100 mg SC Q8W and 200 mg SC Q4W groups, respectively (data derived from Table 4, CSR for Maintenance Study).

14.3. Bioanalytical Method Validation and Performance

14.3.1. PK Bioanalysis

To measure serum guselkumab concentrations in clinical studies, the Applicant used a validated electrochemiluminescence immunoassay using the Meso Scale Discovery platform. This method is the same method that was used to quantify guselkumab in clinical studies supporting prior approvals for the psoriasis and psoriatic arthritis indications.

Briefly, the method uses a streptavidin-coated 96-well plate as the support surface. The well plate is incubated with a biotinylated capture antibody ((b) (4)), a mouse monoclonal antibody specific for the variable region of guselkumab. Following incubation and a wash step, a solution is added containing ((b) (4)), another mouse monoclonal antibody specific for the variable region of guselkumab. The electrochemiluminescent signal is read on the ((b) (4)) reader. The range of the assay is 0.064000 to 0.00100 µg/mL (64.00 to 1.00 ng/mL) with a minimum required dilution of 1:10. Thus, the lowest quantifiable concentration in a sample is 0.0100 µg/mL (10.00 ng/mL).

Validation was described in report CP2014V-027 (Janssen Research & Development, Spring House, PA) and was deemed acceptable.¹²

In the present submission, the Applicant provided 10 new addenda to the bioanalytical method. The addenda provide additional stability data (A24 and A28); partial validation to confirm performance of a new drug stock (A25); incurred sample reanalysis and parallelism assessments from the QUASAR studies (A26, A33, and A37), Study EDI1001 (A27), and Study CRD1003 (A30); partial validation to confirm performance of new recombinant capture and detection reagents (A35); and cross-validation of the method between the Janssen ((b) (4)) ((b) (4)) (A38). The submitted addenda are considered acceptable.

Quantitation of study samples from the China cohorts of the QUASAR study was performed at ((b) (4)) using the same method validated at the Janssen laboratories. Full validation of the bioanalytical method is described in reports SH-J01-R2560 and SH-J01-R2560-A1.

¹² Refer to the clinical pharmacology review in dated July 13, 2017 (DARRTS Reference ID: 4123785).

Table 61. Bioanalytical Validation Summary From Reports SH-J01-R2560 and SH-J01-R2560-A1

Method Parameter	Method Details								
Bioanalytical method review summary	Method validation adequate to support results in study QUASAR								
Materials used for calibration curve, QCs & concentration	(b) (4) standard, Lot #JCS5802, 98 mg/mL; Lot #IJS5100, 101 mg/mL supplied by JNJ Report A1: CNTO (b) (4) [guselkumab] standard, Lot #JCS5802, 98 mg/mL; Lot #KIS5X00, 100 mg/mL; Lot #MGS3D02, 98 mg/mL, supplied by JNJ								
Validated assay range	0.01000 µg/mL (LLOQ) to 0.64000 µg/mL (ULOQ) in human serum (assumed undiluted concentrations as the listed lowest quantifiable concentration in a sample is 0.01000 µg/mL).								
Minimum required dilutions	1:10								
Source & lot of reagents (LBA)	Biotin- (b) (4) (C1644A), Lot #MOS00225073, 1.15 mg/mL, JNJ SulfoTag (b) (4) (C1642A), Lot #MOS00225074, 1.49 mg/mL, JNJ SulfoTag C (b) (4) (C1642A), Lot #MOS00314349, 1.23 mg/mL, JNJ Report A1: • Biotin-C (b) (4) (C1644A), Lot #MOS00225073, 1.15 mg/mL, JNJ • SulfoTag (b) (4) (C1642A), Lot #MOS00314348, 1.12 mg/mL, JNJ • SulfoTag (b) (4) (C1642A), Lot #MOS00314349, 1.23 mg/mL, JNJ								
Regression model & weighting	Log-log quadratic								
Validation parameters	Method validation summary								
Calibration curve performance during accuracy & precision	<table> <tr> <th></th><th>Acceptability</th></tr> <tr> <td>No of standard calibrators from LLOQ to ULOQ</td><td>7 Yes</td></tr> <tr> <td>Cumulative accuracy (%bias) from LLOQ to ULOQ (original report – top; report A1 – bottom)</td><td>-1.7 to 1.2% Yes -3.8 to 3.4%</td></tr> <tr> <td>Cumulative precision (%CV) from LLOQ to ULOQ (original report – top; report A1 – bottom)</td><td>≤3.8% Yes ≤6.8%</td></tr> </table>		Acceptability	No of standard calibrators from LLOQ to ULOQ	7 Yes	Cumulative accuracy (%bias) from LLOQ to ULOQ (original report – top; report A1 – bottom)	-1.7 to 1.2% Yes -3.8 to 3.4%	Cumulative precision (%CV) from LLOQ to ULOQ (original report – top; report A1 – bottom)	≤3.8% Yes ≤6.8%
	Acceptability								
No of standard calibrators from LLOQ to ULOQ	7 Yes								
Cumulative accuracy (%bias) from LLOQ to ULOQ (original report – top; report A1 – bottom)	-1.7 to 1.2% Yes -3.8 to 3.4%								
Cumulative precision (%CV) from LLOQ to ULOQ (original report – top; report A1 – bottom)	≤3.8% Yes ≤6.8%								
QCs performance during accuracy & precision	<table> <tr> <td>Cumulative accuracy (%bias) in 5 QCs (original report – top; report A1 – bottom)</td><td>-5.4 to 5.6% Yes -4.6 to 5.1%</td></tr> <tr> <td>Inter-batch %CV (original report – top; report A1 – bottom)</td><td>≤18.8% Yes ≤17.4%</td></tr> <tr> <td>Percent TE (original report – top; report A1 – bottom)</td><td>≤24.4% Yes ≤22.5%</td></tr> </table>	Cumulative accuracy (%bias) in 5 QCs (original report – top; report A1 – bottom)	-5.4 to 5.6% Yes -4.6 to 5.1%	Inter-batch %CV (original report – top; report A1 – bottom)	≤18.8% Yes ≤17.4%	Percent TE (original report – top; report A1 – bottom)	≤24.4% Yes ≤22.5%		
Cumulative accuracy (%bias) in 5 QCs (original report – top; report A1 – bottom)	-5.4 to 5.6% Yes -4.6 to 5.1%								
Inter-batch %CV (original report – top; report A1 – bottom)	≤18.8% Yes ≤17.4%								
Percent TE (original report – top; report A1 – bottom)	≤24.4% Yes ≤22.5%								
Selectivity & matrix effect	Acceptable selectivity observed in serum from healthy donors, patients with ulcerative colitis, patients with Crohn's disease, and patients with psoriasis (≥9/10 samples passed). Acceptable recovery in 3/3 replicates of lipemic and hemolyzed matrix. All results for unspiked individuals below LLOQ. QC sample concentrations were assessed using standard curves prepared using 10% pooled matrix and 100% pooled matrix. The percent difference ranged from 1.0 to 2.4%. Either 10% or 100% matrix can be used to generate standard curves.								
Hemolysis effect	No observed effect in 1 lot of pooled human serum supplemented with 2% hemolysate Yes								

Method Parameter	Method Details	
Lipemic effect	No observed effect in 1 lot of pooled human serum with triglyceride concentration of 1436 mg/dL	Yes
Dilution linearity & hook effect	A 500 µg/mL sample diluted 1250, 2500, 5000, and 10,000-fold met the acceptance criteria. No hook effect was observed for samples at concentrations up to 500 µg/mL	Yes
Bench-top/process stability	Stable in human serum at room temperature for 48 hours, and at 2 to 8 °C for 48 hours	Yes
Freeze-thaw stability	Established for up to 7 freeze-thaw cycles	Yes
Long-term storage	Established stability in human serum at -20 °C for 861 days and at -70 °C for 861 days	Yes
Parallelism	Acceptable precision in human serum from psoriasis patients, ulcerative colitis patients, and Crohn's disease patients (%CV ≤15.8%)	Yes
Cross-validation	Cross-validation was performed when the PK assay was transferred from the Janssen laboratory (b) (4) 26/30 (87%) spiked matrix samples and 21/30 (70%) incurred subject samples passed acceptance criteria based on percent difference ≤20%	Yes

Source: Validation reports SH-J01-R2560 and SH-J01-R2560-A1.

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantitation; PK, pharmacokinetic; TE, total error; ULQC, upper limit of quantitation

In-study bioanalysis was found to be acceptable in CRD1003, EDI1001, QUASAR Induction Study 1, QUASAR Induction Study 2, and QUASAR Maintenance Study. For QUASAR studies, bioanalysis in (b) (4) was also found to be acceptable.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Immunogenicity following guselkumab treatment was evaluated in subjects with UC with a mMS of 5 to 9 at induction baseline in the QUASAR study, comprised of IS-1, IS-2, and MS. Immunogenicity sample collection in each study is summarized below. Note that for IS-1 and IS-2, samples collected beyond Week I-12 were only applicable to subjects who were not in clinical response at Week I-12.

- IS-1: Weeks I-0, I-4, I-8, I-12, I-24, and at Safety Follow-up. An additional sample could be collected at an early termination visit.
- IS-2: Weeks I-0, I-4, I-8, I-12, I-24, and at Safety Follow-up. An additional sample could be collected at an early termination visit.
- MS: Weeks M-4, M-12, M-20, M-28, M-36, M-44, and at Safety Follow-up. An additional sample could be collected at an early termination visit.

The incidence of ADAs and NAbS following induction treatment with guselkumab in IS-1 and IS-2 and continuous maintenance treatment with guselkumab in MS is shown in [Table 62](#). Among subjects randomized to guselkumab induction at a dose of 200 IV or 400 mg IV in IS-1, no subjects were positive for ADAs by Week I-12. Among subjects randomized to 200 mg IV guselkumab induction in IS-2, 6/409 subjects (1.5%) were positive for ADAs. The overall incidence among all subjects who received induction with 200 mg IV Q4W guselkumab in IS-1

and IS-2 was 1.2% (6/508). None of these subjects were positive for NABs. Five out of six ADA-positive subjects had peak ADA titers of 1:11.25, which was the minimum required dilution of the ADA detection assay. The remaining subject had a peak titer of 1:45.

A total of 501 subjects received continuous treatment with guselkumab induction and maintenance through Week M-44. This number excludes 189 subjects who received guselkumab induction but were randomized to placebo maintenance treatment. Out of 501 subjects, 58 (11.6%) were positive for ADAs. Among Week I-12 induction responders, the incidence of ADAs was comparable between subjects randomized to 100 mg SC Q8W (9.6% – 18/188) or 200 mg SC Q4W (10.5% – 20/190). The remaining ADA-positive subjects were nonrandomized Week I-24 responders, who had a higher ADA incidence rate than randomized induction responders (16.3% – 20/123). Out of 57 ADA-positive subjects who were evaluable for NABs, 9 (15.8%) were positive for NABs. All 9 subjects had received 200 mg SC Q4W, 3 of whom responded to guselkumab induction and were randomized to 200 mg SC Q4W and 6 nonrandomized Week I-24 responders.

A total of 435 subjects with UC received the proposed to-be-marketed (TBM) guselkumab dosage regimen including induction with 200 mg IV Q4W followed by maintenance treatment with either 200 mg SC Q4W or 100 mg SC Q8W. The incidence of ADAs among these subjects was 11.0% (48/435), with comparable incidence irrespective of receiving 100 mg SC Q8W (9.0% – 15/166) or 200 mg SC Q4W (10.1% – 17/168), and greater incidence for nonrandomized Week I-24 responders (15.8% – 16/101). Among ADA-positive subjects, the incidence of NABs was about 17% (n=8). Note that at the time of this review, the drug tolerance of the NAb assay was determined to be inadequate to support NAb assessment for subjects in the China cohort. Among subjects in the China cohort who received the recommended dosage regimens, 10/34 (29%) were ADA-positive. Of these subjects, 2 were NAb-positive (refer to the Applicant's response to IR submitted August 29, 2024). Thus, the NAb incidence excluding ADA-positive subjects in the China cohort is 16% (6/38). See Section 9.1 and the Office of Product Quality Assessment III Review (dated September 5, 2024, located in the Panorama database for additional details).

A summary of peak ADA titers by maintenance dosage regimen among subjects receiving continuous guselkumab treatment with the proposed TBM dosage regimens is shown in [Table 63](#). Among ADA-positive subjects receiving the proposed TBM guselkumab dosage regimens (n=48), most subjects (n=34, 70.8%) had peak ADA titers of 1:11.25, the minimum required dilution. The remaining 14 subjects had higher ADA titers of either 1:22.5 (n=1), 1:90 (n=4), 1:180 (n=2), 1:720 (n=2), 1:1440 (n=1), 1:2880 (n=2), 1:5760 (n=1), or 1:11520 (n=1). Higher titers were observed among subjects who received the 200 mg SC Q4W regimen. A higher proportion of nonrandomized subjects (i.e., subjects who were not in clinical response to guselkumab IV at Week I-12 but were in response at Week I-24) presented with peak ADA titers of 1:720 or greater (observed in 6/16 subjects) relative to randomized subjects (observed in 1/17 subjects randomized to 200 mg SC Q4W).

Table 62. Summary of ADA and NAb Status Following Guselkumab Induction Treatment Through Week I-12 and Maintenance Treatment Through Week M-44

Study ID	Route	Dose Regimen	Incidence of ADA or NAb		
			Participants With Appropriate Samples ^a	ADA ^b	NAb ^b
Through Week I-12					
QUASAR IS-1	IV	400 mg q4w	106	0	0
	IV	200 mg q4w	99	0	0
QUASAR IS-2	IV	200 mg q4w	409	6 (1.5%)	0
Total Through Week I-12			614	6 (1.0%)	0
Through Week M-44 ^c					
QUASAR Maintenance Study	IV+SC	400 mg IV q4w followed by 200 mg SC q4w	22	3 (13.6%)	0
		400 mg IV q4w followed by 100 mg SC q8w	22	3 (13.6%)	0
		400 mg IV q4w followed by 200 mg SC q4w (Week I-24 responders)	22	4 (18.2%)	1 (4.5%)
		200 mg IV q4w followed by 200 mg SC q4w	168	17 (10.1%)	3 (1.8%)
		200 mg IV q4w followed by 100 mg SC q4w	166	15 (9.0%)	0
		200 mg IV q4w followed by 200 mg SC q4w (Week I-24 responders)	101	16 (15.8%)	5 (5.0%)
Total Through Week M-44			501	58 (11.6%)	9 (1.8%)

Source: Table 9, Integrated Summary of Immunogenicity.

Note: Includes only subjects with modified Mayo score of 5 to 9 at induction baseline.

^a Subjects with appropriate samples had one or more samples obtained after their first guselkumab administration through the end of the specified timeframe

^b Denominator was the number of subjects with appropriate samples for antibodies to guselkumab.

^c Includes subjects who received guselkumab induction treatments and continued guselkumab in Maintenance Study. Abbreviations: ADA, antidrug antibody; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; NAb, neutralizing antibody; Q4W, every 4 weeks; Q8W, every 8 weeks; Week I-12, Induction Week 12; Week M-44, Maintenance Week 44

Table 63. Summary of Peak ADA Titers by Maintenance Dosage Regimen Among Subjects Receiving Continuous Guselkumab Treatment With the Proposed TBM Dosage Regimen

Peak Titers	Randomized		Nonrandomized	Total
	100 mg SC Q8W	200 mg SC Q4W	200 mg SC Q4W	
1:11.25	14	13	7	34
1:22.5	0	1	0	1
1:90	1	1	2	4
1:180	0	1	1	2
1:720	0	0	2	2
1:1440	0	0	1	1

Peak Titers	Randomized		Nonrandomized	Total
	100 mg SC Q8W	200 mg SC Q4W	200 mg SC Q4W	
1:2880	0	1	1	2
1:5760	0	0	1	1
1:11520	0	0	1	1

Source: Reviewer's analysis using adis.xpt dataset.

Note: Includes only subjects with modified Mayo score of 5-9 at induction baseline. The dataset includes all subjects who received continuous treatment with the proposed TBM guselkumab dosage regimens, including 200 mg IV Q4W induction then maintenance treatment with either 100 mg SC Q8W or 200 mg SC Q4W. Induction responders at Week I-24 were also included. Responders who were randomized to placebo maintenance are not included.

Abbreviations: ADA, antidrug antibody; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; TBM, to-be-marketed; Week I-#, induction week #

14.4.1. Impact of Immunogenicity on PK

During induction, immunogenicity was not found to impact the PK of guselkumab, although few subjects developed immunogenicity during induction treatment. In IS-2, the median (interquartile range [IQR]) guselkumab concentration at Week I-12 was 9.91 (7.79, 13.0) µg/mL among subjects positive for ADAs (n=6) and 9.30 (6.25, 13.4) µg/mL among subjects who did not develop ADAs (n=330) (data derived from Table TPKIR506, CSR for IS-2).

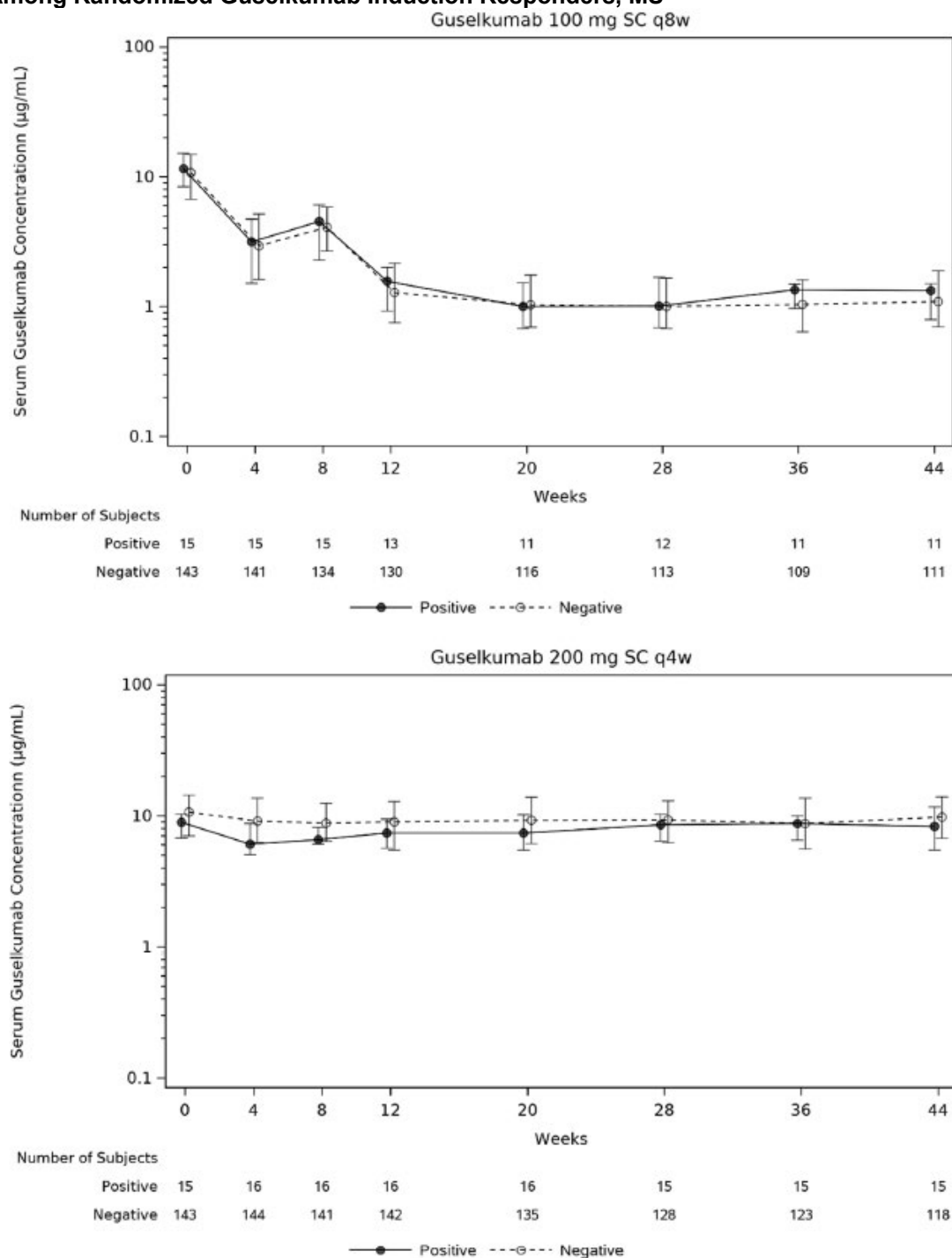
Plots of serum guselkumab concentrations over time during MS by ADA status among randomized subjects who received the proposed TBM dosage regimen (i.e., 200 mg IV Q4W induction and maintenance treatment with 100 mg SC Q8W or 200 mg SC Q4W) are shown in [Figure 9](#). For both maintenance dosage regimens, there was no apparent impact of ADAs on the PK of guselkumab. Among subjects who received 200 mg SC Q4W, median serum guselkumab concentrations were lower in ADA-positive subjects relative to ADA-negative subjects at Weeks M-4 and M-8 but were comparable at other time points. Among subjects randomized to 200 mg SC Q4W, median (IQR) guselkumab trough concentrations at steady state (i.e., Week M-8 through Week M-44) ranged from 6.59 (6.07, 8.16) µg/mL to 8.73 (6.54, 9.98) µg/mL for ADA-positive subjects and from 8.70 (5.59, 13.6) µg/mL to 9.82 (6.70, 13.9) µg/mL for ADA-negative subjects. Among subjects randomized to 100 mg SC Q8W, median (IQR) guselkumab trough concentrations at steady state (i.e., Week M-12 through Week M-44) ranged from 1.00 (0.68, 1.52) µg/mL to 1.57 (0.93, 2.00) µg/mL for ADA-positive subjects and from 1.00 (0.68, 1.66) µg/mL to 1.28 (0.75, 2.15) µg/mL for ADA-negative subjects (data derived from Appendix 21, Summary of Clinical Pharmacology).

No difference in serum guselkumab concentrations was observed between ADA-positive subjects and NAb-positive subjects. Among all subjects with evaluable¹³ NABs as defined by the Applicant (n=9), the median (IQR) serum guselkumab trough concentrations from Week M-8 through Week M-44 ranged from 5.21 (2.70, 8.22) µg/mL to 8.42 (6.14, 11.9) µg/mL (reviewer's analysis using pc.xpt dataset). This range is similar to the range observed among all ADA-positive subjects.

¹³ For the PopPK analysis, the Applicant defined as enrolled subjects as "evaluable" if they had a modified Mayo score between 5 to 9 at induction baseline and received at least 1 dose of guselkumab and had at least 1 valid PK measurement. See study report entitled "Population Pharmacokinetics & Exposure-Response Assessment of Guselkumab in Adults with Moderately to Severely Active Ulcerative Colitis" for full details.

Serum guselkumab concentrations were reduced in subjects with titers of 1:720 or greater (n=7). As previously noted, most ADA-positive subjects with high titers were nonrandomized induction responders. Among all nonrandomized induction responders (n=123), median (IQR) guselkumab serum concentrations from Week M-8 through Week M-44 ranged from 7.50 (4.80, 9.89) µg/mL to 8.64 (5.34, 11.3) µg/mL (data derived from Table TPKCONC601A, CSR for Maintenance Study). Among ADA-positive subjects with titers of 1:720 or greater, the median (IQR) serum guselkumab concentrations from Week M-8 through Week M-44 ranged from 2.75 (1.97, 6.69) µg/mL to 5.83 (2.92, 7.34) µg/mL (reviewer's analysis using pc.xpt dataset). Despite this, a consistent effect of high titer ADAs on serum guselkumab concentrations was not observed when data were examined on an individual level. Serum guselkumab concentrations appeared to decline in two subjects after ADA development. These subjects had peak titers of 1:5760 and 1:11520. Notably, the greatest effect was observed in the subject who developed the highest ADA titers (i.e., 1:11520) and was also NAb-positive. In this subject, a Week I-24 responder, ADAs developed at Week M-0 and this subject remained ADA-positive through Week M-44 with peak titers developing at Week M-20. Serum guselkumab concentrations declined from 8.38 to 8.47 µg/mL at Weeks M-0 and M-4 to falling below the limit of quantitation by Week M-28.

Figure 9. Median (IQR) Serum Guselkumab Concentrations (µg/mL) Over Time by ADA Status in Among Randomized Guselkumab Induction Responders, MS



Source: Figure 16, Summary of Clinical Pharmacology.

Note: Includes only subjects with modified Mayo score of 5-9 at induction baseline. For subjects who were randomized to receive guselkumab 100 mg SC Q8W in Maintenance Study, includes data up to the time of dose adjustment (occurred from Week M-8 through Week M-32) for subjects who had a dose adjustment from 100 mg Q8W to 200 mg Q4W.

Data only includes subjects who responded to induction treatment with 200 mg IV Q4W guselkumab and were randomized to maintenance treatment at a dosage of 200 mg SC Q4W or 100 mg SC Q8W.

Abbreviations: ADA, antidrug antibody; IQR, interquartile range; IV, intravenous; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

In population PK analysis, ADA status was not identified as a significant covariate on the clearance of guselkumab. For additional details, refer to Section [14.5](#).

14.4.2. Impact of Immunogenicity on Efficacy

As few subjects (n=6/409, 1.5%) developed immunogenicity during induction treatment in IS-2, the impact of immunogenicity on induction efficacy could not be determined.

The proportion of subjects achieving efficacy outcomes at Week M-44 by ADA status among subjects who received the proposed TBM induction dosage of 200 mg IV Q4W is shown in [Table 64](#). Among all subjects irrespective of maintenance dosage, a similar proportion of ADA-positive randomized guselkumab induction responders achieved selected efficacy endpoints including clinical remission, symptomatic remission, endoscopic improvement, clinical response, and histologic endoscopic mucosal improvement (HEMI) relative to subjects who did not develop ADAs through Week M-44. A lower proportion of ADA-positive subjects achieved endoscopic remission relative to ADA-negative subjects (7/32, 21.9% versus 105/302, 34.8%, respectively).

Among subjects randomized to guselkumab maintenance with 100 mg SC Q8W, a similar proportion of ADA-positive subjects achieved Week M-44 clinical remission and symptomatic remission as ADA-negative subjects. However, a lower proportion of ADA-positive subjects achieved endpoints of endoscopic improvement (6/15, 40.0% versus 75/151, 49.7%), clinical response (10/15, 66.7% versus 118/151, 78.1%), HEMI (4/15, 26.7% versus 68/151, 45.0%), and endoscopic remission (3/15, 20.0% versus 55/151, 36.4%) ($\geq 10\%$ difference). Among subjects randomized to maintenance treatment with 200 mg SC Q4W, a similar proportion of ADA-positive subjects achieved Week M-44 clinical remission, symptomatic remission, endoscopic improvement, clinical response, and HEMI as ADA-negative subjects. A lower proportion of ADA-positive subjects achieved endoscopic remission (4/17, 23.5% versus 50/151, 33.1%). Among ADA-negative subjects, the proportion of patients achieving efficacy endpoints was similar between subjects randomized to 100 mg SC Q8W or 200 mg SC Q4W. However, among ADA-positive subjects, the proportion of subjects achieving efficacy endpoints was generally lower among subjects randomized to 100 mg SC Q8W relative to subjects randomized to 200 mg SC Q4W, except for clinical remission and endoscopic remission.

Observations of similar proportions of patients achieving Week M-44 efficacy endpoints in the combined group among all ADA-positive and ADA-negative subjects, irrespective of maintenance dosage, received appear to be driven by subjects receiving 200 mg SC Q4W. Although there were generally few ADA-positive randomized induction responders (n=32/334, 9.6%), the data are based on observations in a large phase 3 study. Based on the data, there was no identified clinically significant effect on the efficacy of guselkumab over 56 weeks of treatment in IS-1, IS-2, and MS.

Table 64. Proportion of Subjects Achieving Efficacy Endpoints at Week M-44 by ADA Status Among Randomized Guselkumab Induction Responders

	Anti-guselkumab Antibodies					
	Guselkumab 200 mg IV		Guselkumab 200 mg IV		Guselkumab 200 mg IV	
	100 mg SC q8w (N=166)	200 mg SC q4w (N=168)	Combined (N=334)			
	Negative ^a	Positive ^b	Negative ^b	Positive ^b	Negative ^a	Positive ^b
Number (%) of participants randomized to guselkumab maintenance with appropriate samples ^c	151 (91.0%)	15 (9.0%)	151 (89.9%)	17 (10.1%)	302 (90.4%)	32 (9.6%)
Participants in clinical remission ^{d,e,f,g}	67 (44.4%)	6 (40.0%)	75 (49.7%)	8 (47.1%)	142 (47.0%)	14 (43.8%)
Participants in symptomatic remission ^{h,e,f,g}	104 (68.9%)	10 (66.7%)	102 (67.5%)	13 (76.5%)	206 (68.2%)	23 (71.9%)
Participants with endoscopic healing ^{k,e,f,g}	75 (49.7%)	6 (40.0%)	76 (50.3%)	9 (52.9%)	151 (50.0%)	15 (46.9%)
Participants in clinical response ^{l,e,f,g}	118 (78.1%)	10 (66.7%)	111 (73.5%)	14 (82.4%)	229 (75.8%)	24 (75.0%)
Participants with histologic-endoscopic mucosal healing ^{k,e,f,g}	68 (45.0%)	4 (26.7%)	69 (45.7%)	9 (52.9%)	137 (45.4%)	13 (40.6%)
Participants with endoscopic normalization ^{l,e,f,g}	55 (36.4%)	3 (20.0%)	50 (33.1%)	4 (23.5%)	105 (34.8%)	7 (21.9%)

Source: Table 10, Integrated Summary of Immunogenicity.

Note: Includes only subjects with modified Mayo score 5 to 9 at induction baseline. Data only includes subjects who responded to induction treatment with 200 mg IV Q4W guselkumab and were randomized to maintenance treatment at a dosage of 200 mg SC Q4W or 100 mg SC Q8W.

^a Excludes subjects who were treatment-emergent positive at any time through Week M-44. Denominator was number of subjects negative for antibodies to guselkumab through Week M-44

^b Subjects positive for antibodies to guselkumab includes all subjects who were positive at any time after their first guselkumab administration from Week I-0 through Week M-44. Denominator was number of subjects positive for antibodies to guselkumab through Week M-44.

^c Subjects with appropriate samples had one or more samples obtained after their first guselkumab administration from Week I-0 through Week M-44.

^d Clinical remission was defined as stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and endoscopy subscore of 0 or 1 with no friability present on endoscopy, where the stool frequency subscore had not increased from induction baseline

^e ICE strategies: subjects who had an ostomy or colectomy, a dose adjustment, a prohibited change in UC medications, or discontinued study agent due to lack of efficacy or AE or worsening UC prior to Week M-44 were considered not to have achieved any of the selected efficacy endpoints. For subjects who discontinued due to COVID-19 related reasons or regional crisis in Russia and Ukraine prior to Week M-44, their observed values were used. Subjects who discontinued study agent for other reasons prior to Week M-44 were considered not to have achieved any of the selected efficacy endpoints.

^f Subjects who were missing one or more of the components pertaining to an endpoint at Week M-44 were considered not to have achieved the endpoint. Subjects who had an unevaluable biopsy were considered not to have achieved the histology endpoints

^g Denominator was subjects positive for antibodies to guselkumab through Week M-44

^h Symptomatic remission was defined as a stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0, where the stool frequency subscore had not increased from induction baseline

ⁱ Endoscopic improvement was defined as an endoscopy subscore of 0 or 1 with no friability present on endoscopy

^j Clinical response was defined as a decreased from induction baseline in modified Mayo score by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from induction baseline in rectal bleeding subscore or rectal bleeding subscore of 0 or 1.

^k Histologic endoscopic mucosal healing was defined as achieving a combination of histologic healing and endoscopic improvement. Histologic healing was defined as neutrophil infiltration in $<5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system

^l Endoscopic remission was defined as an endoscopy subscore of 0.

Abbreviations: ADA, antidrug antibody; ICE, intercurrent events; IQR, interquartile range; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; Week I-0, Induction Week 0; Week M-44, Maintenance Week 44; UC, ulcerative colitis

14.4.3. Impact of Immunogenicity on Safety

In IS-2, the proportion of subjects who experienced an adverse event (AE) within one hour of IV infusion by ADA status was assessed. Of the six ADA-positive subjects, no subjects experienced an AE within one hour of IV infusion. Among ADA-negative subjects, 6/403 (1.5%) subjects experienced an AE within 1 hour of infusion (data derived from Table 20, Summary of Clinical Pharmacology). Overall, immunogenicity had no apparent impact on AE incidence within one hour of infusion during induction treatment through Week I-12. Interpretation of the data is limited, as few subjects developed ADAs during induction treatment.

In MS, the proportion of subjects who experienced injection site reactions by ADA status was assessed. Among all subjects randomized to receive SC guselkumab (i.e., including subjects who received induction treatment with 400 mg IV Q4W guselkumab), a greater proportion of ADA-positive subjects experienced injection site reactions (4/38, 10.5%) relative to ADA-negative

subjects (14/340, 4.1%). Among ADA-positive subjects, all four subjects who experienced an injection site reaction had been randomized to 200 mg SC Q4W. Among ADA-negative subjects, most (n=12) were randomized to 200 mg SC Q4W. None of the injection site reactions were classified as severe or serious, and none led to discontinuation of study agent (data derived from Table 11, Integrated Summary of Immunogenicity). In addition, among all treated subjects, there were no cases of treatment-emergent anaphylactic or serum sickness-like reactions through Week M-44 (data derived from LSFAE603, CSR for Maintenance Study).

When considering subjects randomized to the proposed TBM dosage regimens (i.e., 200 mg IV Q4W then maintenance treatment with 100 mg SC Q8W or 200 mg SC Q4W), the conclusions remain unchanged. Among ADA-positive subjects, 4/32 (12.5%), all in the 200 mg SC Q4W group, experienced an injection site reaction. While in ADA-negative subjects, 12/302 (4.0%), 10 of whom received 200 mg SC Q4W, experienced an injection site reaction (data derived from Table 21, Summary of Clinical Pharmacology).

In ADA-positive subjects, there was not an apparent relationship between ADA titers and the occurrence of injection site reactions. In the 4 randomized subjects who experienced an injection site reaction, peak ADA titers were 1:11.25 (n=3) or 1:90 (n=1). Among nonrandomized ADA-positive subjects who experienced an injection site reaction (n=6), peak titers were 1:11.25 (n=4), 1:90 (n=1), or 1:11520 (n=1) (data derived from Table LPKIR601, CSR for Maintenance Study).

Although the proportion of subjects experiencing injection site reactions was greater among ADA-positive subjects, there was a low incidence of experiencing an injection site reaction. As noted above, the data are based on observations in a large phase 3 study. Given the low incidence of experiencing an injection site reaction, immunogenicity was not identified to have a clinically relevant impact on injection site reactions over the treatment duration of 56 weeks in IS-1, IS-2, and MS.

14.5. Pharmacometrics Assessment

14.5.1. Executive Summary

Guselkumab was previously approved for adult patients with moderate-to-severe plaque psoriasis and active psoriatic arthritis. The population pharmacokinetic (PopPK) model submitted in support of the psoriatic arthritis indication was previously reviewed and considered acceptable in 2020. In support of this sBLA, the PopPK model was further modified to facilitate evaluation of guselkumab for the treatment of adult patients with moderately to severely active UC.

To inform induction and maintenance dose selection, the Applicant conducted PopPK and exposure-response (E-R) analyses to evaluate efficacy of the proposed dosages in adults with moderately to severely active UC. The results of the PopPK analyses were found to be acceptable.

Overall, the available PopPK and E-R data supported the 200 mg IV dose for induction therapy in adults with moderately to severely active UC, as the 400 mg IV dose would likely not result in

additional clinical benefit. In addition, positive E-R trends for efficacy were detected for both maintenance dosages evaluated, 200 mg SC Q4W and 100 mg Q8W, across in 4 efficacy endpoints (i.e., clinical response, clinical remission, endoscopic improvement, and HEMI) but appeared to reach a plateau.

14.5.2. PopPK Analysis

Objectives

The PopPK analysis included the following objectives:

- To characterize the PK of guselkumab following IV and SC administration in adults with moderately to severely active UC.
- To identify and quantify the effect of prespecified covariates, including Chinese and Japanese ethnicities, that could significantly influence guselkumab PK in adults with moderately to severely active UC.

Methods

PopPK analyses were performed using nonlinear mixed effects modeling methodology as implemented in the Nonlinear Mixed Effects Modeling (NONMEM) software system, version 7.4. The updated dataset included pooled data from subjects enrolled into IS-1, IS-2, and MS. The first-order conditional estimation (FOCE) method with interaction (FOCE-I) was employed for model runs. Covariates were tested in a stepwise process, which was performed using a forward addition process followed by backward elimination. The performance of the final PopPK model was evaluated for robustness and appropriateness using conventional model convergence criteria, shrinkage, visual predictive check (VPC), and/or prediction-corrected visual predictive check (pcVPC).

Results

The updated final PopPK model was developed using data from a phase 2b induction dose-ranging study (IS-1), a phase 3 induction study (IS-2), and a phase 3 maintenance study (MS) of guselkumab in adults with moderately to severely active UC. The pooled analysis included 10,115 quantifiable concentrations from 859 subjects. The observed PK data was adequately described by a two-compartment linear PopPK model with first-order absorption and first-order elimination with interindividual variability on clearance (CL), volume of distribution of the central compartment (V2), volume of distribution of the peripheral compartment (V3), and absolute bioavailability (F1). No obvious model misspecifications were found in the goodness-of-fit plots ([Figure 10](#)). Concomitant use of immunomodulators (i.e., 6-mercaptopurine, azathioprine, methotrexate) was considered as a potential covariate effect in the initial model, while it was not found to have a statistically significant effect on the CL of guselkumab. In the final model, body weight, baseline serum albumin, baseline C-reactive protein, age, sex, and biologic failure status were found to be statistically significant covariates for the PK of guselkumab. Typical PK parameter estimates from the final population PK model are listed in [Table 65](#) for a participant weighing 70 kg. In the final PopPK model, subjects with

baseline body weight higher than 70 kg, had higher CL and lower predicted exposure ($C_{\text{trough},W44}$) given at either a 200 mg Q4W SC or a 100 mg Q8W SC maintenance dose, which the review team concluded was likely not clinically meaningful. Forest plots showed that none of the statistically significant covariates from the final PopPK model had a clinically relevant effect on trough or average guselkumab concentrations during both induction and maintenance periods.

Conclusions

The review team concluded that the updated PopPK model fitting is generally acceptable. Subjects with baseline body weight higher than 70 kg, had a higher CL. However, the magnitude of effect of the PK covariates on exposure (C_{ave} or C_{trough}) was not clinically meaningful.

Table 65. Parameter Estimates in the PopPK Model for Guselkumab in Participants With Moderately to Severely Active UC

Parameters	Estimate ^a	95% CI	Magnitude of Change ^e
CL (L/day) ^b	0.312 (1.82)	(0.301, 0.323)	--
BWT on CL	0.538 (8.42)	(0.449, 0.627)	-18.3% to +22.5%
ALB on CL	-1.17(13.3)	(-1.48, -0.864)	+23.1% to -14.2%
CRP on CL	0.0365 (21.3)	(0.0213, 0.0517)	-8.2% to +8.2%
AGE on CL	-0.0741 (40.4)	(-0.133, -0.0155)	4.69% to -3.83%
FBIO on CL	0.108 (19.1)	(0.0676, 0.148)	+10.8%
SEX on CL	-0.111 (15.9)	(-0.146, -0.0763)	-11.1%
Q (L/day)	0.298 (8.96)	(0.246, 0.350)	-
V2 (L) ^c	3.38 (0.757)	(3.33, 3.43)	-
BWT on V2	0.512 (5.72)	(0.455, 0.569)	-17.5% to +21.3%
V3 (L) ^d	2.58 (4.19)	(2.37, 2.79)	-
BWT on V3	0.512 (5.72)	(0.455, 0.569)	-17.5% to +21.3%
k _a (1/day)	0.123 (8.02)	(0.104, 0.142)	-
F1	0.588 (3.33)	(0.550, 0.626)	-
IIV of CL (CV%)	25.9% (3.05) [3.34] ^b	(25.9%, 26.7%)	-
IIV of V2 (CV%)	18.1% (4.42) [17.5] ^b	(17.8%, 18.7%)	-
IIV of V3 (CV%)	25.6% (7.24) [32.1] ^b	(24.6%, 27.4%)	-
IIV of F1 (CV%)	31.2% (4.41) [24.6] ^b	(30.6%, 31.7%)	-
Proportional residual error	0.193 (2.43)	(0.184, 0.202%)	-
Additive residual error (µg/mL)	0.0182 (39.3)	(0.00417, 0.0322)	-

AGE=baseline age (years); ALB=baseline serum albumin (g/L); BWT=baseline body weight (kg); CI=confidence interval; CL=clearance; CRP=C-reactive protein (mg/L); CV=coefficient of variation; F1=absolute bioavailability; FBIO=biologic failure status (0=no failure, 1=failure); IIV=interindividual variability, calculated as (variance)^{1/2}*100% except for IIV on F1 (logit scale parameter), which is calculated as (variance)^{1/2}*(1-THETA.F1)*100%; k_a=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling; PK=pharmacokinetics; PopPK=population PK; Q=intercompartmental flow; RSE=relative standard error; SEX=sex (0=male, 1=female); UC=ulcerative colitis; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

^a Mean (RSE%) [Shrinkage %] estimates by NONMEM from the final PK analysis dataset.

^b $CL\left(\frac{L}{day}\right) = 0.312 \times \left(\frac{BWT}{70}\right)^{0.538} \times \left(\frac{ALB}{43}\right)^{-1.17} \times \left(\frac{CRP}{4.28}\right)^{0.0365} \times \left(\frac{AGE}{39}\right)^{-0.0741} \times 1.108^{FBIO} \times 0.889^{SEX}$

^c $V2(L) = 3.38 \times \left(\frac{BWT}{70}\right)^{0.512}$

^d $V3(L) = 2.58 \times \left(\frac{BWT}{70}\right)^{0.512}$

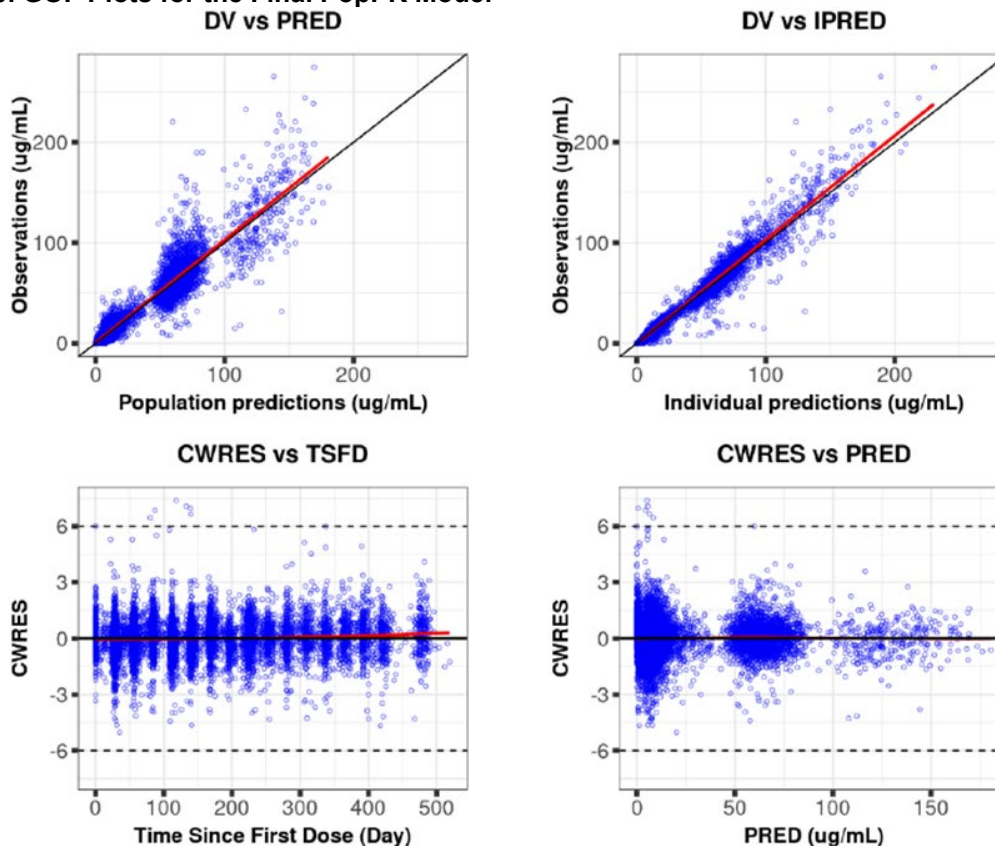
^e The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from the 5th percentile to the 95th percentile of the population.

Source: Applicant's Population Pharmacokinetics & Exposure-Response Modeling Report, Table 7, page 45, Module 5.3.3.5, BLA 761061/S-021.

Abbreviations: PopPK, population pharmacokinetics; UC, ulcerative colitis

Figure 10 shows the population and individual predictions were symmetrically distributed along the line of identity and the conditional weighted residuals (CWRES) were generally centered around zero with homogenous variation relative to the population predictions (PRED) and time.

Figure 10. GOF Plots for the Final PopPK Model
DV vs PRED



Source: Applicant's Population Pharmacokinetics & Exposure-Response Modeling Report, Figure 1, page 46, Module 5.3.3.5, BLA 761061/S-021.

Note: The black solid line is the line of identity or the zero line, and the red full line is the trend line. The blue circles are the observations.

Abbreviations: CWRES, conditional weighted residuals; DV, dependent value or observation; GOF, goodness-of-fit; IPRED, individual predictions; PK, pharmacokinetics; PopPK, population PK; PRED, population predictions; TSFD, time since first dose

14.5.3. Exposure-Response Analyses

Objectives

The primary objectives of the E-R analyses were:

- To provide model-based evidence for 200 mg IV Q4W to support the proposed phase 3 induction dose
- To support the SC maintenance dose selection in adults with UC
- To evaluate the impact of selected covariates, including Chinese and Japanese ethnicities, and the potential need of covariate-based dose adjustment

Methods

Landmark E-R analyses were conducted at two timepoints during the clinical studies (e.g., at Week I-12 for induction and Week M-44 for maintenance) to explore the relationship between four efficacy endpoints including clinical response, clinical remission, endoscopic improvement,

and HEMI and guselkumab exposure in adults with moderately to severely active UC. The final PopPK model was used to simulated individual exposure metrics (C_{trough} and C_{ave}) during induction and maintenance periods for E-R analyses. R and NONMEM were used to generate the histograms, box plots, logistic model and nonlinear function using sigmoid maximum drug effect (E_{max}), which described the relationship between guselkumab exposure and the probability of achieving the selected clinical endpoints. The covariates were tested based on clinical consideration.

Results

The E-R modeling analyses were performed for the efficacy endpoints (i.e., clinical response, clinical remission, endoscopic improvement, and HEMI) at Week I-12 for induction and Week M-44 for maintenance using the individual exposure metrics generated by the final PopPK model. A total of 1,013 subjects were included in the induction E-R analyses. After accounting for individual guselkumab CL or $T_{1/2}$, it was confirmed that no apparent E-R relationships remained for any of the tested efficacy endpoints, regardless of the induction dose group (200 mg or 400 mg IV Q4W). Overall, the induction E-R results supported the use of 200 mg IV for induction, as the data indicate the 400 mg IV would not result in additional clinical efficacy benefit.

Regarding the maintenance E-R analyses, a total of 568 subjects were included. The observed E-R plots indicated positive E-R trends between systemic guselkumab exposures and all the previously specified key efficacy endpoints at Week M-44 following either a 200 mg SC Q4W or a 100 mg SC Q8W maintenance dosage ([Figure 11](#)). The logistic regression modeling results demonstrated consistent E-R relationships across all four selected key efficacy endpoints ([Figure 12](#)). The covariate analysis showed the extent of UC disease (i.e., limited on the left side of colon or extensive based on screening endoscopy or medical history) was an influential factor for E_{max} across all four efficacy endpoints at Week M-44, which indicated that in subjects with extensive disease, higher response rates may be achieved at higher dose levels. No substantial differences in efficacy response rates were identified in subpopulations stratified by additional covariates (e.g., ethnicity, clinical remission at maintenance baseline, failure to prior therapy, corticosteroid use at baseline, endoscopic improvement status at maintenance baseline) for all four efficacy endpoints.

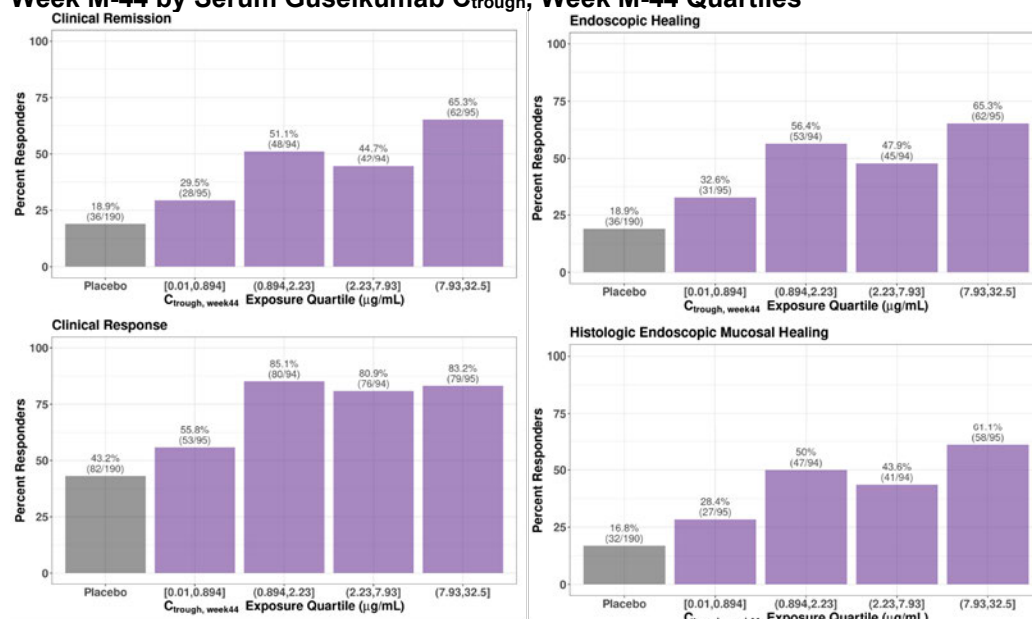
Conclusion

Results of the E-R analyses support the 200 mg IV induction dose, as available data indicate the 400 mg IV dose would likely not result in additional clinical benefit. Positive E-R trends in four efficacy endpoints (i.e., clinical response, clinical remission, endoscopic improvement, and HEMI) were achieved with both maintenance dosages evaluated, 200 mg SC Q4W and 100 mg Q8W. Race did not appear to be a significant covariate across the endpoints assessed in the E-R analyses.

[Figure 11](#) is the positive E-R relationship observed in all 4 efficacy endpoints following the maintenance therapy (either 200 mg Q4W SC or 100 mg Q8W SC). All quartiles demonstrate efficacy over placebo with plateau of effect at higher exposure quartiles (the 3rd to the 4th one), as noted that 50% of the clinical response from 100 mg Q8W SC dose fell into the 2nd exposure

quartile, while 75% of the clinical response from 200 mg Q4W SC dose turned to be the 3rd to the 4th exposure quartile. Overall, the comparable rates of efficacy could be achieved with either dose.

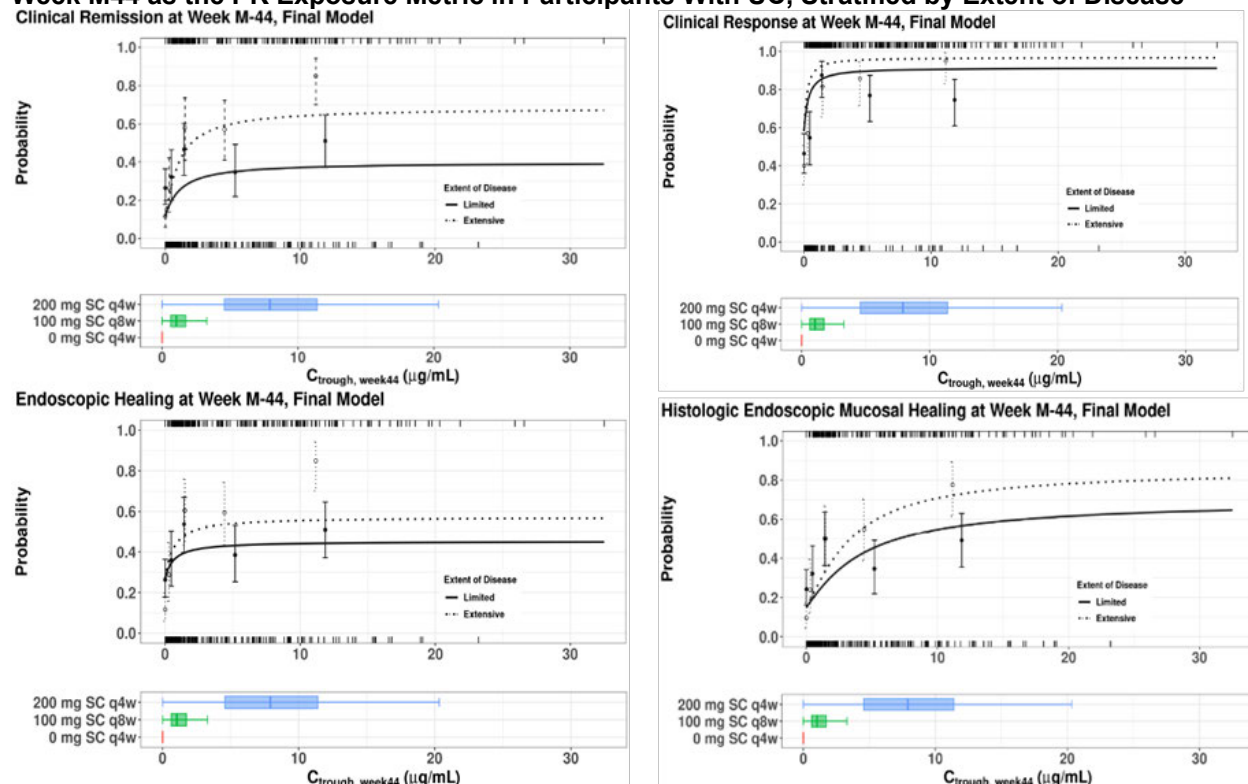
Figure 11. Proportion of Responders in Participants With UC for Each Efficacy Endpoint at Week M-44 by Serum Guselkumab C_{trough}, Week M-44 Quartiles



Source: Applicant's Population Pharmacokinetics & Exposure-Response Modeling Report, Figure 9, page 64-65.
Abbreviations: C_{trough, week44}, trough concentration at Week M-44; UC, ulcerative colitis; Week M-44, Maintenance Week 44

[Figure 12](#) are results from the logistic regression models, which demonstrate the consistent E-R relationships observed across four selected key efficacy endpoints. Meanwhile, a plateau of effect at higher exposure quartiles starting from the second quartile was also detected from the modeling results. The covariate analysis showed participants with the extent of UC disease may have more room for potential increase in the probability of responses when increasing exposure to guselkumab.

Figure 12. Model-Predicted E-R Relationships for Selected Efficacy Endpoints Using C_{trough} , Week M44 as the PK Exposure Metric in Participants With UC, Stratified by Extent of Disease
Clinical Remission at Week M-44, Final Model



Source: Applicant's Population Pharmacokinetics & Exposure-Response Modeling Report, Figure 11, page 69; Figure 14, page 75; Figure 18, page 82; Figure 22, page 90.

The curves represent model-predicted probabilities of achieving clinical response at Week M-44 (dashed curve for subjects with extensive UC disease and solid curve for subjects with limited UC disease). The symbols with error bars represent the observed rate (median with 95% CI) of clinical response in each exposure quartile bin stratified by extent of disease (open circles for subjects with extensive UC disease and closed circles for subjects with limited UC disease).

The box plots at the bottom of the charts represent the distribution of model-predicted $C_{\text{trough, week44}}$ for each of the 2 maintenance dose regimens of 100 mg SC Q8W and 200 mg SC Q4W: the center line of the box is the median $C_{\text{trough, week44}}$; the left and right ends of the box are the 25th and 75th percentiles of $C_{\text{trough, week44}}$, respectively, and the box represents the IQR of $C_{\text{trough, week44}}$; the left and right whiskers of the box cover the bounds of $1.5 \times \text{IQR}$ of $C_{\text{trough, week44}}$.

The smooth curves represent the model-predicted E-R relationships for subgroups stratified by the extent of disease while other covariates were fixed to be the same as the reference group in the final model. In contrast, the symbols with error bars represent the observed efficacy rates for each of the $C_{\text{trough, week44}}$ quartiles stratified by 1 associated covariate, which could be confounded by the effects from other covariates as they were not fixed as in the reference group.

Abbreviations: CI, confidence interval; C_{trough} , Week 44, trough concentration at Week M-44; E-R, exposure response; IQR, interquartile range; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

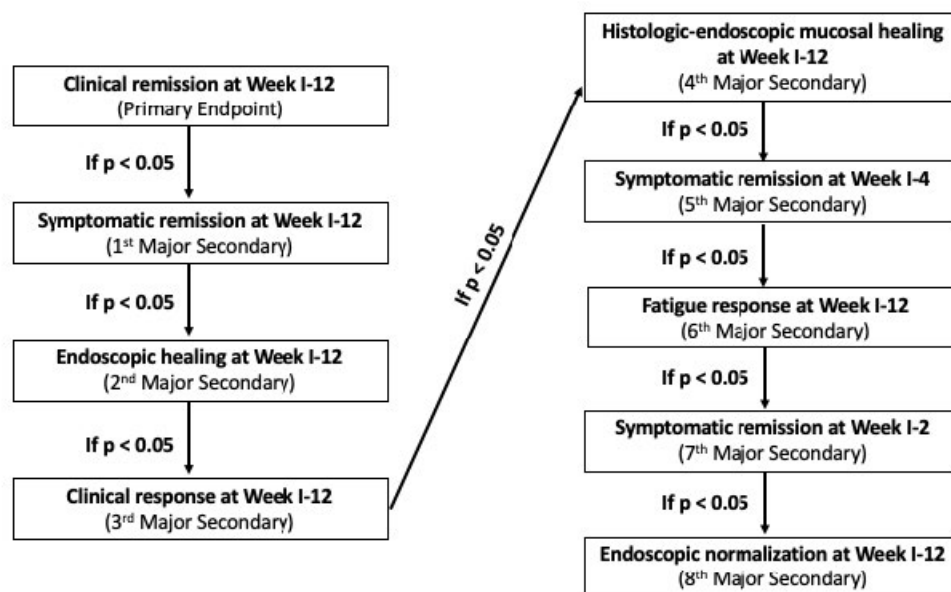
15.1. Multiple Testing Procedure

15.1.1. Multiple Testing Procedure, IS-2

The multiple testing procedure for IS-2 is displayed in [Figure 13](#).

Figure 13. Multiple Testing Procedure, IS-2

Figure 4: US Specific Testing Procedure for the Primary and Major Secondary Endpoints

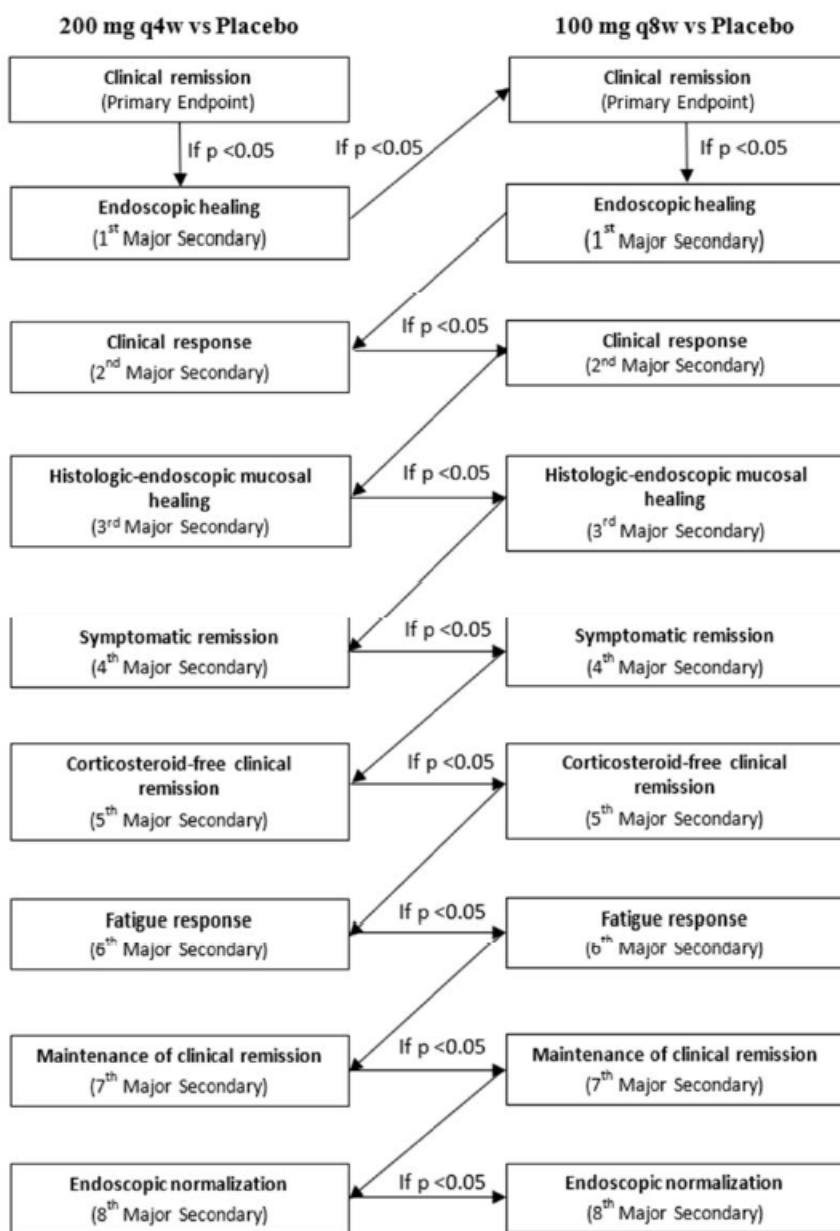


Source: Statistical Analysis Plan (Page 29).
Abbreviations: IS-2, Induction Study 2

15.1.2. Multiple Testing Procedure, MS

The multiple testing procedure for MS is displayed in [Figure 14](#).

Figure 14. Multiple Testing Procedure, MS



Source: Statistical Analysis Plan (Page 38).

Abbreviations: MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks

16. Efficacy

16.1. Efficacy Results Included in the Prescribing Information

The following efficacy results are recommended for inclusion in tabular format in Section 14.3, Ulcerative Colitis of the prescribing information. See Section 6.2.4 and Section 23 for further discussion on suitability of efficacy assessments for inclusion in labeling.

16.1.1. Induction Trial, IS2

Table 66. Proportion of Subjects With Ulcerative Colitis Meeting Efficacy Endpoints at Week 12 in IS-2

Endpoint	Placebo	Guselkumab 200 mg Intravenous Infusion ^a	Treatment Difference (95% CI)
Clinical remission ^b			
Total Population	N=280 (8%)	N=421 (23%)	15% (10%, 20%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 (4%)	N=208 (13%)	
Without prior biologic or JAK inhibitor failure ^e	N=144 (12%)	N=213 (32%)	
Endoscopic improvement ^f			
Total Population	N=280 (11%)	N=421 (27%)	16% (10%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 (5%)	N=208 (15%)	
Without prior biologic or JAK inhibitor failure ^e	N=144 (17%)	N=213 (38%)	
Clinical response ^g			
Total Population	N=280 (28%)	N=421 (62%)	34% (27%, 41%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 (20%)	N=208 (51%)	
Without prior biologic or JAK inhibitor failure ^e	N=144 (35%)	N=213 (71%)	
HEMI ^h			
Total Population	N=280 (8%)	N=421 (24%)	16% (11%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 (4%)	N=208 (13%)	
Without prior biologic or JAK inhibitor failure ^e	N=144 (10%)	N=213 (33%)	

Source: Adapted from the draft USPI submitted to BLA 761061 on August 30, 2024 (SDN 1294).

^a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8

^b A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability

^c p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method (adjusted for stratification factors: biologic and/or JAK-inhibitor failure status and concomitant use of corticosteroids at baseline)

^d Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis

^e Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, only 7 subjects in the placebo group and 11 subjects in the TREMFYA group were previously exposed to, but did not fail, a biologic or JAK inhibitor

^f An endoscopy subscore of 0 or 1 with no friability

^g Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

^h An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Abbreviations: CI, confidence interval; HEMI, histologic endoscopic mucosal improvement; IS-1, Induction Study 1; IS-2, Induction Study 2; JAK, Janus kinase; N, total number of subjects

16.1.2. Maintenance Trial, MS

Table 67. Proportion of Subjects With Ulcerative Colitis Meeting Efficacy Endpoints at Week 44 in MS

Endpoint	Placebo	Guselkumab 100 mg Q8W SC ^a	Guselkumab 200 mg Q4W SC ^b	Treatment Difference vs. Placebo (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission ^c					
Total population ^d	N=190 19%	N=188 45%	N=190 50%	25% (16%, 34%) ^e	30% (21%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 59%		
Corticosteroid-free clinical remission ^h					
Total population ^d	N=190 18%	N=188 45%	N=190 49%	26% (17%, 34%) ^e	29% (20%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 7%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 57%		
Endoscopic improvement ⁱ					
Total population ^d	N=190 19%	N=188 49%	N=190 52%	30% (21%, 38%) ^e	31% (22%, 40%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 45%	N=88 42%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 52%	N=102 60%		
HEMI ^j					
Total population ^d	N=190 17%	N=188 44%	N=190 48%	26% (17%, 34%) ^e	30% (21%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 38%	N=88 39%		
Without prior biologic or JAK inhibitor failure ^g	N=115 23%	N=111 48%	N=102 56%		

BLA 761061/S-021
TREMIFYA (guselkumab)

Endpoint	Placebo	Guselkumab 100 mg Q8W SC ^a	Guselkumab 200 mg Q4W SC ^b	Treatment Difference vs. Placebo (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Maintenance of Clinical Remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction					
Total population ^k	N=59 34%	N=66 61%	N=69 72%	26% (9%, 43%) ^l	38% (23%, 54%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=15 27%	N=20 60%	N=18 56%		
Without prior biologic or JAK inhibitor failure ^m	N=44 36%	N=46 61%	N=51 78%		

Source: Adapted from the draft USPI submitted to BLA 761061 on August 30, 2024 (SDN 1294).

^a TREMFYA 100 mg as a subcutaneous injection every 8 weeks after the induction regimen

^b TREMFYA 200 mg as a subcutaneous injection every 4 weeks after the induction regimen

^c A stool frequency subscore of 0 or 1 and not increased from induction baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability

^d Subjects who achieved clinical response 12 weeks following the intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3

^e p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization

stratification factors

^f Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis

^g Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, only 7 subjects in the placebo group, 6 subjects in the TREMFYA 100 mg group, and 6 subjects in the TREMFYA 200mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor

^h Not requiring any treatment with corticosteroids for at least 8 weeks prior to week 44 and also meeting the criteria for clinical remission at week 44

ⁱ An endoscopy subscore of 0 or 1 with no friability

^j An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤3.1 (indicating neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

^k Subjects who achieved clinical remission 12 weeks following intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3

^l p <0.01, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors

^m Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, only 3 subjects in the placebo group, 3 subjects in the TREMFYA 100 mg group, and 3 subjects in the TREMFYA 200 mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor.

Abbreviations: CI, confidence interval; HEMI, histologic endoscopic mucosal improvement; JAK, Janus kinase; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

16.2. Assessment Tools

16.2.1. Mayo Scoring Assessment

The Mayo score was defined according to [Figure 15](#).

Figure 15. Mayo Scoring System

Mayo scoring system for assessment of ulcerative colitis activity

Stool frequency^a

- 0 = Normal number of stools for this patient
- 1 = 1-2 stools more than normal
- 2 = 3-4 stools more than normal
- 3 = 5 or more stools more than normal

Rectal bleeding^b

- 0 = No blood seen
- 1 = Streaks of blood with stool less than half the time
- 2 = Obvious blood with stool most of the time
- 3 = Blood alone passed

Findings of endoscopy

- 0 = Normal or inactive disease
- 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
- 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
- 3 = Severe disease (spontaneous bleeding, ulceration)

Physician's global assessment^c

- 0 = Normal
- 1 = Mild disease
- 2 = Moderate disease
- 3 = Severe disease

^a At the screening visit, each person indicates the number of stools he/she passed in a 24-hour period when in remission or before his/her UC diagnosis, thereby serving as his/her own control to establish the degree of abnormality of stool frequency.

^b The daily bleeding score represents the most severe bleeding of the day.

^c The physician's global assessment acknowledges the 3 other criteria, the patient's recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Source: Protocol Appendix 10 (page 174).

Abbreviations: UC, ulcerative colitis

16.2.2. Geboes Grading System

The Geboes Grading System is defined according to [Figure 16](#).

Figure 16. Geboes Grading System

Grade 0	Structural (architectural change)
Subgrades	
0.0	No abnormality
0.1	Mild abnormality
0.2	Mild or moderate diffuse or multifocal abnormalities
0.3	Severe diffuse or multifocal abnormalities
Grade 1	Chronic inflammatory infiltrate
Subgrades	
1.0	No increase
1.1	Mild but unequivocal increase
1.2	Moderate increase
1.3	Marked increase
Grade 2	Lamina propria neutrophils and eosinophils
2A Eosinophils	
2A.0	No increase
2A.1	Mild but unequivocal increase
2A.2	Moderate increase
2A.3	Marked increase
2B Neutrophils	
2B.0	None
2B.1	Mild but unequivocal increase
2B.2	Moderate increase
2B.3	Marked increase
Grade 3	Neutrophils in epithelium
3.0	None
3.1	< 5% crypts involved
3.2	< 50% crypts involved
3.3	> 50% crypts involved
Grade 4	Crypt destruction
4.0	None
4.1	Probable—local excess of neutrophils in part of crypt
4.2	Probable—marked attenuation
4.3	Unequivocal crypt destruction
Grade 5	Erosion or ulceration
5.0	No erosion, ulceration, or granulation tissue
5.1	Recovering epithelium+adjacent inflammation
5.2	Probable erosion—focally stripped
5.3	Unequivocal erosion
5.4	Ulcer or granulation tissue

Source: Statistical Analysis Plan Attachment 3 (page 66).

16.2.3. Patient Global Impression of Severity (PGIS)

Figure 17. Patient Global Impression of Severity

Patient's Global Impression of Severity of Ulcerative Colitis

Overall, how would you rate the severity of your Ulcerative Colitis currently? (Please select one response)

☐	1. None
☐	2. Mild
☐	3. Moderate
☐	4. Severe
☐	5. Very Severe

Source: PRO Evidence Fatigue Study Report 12 (page 33).

16.2.4. Patient Global Impression of Change

Figure 18. Patient Global Impression of Change

Patient's Global Impression of Change (PGIC) of Ulcerative Colitis Severity

Compared to when you received the first treatment in this study, how has your Ulcerative Colitis changed? (Please select one response)

- ☐ 1. A lot better now
- ☐ 2. Moderately better now
- ☐ 3. A little better now
- ☐ 4. Neither better, nor worse (no change)
- ☐ 5. A little worse now
- ☐ 6. Moderately worse now
- ☐ 7. A lot worse now

Source: PRO Evidence Fatigue Study Report 12 (page 31).

Abbreviations: PGIC, Patient's Global Impression of Change

16.2.5. PROMIS-29 (Fatigue)

Figure 19. Fatigue Domain Items of PROMIS-29
PROMIS-29 Profile v2.0

Fatigue			Not at all	A little bit	Somewhat	Quite a bit	Very much
In the past 7 days...							
FATEX241 15	How run-down did you feel on average? ...	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
FATEX242 16	How fatigued were you on average?	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
Sleep Disturbance							
In the past 7 days...			Very poor	Poor	Fair	Good	Very good
Sleep109 17	My sleep quality was	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
In the past 7 days...			Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116 18	My sleep was refreshing	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
Sleep20 19	I had a problem with my sleep	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
Sleep44 20	I had difficulty falling asleep	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
Ability to Participate in Social Roles and Activities							
			Never	Rarely	Sometimes	Usually	Always
SRPPR111 _CAPS 21	I have trouble doing all of my regular leisure activities with others	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
SRPPR118 _CAPS 22	I have trouble doing all of the family activities that I want to do	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
SRPPR123 _CAPS 23	I have trouble doing all of my usual work (include work at home)	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
SRPPR145 _CAPS 24	I have trouble doing all of the activities with friends that I want to do	☐	☐	☐	☐	☐	☐
		5	4	3	2	1	
Pain Interference							
In the past 7 days...			Not at all	A little bit	Somewhat	Quite a bit	Very much
PAINING 25	How much did pain interfere with your day to day activities?	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
PAINING22 26	How much did pain interfere with work around the home?	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
PAINING31 27	How much did pain interfere with your ability to participate in social activities? ..	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	
PAINING34 28	How much did pain interfere with your household chores?	☐	☐	☐	☐	☐	☐
		1	2	3	4	5	

16.2.6. PROMIS-Fatigue 7-Item Short Form

The Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Short Form (SF)-7a ([Figure 20](#)) contains seven items evaluating fatigue-related symptoms (i.e., tiredness, exhaustion, mental tiredness, and lack of energy) and associated impacts on daily activities (i.e., activity limitations related to work, self-care, and exercise). PROMIS-Fatigue SF-7a has a recall period of the past seven days.

Figure 20. PROMIS-Fatigue Short Form 7a
Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Source: PRO Evidence Fatigue Study Report 9 (page 19).

Abbreviations: PROMIS, Patient-Reported Outcomes Measurement Information System

16.2.6.1. Quantitative Validity and Reliability Evidence for PROMIS-Fatigue SF-7a

During the IND phase, the Agency communicated concerns regarding the content relevance of items six and seven of the PROMIS-Fatigue SF-7a and suggested the Applicant explore different scoring algorithms (e.g., excluding items six and seven) using data from IS-1 to help inform the scoring algorithm for fatigue-based endpoint(s) in phase 3 trials. The Applicant created the PROMIS-Fatigue SF-5a, a five-item custom short form excluding items six and seven from the original PROMIS-Fatigue SF-7 measure. The full PROMIS-Fatigue SF-7a was administered in IS-1, IS-2, and MS, and the Applicant calculated scores for both the PROMIS-Fatigue SF-7a and PROMIS-Fatigue SF-5a. The Applicant provide quantitative validity and reliability for both scores using data from IS-1.

The Applicant used standardized T-scores based on a raw score conversion table for the PROMIS-Fatigue SF-7a and a response-pattern scoring approach for the PROMIS-Fatigue SF-5a. The psychometric results from the PROMIS-Fatigue SF-7a and PROMIS-Fatigue SF-5a are not directly comparable, and the psychometric evidence for the PROMIS-Fatigue SF-7a should be interpreted within the context of the limitations of the scoring approach.

The review team evaluated the Applicant's quantitative validity and reliability evidence, generated using data from IS-1, for both PROMIS-Fatigue SF-7a and PROMIS-Fatigue SF-5a scores. Based on the quantitative validity and reliability evidence, along with the content validity evaluation, the review team concluded that the PROMIS-Fatigue SF-7a is fit-for-purpose for use in participants with moderately to severely active UC. The results of these psychometric analyses are not included in this review. See DCOA review memo by Susan Pretko uploaded on September 3, 2024 (DARRTS Reference ID: 5440631).

16.3. Additional Analyses To Support Efficacy

16.3.1. Additional Analyses, IS-2

Intercurrent Events, IS-2

The following intercurrent events (ICEs) were defined for IS-2:

- (1) An ostomy or colectomy (partial or total).
- (2) Prohibited change in UC medication.
- (3) Discontinuation of study intervention due to lack of efficacy or an AE of worsening of UC.
- (4) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine.
- (5) Discontinuation of study intervention due to reasons other than those in ICEs 3 and 4.

The number of subjects experiencing each ICE is listed in [Table 68](#). Subjects in the placebo IV group were more likely to experience ICE 2, as compared to subjects in the guselkumab 200 mg IV group. The rates of other ICE were similar across treatment groups.

Table 68. Intercurrent Events (FAS), IS-2

Intcurrent Event	Placebo IV Q4W N=280 n (%)	Guselkumab 200 mg IV Q4W N=421 n (%)	Total N=701 n (%)
Any Intcurrent Event	34 (12.1)	21 (5.0)	55 (7.8)
ICE 1	2 (0.7)	2 (0.5)	4 (0.6)
ICE 2	20 (7.1)	9 (2.1)	29 (4.1)
ICE 3	7 (2.5)	3 (0.7)	10 (1.4)
ICE 4	1 (0.4)	1 (0.2)	2 (0.3)
ICE 5	14 (5.0)	13 (3.1)	27 (3.9)

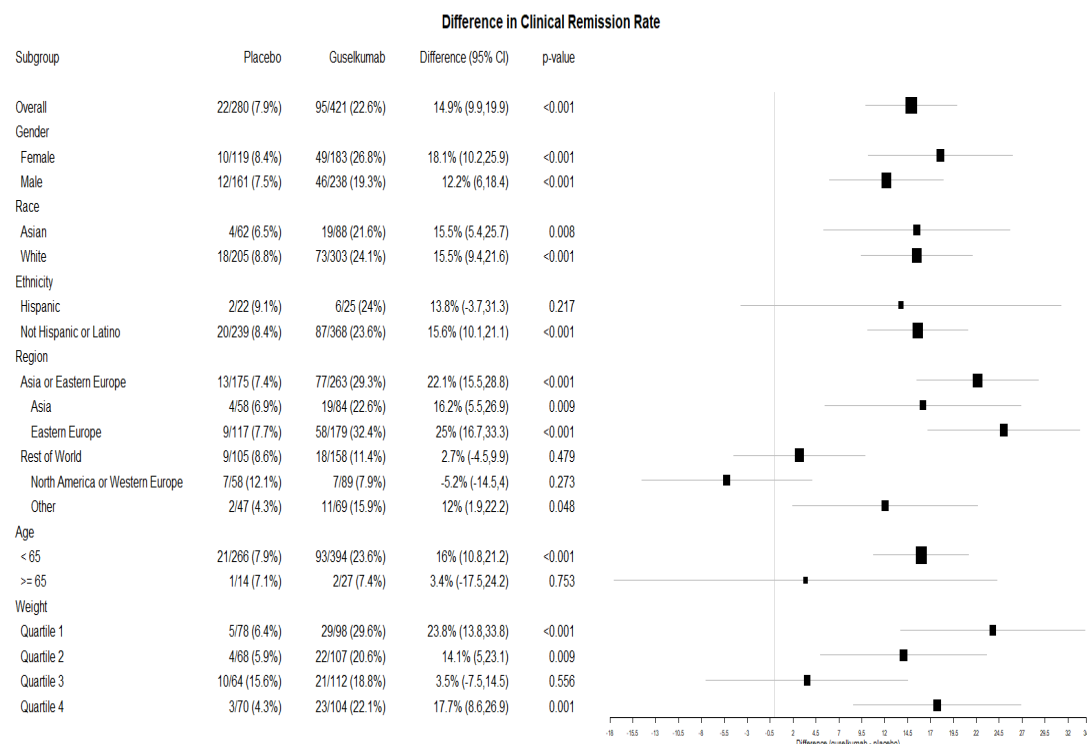
Source: Generated by reviewer using ADICE.xpt.

Abbreviations: ICE, intercurrent events; IS-2, Induction Study 2; IV, intravenous; FAS, full analysis set; Q4W, every 4 weeks; Q8W, every 8 weeks

Subgroup Analyses, IS-2

The primary analysis was repeated in subgroups defined by demographic characteristics (Figure 21). In evaluated subgroups, the proportion of subjects in clinical remission at Week I-12 tended to favor guselkumab relative to placebo.

Figure 21. Clinical Remission^a at Week I-12 by Demographic Subgroup (FAS), IS-2



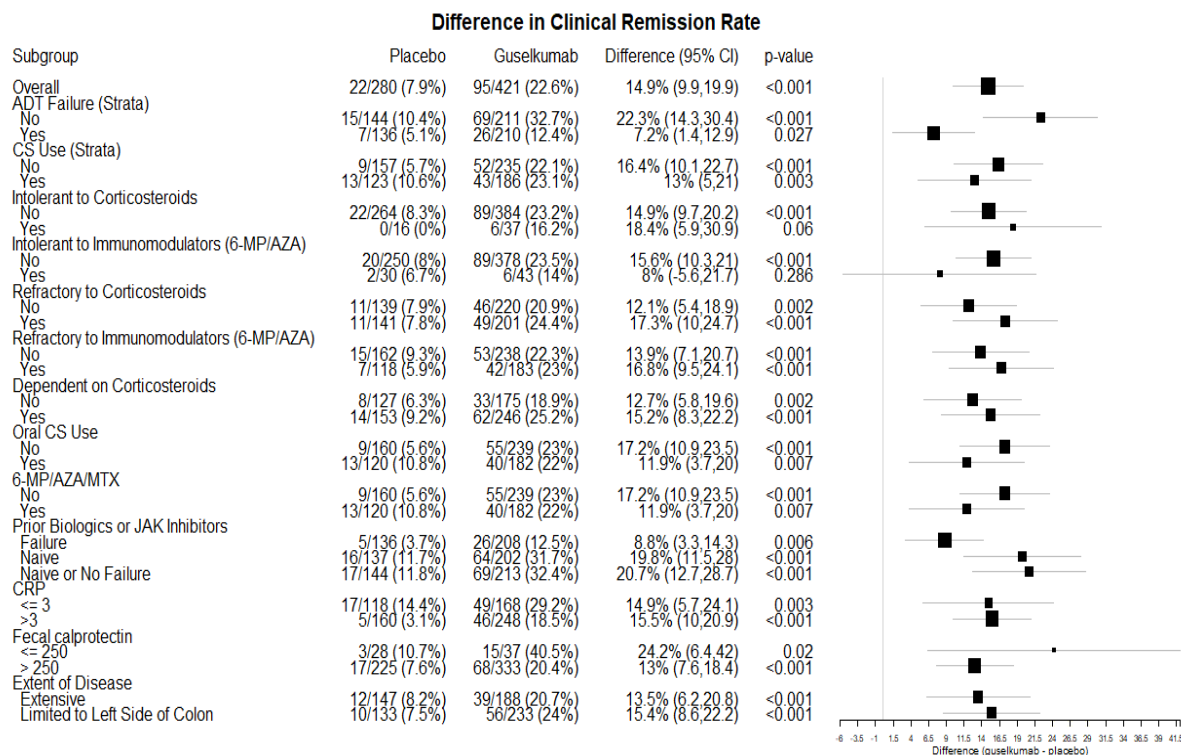
Source: Based on Clinical Study Report Table GEFCREM502 (page 211-213). Verified by reviewer using ADEFF.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-2, Induction Study 2; MH, Mantel-Haenszel

The primary analysis was repeated in subgroups defined by baseline UC characteristics ([Figure 22](#)). In all evaluated subgroups, the proportion of subjects in clinical remission at Week I-12 favored guselkumab relative to placebo.

Figure 22. Clinical Remission^a at Week I-12 by UC Baseline Characteristic Subgroup (FAS), IS-2



Source: Based on Clinical Study Report Table GEFCREM504 (page 214-216), Table GEFCREM505 (page 217-223). Verified by reviewer using ADADT.xpt, ADBDC.xpt, ADEFF.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CS, corticosteroids; FAS, full analysis set; MH, Mantel-Haenszel; UC, ulcerative colitis

The secondary endpoints were evaluated separately in subjects with prior therapeutic biologic product and/or JAK inhibitor failure and subjects without prior therapeutic biologic product or JAK inhibitor failure. [Table 69](#) shows the number of responders for each secondary endpoint in each of these two subgroups.

Table 69. Secondary Endpoints by Prior Therapeutic Biologic Products or JAK Inhibitors Status (FAS), IS-2

Secondary Endpoint	Placebo IV Q4W n/N (%)	Guselkumab 200 mg IV Q4W n/N (%)
Prior failure to therapeutic biologic products and/or JAK inhibitors		
Symptomatic remission at W12	19/136 (14%)	80/208 (38.5%)
Endoscopic improvement at W12	7/136 (5.1%)	31/208 (14.9%)
Clinical response at W12	27/136 (19.9%)	107/208 (51.4%)
Histologic endoscopic mucosal improvement at W12	6/136 (4.4%)	28/208 (13.5%)
Symptomatic remission at W4	11/136 (8.1%)	31/208 (14.9%)
Fatigue response at W12	18/136 (13.2%)	80/208 (38.5%)
Symptomatic remission at W2	7/136 (5.1%)	16/208 (7.7%)
Endoscopic remission at W12	3/136 (2.2%)	18/208 (8.7%)
No prior failure to therapeutic biologic products and/or JAK inhibitors		
Symptomatic remission at W12	39/144 (27.1%)	130/213 (61%)
Endoscopic improvement at W12	24/144 (16.7%)	82/213 (38.5%)
Clinical response at W12	51/144 (35.4%)	152/213 (71.4%)
Histologic endoscopic mucosal improvement at W12	15/144 (10.4%)	71/213 (33.3%)
Symptomatic remission at W4	25/144 (17.4%)	64/213 (30%)
Fatigue response at W12	42/144 (29.2%)	93/213 (43.7%)
Symptomatic remission at W2	19/144 (13.2%)	35/213 (16.4%)
Endoscopic remission at W12	11/144 (7.6%)	45/213 (21.1%)

Source: Generated by reviewer using ADADT.xpt, ADEFF.xpt, ADHIST1.xpt, ADIBDQI.xpt, ADPROMSI.xpt, ADSL.xpt.
Abbreviations: FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks

Supplementary Analyses for Fatigue Response, IS-2

The review team performed additional supplementary analyses for the fatigue endpoint to address various concerns. First, the prespecified analysis used the raw score conversion table to calculate the PROMIS-Fatigue SF-7a score, whereas the FDA preferred scoring method uses the response pattern scoring approach. Second, as discussed in Section 16.4, there may not be a single clinically meaningful threshold for the binary definition of “fatigue response” and the appropriate threshold may depend on baseline symptom severity. To address these first two concerns, the review team repeated the primary analysis for fatigue response using the response pattern scoring approach and a range of thresholds (Table 70) to define response, in addition to evaluating the PROMIS-Fatigue SF-7a score as a continuous outcome (Table 71). Results from all analyses remained nominally statistically significant with p-values below 0.001.

Table 70. Efficacy Results for Fatigue Endpoint Over a Range of PROMIS-Fatigue SF-7a Score^a Thresholds (FAS), IS-2

Threshold	Placebo IV Q4W N=280 n (%)	Guselkumab 200 mg IV Q4W N=421 n (%)	Adjusted Treatment Difference (95% CI) ^b	p-Value ^c
9.8	33 (11.8%)	131 (31.1%)	19.4% (13.7,25.2)	<0.001
9	45 (16.1%)	141 (33.5%)	17.5% (11.4,23.7)	<0.001
8.05	54 (19.3%)	158 (37.5%)	18.4% (11.9,24.9)	<0.001
7	64 (22.9%)	173 (41.1%)	18.3% (11.6,25.1)	<0.001
6.8	66 (23.6%)	175 (41.6%)	18.1% (11.3,24.9)	<0.001
2.7	99 (35.4%)	247 (58.7%)	23.4% (16.2,30.7)	<0.001

Source: Table 21 in a response to Information Request submitted on 7/8/24. Verified by reviewer using ADPRMRI2.xpt also submitted on July 8, 2024.

^a Used response-pattern scoring approach

^b The treatment difference was based on the common risk difference stratified by prior therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by prior therapy failure status and concomitant use of corticosteroids

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; IS-2, Induction Study 2; IV, intravenous; MH, Mantel-Haenszel; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; SF, Short Form

Table 71. Summary of Change From Induction Baseline in PROMIS-Fatigue SF-7a Score^a (FAS), IS-2

Parameter	Placebo IV Q4W N=280	Guselkumab 200 mg IV Q4W N=421
Induction Baseline ^b		
Mean ^b (SD)	56.5 (9.3)	56.1 (9.3)
Median	57.5	56.0
IQR	50.1, 62.9	49.5, 62.9
Min, Max	29, 83	29, 83
Missing	9	14
Week I-12 ^b		
Mean (SD)	54.3 (10.4)	49.8 (10.6)
Median	54.1	49.1
IQR	47.3, 60.8	42.7, 57.6
Min, Max	29, 83	29, 83
Missing	13	5
Change from baseline		
Mean (SD)	-2.3 (8.0)	-6.1 (9.4)
Median	-0.7	-5.4
IQR	-6.9, 1.9	-12.1, 0.0
Min, Max	-36, 20	-39, 23
Missing	20	16
Treatment Difference ^c (95% CI)		-4.0 (-5.3, -2.7)
p-Value		<0.001

Source: Response to Information Request (IR) submitted on 5/15/24. Verified by reviewer using ADPROMRI.xpt.

^a Used response-pattern scoring approach

^b ICE Strategies: Subjects who had an ostomy or colectomy (ICE 1), a prohibited change in UC medications (ICE 2), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 3) prior to Week I-12 had their baseline value carried forward from the time of the event onward. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 4) prior to Week I-12, their observed values were used, if available. Subjects who experienced ICE 5 (discontinued study agent due to reasons other than those in ICEs 3 and 4) prior to Week I-12 had their baseline value carried forward from the time of the event onward.

^c The treatment difference was based on an ANCOVA with treatment group, prior therapeutic biologic and/or JAK inhibitor therapy failure status (Yes/No), concomitant use of corticosteroids (Yes/No), and baseline value as covariates. ANCOVA used observed data without imputation.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; ICE, incurrent event; IQR, interquartile range; IS-2, Induction Study 2; IV, intravenous; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation; SF, Short Form; UC, ulcerative colitis

Supplementary Analyses for Stool Frequency and Rectal Bleeding Subscores by Week, IS-2

The mean change from baseline in the stool frequency and rectal bleeding subscores at Weeks I-2, I-4, I-8, and I-12 are presented in [Table 72](#). For both subscores and at each week, the change from baseline was larger (i.e., more negative) in the 200 mg guselkumab group, as compared to the placebo group. A Mixed-Effect Repeated Measures (MMRM) compared the mean change from baseline between the 200 mg guselkumab and placebo groups. The LS mean differences were nominally significant for both subscores at each evaluated time point, although the results for the Week I-2 stool frequency subscore were not as persuasive as the results at subsequent timepoints.

Table 72. Change From Induction Baseline in Stool Frequency and Rectal Bleeding Subscores (FAS), IS-2

Mayo Subscore	Placebo IV Q4W	Guselkumab 200 mg IV Q4W	LS Mean Differenc (95% CI) ^{a,b}	p- Value ^{a,b}
Stool frequency, mean (95% CI) ^{a,c}				
Week I-2	-0.25 (-0.34, -0.15)	-0.39 (-0.46, -0.31)	-0.14 (-0.25, -0.02)	0.020
Week I-4	-0.34 (-0.44, -0.24)	-0.66 (-0.75, -0.58)	-0.32 (-0.45, -0.20)	<0.001
Week I-8	-0.48 (-0.58, -0.37)	-0.93 (-1.02, -0.84)	-0.47 (-0.60, -0.33)	<0.001
Week I-12	-0.49 (-0.61, -0.37)	-1.11 (-1.21, -1.01)	-0.63 (-0.78, -0.48)	<0.001
Rectal bleeding, mean (95% CI) ^{a,c}				
Week I-2	-0.45 (-0.56, -0.35)	-0.61 (-0.69, -0.53)	-0.18 (-0.30, -0.06)	0.003
Week I-4	-0.50 (-0.61, -0.39)	-0.85 (-0.93, -0.76)	-0.37 (-0.49, -0.24)	<0.001
Week I-8	-0.65 (-0.76, -0.53)	-1.11 (-1.20, -1.02)	-0.49 (-0.61, -0.36)	<0.001
Week I-12	-0.57 (-0.67, -0.46)	-1.21 (-1.30, -1.12)	-0.68 (-0.80, -0.55)	<0.001

Source: Clinical Study Report Table TEFMAYO504 (page 662-666). Verified by reviewer using ADICE.xpt, ADMAYO.xpt

^a Intercurrent Event (ICE) Strategies: Subjects who had an ostomy or colectomy (ICE 1), a prohibited change in UC medications (ICE 2), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 3) prior to the designated timepoint had their baseline value carried forward from the time of the event onward. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 4) prior to the designated timepoint, their observed values were used, if available. Subjects who experienced ICE 5 (discontinued study agent due to reasons other than those in ICEs 3 and 4) prior to the designated timepoint had their baseline value carried forward from the time of the event onward.

^b A Mixed-Effect Model Repeated Measures (MMRM) was used with covariates for baseline value, prior therapeutic biologic and/or JAK inhibitor failure status and concomitant use of corticosteroids; p-values were based on the results from the MMRM model.

^c The confidence intervals for the mean in each treatment group were based on the normal approximation.

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, Coronavirus disease of 2019; ICE, intercurrent event; IS-2, Induction Study 2; IV, intravenous; JAK, Janus kinase; LS Mean, Least Squares Mean; MMRM, Mixed-Effect Model Repeated Measures; Q4W, every four weeks; UC ulcerative colitis

16.3.2. Additional Analyses, MS

Intercurrent Events, MS

The ICEs in MS were the following:

- (1) An ostomy or colectomy (partial or total)
- (2) Have a dose adjustment (including sham adjustment)
- (3) Prohibited change in UC medication
- (4) Discontinuation of study intervention due to lack of efficacy or an AE of worsening of UC
- (5) Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine
- (6) Discontinuation of study intervention due to reasons other than those in ICEs 4 and 5

The number of subjects experiencing each ICE is listed in [Table 73](#). Subjects in the placebo group were more likely to experience ICE 2 and ICE 3, as compared to subjects in the guselkumab groups. The rates of other ICE were similar across treatment groups.

Table 73. Intercurrent Events (RFAS), MS

Intercurrent Event	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Total N=568 n (%)
Any Intercurrent Event	93 (48.9)	35 (18.6)	44 (23.2)	172 (30.3)
ICE 1	0	0	0	0
ICE 2	69 (36.3)	19 (10.1)	30 (15.8)	118 (20.8)
ICE 3	29 (15.3)	15 (8.0)	13 (6.8)	57 (10.0)
ICE 4	13 (6.8)	6 (3.2)	9 (4.7)	28 (4.9)
ICE 5	0	0	0	0
ICE 6	13 (6.8)	13 (6.9)	13 (6.8)	39 (6.9)

Source: Generated by reviewer using ADICE.xpt.

Abbreviations: ICE, intercurrent events; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous

Sensitivity Analyses, MS

[Table 74](#) includes the results for two sensitivity analyses for the primary endpoint of clinical remission. The first sensitivity analysis used is the FDA preferred method for calculating the mMS. The second sensitivity analysis excluded subjects randomized to receive guselkumab 400 mg IV Q4W during the induction study.

Table 74. Sensitivity Analyses for Primary Endpoint (RFAS), MS

Secondary Endpoints	Placebo SC Q4W n/N (%)	Guselkumab 100 mg SC Q8W n/N (%)	Guselkumab 200 mg SC Q4W n/N (%)
FDA Preferred Definition ^a			
Clinical remission at Week M-44	34/190 (17.9%)	86/188 (45.7%)	95/190 (50.0%)
Adjusted tx difference (95% CI) ^b		26.9% (18.1, 35.6) ^c	30.7% (22.1, 39.2) ^c
200 mg Q4W Induction Dose			
Clinical remission at Week M-44	32/169 (18.9%)	73/166 (44%)	83/168 (49.4%)
Adjusted tx difference (95% CI) ^b		24.0% (14.6, 33.3) ^c	29.2% (20, 38.4) ^c

Source: Generated by reviewer using ADEFF.xpt, ADSL.xpt.

^a The FDA preferred approach is to calculate the rectal bleeding and stool frequency subscores by averaging all daily values from the 7-day window prior to the visit excluding the day of bowel preparation and the day of endoscopy.

^b The treatment difference was based on the common risk difference stratified by induction dose treatment and clinical remission status at maintenance baseline using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and, when applicable, the induction treatment.

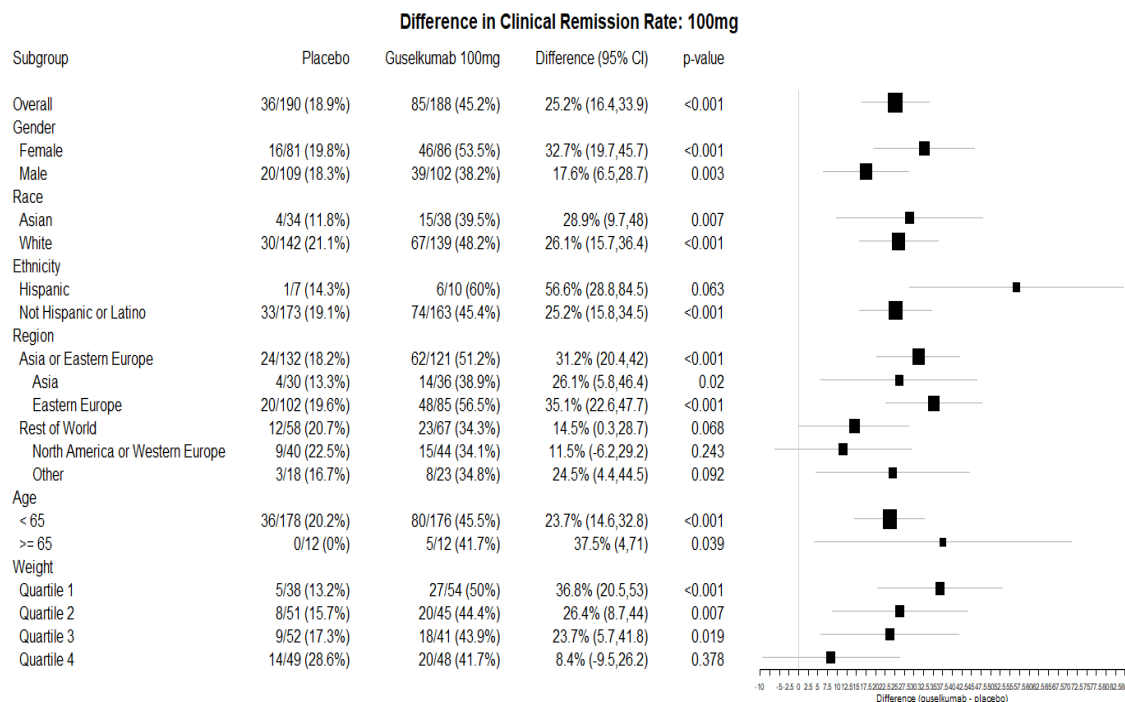
^c p-value<0.001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; MH, Mantel-Haenszel; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; tx, treatment

Subgroup Analyses, MS

The primary analysis was repeated in subgroups defined by demographic characteristics ([Figure 23](#), [Figure 24](#)). In all evaluated subgroups, the proportion of subjects in clinical remission at Week M-44 favored the guselkumab groups, as compared to the placebo group.

Figure 23. Clinical Remission^a at Week M-44 by Baseline Demographic Subgroup Comparing Placebo and Guselkumab 100 mg Groups (RFAS), MS

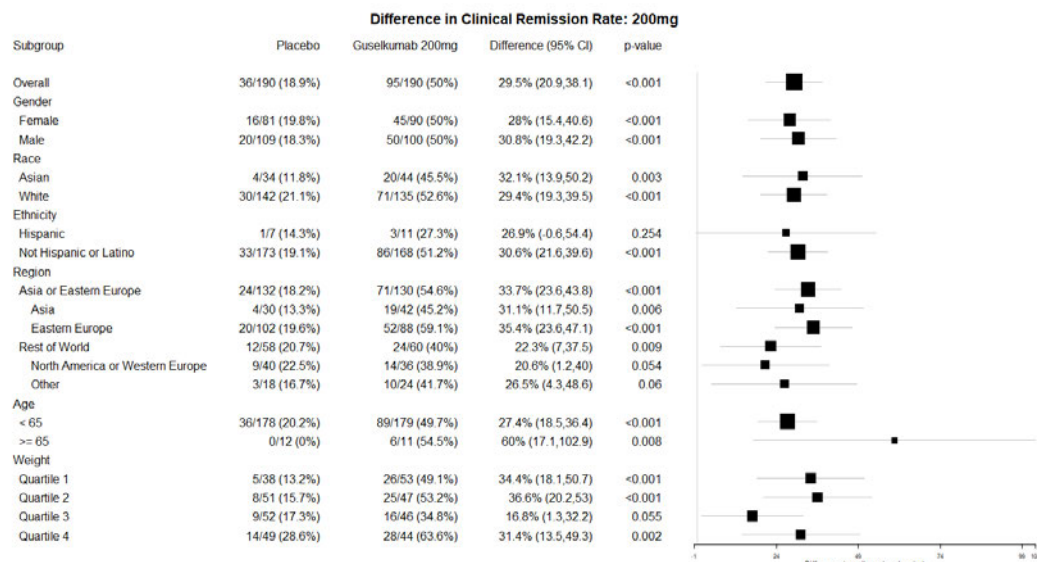


Source: Based on Clinical Study Report Table GEFCREM608B (pages 231-233). Verified by reviewer using ADEFF.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by clinical remission status at maintenance baseline and induction treatment using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; RFAS, randomized full analysis set

Figure 24. Clinical Remission^a at Week M-44 by Baseline Demographic Subgroup Comparing Placebo and Guselkumab 200 mg Groups (RFAS), MS



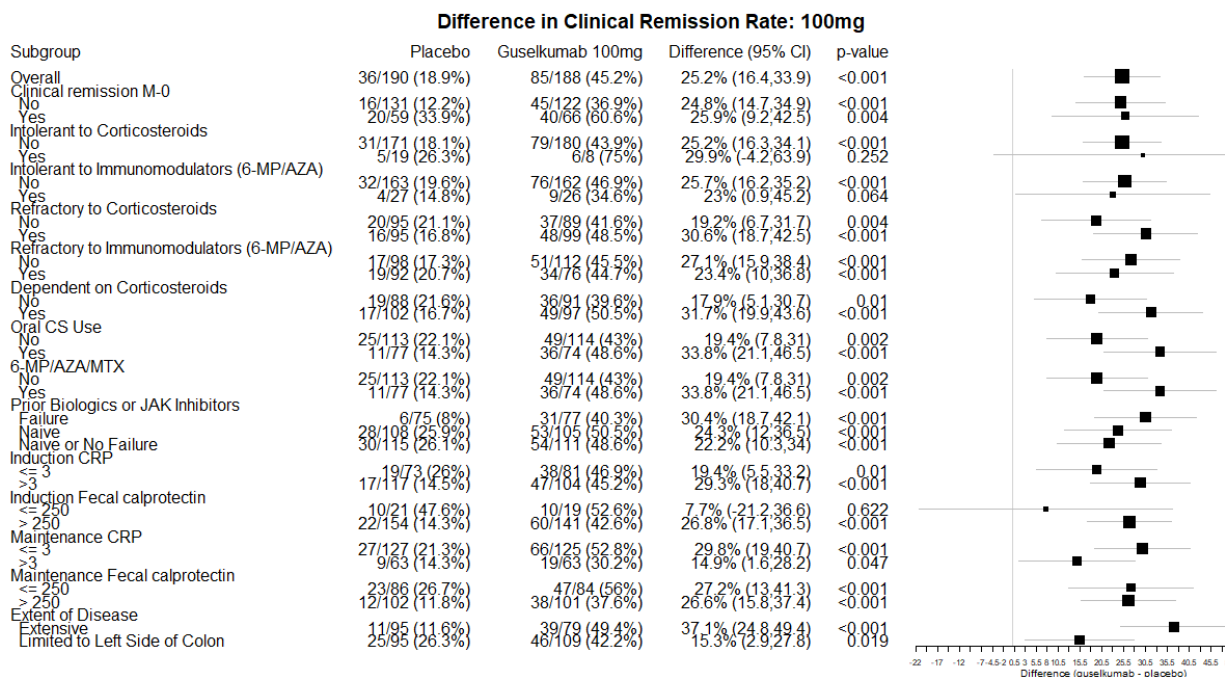
Source: Based on Clinical Study Report Table GEFCREM608A (pages 2328-230). Verified by reviewer using ADEFF.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by clinical remission status at maintenance baseline and induction treatment using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; RFAS, randomized full analysis set

The primary analysis was repeated in subgroups defined by UC characteristics, measured at the baseline of either IS-2 or MS. In all evaluated subgroups, the proportion of subjects in clinical remission at Week M-44 favored the guselkumab groups, as compared to the placebo group.

Figure 25. Clinical Remission^a at Week M-44 by UC Characteristic Subgroup Comparing Placebo and Guselkumab 100 mg Groups (RFAS), MS



Source: Based on Clinical Study Report Table GEFCREM609B (pages 239-243), GEFCREM610B (pages 247-249), GEFCREM611B (pages 258-265) and GEFCREM613B (pages 273-275). Verified by reviewer using ADADT.xpt, ADBDC.xpt, ADEFF.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by clinical remission status at maintenance baseline and induction treatment using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CS, corticosteroids; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; RFAS, randomized full analysis set; UC, ulcerative colitis

Figure 26. Clinical Remission^a at Week M-44 by UC Characteristic Subgroup Comparing Placebo and Guselkumab 200 mg Groups (RFAS), MS



Source: Based on Clinical Study Report Table GEFCREM609A (pages 234-238), GEFCREM610A (pages 244-246), GEFCREM611A (pages 250-257) and GEFCREM613A (pages 270-272). Verified by reviewer using ADADT.xpt, ADBDC.xpt, ADEFF.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by clinical remission status at maintenance baseline and induction treatment using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CRP, C-reactive protein; MH, Mantel-Haenszel; MS, Maintenance Study; RFAS, randomized full analysis set; UC, ulcerative colitis

The secondary endpoints were evaluated separately in subjects with prior therapeutic biologic product or JAK inhibitor failure and subjects without prior therapeutic biologic product or JAK inhibitor failure. [Table 75](#) shows the number of responders for each secondary endpoint in each of these two subgroups.

Table 75. Secondary Endpoints by Prior Use of Therapeutic Biologic Product and/or JAK Inhibitor (RFAS), MS

Secondary Endpoints	Placebo SC n/N (%)	Guselkumab 100 mg SC Q8W n/N (%)	Guselkumab 200 mg SC Q4W n/N (%)
Prior failure to therapeutic biologic products and/or JAK inhibitors			
Endoscopic improvement at W44	6/75 (8%)	35/77 (45.5%)	37/88 (42%)
Clinical response at W44	21/75 (28%)	54/77 (70.1%)	59/88 (67%)
Histologic endoscopic mucosal improvement at W44	6/75 (8%)	29/77 (37.7%)	34/88 (38.6%)
Symptomatic remission at W44	18/75 (24%)	50/77 (64.9%)	53/88 (60.2%)
Corticosteroid-free clinical remission at W44	5/75 (6.7%)	31/77 (40.3%)	35/88 (39.8%)
Fatigue response at W44	14/75 (18.7%)	36/77 (46.8%)	28/88 (31.8%)
Maintenance of clinical remission at W44	4/15 (26.7%)	12/20 (60%)	10/18 (55.6%)
Endoscopic remission at W44	6/75 (8%)	24/77 (31.2%)	21/88 (23.9%)
No prior failure to therapeutic biologic products or JAK inhibitors			
Endoscopic improvement at W44	30/115 (26.1%)	58/111 (52.3%)	61/102 (59.8%)
Clinical response at W44	61/115 (53%)	92/111 (82.9%)	83/102 (81.4%)
Histologic endoscopic mucosal improvement at W44	26/115 (22.6%)	53/111 (47.7%)	57/102 (55.9%)
Symptomatic remission at W44	53/115 (46.1%)	82/111 (73.9%)	78/102 (76.5%)
Corticosteroid-free clinical remission at W44	30/115 (26.1%)	54/111 (48.6%)	58/102 (56.9%)
Fatigue response at W44	42/115 (36.5%)	59/111 (53.2%)	54/102 (52.9%)
Maintenance of clinical remission at W44	16/44 (36.4%)	28/46 (60.9%)	40/51 (78.4%)
Endoscopic remission at W44	23/115 (20%)	41/111 (36.9%)	43/102 (42.2%)

Source: Generated by reviewer using ADADT.xpt, ADEFF.xpt, ADHIST1.xpt, ADIBDQ1.xpt, ADPROMS1.xpt, ADSL.xpt.
Abbreviations: MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks RFAS, randomized full analysis set;
SC, subcutaneous

The secondary endpoint of corticosteroid-free clinical remission at Week M-44 was evaluated among subjects using corticosteroids at induction baseline. In this subpopulation, the guselkumab 100 mg and guselkumab 200 mg groups had larger percentages of subjects with corticosteroid-free clinical remission at Week M-44, as compared to the placebo group (Table 76).

Table 76. Efficacy Results for Corticosteroid-Free Clinical Remission at Week M-44 Among Subjects Using Corticosteroids at Induction Baseline (RFAS), MS

Endpoint	Placebo SC Q4W n/N (%)	Guselkumab 100 mg SC Q8W n/N (%)	Guselkumab 200 mg SC Q4W n/N (%)
Corticosteroid-free clinical remission at W44	10/77 (13.0%)	36/74 (48.6%)	30/76 (39.5%)
Adjusted tx dif (95% CI) ^a		35.2% (22.5,47.8) ^b	26.1% (13.8,38.5) ^b

Source: Reviewer generated using ADEFF.xpt, ADSL.xpt.

^a The treatment difference was based on the common risk difference stratified by induction dose treatment and clinical remission status at maintenance baseline using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment.

^b p-value<0.001

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; N, number of subjects using corticosteroids at induction baseline; n, number of subjects meeting criteria; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; tx dif, treatment difference

Supplementary Analyses for Fatigue Response

The review team performed additional supplementary analyses for the fatigue endpoint to address various concerns. First, the prespecified analysis used the raw score conversion table to calculate the PROMIS-Fatigue SF-7a score, whereas the FDA preferred scoring method uses the response pattern scoring approach. Second, as discussed in Section 16.4 there may not be a single clinically meaningful threshold for the binary definition of “fatigue response” and the appropriate threshold may depend on baseline symptom severity. To address these first two concerns, the review team repeated the primary analysis for fatigue response using the response pattern scoring approach and a range of thresholds (Table 77) to define response. Of note, the results were no longer nominally significant (i.e., $p > 0.05$) for higher thresholds (i.e., 12.8, 14.5) when evaluating the guselkumab 200 mg SC Q4W dose.

Table 77. Efficacy Results for Fatigue Endpoint Over a Range of PROMIS-Fatigue SF-7a Score^a Thresholds (RFAS), MS

Placebo SC N=190		Guselkumab 100 mg SC Q8W N=188			Guselkumab 200 mg SC Q4W N=190		
		Adjusted Treatment Difference (95% CI) ^b			Adjusted Treatment Difference (95% CI) ^b		
T	n (%)	n (%)		p-Value ^c	n (%)		p-Value ^c
14.5	32 (16.8%)	48 (25.5%)	8.3% (0.3,16.2)	0.048	46 (24.2%)	6.5% (-1.4,14.5)	0.11
12.8	37 (19.5%)	54 (28.7%)	8.8% (0.4,17.1)	0.045	53 (27.9%)	7.5% (-0.8,15.8)	0.081
9.9	43 (22.6%)	77 (41.0%)	17.5% (8.5,26.6)	<0.001	66 (34.7%)	11.1% (2.3,19.9)	0.015
8.2	52 (27.4%)	90 (47.9%)	19.5% (10.2,28.8)	<0.001	74 (38.9%)	10.5% (1.4,19.7)	0.027
7	55 (28.9%)	95 (50.5%)	20.4% (11.1,29.7)	<0.001	85 (44.7%)	14.7% (5.4,24.0)	0.002
6.75	56 (29.5%)	96 (51.1%)	20.4% (11.1,29.8)	<0.001	86 (45.3%)	14.7% (5.4,24.0)	0.002

Source: Table 22 in a response to Information Request submitted on 7/8/24. Verified by reviewer using ADPRMRI2.xpt also submitted on 7/8/24.

^a Used response-pattern scoring approach.

^b The treatment difference was based on the common risk difference stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids using MH weights and was reported with a Wald-type 95% CI.

^c The p-value was based on the CMH chi-square test, stratified by prior therapeutic biologic and/or JAK inhibitor therapy failure status and concomitant use of corticosteroids

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; MH, Mantel-Haenszel; MS, Maintenance Study; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; SF, Short Form; T, threshold

Furthermore, the review team evaluated the PROMIS-Fatigue SF-7a score as a continuous outcome (Table 78) with the score calculated using the response pattern approach.

Table 78. Summary of Change From Induction Baseline in PROMIS-Fatigue SF-7a Score^a (RFAS), MS

Parameter	Placebo SC N=190	Guselkumab 100 mg SC Q8W N=188	Guselkumab 200 mg SC Q4W N=190
Induction Baseline ^b			
Mean (SD)	55.8 (8.6)	56.5 (9.6)	56.7 (10.0)
Median	56.0	57.2	57.0
IQR	49.8, 61.7	50.0, 63.6	49.5, 64.0
Min, Max	32, 76	29, 83	29, 81
Missing	5	9	8

Parameter	Placebo SC N=190	Guselkumab 100 mg SC Q8W N=188	Guselkumab 200 mg SC Q4W N=190
Week M-44 ^b			
Mean (SD)	50.5 (10.7)	47.5 (10.7)	48.3 (11.1)
Median	51.3	47.3	47.3
IQR	43.3, 58.0	38.4, 54.8	40.4, 56.6
Min, Max	29, 76	29, 83	29, 81
Missing	5	4	8
Change from baseline			
Mean (SD)	-5.2 (8.5)	-9.0 (9.4)	-8.2 (10.5)
Median	0.0	-8.6	-5.6
IQR	-9.1, 0.0	-15.2, 0.0	-14.9, 0.0
Min, Max	-42, 10	-32, 15	-47, 17
Missing	9	12	13
Treatment Difference ^c (95% CI)		-3.30 (-5.14, -1.47)	-2.57 (-4.40, -0.73)
p-Value		<0.001	0.006

Source: Response to Information Request (IR) submitted on May 15, 2024. Independent analyses by reviewer using ADPROMRI.xpt produced similar results.

^a Used response-pattern scoring approach.

^b ICE Strategies: Subjects who had an ostomy or colectomy (ICE 1), a dose adjustment (including a sham dose adjustment) (ICE 2), a prohibited change in UC medications (ICE 3), or discontinued study agent due to lack of efficacy or an AE of worsening of UC (ICE 4) prior to the designated timepoint had their induction baseline value carried forward from the time of the event onward. For subjects who discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis in Russia and Ukraine (ICE 5) prior to the designated timepoint, their observed values (if available) were used. Subjects who experienced ICE 6 (discontinued study agent due to reasons other than those in ICEs 4 and 5) prior to the designated timepoint had their induction baseline value carried forward from the time of the event onward.

^c The treatment difference was based on an MMRM with treatment group, clinical remission status at maintenance baseline (Yes/No), induction dose treatment (guselkumab 400 mg, guselkumab 200 mg, placebo crossover to guselkumab 200 mg), and baseline value as covariates.

Abbreviations: CI, confidence interval; ICE, intercurrent event; MMRM, mixed-effect model with repeated measurements; PROMIS, Patient-Reported Outcomes Measurement Information System; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; SF, Short Form

A third concern was the use of non-responder imputation to handle ICE. As discussed earlier in this review (i.e., refer to [Table 23](#)), a larger percentage of subjects in the placebo group (48.9%) experienced an ICE, as compared to either the guselkumab 100 mg SC (18.6%) or the guselkumab 200 mg SC (23.2%) groups. Percentages were similar when using the response pattern scoring approach to calculate the PROMIS-Fatigue SF-7a Score ([Table 79](#)).

Table 79. Efficacy Results for Fatigue Endpoint^a (RFAS), MS

Fatigue Endpoint	Placebo SC Q4W N=190 n (%)	Guselkumab 100 mg SC Q8W N=188 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)
Fatigue responders	56 (29.5%)	95 (50.5%)	82 (43.2%)
Fatigue non-responders	134 (70.5%)	93 (49.5%)	108 (56.8%)
ICE	93 (48.9%)	35 (18.6%)	44 (23.2%)
<7 point change in PROMIS-Fatigue score ^b	41 (21.6%)	58 (30.9%)	64 (33.7%)

Source: Reviewer generated using ADPROMRI.xpt submitted on May 15, 2024 as part of a response to an Information Request.

^a Calculation of the PROMIS-Fatigue score used the response-pattern scoring approach.

^b Includes subjects with missing data after accounting for ICE.

Abbreviations: ICE, intercurrent event; MS, Maintenance Study; PROMIS, Patient-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous

Therefore, additional reviewer-initiated analyses were performed to understand if the estimated treatment effect on fatigue reflected an effect on the targeted endpoint (i.e., fatigue) and/or an effect on the occurrence of an ICE (e.g., needing a dose adjustment due to loss of clinical

response). [Table 80](#) shows the results from analyses of the fatigue endpoint using alternative methods for handling ICE. The first analysis uses a treatment policy strategy¹⁴ to handle ICE and the second analysis omits subjects with an ICE. Both analyses failed to produce nominally significant results. However, we acknowledge that both analyses are likely conservative for assessing the effect of the guselkumab compared to placebo at Week 48. For the treatment policy analysis, some placebo subjects were crossed over to active treatment and for the analysis omitting ICE subjects, subjects experiencing an ICE tended to have relatively lower fatigue scores. Analyses were repeated using both the raw score conversion table and the response pattern scoring approach.

Table 80. Efficacy Results for Fatigue Endpoint Using Alternative Methods for Handling ICE (RFAS), MS

Fatigue Endpoint	Placebo SC Q4W n/N (%)	Guselkumab 100 mg SC Q8W n/N (%)	Guselkumab 200 mg SC Q4W n/N (%)
Raw Score Conversion Table			
Treatment policy strategy			
Fatigue response at Week M-44	92/190 (48.4%)	103/188 (54.8%)	94/190 (49.5%)
Adjusted tx dif (95% CI) ^a		5.7% (-4.1,15.5)	0.4% (-9.5,10.2)
Omitting subjects with ICE			
Fatigue response at Week M-44	56/97 (57.7%)	95/153 (62.1%)	82/146 (56.2%)
Adjusted tx dif (95% CI) ^a		4.1% (-8,16.1)	-1.3% (-13.4,10.9)
Response Pattern Scoring			
Treatment policy strategy			
Fatigue response at Week M-44	90/190 (47.4%)	103/188 (54.8%)	97/190 (51.1%)
Adjusted tx dif (95% CI) ^a		6.6% (-3.2,16.4)	3.1% (-6.8,12.9)
Omitting subjects with ICE			
Fatigue response at Week M-44	55/97 (56.7%)	95/153 (62.1%)	85/146 (58.2%)
Adjusted tx dif (95% CI) ^a		5.3% (-6.7,17.2)	1.8% (-10.2,13.9)

Source: Reviewer generated using ADPROMIS.xpt ADPROMSI.xpt and using ADPROMRI.xpt and ADPROMR.xpt submitted on May 15, 2024 as part of a response to an Information Request.

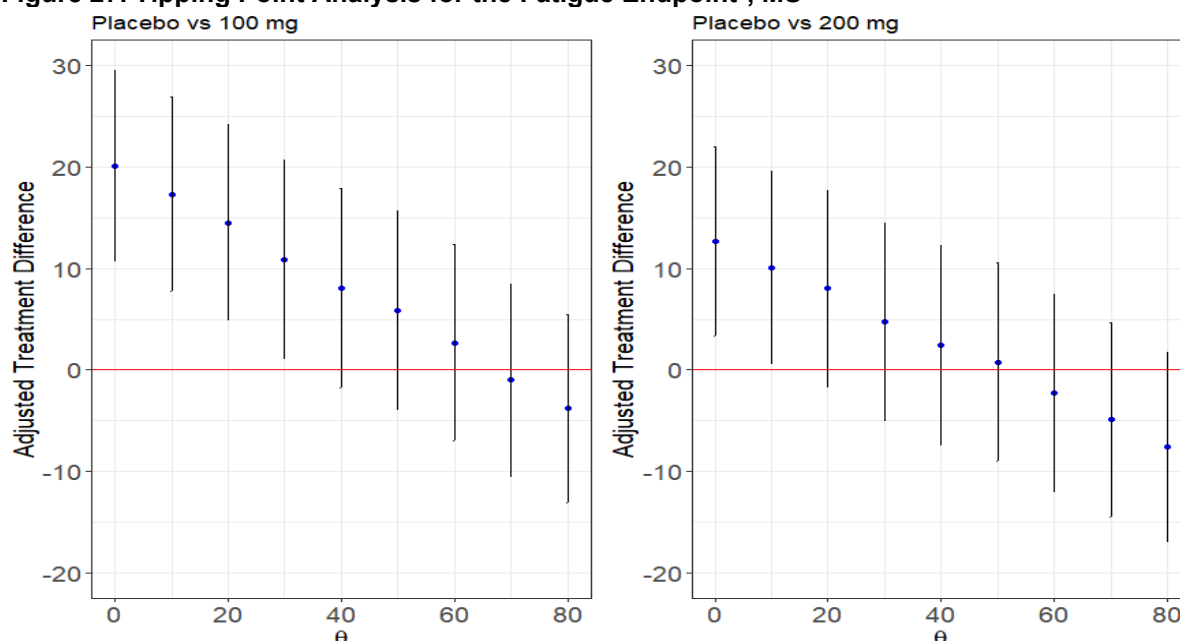
^a The treatment difference was based on the common risk difference stratified by induction dose treatment and clinical remission status at maintenance baseline using MH weights and was reported with a Wald-type 95% CI. The p-value was based on the CMH chi-square test, stratified by clinical remission status at maintenance baseline and induction treatment
Abbreviations: CMH, Cochran-Mantel-Haenszel; ICE, intercurrent event; MH, Mantel-Haenszel; MS, Maintenance Study; Q4W, every 4 weeks; Q8W, every 8 weeks; RFAS, randomized full analysis set; SC, subcutaneous; tx dif, treatment difference

Tipping point analyses were also performed. Results are based on analyses using the raw score conversion table to calculate the PROMIS-Fatigue score; however, results based on using the response pattern scoring approach were similar. A one-dimensional tipping point analysis was performed to examine what percentage of subjects with an ICE would have needed to meet criteria for fatigue response in order to change efficacy conclusions. Let Θ denote the percentage of ICE subjects who would be fatigue responders (i.e., ≥ 7 -point improvement in the PROMIS-Fatigue score) had they continued on their assigned treatment and assessed at Week M-44. Note Θ is assumed to be the same for both treatment groups. [Figure 27](#) shows the adjusted treatment differences over a range of Θ values. Note, $\Theta = 0$ produces results similar to the primary analysis and $\Theta \approx 60\%$ produces results similar to the analysis omitting ICE subjects. The key point is Θ would have to be relatively small for the results to have remained nominally significant, especially in the analysis of the guselkumab 200 mg SC group. We acknowledge that

¹⁴ Non-responder imputation was still used for the 102 subjects (33 in the placebo group, 34 in the guselkumab 100mg SC group, and 35 in the guselkumab 200 mg SC group) with missing data.

it is difficult to predict the actual value of Θ or to predict if Θ would be similar across treatment groups. However, among subjects with an ICE after Week M-28, 22/50 (44.0%) subjects had a ≥ 7 point improvement in the PROMIS-Fatigue score at Week M-28 (3/7 [42.8%] in guselkumab 100 mg SC group, 7/10 [70.0%] in the guselkumab 200 mg group, and 12/32 [37.5%] in the placebo group), suggesting that larger values of Θ (i.e., $\sim 44\%$) may be plausible and the occurrence of an ICE may not necessarily indicate a subject was having severe fatigue prior to the ICE.

Figure 27. Tipping Point Analysis for the Fatigue Endpoint^a, MS



Source: Reviewer generated using ADPROMSI.xpt.

^a The primary analysis of the fatigue endpoint was repeated on 100 MI datasets. In each MI dataset, the responses for subjects with an ICE were imputed with a probability of $\Theta/100$. The results for the MI datasets were combined using Rubin's rules. The estimates of the adjusted treatment differences are indicated by blue points and the 95% confidence intervals are indicated by black lines. Abbreviations: ICE, intercurrent event; MI, multiply imputed; MS, Maintenance Study

A two-dimensional tipping point analysis was also conducted for the fatigue endpoint in the MS. Of note, the varied parameter was the response rate in subjects with an ICE, as opposed to the response rate in subjects with missing data. Let Θ_0 and Θ_1 denote the percentage of ICE subjects who would be fatigue responders (i.e., a ≥ 7 point improvement in the PROMIS-Fatigue score) in the placebo and guselkumab SC groups, respectively, had they continued on their assigned treatment and been assessed at Week M-44. The primary analysis of the fatigue endpoint was repeated on 100 multiply imputed (MI) datasets. In each MI dataset, the response in the placebo subjects with an ICE was imputed with probability $\Theta_0/100$ and the response in the guselkumab subjects with an ICE was imputed with probability $\Theta_1/100$. [Table 81](#) and [Table 82](#) show the results from analyses evaluating guselkumab 100 mg SC and guselkumab 200 mg SC, respectively. The bolded values in the tables indicate nominally significant results (i.e., $p \leq 0.05$) with the guselkumab SC group having the higher response rate. Of note, the points $\Theta_0=0.375$ and $\Theta_1=0.588$ were included because these values reflect the fatigue response rates observed at Week 28 among subjects who had an ICE after Week 28.

Table 81. Tipping Point Analysis for the Fatigue Endpoint, Guselkumab 100 mg SC Q4W

$\Theta_0 \backslash \Theta_1$	0	0.1	0.2	0.3	0.375	0.4	0.5	0.588	0.6	0.7	0.8
0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.2	0.04	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.3	0.24	0.14	0.06	0.03	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.375	0.68	0.42	0.29	0.13	0.07	0.06	0.02	<0.01	<0.01	<0.01	<0.01
0.4	0.92	0.57	0.38	0.21	0.11	0.14	0.04	0.02	0.02	<0.01	<0.01
0.5	0.35	0.68	0.92	0.75	0.57	0.51	0.29	0.17	0.13	0.06	0.03
0.588	0.08	0.19	0.31	0.56	0.76	0.9	0.85	0.59	0.54	0.33	0.17
0.6	0.07	0.15	0.3	0.49	0.71	0.77	0.9	0.7	0.62	0.33	0.15
0.7	<0.01	0.01	0.04	0.09	0.18	0.18	0.39	0.52	0.65	0.92	0.74
0.8	<0.01	<0.01	<0.01	<0.01	0.02	0.02	0.06	0.11	0.14	0.26	0.48

Source: Reviewer generated with ADICE.xpt, ADPROMSI.xpt, ADSL.xpt.

Abbreviations: Q4W, every 4 weeks; SC, subcutaneous

Table 82. Tipping Point Analysis for the Fatigue Endpoint, Guselkumab 200 mg SC Q4W

$\Theta_0 \backslash \Theta_1$	0	0.1	0.2	0.3	0.375	0.4	0.5	0.588	0.6	0.7	0.8
0	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.1	0.1	0.04	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.2	0.6	0.29	0.12	0.05	0.02	0.01	<0.01	<0.01	<0.01	<0.01	<0.01
0.3	0.75	0.95	0.56	0.36	0.17	0.12	0.05	0.02	0.01	<0.01	<0.01
0.375	0.28	0.54	0.83	0.79	0.5	0.49	0.2	0.11	0.08	0.02	<0.01
0.4	0.16	0.4	0.68	0.94	0.7	0.67	0.33	0.17	0.17	0.05	0.01
0.5	0.01	0.08	0.18	0.34	0.59	0.63	0.96	0.67	0.58	0.3	0.14
0.588	<0.01	<0.01	0.02	0.08	0.16	0.18	0.39	0.72	0.74	0.87	0.52
0.6	<0.01	<0.01	0.02	0.06	0.12	0.14	0.33	0.56	0.71	0.93	0.58
0.7	<0.01	<0.01	<0.01	<0.01	0.01	0.01	0.05	0.12	0.15	0.31	0.66
0.8	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	0.01	0.04	0.15

Source: Reviewer generated with ADICE.xpt, ADPROMSI.xpt, ADSL.xpt.

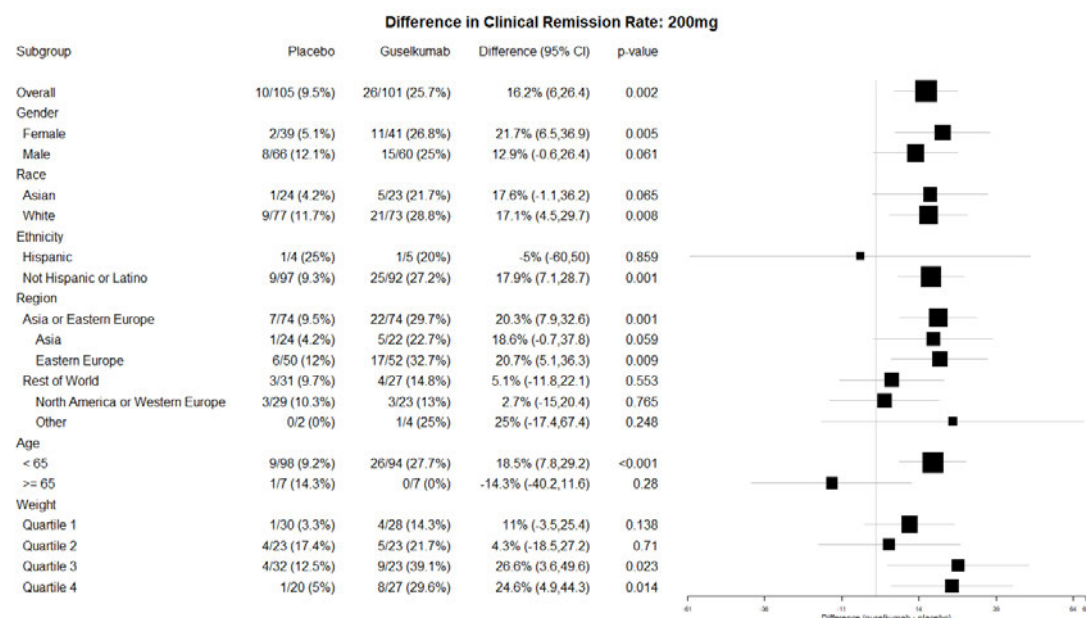
Abbreviations: Q4W, every 4 weeks; SC, subcutaneous

16.3.3. Additional Analyses, IS-1

Subgroup Analyses, IS-1

The primary analysis of the clinical remission endpoint was repeated in subgroups defined by demographic characteristics ([Figure 28](#) and [Figure 29](#)). In most evaluated subgroups, the proportion of subjects in clinical remission at Week I-12 favored guselkumab relative to the placebo.

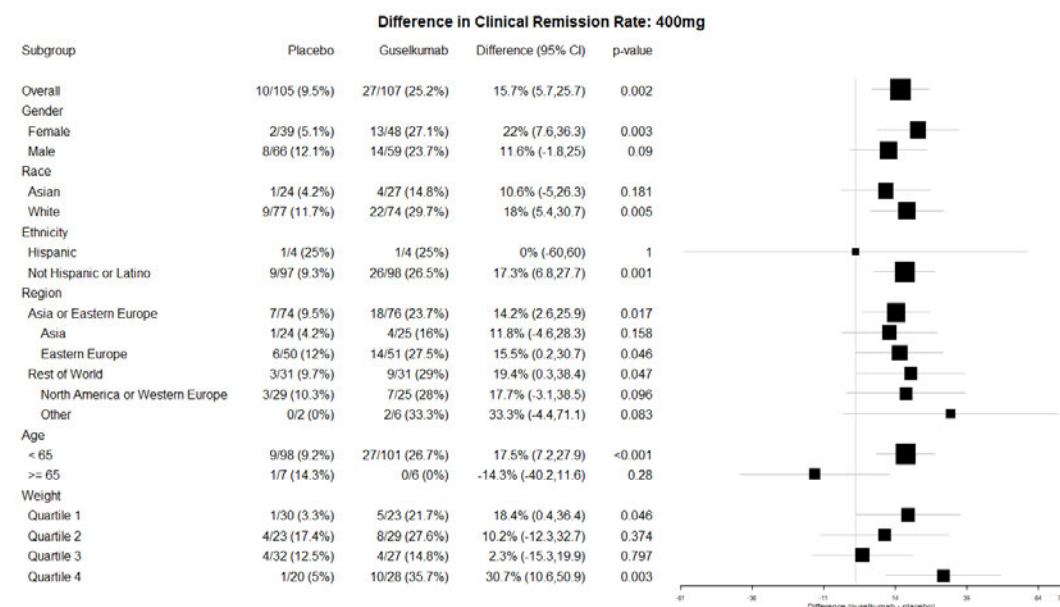
Figure 28. Clinical Remission^a at Week I-12 by Demographic Subgroup Comparing Placebo and Guselkumab 200 mg Groups (FAS), IS-1



Source: Generated by reviewer using ADEFF.xpt, ADSL.xpt.

^a The unadjusted treatment difference was reported with a Wald-type 95% CI. The p-value was based on the Wald statistic. Abbreviations: CI, confidence interval; FAS, full analysis set; IS-1, Induction Study 1

Figure 29. Clinical Remission^a at Week I-12 by Demographic Subgroup Comparing Placebo and Guselkumab 400 mg Groups (FAS), IS-1



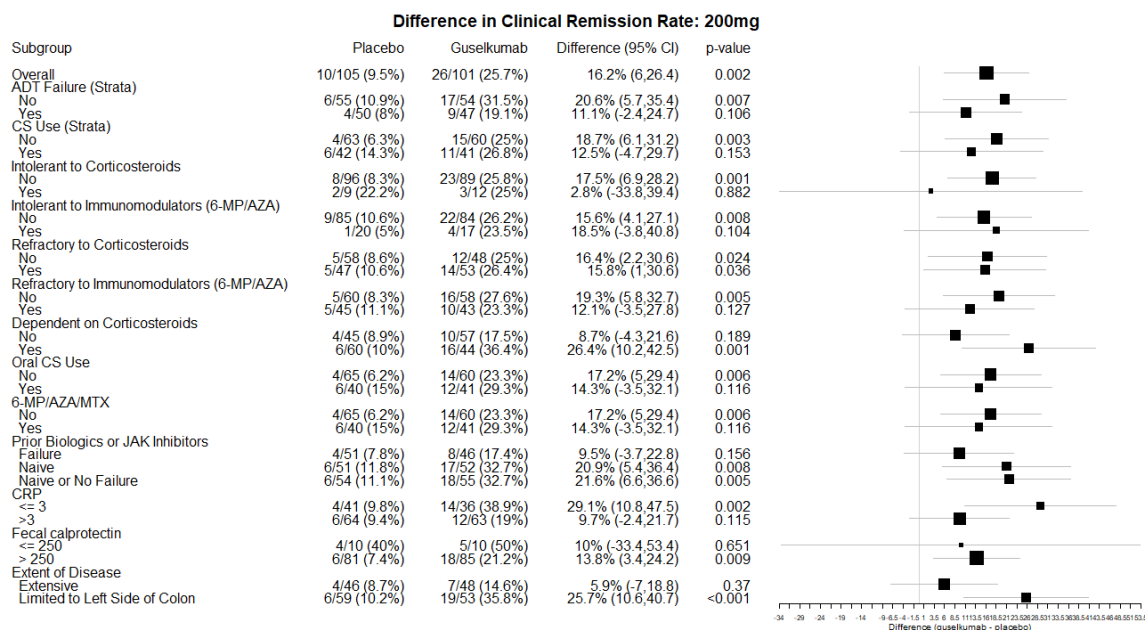
Source: Generated by reviewer using ADEFF.xpt, ADSL.xpt.

^a The unadjusted treatment difference was reported with a Wald-type 95% CI. The p-value was based on the Wald statistic. Abbreviations: CI, confidence interval; FAS, full analysis set; IS-1, Induction Study 1

The primary analysis of the clinical remission endpoint was repeated in subgroups defined by baseline UC characteristics ([Figure 30](#) and [Figure 31](#)). In most evaluated subgroups, the

proportion of subjects in clinical remission at Week I-12 favored guselkumab relative to the placebo.

Figure 30. Clinical Remission^a at Week I-12 by UC Baseline Characteristic Subgroup Comparing Placebo and Guselkumab 200 mg Groups (FAS), IS-1

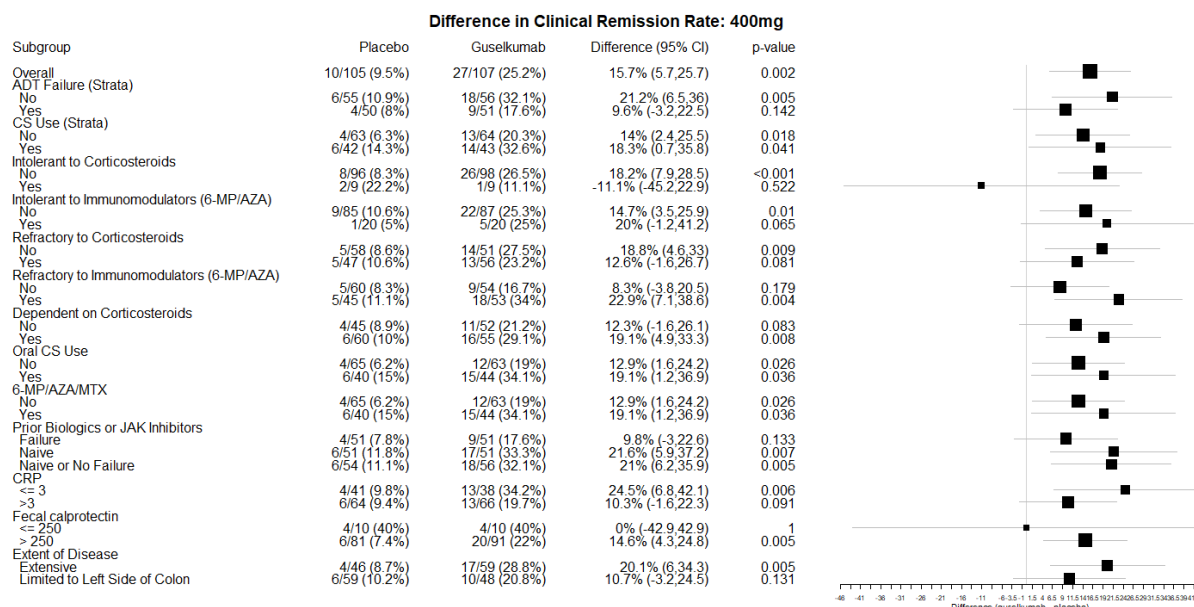


Source: Generated by reviewer using ADADT.xpt, ADBDC.xpt, ADEFF.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a The unadjusted treatment difference was reported with a Wald-type 95% CI. The p-value was based on the Wald statistic.

Abbreviations: CI, confidence interval; FAS, full analysis set; IS-1, Induction Study 1

Figure 31. Clinical Remission^a at Week I-12 by UC Baseline Characteristic Subgroup Comparing Placebo and Guselkumab 400 mg Groups (FAS), IS-1



Source: Generated by reviewer using ADADT.xpt, ADBDC.xpt, ADEFF.xpt, ADMEDRVW.xpt, ADSL.xpt.

^a The unadjusted treatment difference was reported with a Wald-type 95% CI. The p-value was based on the Wald statistic.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; CS, corticosteroid; FAS, full analysis set; IS-1, Induction Study 1

16.4. Additional Analyses To Support “Fatigue Response”

16.4.1. Background

The Agency reviewed the evidence provided in the application regarding whether the Applicant’s binary responder endpoint (i.e., fatigue response defined as a ≥ 7 point improvement on the PROMIS-Fatigue SF-7a) is appropriate to assess fatigue. Specifically, the review team examined whether a single responder threshold (i.e., 7 points) constitutes a clinically meaningful within-subjects change in the target patient population.

In defining the responder endpoint based on fatigue, the Applicant conducted anchor-based analyses supplemented by empirical cumulative distribution function (eCDF) curves using four anchors, (i.e., PGIS [Figure 17], Subjects Global Impression of Change [PGIC; Figure 18], and two PROMIS-29 fatigue-specific items [Item FATEXP40 and Item HI7; Figure 19], with PGIC as the primary anchor). For the analyses, the Applicant used the PROMIS-Fatigue SF-7a T-scores based on the raw score conversion table in IS-1.

The Applicant concluded that the meaningful change thresholds range from -7.8 to -5.8, based on the target anchor change category of “Moderately better” in PGIC and 1-point improvement in the other anchors. It was unclear how the Applicant derived the specific threshold values, as the Applicant did not specify which statistic (e.g., mean, median) of the change in the PROMIS-Fatigue SF-7a T-scores corresponding to the target anchor change category was used.

Given this result, the Applicant proposed a single threshold of a seven-point improvement to define fatigue response. Additionally, the Applicant noted that the meaningful change thresholds range from -14.2 to -9.6 when using a target anchor change category of “a lot better” in PGIC and 2-point improvement in the other anchors. Based on these results, the Applicant suggested using a range of cut-off from 6 to 14 points change as a sensitivity analysis.

- The Applicant’s analyses were based on the use of the raw score conversion table, not the FDA preferred scoring approach for PROMIS measures, response-pattern scoring. PROMIS measures were developed using a response-pattern scoring approach, which more effectively handles item-level missing data and facilitates comparisons across PROMIS measures. Additionally, the Applicant’s analyses used two anchor scales, PGIS and PGIC, which have the following limitations which reduces their utility in aiding in the interpretation of PROMIS-Fatigue SF-7a scores.
 - The concept assessed by the PGIC and PGIS scales (i.e., severity of UC) is not aligned with the concept of interest measured by the PROMIS-Fatigue SF-7a (i.e., fatigue-related symptoms and impacts).
 - The recall period of the PGIS scale (i.e., “currently”) is not aligned with the assessment time period of the PROMIS-Fatigue SF-7a-based endpoint (i.e., recall period of seven days).
 - PGIC is susceptible to potential recall error, as subjects are asked to compare their current status to their status 12 weeks ago (i.e., at Week I-12) and 44 weeks ago (i.e., at Week M-44).

The results of the Applicant’s analyses also suggest meaningful improvement in PROMIS-Fatigue SF-7a scores is better characterized by a range of change scores rather than a single threshold value, making a binary responder endpoint inappropriate. To address these concerns, FDA issued an information request on May 10, 2024, asking the Applicant to conduct anchor-based meaningful change analyses for the PROMIS-Fatigue SF-7a T-score based on the response-pattern scoring approach (referred to as PROMIS-Fatigue SF-7a rT-score herein) in IS-2 and MS, using two PROMIS-29 fatigue-specific items (Item FATEXP40 and Item HI7) as the anchors. The concept and recall period of the two PROMIS-29 fatigue-specific items are aligned with the PROMIS-Fatigue SF-7a.

16.4.2. Clinically Meaningful Benefit in Change from Baseline in PROMIS-Fatigue SF-7a rT-scores

16.4.2.1. Anchor-Based Analyses, IS-2 and MS

The Agency used anchor-based methods supplemented with eCDF curves to evaluate the clinically meaningful within-subjects change in the PROMIS-Fatigue SF-7a rT-score from Baseline to Week I-12. The anchor-based analyses were conducted on the full analysis set of IS-2 and the randomized full analysis set of MS. In IS-2, the full analysis set includes all randomized subjects with a mMS of 5 to 9 who received at least one (partial or complete) dose of

study intervention. In MS, the randomized full analysis set includes all participants with a mMMS of 5 to 9 who are randomized (i.e., guselkumab clinical responders at Week I-12 and placebo crossover responders at Week I-24 in an induction study) in MS and receive at least one (partial or complete) dose of study intervention in MS.

Baseline PROMIS-Fatigue SF-7a rT-Score

In order to understand the amount of improvement in the PROMIS-Fatigue SF-7a rT-score that is considered meaningful to subjects, it is important to first examine the distribution of baseline scores by treatment arm ([Table 83](#)). In the target patient population, the PROMIS-Fatigue SF-7a rT-score ranged from 29.4 to 82.7.¹⁵ The means and medians for both groups were similar, with the placebo group having slightly lower scores.

Table 83. Distribution of Baseline PROMIS-Fatigue SF-7a rT-Score by Treatment Arm

Treatment	N (%)	Mean	SD	Min	Max	Percentiles					N _{missing} (%)
						10 th	25 th	50 th	75 th	90 th	
Guselkumab 200 mg	271 (96.8%)	56.5	9.3	29.4	82.7	45.6	50.1	57.5	62.9	66.9	9 (3.2%)
Placebo	407 (96.7%)	56.1	9.3	29.4	82.7	43.9	49.5	56.0	62.9	67.3	14 (3.3%)

Source: Analyst generated table modified from Table GEFPROMIS9501A of the Applicant's response to FDA IR dated May 22, 2024. Verified using Applicant submitted adpromr.xpt and adsl.xpt.
Abbreviations: N, number of subjects; n (%), number (percentage) of subjects in subset; PROMIS, Subjects-Reported Outcomes Measurement Information System; SD, standard deviation

Evaluation of Anchor Measures

The review team evaluated the relationship between the anchor items (PROMIS-29 Item FATEXP40 and PROMIS-29 Item HI7) and endpoint scores. [Table 84](#) shows polyserial correlations were calculated for the relationship between the anchor items and Fatigue SF-7a rT-score at Baseline, Week I-12, and Week M-44, and Spearman correlations were calculated for the change in scores between the anchor items and Fatigue SF-7a (i.e., change from Baseline to Week I-12 and change from Baseline to Week M-44). Overall, the correlations between the two PROMIS-29 fatigue items and the PROMIS-Fatigue SF-7a rT-scores were consistently moderately high to high across all timepoints and in change scores in both studies, suggesting the two PROMIS-29 fatigue items are informative anchors to use for anchor-based analyses.

¹⁵ Theoretically, standardized theta scores, which form the T-score metric through a linear transformation, can range from -∞ to ∞. However, respondents typically fall within a range of -3 to 3. Consequently, the possible range of PROMIS-Fatigue SF-7a scores (T-scores) is not fixed and vary by the target patient population. Although not directly comparable, the T-scores based on raw score conversion table can range from 30.3 to 84.

Table 84. Polyserial Correlation and Spearman Correlation Coefficients Between PROMIS-Fatigue SF-7a rT-Scores and Anchor Items (PROMIS-29 Item FATEXP40 and PROMIS-29 Item HI7) by Study

Time point	PROMIS-29 Item FATEXP40		PROMIS-29 Item HI7	
	IS-2 (n=701)	MS (n=568)	IS-2 (n=701)	MS (n=568)
Baseline	0.825		0.771	
Week I-12	0.854		0.831	
Week M-44	0.830		0.819	
Change from Baseline to Week I-12	0.634 ^a		0.620*	
Change from Baseline to Week M-44	0.619 ^a		0.611 ^a	

Source: Analyst generated table based on Tables TEFPROMIS9511A, TEFPROMIS9511B, TEFPROMIS9613A, and TEFPROMIS9613B submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted adpromr.xpt, adsl.xpt, and adpromis.xpt.

^a Spearman correlation coefficient

Abbreviations: IS-2, Induction Study 2; MS, Maintenance Study; PROMIS, Subjects-Reported Outcomes Measurement Information System

Target Anchor Change Categories

The Applicant did not prespecify a target anchor change category on the PROMIS-29 Fatigue Item FATEXP40 and PROMIS-29 Item HI7 that represents a meaningful within-subjects change (improvement or worsening) in fatigue severity as neither was a primary anchor for their original analysis. Instead, the Applicant selected a one-point improvement in PROMIS-29 Fatigue Item FATEXP40 and PROMIS-29 Item HI7, as these correspond to “moderately better” in PGIC, which was prespecified as the target change category by the Applicant.

To examine the distribution of change in global fatigue symptom severity between Baseline and Week I-12 and between Baseline and Week M-44, a crosstabulation was performed at Week I-12 and Week M-44 for each anchor.

PROMIS-29 Fatigue Item FATEXP40

Most subjects reported “a little bit” and “somewhat” fatigue at Baseline, followed by “quite a bit” ([Table 85](#) and [Table 86](#)). [Table 85](#) displays category change from Baseline to Week I-12. Most subjects experienced a one-category improvement across all baseline symptom severity from “a little bit” to “very much.” However, subjects who had “a little bit” of fatigue at baseline mostly experienced “no change,” followed by a one-category improvement. [Table 86](#) displays category change from Baseline to Week M-44. Most subjects with baseline symptom severity of “a little bit” and “somewhat” experienced a one-category improvement. However, subjects with baseline symptom severity of “quite a bit” and “very much” predominantly reported two-category and three-category improvements, respectively, followed by a one-category improvement. The relatively large proportion of subjects in the high improvement categories (e.g., two-category, three-category) from Baseline to Week M-44 should be interpreted with caution, as a large percentage of subjects had an ICE and were no longer on their originally assigned treatment at Week M-44.

Table 85. Category Change (n (%)) in PROMIS-29 Fatigue Item FATEXP40 From Baseline to Week I-12 by Baseline PROMIS-29 Fatigue Item FATEXP40

PROMIS-29 Fatigue Item FATEXP40 at Baseline	PROMIS-29 Fatigue Item FATEXP40 Change From Baseline to Week I-12							Missing
	Worsened ≥3 Categories	Worsened 2 Categories	Worsened 1 Category	No Change	Improved 1 Category	Improved 2 Categories	Improved ≥3 Categories	
Not at all (n=50)	1 (2.0%)	2 (4.0%)	17 (34.0%)	28 (56.0%)	0	0	0	2 (4.0%)
A little bit (n=196)	1 (0.5%)	10 (5.1%)	26 (13.3%)	95 (48.5%)	50 (25.5%)	0	0	14 (7.1%)
Somewhat (n=209)	0	4 (1.9%)	28 (13.4%)	68 (32.5%)	76 (36.4%)	19 (9.1%)	0	14 (6.7%)
Quite a bit (n=161)	0	0	10 (6.2%)	34 (21.1%)	49 (30.4%)	37 (23.0%)	20 (12.4%)	11 (6.8%)
Very much (n=62)	0	0	0	12 (19.4%)	17 (27.4%)	9 (14.5%)	13 (21.0%)	11 (17.7%)

Source: Analyst generated table modified from Table TEFPROMIS9522B submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted adsl.xpt and adpromis.xpt.

Abbreviations: n, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System

Table 86. Category Change (n (%)) in PROMIS-29 Fatigue Item FATEXP40 From Baseline to Week M-44 by Baseline PROMIS-29 Fatigue Item FATEXP40

PROMIS-29 Fatigue Item FATEXP40 at Baseline	PROMIS-29 Fatigue Item FATEXP40 Change From Baseline to Week M-44							Missing
	Worsened ≥3 Categories	Worsened 2 Categories	Worsened 1 Category	No Change	Improved 1 Category	Improved 2 Categories	Improved ≥3 Categories	
Not at all (n=40)	0	1 (2.5%)	10 (25.0%)	21 (52.5%)	0	0	0	8 (20.0%)
A little bit (n=166)	0	4 (2.4%)	10 (6.0%)	58 (34.9%)	69 (41.6%)	0	0	25 (15.1%)
Somewhat (n=153)	0	0	3 (2.0%)	30 (19.6%)	68 (44.4%)	38 (24.8%)	0	14 (9.2%)
Quite a bit (n=140)	0	0	3 (2.1%)	14 (10.0%)	31 (22.1%)	44 (31.4%)	22 (15.7%)	26 (18.6%)
Very much (n=47)	0	0	0	5 (10.6%)	9 (19.1%)	8 (17.0%)	18 (38.3%)	7 (14.9%)

Source: Analyst generated table modified from Table TEFPROMIS9624B submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted adsl.xpt and adpromis.xpt.

Abbreviations: n, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System

PROMIS-29 Fatigue Item HI7

Most subjects reported “a little bit” to “somewhat” fatigue at Baseline, followed by “quite a bit” ([Table 87](#) and [Table 88](#)). [Table 87](#) displays category change from Baseline to Week I-12. Most subjects experienced a one-category improvement. However, subjects who reported with “a little bit” of fatigue at Baseline mostly experienced “no change,” followed by a one-category improvement; for those with baseline symptom severity of “quite a bit,” a similar percentage of subjects experienced one- and two-category improvements. [Table 88](#) displays category change from Baseline to Week M-44. Most subjects experienced a two-category improvement, with the exception of subjects with baseline symptom severity of “very much,” where a three-category improvement was most common. The difference in the percentage of subjects experiencing two- and three-category improvements was minimal, however. The relatively large proportion of subjects in the high improvement categories from Baseline to Week M-44 should be interpreted with caution, as a large percentage of subjects had an ICE and were no longer on their originally assigned treatment at Week M-44.

Table 87. Category Change (n (%)) in PROMIS-29 Fatigue Item HI7 From Baseline to Week I-12 by Baseline PROMIS-29 Fatigue Item HI7

PROMIS-29 Fatigue Item HI7 Change From Baseline to Week I-12								
PROMIS-29 Fatigue Item HI7 at Baseline	Worsened ≥3 Categories	Worsened 2 Categories	Worsened 1 Category	No Change	Improved 1 Category	Improved 2 Categories	Improved ≥3 Categories	Missing
Not at all (n=63)	1 (1.6%)	9 (14.3%)	18 (28.6%)	33 (52.4%)	0	0	0	2 (3.2%)
A little bit (n=181)	0	9 (5.0%)	24 (13.3%)	78 (43.1%)	54 (29.8%)	0	0	16 (8.8%)
Somewhat (n=193)	0	6 (3.1%)	14 (7.3%)	56 (29.0%)	78 (40.4%)	27 (14.0%)	0	12 (6.2%)
Quite a bit (n=164)	0	0	15 (9.1%)	35 (21.3%)	44 (26.8%)	45 (27.4%)	14 (8.5%)	11 (6.7%)
Very much (n=77)	0	0	0	15 (19.5%)	20 (26.0%)	13 (16.9%)	18 (23.4%)	11 (14.3%)

Source: Analyst generated table modified from Table TEFPROMIS9522A submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted adsl.xpt and adpromis.xpt.

Abbreviations: n, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System

Table 88. Category Change (n (%)) in PROMIS-29 Fatigue Item HI7 From Baseline to Week M-44 by Baseline PROMIS-29 Fatigue Item HI7

PROMIS-29 Fatigue Item HI7 Change From Baseline to Week M-44								
PROMIS-29 Fatigue Item HI7 at Baseline	Worsened ≥3 Categories	Worsened 2 Categories	Worsened 1 Category	No Change	Improved 1 Category	Improved 2 Categories	Improved ≥3 Categories	Missing
Not at all (n=50)	0	2 (4.0%)	10 (20.0%)	30 (60.0%)	0	0	0	8 (16.0%)
A little bit (n=150)	0	1 (0.7%)	9 (6.0%)	52 (34.7%)	63 (42.0%)	0	0	25 (16.7%)
Somewhat (n=161)	0	2 (1.2%)	6 (3.7%)	30 (18.6%)	58 (36.0%)	51 (31.7%)	0	14 (8.7%)
Quite a bit (n=127)	0	0	6 (4.7%)	10 (7.9%)	31 (24.4%)	33 (26.0%)	22 (17.3%)	25 (19.7%)
Very much (n=58)	0	0	0	5 (8.6%)	12 (20.7%)	10 (17.2%)	23 (39.7%)	8 (13.8%)

Source: Analyst generated table modified from Table TEFPROMIS9624A submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted adsl.xpt and adpromis.xpt.

Abbreviations: n, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System

The review team determined that a one-category improvement on the PROMIS-29 Fatigue Item FATEXP40 and Item HI7 was acceptable to support further anchor-based meaningful change analyses. A one-category improvement in these anchor items corresponds to the target anchor change category of “moderately better” in PGIC. A one-category improvement on the five-category PROMIS-29 Fatigue Item FATEXP40 and PROMIS-29 Fatigue Item HI7 could occur in the following ways:

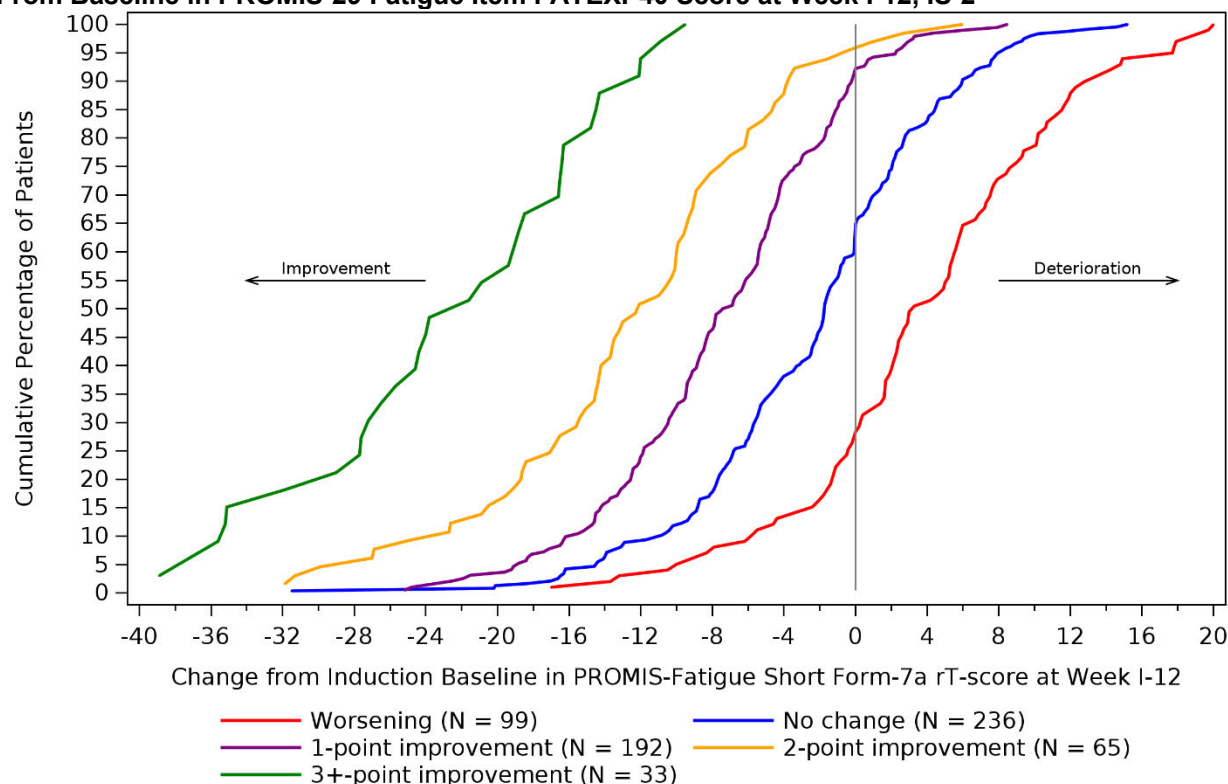
- Change from “very much” to “quite a bit”
- Change from “quite a bit” to “somewhat”
- Change from “somewhat” to “a little bit”
- Change from “a little bit” to “not at all”

Meaningful Change Threshold Range: IS-2

PROMIS-29 Fatigue Item FATEXP40 as the Anchor

[Figure 32](#) shows the empirical cumulative distribution function (eCDF) plot of change from Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score by PROMIS-29 Fatigue Item FATEXP40 category of change at Week I-12. The eCDF plot shows a clear and consistent separation between one-category improvement and “no change” and worsening. The median change in the PROMIS-Fatigue SF-7a rT-scores for subjects who had a one-category improvement in fatigue is -7.15. While using a meaningful change threshold of -7.15 would allow 50% of subjects who reported a one category improvement to be correctly classified as having experienced a meaningful improvement, it would also result in misclassifying more than 20% of subjects who reported no change or worsening. To minimize the misclassification rate, a threshold of -9 is necessary.

Figure 32. eCDF Curves for Change From Baseline in PROMIS-Fatigue SF-7a rT-score by Change From Baseline in PROMIS-29 Fatigue Item FATEXP40 Score at Week I-12, IS-2



Source: Analyst figure, verified with Figure GEFPROMISS9503B of the Applicant's response to FDA IR dated May 10, 2024. Analysis was verified using Applicant submitted adppromr.xpt and qs.xpt. Abbreviations: eCDF, empirical cumulative distribution function; IS-2, Induction Study 2; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

What subjects consider to be clinically meaningful improvement may be impacted by the subjects' baseline fatigue symptom severity. Therefore, subjects' baseline symptom severity should be considered when determining clinically meaningful within-subjects improvement thresholds. [Table 89](#) shows the change from Baseline to Week-12 in PROMIS-Fatigue SF-7a rT-score for subjects with a one-category of improvement in PROMIS-29 Fatigue Item FATEXP40 by Baseline PROMIS-29 Fatigue Item FATEXP40 score. When subjects' baseline fatigue severity is taken into account, the median change from Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score for different baseline symptom severity varies, especially for subjects who had baseline fatigue "very much." Notably, subjects with higher symptom severity require smaller changes to be considered meaningfully improved compared to those with less severe symptoms. FDA's assessment concluded that a clinically meaningful improvement range in PROMIS-Fatigue SF-7a rT-scores based on PROMIS-29 Fatigue Item FATEXP40 should be between -9.8 to -2.7.

Table 89. Change From Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score for Subjectss With a 1-Category of Improvement in PROMIS-29 Fatigue Item FATEXP40 by Baseline PROMIS-29 Fatigue Item FATEXP40 Score, IS-2

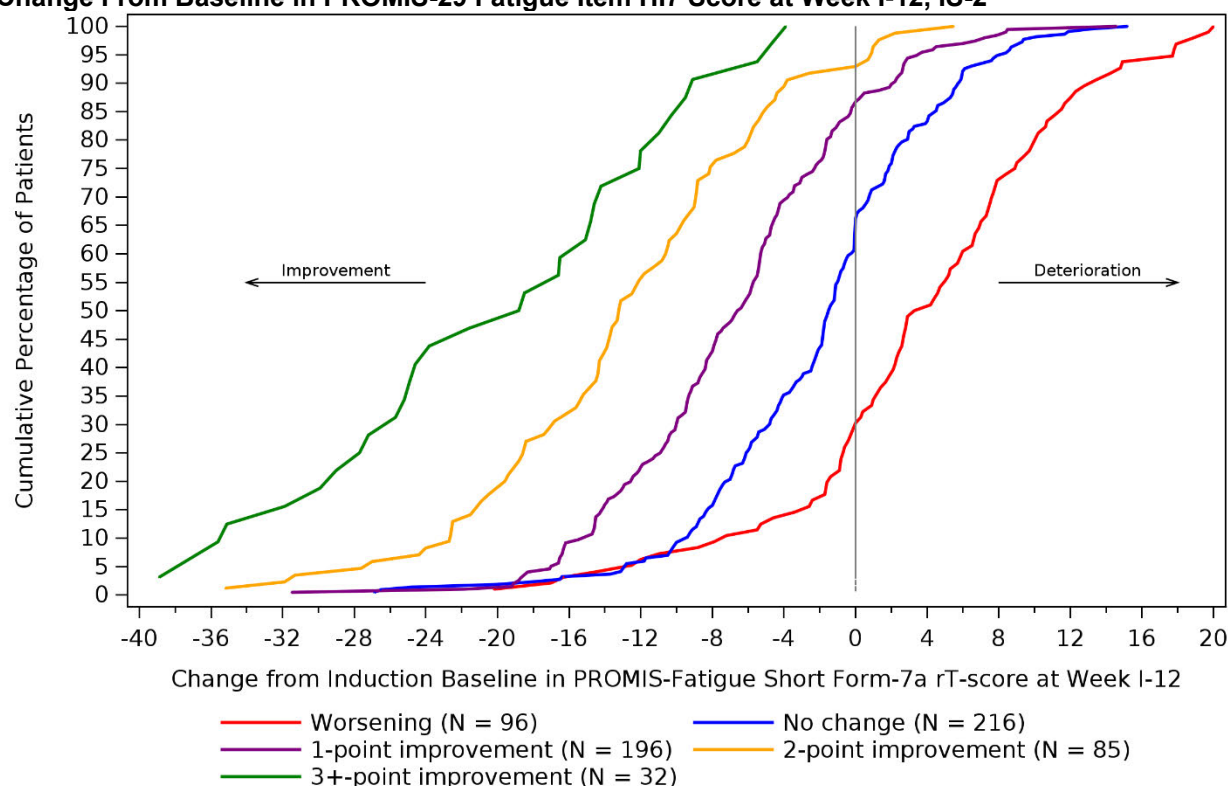
Score	Percentile Rank	Baseline PROMIS-29 Fatigue Item FATEXP40 Response Category				Total
		A Little Bit (N=33)	Somewhat (N=47)	Quite a Bit (N=32)	Very Much (N=8)	
Change from baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score	10 percentile	-17.6	-17.4	-13.1	-10	-15.50
	25 percentile	-14.5	-10.6	-11	-7.4	-11.80
	50 percentile	-9.8	-7.7	-6.8	-2.7	-7.15
	75 percentile	-4.6	-3.4	-3.4	-0.7	-3.25
	90 percentile	-0.65	0	-0.3	2.6	-0.20

Source: Analyst table modified from Table TEFPR0MIS9517B submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted datasets; adpromr.xpt, adsl.xpt, and adpromis.xpt. Abbreviations: IS-2, Induction Study 2; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System

PROMIS-29 Fatigue Item HI7 as the Anchor

[Figure 33](#) shows the eCDF plot of change from baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score by PROMIS-29 Fatigue Item HI7 category of change at Week I-12. The eCDF plot shows a clear and consistent separation between one-category improvement and no change and worsening. The median change in the PROMIS-Fatigue SF-7a rT-scores for subjects who had a one-category improvement in fatigue is -6.50. While using a meaningful change threshold of -6.50 would allow 50% of subjects who reported a one category improvement to be correctly classified as having experienced a meaningful improvement, using -6.50 as the threshold would result in misclassifying more than 20% of subjects who reported no change or worsening on the anchor. To minimize the misclassification rate, a threshold of -9 is necessary.

Figure 33. eCDF Curves for the Change From Baseline in PROMIS-Fatigue SF-7a rT-score by Change From Baseline in PROMIS-29 Fatigue Item HI7 Score at Week I-12, IS-2



Source: Analyst figure, verified with Figure GEFPROMISS9503A of the Applicant's response to FDA IR dated May 10, 2024.

Analysis was verified using Applicant submitted adppromr.xpt and qs.xpt.

Abbreviations: eCDF, empirical cumulative distribution function; IS-2, Induction Study 2; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

[Table 90](#) shows the change from Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score for subjects with one-category of improvement in PROMIS-29 Fatigue Item HI7 by Baseline PROMIS-29 Fatigue Item HI7 score. When subjects' baseline fatigue severity is taken into account, the change from Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score for different baseline symptom severity vary. Subjects with higher symptom severity require smaller changes to be considered meaningfully improved compared to those with less severe symptoms. FDA's assessment concluded that a clinically meaningful within-subjects improvement range in PROMIS-Fatigue SF-7a rT-scores based on the PROMIS-29 Fatigue Item HI7 should be between -9 to -4.65.

Table 90. Change From Baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score for Subjects With a 1-Category Improvement in PROMIS-29 Fatigue Item HI7 by Baseline PROMIS-29 Fatigue Item HI7 Score, IS-2

Score	Percentile Rank	Baseline PROMIS-29 Fatigue Item HI7 Response Category				Total
		A Little Bit (N=33)	Somewhat (N=47)	Quite a Bit (N=32)	Very Much (N=8)	
Change from baseline to Week I-12 in PROMIS-Fatigue SF-7a rT-score	10 percentile	-16.20	-14.50	-13.50	-9.85	-14.70
	25 percentile	-14.50	-10.60	-10.20	-8.60	-10.85
	50 percentile	-8.05	-6.75	-4.75	-4.65	-6.50
	75 percentile	-4.50	-3.00	-1.45	-1.15	-2.25
	90 percentile	0.50	1.30	2.40	5.85	2.20

Source: Analyst generated table modified from Table TEFROMIS9517A submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted datasets; adpromr.xpt, adsl.xpt, and adpromis.xpt. Abbreviations: IS-2, Induction Study 2; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

Conclusion, IS-2

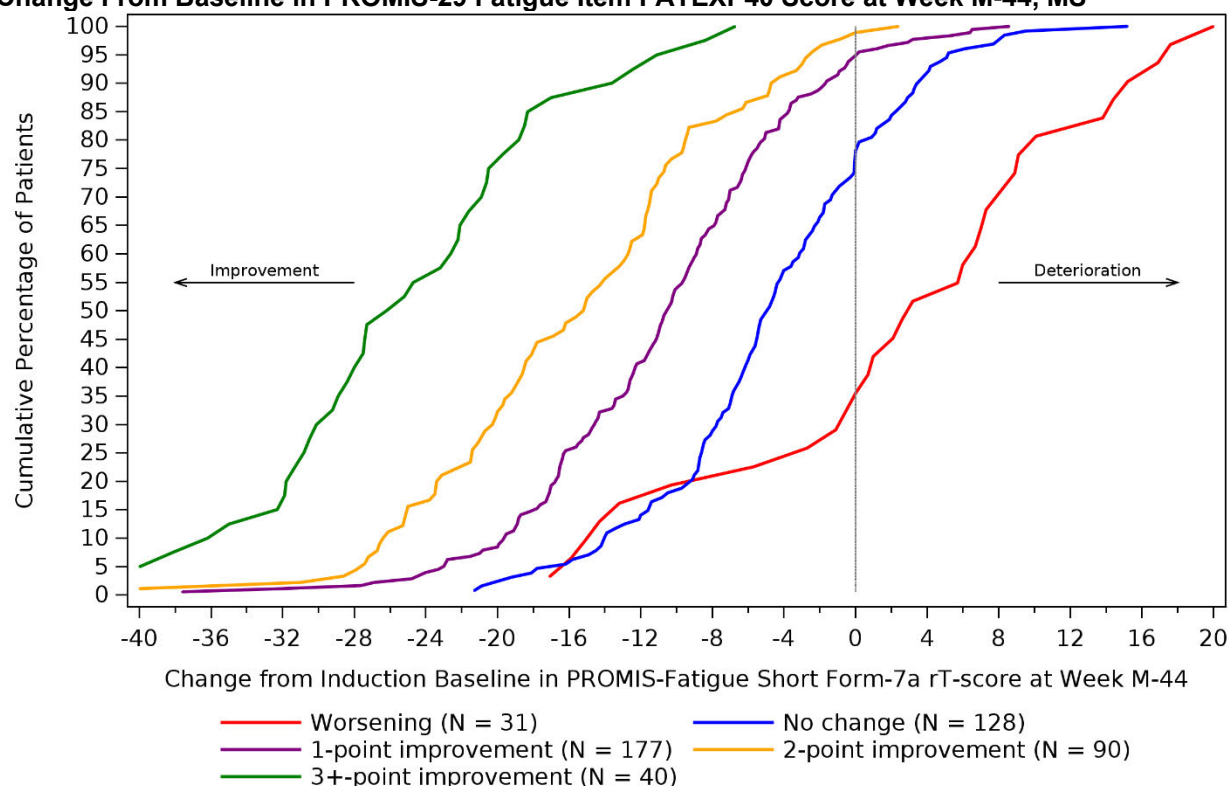
Based on the results of the anchor-based analyses using the two fatigue anchor scales (PROMIS-29 Fatigue Item FATEXP40 and PROMIS-29 Fatigue Item HI7), the review team concluded the final meaningful within-subjects improvement range should be between -9.8 to -2.7 to appropriately account for subjects at all levels of baseline fatigue severity and minimize the misclassification of subjects who experienced no change or worsening.

Meaningful Change Threshold Range: MS

PROMIS-29 Fatigue Item FATEXP40 as the Anchor

[Figure 34](#) shows the eCDF plot of change from Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score by PROMIS-29 Fatigue Item FATEXP40 category of change at Week M-44. The eCDF plot shows a clear and consistent separation between one-category improvement and no change and worsening. The median change in the PROMIS-Fatigue SF-7a rT-scores for subjects who had a 1-category improvement in fatigue is -10.5. However, using -10.5 as the threshold would result in misclassifying more than 20% of subjects who reported no change or worsening on the anchor. To minimize the misclassification rate, a threshold of -14.5 is necessary.

Figure 34. eCDF Curves for the Change From Baseline in PROMIS-Fatigue SF-7a rT-score by Change From Baseline in PROMIS-29 Fatigue Item FATEXP40 Score at Week M-44, MS



Source: Analyst figure, verified with Figure GEFPROMISS9603B of the Applicant's response to FDA IR dated May 10, 2024.

Analysis was verified using Applicant submitted adppromr.xpt and qs.xpt.

Abbreviations: eCDF, empirical cumulative distribution function; MS, Maintenance Study; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

[Table 91](#) shows the change from Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for subjects with a one-category improvement in Item FATEXP40 by Baseline Item FATEXP40 score. When subjects' baseline fatigue severity is taken into account, the median change from Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for different baseline symptom severity vary, especially for subjects who had baseline fatigue "a little bit". Subjects with higher symptom severity requires smaller changes to be considered meaningfully improved compared to those with less severe symptoms. The review team concluded that a meaningful within-subjects improvement range in PROMIS-Fatigue SF-7a rT-scores based on Item FATEXP40 should be between -14.5 to -8.2.

Table 91. Change From Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for Subjectss With a 1-Category of Improvement in PROMIS-29 Fatigue Item FATEXP40 by Baseline PROMIS-29 Fatigue Item FATEXP40 Score, MS

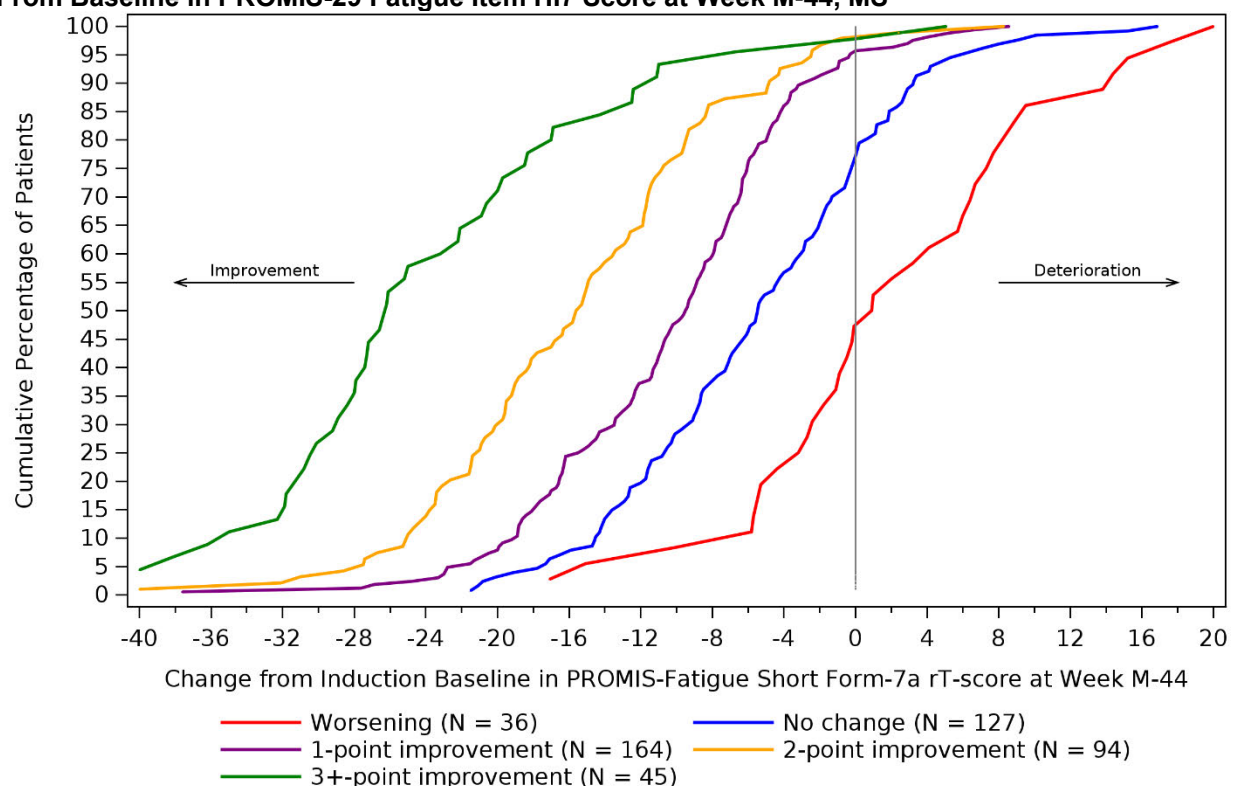
Score	Percentile Rank	Baseline PROMIS-29 Fatigue Item FATEXP40 Response Category				Total
		A Little Bit (N=33)	Somewhat (N=47)	Quite a Bit (N=32)	Very Much (N=8)	
Change from baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score	10 percentile	-22.80	-18.20	-15.50	-10.80	-19.50
	25 percentile	-17.80	-14.80	-11.30	-9.30	-16.20
	50 percentile	-12.80	-9.90	-8.80	-8.20	-10.50
	75 percentile	-7.80	-6.10	-3.80	-5.30	-6.00
	90 percentile	-1.60	-3.30	-0.60	-0.20	-1.60

Source: Analyst table modified from Table TEFROMIS9619B submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted datasets; adpromr.xpt, adsl.xpt, and adpromis.xpt. Abbreviations: MS, Maintenance Study; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

PROMIS-29 Fatigue Item HI7 as the Anchor

[Figure 35](#) shows the eCDF plot of change from Baseline to Week 44 in PROMIS-Fatigue SF-7a rT-score by Fatigue Item HI7 category of change at Week 44. The eCDF plot shows a clear and consistent separation between 1-category improvement and No Change and Worsening. The median change in the PROMIS-Fatigue SF-7a rT-scores for subjects who had 1-category improvement in fatigue is -9.45. However, using -9.45 as the threshold would result in misclassifying more than 20% of subjects who reported no change or worsening on the anchor. To minimize the misclassification rate, a threshold of -14 is necessary.

Figure 35. eCDF Curves for Change From Baseline in PROMIS-Fatigue SF-7a rT-score by Change From Baseline in PROMIS-29 Fatigue Item HI7 Score at Week M-44, MS



Source: Analyst figure, verified with Figure GEFPROMIS9603A of the Applicant's response to FDA IR dated May 10, 2024. Analysis was verified using Applicant submitted adppromr.xpt and qs.xpt.
Abbreviations: eCDF, empirical cumulative distribution function; MS, Maintenance Study; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

[Table 92](#) shows the change from Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for subjects with a 1-category of improvement in PROMIS-29 Fatigue Item HI7 by Baseline PROMIS-29 Fatigue Item HI7 score. When subjects' baseline fatigue severity is taken into account, the median change from Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for different baseline symptom severity varies, especially for subjects who had baseline fatigue of "a little bit". Subjects with higher symptom severity requires smaller changes to be considered meaningful compared to those with less severe symptoms. The review team concluded that a clinically meaningful within-subjects improvement range in PROMIS-Fatigue SF-7a rT-scores based on the anchor, PROMIS-29 Fatigue Item HI7, should be between -14 to -6.75.

Table 92. Change From Baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score for Subjects With a 1-Category of Improvement in PROMIS-29 Fatigue Item HI7 by Baseline PROMIS-29 Fatigue Item HI7 Score, MS

Score	Percentile Rank	Baseline PROMIS-29 Fatigue Item HI7 Response Category				Total
		A Little Bit (N=33)	Somewhat (N=47)	Quite a Bit (N=32)	Very Much (N=8)	
Change from baseline to Week M-44 in PROMIS-Fatigue SF-7a rT-score	10 percentile	-21.5	-18.6	-16.7	-10.8	-18.90
	25 percentile	-17.1	-14.9	-11	-9	-15.35
	50 percentile	-12.5	-9.15	-6.8	-6.75	-9.45
	75 percentile	-8.1	-6.1	-3.6	-3.8	-6.00
	90 percentile	-4.6	-3.7	-0.9	-2.8	-2.80

Source: Analyst table modified from Table TEFPROMIS9619A submitted by Applicant in response to FDA IR dated May 10, 2024. Verified using Applicant submitted datasets; adpromr.xpt, adsl.xpt, and adpromis.xpt. Abbreviations: MS, Maintenance Study; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

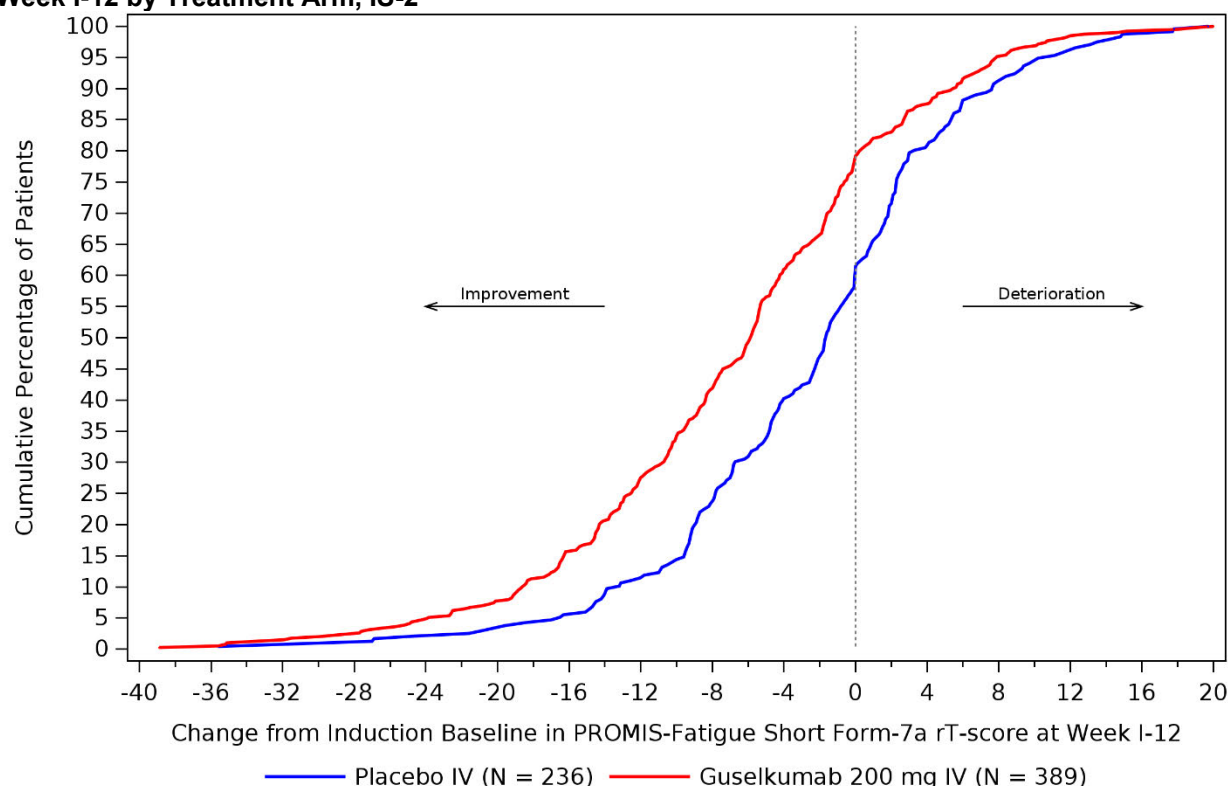
Conclusion, MS

Considering the results from the anchor-based analyses, using the two fatigue anchor scales (PROMIS-29 Fatigue Item FATEXP40 and PROMIS-29 Fatigue Item HI7), the review team concluded the final meaningful within-subjects improvement range in PROMIS-Fatigue SF-7a rT-scores should be between -14.5 to -6.75 to appropriately account for subjects at all levels of baseline fatigue severity and minimize the misclassification of subjects who experienced no change or worsening.

16.4.2.2. Conclusion, IS-2 and MS

To determine how much more likely an average subjects given guselkumab over placebo would experience a meaningful improvement in their fatigue symptoms, the review team examined the eCDF plot of changes in the PROMIS-Fatigue SF-7a rT-score from baseline to Week I-12 by the treatment arm. [Figure 36](#) shows the eCDF plot of changes in PROMIS-Fatigue SF-7a rT-score from baseline to Week I-12 by treatment arm. there is adequate, sustained separation between the eCDF curves for the two treatment arms in the range subjects consider meaningful (i.e., -9.8 to -2.7). The review team concluded that the observed treatment effect substantiated a clinically meaningful within-subjects improvement in subjects receiving drug versus placebo in IS-2.

Figure 36. eCDF Curves for the Change From Baseline in PROMIS-Fatigue SF-7a rT-score at Week I-12 by Treatment Arm, IS-2

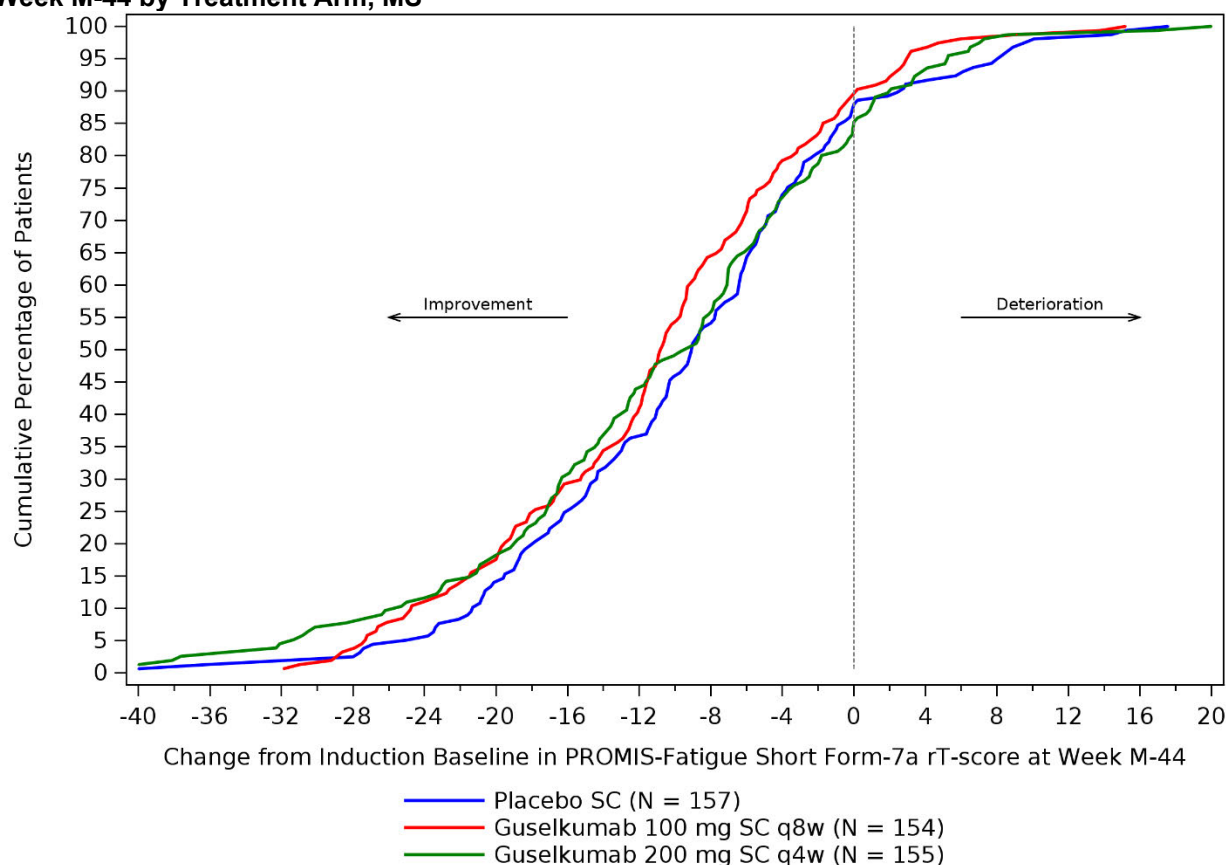


Source: Analyst figure using Applicant submitted adppromr.xpt and qs.xpt.

Abbreviations: eCDF, empirical cumulative distribution function; IS-2, Induction Study 2; IV, intravenous; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; SF, Short Form

[Figure 37](#) shows the eCDF plot of changes in the PROMIS-Fatigue SF-7a rT-scores from Baseline to Week M-44 by treatment arm. There is no clear or consistent separation between treatment arms in the FDA-derived meaningful change threshold range of -14.5 to -6.75. The review team concluded that there is not sufficient evidence to support that the treatment effect at Week M-44 represents a meaningful change in fatigue to subjects in MS.

Figure 37. eCDF Curves for the Change From Baseline in PROMIS-Fatigue SF-7a rT-score at Week M-44 by Treatment Arm, MS



Source: Analyst figure using Applicant submitted adppromr.xpt and qs.xpt.

Abbreviations: eCDF, empirical cumulative distribution function; MS, Maintenance Study; N, number of subjects; PROMIS, Subjects-Reported Outcomes Measurement Information System; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SF, Short Form

17. Clinical Safety

17.1. Safety Analysis by Demographic Subgroup

17.1.1. Sex

In the primary induction database, 224/522 (42.9%) subjects in the guselkumab 200 mg IV treatment arm, 48/107 (44.9%) subjects in the guselkumab 400 mg IV treatment arm, and 158/385 (41.0%) subjects in the placebo arm were female; 298/522 (57.1%) subjects in the guselkumab 200 mg IV treatment arm, 59/107 (55.1%) subjects in the guselkumab 400 mg IV treatment arm, and 227/385 (59%) subjects in the placebo arm were male.

In the primary maintenance database, 85/186 (45.7%) subjects in the guselkumab 100 mg SC treatment arm, 90/190 (47.4%) subjects in the guselkumab 200 mg SC treatment arm, and 82/192 (42.7%) subjects in the placebo arm were female; 101/186 (54.3%) subjects in the guselkumab

100 mg SC treatment arm, 100/190 (52.6%) subjects in the guselkumab 200 mg SC treatment arm, and 110/192 (57.3%) subjects in the placebo arm were male.

[Table 93](#) and [Table 94](#) show an overview of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs leading to discontinuation of study, AEs leading to interruption of study drug, and SAEs with fatal outcome, based on sex, that were reported across treatment arms during the induction and maintenance treatment periods, respectively.

Table 93. Overview of Adverse Events in Subjects by Sex, Safety Population, IS-1 and IS-2 (Pooled)

Event Category	Female			Male		
	Guselkumab 200 mg IV N=224 n (%)	Guselkumab 400 mg IV N=48 n (%)	Placebo IV N=158 N (%)	Guselkumab 200 mg IV N=298 n (%)	Guselkumab 400 mg IV N=59 n (%)	Placebo IV N=227 n (%)
Any AE	121 (54)	28 (58.3)	87 (55.1)	132 (44.3)	25 (42.4)	110 (48.5)
Any SAE	6 (2.7)	2 (4.2)	14 (8.9)	7 (2.3)	1 (1.7)	12 (5.3)
AE leading to discontinuation of study drug	2 (0.9)	0	7 (4.4)	6 (2)	0	7 (3.1)
AE leading to interruption of study drug	5 (2.2)	0	1 (0.6)	4 (1.3)	0	3 (1.3)
SAEs with fatal outcome	1 (0.4)	0	2 (1.3)	0	0	0

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as events that begin or worsen either on or after the first dose of the study drug in IS-1 or IS-2.

Duration is 12 weeks.

Includes all subjects that have received at least one dose of study drug in the double-blind, placebo-controlled 12-week induction studies, IS-1 and IS-2 (pooled).

Abbreviations: AE, adverse event; IS-1 Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of patients in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event

Table 94. Overview of Adverse Events in Subjects by Sex, Safety Population, MS

Event Category	Female			Male		
	Guselkumab 100 mg SC N=85 n (%)	Guselkumab 200 mg SC N=90 n (%)	Placebo SC N=82 N (%)	Guselkumab 100 mg SC N=101 n (%)	Guselkumab 200 mg SC N=100 n (%)	Placebo SC N=110 n (%)
Any AE	62 (72.9)	68 (75.6)	60 (73.2)	58 (57.4)	65 (65.0)	71 (64.5)
Any SAE	4 (4.7)	6 (6.7)	0	1 (1.0)	6 (6.0)	1 (0.9)
AE leading to discontinuation of study drug	4 (4.7)	4 (4.4)	8 (9.8)	3 (3.0)	1 (1.0)	5 (4.5)
AE leading to interruption of study drug	2 (2.4)	2 (2.2)	1 (1.2)	2 (2.0)	0	1 (0.9)
SAEs with fatal outcome	0	0	0	0	0	0

Source: adae.xpt; Software: R.

Includes all subjects that received at least one dose of study drug and who had a modified Mayo score of 5 to 9 who were randomized and treated in MS

Abbreviations: AE, adverse event; IV, intravenous; MS, Maintenance Study; N, number of patients in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous

During the induction studies, a higher proportion of TEAEs were reported females than males, and a similar proportion of female and male subjects reported TEAEs in MS. The number of SAEs, AEs leading to study discontinuation, or AEs leading to interruption of study reported between were too small to draw conclusions regarding differences in safety profile within the subgroup across treatment and/or placebo arms.

17.1.2. Age

In the primary induction safety database, 488/522 (93.5%) subjects in the guselkumab 200 mg IV group, 101/107 (94.4%) subjects in the guselkumab 400 mg IV group, and 364/385 (94.5%) subjects in the placebo group were age <65 years; and 34/522 (6.5%) subjects in the guselkumab 200 mg IV group, 6/107 (5.6%) subjects in the guselkumab 400 mg IV group, and 21/385 (5.5%) subjects in the placebo group were age ≥65 years.

In the primary maintenance safety database, 174/186 (93.5%) subjects in the guselkumab 100mg SC treatment arm, 179/190 (94.2%) subjects in the guselkumab 200 mg SC treatment arm, and 180/192 (93.8%) subjects in the placebo arm were age <65 years; and 12/186 (6.5%) subjects in the guselkumab 100 mg SC treatment arm, 11/190 (5.8%) subjects in the guselkumab 200 mg SC treatment arm, and 12/192 (6.2%) subjects in the placebo arm were age ≥65 years.

[Table 95](#) and [Table 96](#) show an overview of TEAEs, SAEs, AEs leading to discontinuation of study, AEs leading to interruption of study drug, and SAEs with fatal outcome in subjects <65 years and ≥65 years of age, that were reported across treatment arms during the induction and maintenance treatment periods, respectively.

Table 95. Overview of Adverse Events in Subjects by Age, Safety Population, IS-1 and IS-2 (Pooled)

Event Category	Age <65 Years			Age ≥65 Years		
	Guselkumab 200 mg IV N=488 n (%)	Guselkumab 400 IV N=101 n (%)	Placebo IV N=364 N (%)	Guselkumab 200 mg IV N=34 n (%)	Guselkumab 400 mg IV N=6 n (%)	Placebo IV N=21 n (%)
Any AE	233 (47.7)	49 (48.5)	185 (50.8)	20 (58.8)	4 (66.7)	12 (57.1)
Any SAE	13 (2.7)	2 (2)	22 (6)	0	1 (16.7)	4 (19)
AE leading to discontinuation of study drug	8 (1.6)	0	14 (3.8)	0	0	0
AE leading to interruption of study drug	8 (1.6)	0	4 (1.1)	1 (2.9)	0	0
SAEs with fatal outcome	1 (0.2)	0	0	0	0	2 (9.5)

Source: adae.xpt; Software: R.

Treatment-emergent adverse events defined as events that begin or worsen either on or after the first dose of the study drug in IS-1 or IS-2.

Duration is 12 weeks.

Includes all subjects that have received at least one dose of study drug in the double-blind, placebo-controlled 12-week induction studies, IS-1 and IS-2 (pooled).

Abbreviations: AE, adverse event; CI, confidence interval; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of patients in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event

Table 96. Overview of Adverse Events in Subjects by Age, Safety Population, MS

Event Category	Age <65 Years			Age ≥65 Years		
	Guselkumab 100 mg SC N=174 n (%)	Guselkumab 200 mg SC N=179 n (%)	Placebo SC N=180 N (%)	Guselkumab 100 mg SC N=12 n (%)	Guselkumab 200 mg SC N=11 n (%)	Placebo SC N=12 n (%)
Any AE	109 (62.6)	126 (70.4)	119 (66.1)	11 (91.7)	7 (63.6)	12 (100.0)
Any SAE	4 (2.3)	10 (5.6)	0	1 (8.3)	2 (18.2)	1 (8.3)
AE leading to discontinuation of study drug	7 (4.0)	4 (2.2)	10 (5.6)	0	1 (9.1)	3 (25.0)
AE leading to interruption of study drug	4 (2.3)	1 (0.6)	2 (1.1)	0	1 (9.1)	0
SAEs with fatal outcome	0	0	0	0	0	0

Source: adae.xpt; Software: R.

Includes all subjects that received at least one dose of study drug and who had a modified Mayo score of 5 to 9 who were randomized and treated in MS.

Abbreviations: AE, adverse event; CI, confidence interval; MS, Maintenance Study; N, number of patients in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous

In the induction and maintenance periods, the proportion of any TEAEs reported were comparable between arms among subjects age <65 years. However, given that a small number of subjects aged ≥65 years were enrolled in either study, clinical inference of potential differences in safety profiles within the two age cohorts is limited.

17.1.3. Race

In the primary induction safety database, 376/522 (72.0%) of the subjects who received guselkumab 200 mg IV were White, 111/522 (21.3) subjects were Asian, 5/522 (1%) subjects were Black, 2/522 (0.4%) subjects were of multiple races, 2/522 (0.4%) subjects were Native Hawaiian or Other Pacific Islander, 1/522 (0.2%) subjects were American Indian or Alaskan Native, and 25/522 (4.8%) subjects did not report race. Of the subjects who received guselkumab 400 mg IV, 74/107 (69.2%) subjects were White, 27/107 (25.2%) subjects were Asian, 1/107 (0.9%) subjects were Black, and 5/107 (4.7%) subjects did not report race. Of the subjects who received placebo, 282/385 (73.2%) subjects were White, 86/385 (22.3%) subjects were Asian, 4/385 (1.0) were Black, and 13/385 (3.4%) of subjects did not report race.

In the primary maintenance safety database, of the 137/186 (73.7%) subjects who received guselkumab 100 mg SC were White, 38/186 (20.4%) subjects were Asian, 2/186 (1.1%) were Black, and 9/186 (4.8%) of subjects did not report race. Of the subjects who received guselkumab 200 mg SC, 135/190 (71.1%) subjects were White, 44/190 (23.2) subjects were Asian, 2/190 (1.1%) were subjects Black, and 9/190 (4.7%) subjects did not report race. Of the subjects who received placebo, 144/192 (75%) subjects were White, 34/192 (17.7%) were Asian, 2/192 (1%) subjects were Black, 1/192 (0.5%) subjects were Native Hawaiian or other Pacific Islander, 1/192 (0.5%) subjects were of multiple races, and 10/192 (5.2%) of subjects did not report race.

[Table 97](#) and [Table 98](#) show an overview of TEAEs, SAEs, AEs leading to discontinuation of study, AEs leading to interruption of study drug, and SAEs with fatal outcome based on race that were reported across treatment arms during the induction and maintenance treatment periods, respectively.

Table 97. Overview of Adverse Events in Subjects by Race, Safety Population, IS-1 and IS-2 (Pooled)

Event Category	White			Non-White		
	Guselkumab 200 mg IV N=376 n (%)	Guselkumab 400 IV N=74 n (%)	Placebo IV N=282 N (%)	Guselkumab 200 mg IV N=121 n (%)	Guselkumab 400 mg IV N=28 n (%)	Placebo IV N=90 n (%)
Any AE	171 (45.5)	35 (47.3)	140 (49.6)	82 (56.2)	18 (54.5)	57 (55.3)
Any SAE	7 (1.9)	2 (2.7)	21 (7.4)	6 (4.1)	1 (3.0)	5 (4.9)
AE leading to discontinuation of study drug	6 (1.6)	0	12 (4.3)	2 (1.4)	0	2 (1.9)
AE leading to interruption of study drug	8 (2.1)	0	3 (1.1)	1 (0.7)	0	1 (1.0)
SAEs with fatal outcome	0	0	2 (0.7)	1 (0.7)	0	0

Source: adae.xpt; Software: R.

Subjects that did not report race are included in the "Non-White" subgroup.

Abbreviations: AE, adverse event; CI, confidence interval; IS-1, Induction Study 1; IS-2, Induction Study 2; IV, intravenous; N, number of patients in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event

Table 98. Overview of Adverse Events in Subjects by Race, Safety Population, MS

Event Category	White			Non-White		
	Guselkumab 100 mg SC N=137 n (%)	Guselkumab 200 mg SC N=135 n (%)	Placebo SC N=144 N (%)	Guselkumab 100 mg SC N=40 n (%)	Guselkumab 200 mg SC N=46 n (%)	Placebo SC N=38 n (%)
Any AE	88 (64.2)	85 (63.0)	94 (65.3)	32 (65.3)	48 (87.3)	37 (77.1)
Any SAE	4 (2.9)	5 (3.7)	0	1 (2.0)	7 (12.7)	1 (2.1)
AE leading to discontinuation of study drug	4 (2.9)	5 (3.7)	9 (6.2)	3 (6.1)	0	4 (8.3)
AE leading to interruption of study drug	4 (2.9)	2 (1.5)	2 (1.4)	0	0	0
SAEs with fatal outcome	0	0	0	0	0	0

Source: adae.xpt; Software: R.

Subjects that did not report race are included in the "Non-White" subgroup.

Includes all subjects that received at least one dose of study drug and who had a modified Mayo score of 5 to 9 who were randomized and treated in MS.

Abbreviations: AE, adverse event; CI, confidence interval; MS, Maintenance Study; N, number of subjects in treatment arm; n, percentage of subjects with at least one event; SAE, serious adverse event; SC, subcutaneous

Given that a small number of Non-White subjects were enrolled, clinical inference of potential differences in safety profiles among treatment arms for this subgroup is limited.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Guselkumab is a human monoclonal IgG1 λ (lambda) antibody that selectively binds the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. Per the Applicant, IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

21. Other Drug Development Considerations

Not applicable.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Division of New Drug Study Integrity within the Office of Scientific Investigations (OSI) was consulted, and on-site inspections at two investigational sites for IS-2 and MS: Site #PL10008 (Adam Kropon, MD; Torun, Kujawsko-Pomorskie, 87-100, Poland) and Site #PL10021 (Juliusza Słowackiego 19 Szczecin, 71-434, Poland). Minor protocol deviations were found, which the review team deemed appeared unlikely to impact interpretation of efficacy and safety results. OSI ultimately determined that no major issues regarding data integrity or submission quality were identified. See Clinical Inspection Summary uploaded by Glenn Mannheim, M.D., on August 13, 2024, (DARRTS Reference ID: 5429095).

OSIS was consulted and completed an inspection of the analytical portion of in vivo bioequivalence studies CNT01959EDI1001 and CNT01959CRD1003 performed at Janssen Research & Development, Spring House, PA, submitted to support guselkumab solution for infusion 10 mg/ml and solution for injection 200 mg/2 ml. No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out meeting. However, two findings were observed during the study. See Bioequivalence Establishment Inspection Report

review uploaded by Sri Rama Krishnaiah Yellela, on July 16, 2024, (DARRTS Reference ID: 5414634).

- Pre-dose ADA titers for subjects #100130 and #100154 were not reported in the bioanalytical quality summary [BQS] report submitted to FDA for Study CNTO1959EDI1001
- ADA titers were not included in BQS report submitted to the FDA for Study CNTO1959CRD1003

Based on the review of inspection findings, exhibits, and the site's response during the inspection, ADA titers for both studies are reliable. No issues were identified with source records regarding ADA titers used to confirm ADA positive subjects.¹⁶ An IR was sent to the Applicant for explanation of why these were not included in the BQS reports, and potential impact on assessment of ADA assessment. The Applicant's response was deemed adequate, and the review team concluded that the interpretability of study results (including assessment of immunogenicity) was not impacted.

In addition, OSIS deemed on-site inspections were not needed for CRS Manheim and CRS Berlin as site inspections for these sites had been conducted in June 2024 and July 2024, respectively, for BLA 761379. After review, OSIS concluded that there were no human subject safety concerns and data from the reviewed study was reliable. See Bioequivalence Establishment Inspection Report review uploaded by James Lumalcuri, on September 6, 2024, (DARRTS Reference ID: 5442598).

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI and the Applicant's draft PI for the proposed new indication of "adult patients with moderately to severely active ulcerative colitis" ([Table 99](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

¹⁶ Bioequivalence Establishment Inspection Report Review by Sri Rama Krishnaiah Yellela, Ph.D. dated July 16, 2024 for full details (DARRTS Reference ID: 5414634)

Table 99. Key Labeling Changes and Considerations Related to the Ulcerative Colitis Indication

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
2 DOSAGE AND ADMINISTRATION	<u>2.4 Recommended Dosage for Ulcerative Colitis</u> Following induction with 200 mg administered by intravenous infusion at Weeks 0, 4 and 8, the Applicant proposed two subcutaneous maintenance dosage regimens (b) (4) (b) (4) compared to placebo for the primary efficacy endpoint and other ranked, secondary endpoints in the clinical trials. While the size of and duration of exposure in the premarket safety database are adequate to support approval, uncertainties remain regarding the risk, and potential dose-dependence, of some adverse events of special interest, including malignancy, as these events occur infrequently and may be more likely to occur after prolonged exposure. Therefore, the text was revised to describe the lower dosage (100 mg Q8W) before the higher dosage (200 mg Q4W) and to emphasize to “use the lowest effective recommended dosage needed to maintain therapeutic response.” Approval of both maintenance dosages along with the phrase, “Use the lowest effective recommended dosage to maintain therapeutic response,” allows providers flexibility and encourages reassessment of response during maintenance therapy in order to avoid the potential risks of long-term drug exposure to a higher dosage if patients are able to maintain therapeutic response with the lower dosage. See Section 6.3.2 for discussion on selection of maintenance dosage and Section 7.6.2 for safety review completed to support the maintenance dosages. <u>2.5 Preparation and Administration Instructions for Subcutaneous Injection</u> The proprietary name was revised to include “TREMIFYA PEN” for the prefilled pen presentation to be consistent with the proposed name, label, and labeling.
5 WARNINGS AND PRECAUTIONS	<u>5.4 Immunizations</u> The wording was revised from (b) (4) to “complete” all age-appropriate immunizations according to current immunization guidelines prior to initiating TREMIFYA and to add additional rationale (“Medications that interact with the immune system may increase the risk of infection following administration of live vaccines”). These revisions are consistent with labeling for other approved immunomodulatory therapies.
6 ADVERSE REACTIONS	<u>6.1 Clinical Trials Experience</u> The description of the clinical trials and was revised to include the clinical response criteria for the maintenance study (Maintenance Study, called UC2) which followed the induction studies (Induction Study 2 [IS-2], called UC1 and Induction Study 1 [IS-1], called UC3). The statement that the safety profile in subjects with UC treated with TREMIFYA was similar to subjects with psoriasis and psoriatic arthritis was removed because - with the exception of

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
	respiratory tract infections, injection site reactions, and arthralgia - the other adverse reactions reported in subjects with psoriasis and psoriatic arthritis were not reported in the UC trials. Furthermore, there may be potential differences in safety profile in patients with UC compared to patients with psoriasis and psoriatic arthritis that are not yet known and the dosage regimens for UC are higher than for the other two indications. Safety analysis of the induction studies indicated that the only adverse reaction reported in $\geq 2\%$ of subjects was respiratory tract infections (defined as COVID-19, upper respiratory tract infection, nasopharyngitis, influenza, respiratory tract infection viral, and respiratory tract infection). Rash, as proposed by the Applicant was not higher in the TREMFYA group compared to the placebo group (2.1% vs 1.6%) and did not meet the definition of an adverse reaction. Rash is included in the currently approved PI in Section 6.2 <i>Postmarketing Experience</i>. Adverse reactions terms in the maintenance study, as proposed by the Applicant, were confirmed by the safety review. The rates of injection site reactions were increased across arms based on analysis of multiple similar terms (defined as injection site reaction, injection site pruritus, injection site erythema, injection site pain, administration site pain, injection site hypersensitivity, injection site rash, injection site urticaria, injection site hematoma, and injection site hemorrhage). Of note, in the maintenance trial (UC2) the 200 mg dosage was administered as two injections of 100 mg, which may impact the rates of injection site reactions. A footnote was added to describe how the 200 mg dosage was administered.
7 DRUG INTERACTIONS	<u>7.1 CYP450 Substrates</u> The Applicant proposed removal of this subsection describing the potential interaction between TREMFYA and patients receiving concomitant CYP450 substrates as found in the currently approved PI. No new drug-drug studies have been conducted with guselkumab and it is not clear that the findings from other monoclonal antibody products, as cited by the Applicant, can be extrapolated to predict the interaction potential of guselkumab. Therefore, the currently approved text was reinserted.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	<u>8.1 Pregnancy</u> <u>Risk Summary</u> The currently approved text states that there (b) (4) However, there are available data from literature, postmarketing reports, and the ongoing TREMFYA pregnancy registry. Therefore, the statement was revised to state that the available data are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. See Section 8.4 and review memo uploaded by Tamara Johnson, MD, MS on July 29, 2024 (DARRTS Reference ID: 5420342).

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
	(b) (4) <i>Clinical Considerations</i> A new subsection describing the risk of adverse pregnancy outcomes and embryo/fetal risk associated with guselkumab exposure in patients with inflammatory bowel disease was added and is consistent with information in approved labeling for other products with IBD indication(s). <u>8.5 Geriatric Use</u> This section was revised to follow the guidance for industry on Geriatric Use when there are insufficient numbers of subjects 65 years of age and older within an indication to determine whether they respond differently from younger adult subjects. In addition, a statement was added to communicate no clinically meaningful differences in PK of guselkumab were observed based on age with a cross-reference to the additional discussion in Section 12.3 <i>Pharmacokinetics</i> of the approved PI.
10 OVERDOSAGE	The Applicant was requested to remove this section. According to the labeling regulations (21 CFR 201.57), the section must be based on human data. If there are no human data, this section should be removed.
12 CLINICAL PHARMACOLOGY	<u>12.2 Pharmacodynamics</u> (b) (4) <u>12.3 Pharmacokinetics</u> (b) (4) <u>12.6 Immunogenicity</u>

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
	The language of the introductory paragraph was altered to be consistent with recommendations in the draft guidance for industry – <i>Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling – Content and Format</i> (February 2022). The Applicant proposed language describing immunogenicity incidence and the impact on pharmacokinetics, efficacy, and safety in patients with UC. The proposed language regarding the immunogenicity incidence in subjects with UC was revised to only include subjects who received the proposed induction regimen. Language was also revised to describe the impact of immunogenicity on guselkumab exposure in patients with high ADA titers (i.e., two subjects with higher titers had lower trough concentrations of guselkumab). Up to Week 56 in Studies UC1, UC2 and UC3, there were no identified clinically significant effect of anti-drug antibodies on injection site reactions, or effectiveness of guselkumab in subjects with UC.
13 NONCLINICAL TOXICOLOGY	<u>Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</u> The Applicant proposed changes to this subsection to state that no effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 100 mg/kg twice weekly. The NOAEL in the currently approved PI is based on a previous review with a dose of 25 mg/kg, and there are no additional data submitted to justify the change of dose to 100 mg/kg with associated human dose multiples. The applicant agreed to revise the dose back to 25 mg/kg and proposed revising the human dose multiples using an AUC, rather than a mg/kg, basis and this was acceptable.
14 CLINICAL STUDIES	<u>14.3 Ulcerative Colitis</u> This Applicant proposed to include a description of Induction Study 2 (IS-2; UC1), Maintenance Study (UC2) to support the efficacy and safety of guselkumab in adults with UC. In addition, a description of Induction Study 1 (IS-1; UC3) was also included, although no results were presented. The description of IS-1 (UC3) was removed from this section and only mentioned to give context to the study population in UC2 because the study was not used as substantial evidence of effectiveness. <u>Induction Trial (UC1)</u> A description of the study was revised to include a description of how disease activity was assessed and defined. Subjects with prior exposure to biologic and/or JAK inhibitor but who did not meet criteria for failure were not included in the Applicant's table of results (Table 8). Table 8 was revised to include data generated from the entire primary efficacy population based on the following groups/subgroups: 1. Total population 2. Subjects without prior biologic and/or JAK inhibitor

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
	failure (i.e., subjects that are biologic and/or JAK inhibitor naïve, and subjects with biologic and/or JAK inhibitor exposure but who did not meet criteria for failure) 3. Subjects with prior biologic and/or JAK inhibitor failure The endpoint of fatigue response was removed from Table 8. Although it was included as a ranked secondary endpoint in the study and achieved a statistically significant result for the comparison of guselkumab 200 mg versus placebo, the results may be impacted by confounding factors. Instead, results were included descriptively in text below the table. The applicant proposed to include results for the endpoint of histologic endoscopic mucosal improvement in Table 8, which was acceptable; however, a disclaimer statement was added below the table that Study UC1 was not designed to evaluate the relationship between histologic improvement at Week 12 and long-term clinical outcomes. Study UC1 enrolled subjects with a baseline mMS of 4 which did not meet the severity criteria for moderately to severely active disease. These subjects were excluded from the efficacy population and results in Table 8. However, the applicant proposed including descriptive text below the table describing efficacy results in this subpopulation. Because a mildly active disease population is not consistent with the proposed indication, and could promote off-label use, the results for this subgroup were not included. The Applicant proposed (b) (4) (b) (4) (b) (4) The text was revised to state that decreases were observed as early as Week 4, without mention of Week 12, based on additional analyses evaluating change of rectal bleeding scores and stool frequency subscores from baseline to Week 4 compared to placebo. See Section 16.3.1. Week 12 results for clinical response/remission are included in Table 8 and these endpoints include rectal bleeding and stool frequency symptoms in the modified Mayo Score. The Applicant proposed (b) (4) (b) (4) <u>Maintenance Study</u> Table 9 was revised to include data generated from the entire primary efficacy population based on the following groups/subgroups: 1. Total population

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Currently Approved PI and Applicant's Draft PI
	2. Subjects without prior biologic and/or JAK inhibitor failure (i.e., subjects that are biologic and/or JAK inhibitor naïve, and subjects with biologic and/or JAK inhibitor exposure but who did not meet criteria for failure) 3. Subjects with prior biologic and/or JAK inhibitor failure The Applicant proposed (b) (4) (b) (4) (b) (4) The Applicant proposed (b) (4) (b) (4) (b) (4) These results were removed. A disclaimer statement about the endpoint of histologic endoscopic mucosal improvement at Week 44 was added. Refer to comments under "Induction Studies", above. The Applicant proposed (b) (4) (b) (4)
17 PATIENT COUNSELING INFORMATION	<u>Pregnancy</u> Added text that patients be advised that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to guselkumab during pregnancy.

Source: Prescribing Information submitted March 11, 2024, comments sent to the Applicant on August 6, 2024, and response received August 22, 2024.

¹ Some sections may not be included because those sections may not have major issues (or changes).

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviation(s): PI, Prescribing Information

23.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Instructions for Use (two documents)
- 200mg/2mL Prefilled Syringe
- 200mg/2mL Prefilled Pen

24. Postmarketing Requirements and Commitments

The following postmarketing requirements will be issued under the Pediatric Research Equity Act.

- 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

The following postmarketing requirements will be issued under 505(o)(3) of the Federal FDCA.

- 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.

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.

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.

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.

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

The following postmarketing commitments will be issued.

- 4695-1** Perform a supplemental low endotoxin recovery (LER) study to examine the effects of hold time at 15-25°C on endotoxin recovery using 3 batches of 20 mg/mL guselkumab FVP spiked with RSE or CSE and stored at 20-25°C to verify that the longest duration for the DP manufacturing process has no impact on endotoxin recovery.

Final Report Submission: 02/2025

25. Financial Disclosure

Table 100. Covered Clinical Studies: IS-1, IS-2, and Maintenance Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1688		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Source: Applicant response to information request dated May 20, 2024.

Abbreviations: IS-1, Induction Study 1; IS-2, Induction Study 2; MS, Maintenance Study

26. References

Journal Articles

Barreiro-de Acosta, M, N Vallejo, D de la Iglesia, L Uribarri, I Baston, R Ferreiro-Iglesias, A Lorenzo, and JE Dominguez-Munoz, 2016, Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study, *J Crohns Colitis*, 10(1):13-19.

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27. Review Team

Table 101. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Andrew Chi
Nonclinical Reviewer	Blessy George
Nonclinical Team Leader	Sushanta Chakder
Pharmacometrics Reviewer	Hui Wei
Pharmacometrics Team Leader	Jiang Liu
OCP Reviewer	Amer Al-Khouja

BLA 761061/S-021
TREMFA (guselkumab)

Role	Name(s)
OCP Team Leader	Shen (Steven) Li
Clinical Reviewer	Jaime Wolfe
Clinical Secondary Reviewer	Suruchi Batra
PFSS Reviewer	Seungwon Chung
PFSS Team Leader	Monica Morell
Biometrics Reviewer	Joshua Sampson
Biometrics Analyst	Susan Jin
Biometrics Team Leader	Paul Imbriano
Associate Director for Labeling	Joette Meyer
Deputy Director for Safety	Joyce Korvick Jacqueline Lee-Hoffman (Safety RPM)
Cross-Discipline Team Leader	Suruchi Batra
Designated Signatory	Erica Lyons
Associate Director for Therapeutic Review	

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; PFSS, Patient Focused Statistical Scientists

Table 102. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Yun Wu Willie Wilson III
Microbiology	Bingchen (Ben) Du Maxwell Van Tassell Zhong Li
CDRH	Jillian Socea Shruti Mistry
OND Clinical Data Scientists	Salman Hosain Ling Cao
DCOA	Susan Pretko Onyekachukwu Illoh
DPV	Suraj Rajasimhan Michelle Hines
DPMH	Sarah Sheikh Tamara Johnson
DHN	Eileen Navarro Almarino Paul Hayashi
OCP	Bindi Nikhar
OPDP	Montherson Saint Juste Quynh-Nhu Capasso James Dvorsky
DMPP	Nyedra Booker Marcia Williams
OSI	Glenn Manheim Min Lu
OSIS	James J Lumalcuri Sri Rama Krishnaiah Yellela Charles R Bonapace
OSE/DEPI	Alvis Dunson Joel Wessfield Benjamin Booth

Office or Discipline	Name(s)
OSE/DMEPA	Sherly Abraham Tianyi (Tim) Zhang Damon Birkemeier Murewa Oguntimein

Abbreviations: CDRH, Centers for Devices and Radiologic Health; DCOA, Division of Clinical Outcome Assessment; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance; OND, Office of New Drugs; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OPQ IIIA OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-103 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Monica Morell OB DBIII	Sections: Section 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Monica Morell		Digitally signed by Monica Morell		
		Date: 9/9/2024 4:04 PM EDT GUID: 20249920420		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Paul Imbriano OB DBIII	Sections: 6.2, 6.3, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Paul Imbriano Digitally signed by Paul Imbriano Date: 9/9/2024 4:07 PM EDT GUID: 2024992077				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Joette Meyer OII DG	Sections: 23 Labeling	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joette Meyer Digitally signed by Joette Meyer Date: 9/9/2024 4:08 PM EDT GUID: 20249920846				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Joette Meyer OII DG	Sections: 23 Labeling	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joette Meyer Digitally signed by Joette Meyer Date: 9/9/2024 4:09 PM EDT GUID: 20249920919				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Amer Al-Khouja OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14.2, 14.3, 14.4	Based on my assessment of the application: ✓ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Amer Al-Khouja Digitally signed by Amer Al-Khouja Date: 9/9/2024 4:09 PM EDT GUID: 20249920922				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Joshua Sampson OB DBIII	Sections: 2, 6.2.1, 6.2.2, 6.2.3, 6.3.1, 6.3.2, 15, 16.1, 16.2, 16.3	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Joshua Sampson Digitally signed by Joshua Sampson Date: 9/9/2024 4:59 PM EDT GUID: 202499205918				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Shen Li OCP DIIP	Sections: 5.2, 6.1, 6.3, 8.1, 8.2, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Shen Li Digitally signed by Shen Li Date: 9/9/2024 5:50 PM EDT GUID: 202499215042				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Group Discipline Primary Reviewer	Seung Won Chung OB DBIII	Sections: Section 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Seung Won Chung Digitally signed by Seung Won Chung Date: 9/9/2024 7:16 PM EDT GUID: 202499231649				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Primary Reviewer	Blessy George OII DPTII	Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Blessy George Digitally signed by Blessy George Date: 9/9/2024 8:31 PM EDT GUID: 202491003119				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Sushanta Chakder OII DPTII	Sections: 5.1, 7.1, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sushanta Chakder		Digitally signed by Sushanta Chakder Date: 9/10/2024 9:05 AM EDT GUID: 202491013546		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Jiang Liu OCP DPM	Sections: 2, 5, 6, 7, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jiang Liu		Digitally signed by Jiang Liu Date: 9/10/2024 9:38 AM EDT GUID: 202491013381		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Primary Reviewer	Hui Wei OCP DPM	Sections: 14.5	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Hui Wei		Digitally signed by Hui Wei Date: 9/10/2024 10:22 AM EDT GUID: 2024910142213		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Erica Lyons OII DG	Sections: 1, 2, 3, 4, 6, 7, 10, 11, 16.1, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Erica Lyons		Digitally signed by Erica Lyons Date: 9/10/2024 10:34 AM EDT GUID: 2024910143416		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Jaime Wolfe OII DG	Sections: 1, 2, 3, 4, 6, 7, 8.3, 8.4, 10, 11, 12, 16.1, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jaime Wolfe Digitally signed by Jaime Wolfe Date: 9/10/2024 10:41 AM EDT GUID: 2024910144142				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Suruchi Batra OII DG	Sections: 1, 2, 3, 4, 6, 7, 8.3, 8.4, 10, 11, 12, 17, 20, 22, 23, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Suruchi Batra Digitally signed by Suruchi Batra Date: 9/10/2024 11:12 AM EDT GUID: 2024910151248				

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/

SURUCHI K BATRA
09/10/2024 12:35:30 PM

ERICA M LYONS
09/10/2024 01:06:38 PM

HUMAN FACTORS STUDY REPORTS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 15, 2024
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761061/S-021
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form, and Strength:	Tremfya (guselkumab) Injection, 200 mg/2 mL
Device Constituent:	Autoinjector and prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Research & Development, LLC (Janssen)
Submission Date:	March 11, 2024
TTT ID #:	2024-8736
DMEPA 1 Safety Evaluator:	Tianyi Zhang, PhD, MS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results submitted under prior approval supplement BLA 761061/S-021 for Tremfya (guselkumab) Autoinjector (AI) and prefilled syringe (PFS). The HF validation study included Ulcerative Colitis (UC) and Crohn's Disease (CD) participants. However, for this supplement, Janssen is only proposing to expand the indication of Tremfya to include the treatment of adult patients with UC. Tremfya is currently approved for the indications listed in Table 2 below.

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Human Factors Study Reports	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C
Detailed List of Use Errors, Use Difficulties, And Close Calls for Section 3.1	Appendix D

1.1 PRODUCT DESCRIPTION

Table 2 presents relevant product information for Tremfya that Janssen submitted on March 11, 2024.

Table 2. Relevant Product Information for Tremfya	
Initial Approval Date	July 13, 2017
Application Number	BLA 761061
Active Ingredient	guselkumab
Indication	Approved: For the treatment of adult patients with: • moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • active psoriatic arthritis Proposed: • Treatment of adult patients with Ulcerative Colitis (UC)
Route of Administration	Subcutaneous and intravenous infusion
Dosage Form	Injection
Strength	<u>Approved:</u> 100 mg/mL

	<u>Proposed:</u> 200 mg/mL
Dose and Frequency	<u>Approved:</u> <u>Plaque Psoriasis:</u> 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. <u>Psoriatic Arthritis:</u> 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. Tremfya can be used alone or in combination with a conventional DMARD (e.g., methotrexate). <u>Proposed:</u> <u>Ulcerative Colitis:</u> - Induction: 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8. - Maintenance: 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.
How Supplied	<u>Approved:</u> - Subcutaneous injection: Single-dose 100 mg/mL prefilled syringe (PFS) assembled with the UltraSafe Plus needle safety guard - Subcutaneous injection: Single-dose 100 mg/mL PFS assembled with the One-Press patient-controlled injector <u>Proposed:</u> - Subcutaneous injection: single-dose 200 mg/2 mL PFS assembled with the UltraSafe Plus needle safety guard - Subcutaneous injection: single-dose 200 mg/2 mL AI - Intravenous infusion: single-dose 200 mg/20 mL (10 mg/mL) solution vial
Storage	The entire carton should be stored in the refrigerator (36°–46°F; 2°–8°C) and protected from light. Keep out of reach of children Do not freeze Do not shake
Container Closure/Device Constituent	<u>AI:</u> - Available in cartons containing one AI <u>PFS:</u> - Available in cartons containing one PFS

	<table border="1"> <thead> <tr> <th>AI</th><th>PFS</th></tr> </thead> <tbody> <tr> <td></td><td></td></tr> </tbody> </table>	AI	PFS		
AI	PFS				
					
Intended Users	Healthcare professionals (HCPs), patients, caregivers				
Intended Use Environment	Hospital/clinic, home				

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On May 3, 2024, we searched previous DMEPA reviews and FDA/Janssen interactions relevant to this current review using the terms, “Tremfya” and “BLA 761061”. See details below.

- On November 16, 2016, Janssen submitted Biologics License Application (BLA) 761061 for the indication of moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This submission included two HF study reports to support Tremfya (guselkumab) injection 100 mg/mL. We reviewed the two HF validation study results reports and did not have any recommendations.¹
- On July 13, 2017, the Agency approved Tremfya (guselkumab) injection 100 mg/mL PFS under BLA 761061.²
- On February 21, 2019, Janssen submitted a Type C meeting request to discuss the development of guselkumab injection 200 mg/2 mL in PFS and AI presentations for the treatment of CD under IND 133845.

¹ Mena-Grillasca, CM. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. OSE RCM No.: 2016-2621 and 2016-2649.

² Beitz, J. Approval letter for Tremfya (guselkumab) injection 100 mg/mL (BLA 761061). Silver Spring (MD): FDA, CDER, OND, OII, DDD (US); 2017 JUL 13. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8044a998>.

- We met with Janssen on May 9, 2019. In the meeting minutes dated May 24, 2019, we recommended that Janssen submit a comprehensive use-related risk analysis (URRA) and their justification that the proposed product and platforms can be used safely in the proposed investigational studies.³
- On April 21, 2020, Janssen submitted a URRA and their justification that the proposed product and platforms can be used safely in the proposed investigational studies under IND 133845.
 - On June 16, 2020, we reviewed the URRA and Janssen’s justification that the information provided is sufficient to “*support safe clinical use of the subcutaneous injection devices in the proposed investigational studies.*” We agreed with Janssen’s determination and noted that we did not have any specific concerns that would warrant Janssen to submit results from a HF study to the Agency prior to the introduction of the proposed devices into the clinical study/studies.⁴
- On November 2, 2022, Janssen submitted HF validation study protocols for guselkumab injection 200 mg/2 mL PFS and AI for the treatment of CD and UC under IND 133845. We reviewed the protocol and provided recommendations.⁵
- On March 11, 2024, Janssen submitted BLA 761061/S-021 for Tremfya 200 mg/2 mL PFS and AI for the treatment of UC. This submission included HF validation study result reports, which are the subjects of the review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 3 presents a summary of the HF validation study designs. See Appendix A for more details on the study designs.

Table 3. Study Methodology for the Human Factors (HF) Validation Studies	
Study Design Elements	Details provided by Applicant
User Groups	PFS HF Validation Study ● Adult (≥ 18 years of age, n=15) patients diagnosed with and treating UC and/or CD ● Adult (≥ 18 years of age, n=15) caregivers of patients diagnosed with and treating UC and/or CD (half injection-naïve and half injection-experienced).

³ Allan, LW. Meeting Minutes for Guselkumab (IND 133845). Silver Spring (MD): FDA, CDER, OND, OII, DG (US); 2019 MAY 24. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804f74f2>.

⁴ Barlow M. Use-Related Risk Analysis (URRA) Review for guselkumab injection (IND 133845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 16. TTT ID No.: 2020-837.

⁵ Fung M. Guselkumab HF Protocol Review (IND 133845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2023 OCT 5. TTT ID No.: 2022-2716.

	- Adult (≥ 18 years of age, n=15) nurses specializing in gastroenterology or primary care AI HF Validation Study - Adult (≥ 18 years of age, n=15) patients diagnosed with and treating UC and/or CD - Adult (≥ 18 years of age, n=15) caregivers of patients diagnosed with and treating UC and/or CD (half injection-naïve and half injection-experienced). - Adult (≥ 18 years of age, n=15) nurses specializing in gastroenterology or primary care																																
Training	No training was provided																																
Test Environment and Materials	<table border="1"> <thead> <tr> <th colspan="2">Simulated Use Environment for Hospital and Clinic Environments</th> </tr> </thead> <tbody> <tr> <td>Environment Variables</td><td>Simulated Use Environment</td> </tr> <tr> <td>Noise and Distraction</td><td>Standard variable background noise and activity level typical of a hospital/clinic setting</td> </tr> <tr> <td>Storage</td><td>Product should be refrigerated at 36°F to 46°F (2° to 8°C)</td> </tr> <tr> <td>Conditions of Visibility</td><td>Standard variable lighting conditions found in a hospital/clinic environment</td> </tr> <tr> <td>Physical</td><td>Standard temperature and humidity ranges found in a hospital or clinic environment</td> </tr> <tr> <td>Mobility</td><td>Table surface was provided to prepare and administer the injection.</td> </tr> <tr> <td>Disposal</td><td>A sharps container was provided</td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th colspan="2">Simulated Use Environment for Home Environments</th> </tr> </thead> <tbody> <tr> <td>Environment Variables</td><td>Simulated Use Environment</td> </tr> <tr> <td>Noise and Distraction</td><td>Standard variable background noise and activity level typical of a home setting</td> </tr> <tr> <td>Storage</td><td>Product should be refrigerated at 36°F to 46°F (2° to 8°C)</td> </tr> <tr> <td>Conditions of Visibility</td><td>Standard variable lighting conditions found in a home environment</td> </tr> <tr> <td>Physical</td><td>Standard temperature and humidity ranges found in a home environment</td> </tr> <tr> <td>Mobility</td><td>Table surface was provided to prepare and administer the injection.</td> </tr> <tr> <td>Disposal</td><td>A sharps container was provided</td> </tr> </tbody> </table>	Simulated Use Environment for Hospital and Clinic Environments		Environment Variables	Simulated Use Environment	Noise and Distraction	Standard variable background noise and activity level typical of a hospital/clinic setting	Storage	Product should be refrigerated at 36°F to 46°F (2° to 8°C)	Conditions of Visibility	Standard variable lighting conditions found in a hospital/clinic environment	Physical	Standard temperature and humidity ranges found in a hospital or clinic environment	Mobility	Table surface was provided to prepare and administer the injection.	Disposal	A sharps container was provided	Simulated Use Environment for Home Environments		Environment Variables	Simulated Use Environment	Noise and Distraction	Standard variable background noise and activity level typical of a home setting	Storage	Product should be refrigerated at 36°F to 46°F (2° to 8°C)	Conditions of Visibility	Standard variable lighting conditions found in a home environment	Physical	Standard temperature and humidity ranges found in a home environment	Mobility	Table surface was provided to prepare and administer the injection.	Disposal	A sharps container was provided
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	• Tremfya 200 mg/2 mL PFS/AI pack - o Carton - o Tray - o Tremfya 200 mg/2 mL PFS/AI containing active medication - o IFU - o Mock PI • Tremfya One-Press packaging and device (for HCP product-differentiation task only) • Tremfya 2 mL Autoinjector packaging and device (for HCP product differentiation task only) • Mock prescription • Alcohol wipes • Mock sink/hand sanitizer • Gloves • Band-aids • Gauze pads/cotton balls • Injection pad • Manikin (for HCP and caregiver participants only) • Sharps container • Trash bin (to capture potential use errors) • Mock Refrigerator (for HCP participants only)
Sequence of Study	1. Differentiation/Confirmation Tasks - o HCP only: Product and dose differentiation (packaged product) - o HCP only: Product and dose differentiation (device only) - o Patient and caregiver only: product and dose confirmation (packaged product) - o Root cause probing 2. Simulated-Use Scenarios - o Trial 1 (IFU optional) - o Trial 2 (IFU mandatory) - o Root cause probing - o Knowledge tasks (IFU optional and IFU mandatory) - o Root cause probing - o Subjective feedback

3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use error, close calls, use difficulty), Janssen's URRAs, the participants' subjective feedback, Janssen's root cause analysis, Janssen's post HF validation study mitigations and Janssen's comments to

determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. We provide a discussion of the identified use tasks below where we agree with Janssen's conclusions and have no further recommendation or comment.

3.1 ANALYSIS OF THE IDENTIFIED ISSUES

The HF validation study reports showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), Janssen's root cause analysis, Janssen's post-HF validation study mitigations, and our evaluation of the residual risks, we find the proposed user interface has been appropriately designed. The labels and labeling include information that is prominent, and we did not identify recommendations to address the identified issues with the tasks in Appendix D.

Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under a separate cover⁶.

4 CONCLUSIONS

The results of the HF validation study demonstrated several use errors with critical tasks that may result in harm. However, based on our review of the available participants' and subjective feedback, and root cause analysis from the HF validation study, and Janssen's post-HF validation study mitigations, we did not identify additional risk mitigations to address the use errors. We find that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. As such, we have no recommendations for this prior approval supplement.

⁶ Abraham, S. Label and Labeling Packaging Review for Tremfya (guselkumab) BLA 761061/S-021. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 July 2. TTT ID #: 2024-8735.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

Prefilled syringe: <\\CDSESUB1\EVSPROD\bla761061\0700\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uc\5354-other-stud-rep\pfs-u-2ml\pfs-u-2ml-study-report-2.pdf>

Autoinjector: <\\CDSESUB1\EVSPROD\bla761061\0700\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uc\5354-other-stud-rep\pfs-y-2ml\pfs-y-2ml-study-report-2.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Tremfya labels and labeling submitted by Janssen.

Autoinjector container label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-y-label.pdf
Autoinjector carton label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-y-carton.pdf
Autoinjector instructions for use (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-y.pdf
Prefilled syringe container label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-u-label.pdf
Prefilled syringe carton label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-u-carton.pdf
Prefilled Syringe instructions for use (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-u.pdf

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3.1

- Autoinjector simulated use tasks:
 - Inspect liquid in window to see that it is clear to slightly yellow
 - Choose an injection site
 - Wash hands
 - Clean injection site
 - Remove cap
 - Inject medication: there were 5 use errors, 1 close call, 1 use difficulty observed for this task. The root cause analysis indicated these use errors, close call, and use difficulty were due to:
 - Negative transfer:
 - A participant initially looked for an activation button but subsequently successfully completed the injection after referring to the IFU images
 - A participant removed the AI before the second click due to their previous experience with AIs that are quick and only click once
 - Mistaking the first click as the second click
 - Mental model
 - A participant expected the device to dispense the medication faster and removed the AI before the second click
 - A participant didn't position the AI with the viewing window facing them
 - A participant removed the AI before the second click because they were trying to inspect the viewing window during injection, but the viewing window was not visible to them
 - Inconspicuous instruction
 - The instructions for use (IFU) does not saliently instruct users regarding what to do if two injections are required
 - Study artifact (participants did not think the needle would activate since it was a simulation).

We note that Janssen stated that the injection completion time ranges from 4 seconds to 5.2 seconds with the mean of 4.6 seconds. Two of the five participants in Trial 1 (IFU optional) who experienced use difficulty or use errors with this task had an injection time (i.e., 10 seconds and 5 seconds, respectively) of more than 4.6 seconds. Two participants in Trial 2 (IFU mandatory) who experienced close call or use error with this task had an injection time (i.e., 12 seconds and 8 seconds, respectively) of more than 4.6 seconds. Based on this information, we note that these participants would have received the full dose. Based on the errors observed and the root cause analysis, Janssen added (b) (4)

(b) (4)

to IFU Step 3e, in red font to remind users to follow the same steps for the second device, if required. We acknowledge Janssen's mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close call, and use difficulty, and have no recommendations at this time.

- o Remove injection device: there was 1 use difficulty observed for this task. The root cause analysis indicated that the user failed to notice the second click but was still able to complete the injection. Based on our review of the user interface, we did not identify any additional mitigations to address this use difficulty and have no recommendations at this time.
 - o Check injection site
 - o Dispose of the device
- Autoinjector study knowledge task assessment:
 - o When, if ever, should you shake the injection device? Answer: user must indicate do not shake/never.
 - o If your prescribed dose requires two injection devices, where, if anywhere, should the second injection be given? Answer: user must indicate not to inject into the same injection site or different acceptable site or at least 2 inches way from first injection site.
 - o Into which area or areas on the body can you inject with this injection device? Answer: upper thigh, lower abdomen, and/or back of arms. There was 1 use error observed for this question. The root cause analysis indicated the use error was due to the misleading IFU image (the participant thought the image of the appropriate injection locations showed the side of the arm instead of the back of the upper arm). Based on the errors and root cause analysis, Janssen changed the blue area on the arm to be smaller, so it looks more like the back of the upper arm rather than the side of upper arm. We acknowledge Janssen's mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
 - o What, if anything, should you do with the injection device if it is dropped? Answer: user must indicate they would not use the injection device or get a new device.
 - o What, if anything, should you not do while the medication is being injected into the skin? Answer: do not lift the device during the injection. There was 1 use error observed for this question. The root cause analysis was incomplete because Janssen did not investigate why the participant gave the answer "*they should not shake or move the device*". However, based on our review of the user

interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.

- PFS simulated use tasks:
 - Inspect liquid in window
 - Choose an injection site
 - Wash hands
 - Clean injection site
 - Remove needle cover
 - Pinch skin and insert needle: there were 42 use errors. The root cause analysis indicated these use errors were due to negative transfer (Participants recalled previous experience seeing/performing an injection or using autoinjectors and determined inserting at 90 degrees was correct or no pinching was necessary.), study artifact (participants did not pinch the skin because it was not their skin), and inconspicuous image depicting pinching the skin (the image of the appropriate technique with pinching did not look like pinching). Based on the use errors and root cause analysis, Janssen changed the image to depict a larger amount of skin being pinched and increased font size of “45” in the IFU Step 3b image. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
 - Inject medication: there were 7 use errors, 1 close call and 4 use difficulties, observed for this task. The root cause analysis indicated that the use errors, close call and use difficulties were due to negative transfer (A participant relied on their previous experience with injections leading them to prime the device. Another participant stated they typically draw back on the syringe to ensure there’s no blood for all injections and performed a draw to ensure there’s no blood in the study) and the confusing order of steps in the IFU (instruction “If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second prefilled syringe” was after Step 4b – *Dispose of your prefilled syringe*). Based on the use errors and root cause analysis, Janssen moved the text “*If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second prefilled syringe*” to the Step 3d. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close call and use difficulties, and have no recommendations at this time.
 - Check injection site
 - Dispose of the device

- PFS study knowledge task assessment:
 - o When, if ever, should you shake the injection device? Answer: user must indicate do not shake/never.
 - o Into which area or areas on the body can you inject with this injection device? Answer: upper thigh, lower abdomen, and/or back of arms. There was 1 use error observed for this question. The root cause analysis indicated the use error was due to the inconspicuous IFU Step 2 image (the image of the appropriate injection location does not sufficiently depict the back of the upper arm). Based on the error and root cause analysis, Janssen made the image of the blue area of the arm smaller so it looks more like the back of upper arms. We acknowledge Janssen's mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
 - o What, if anything, should you do with the injection device if it is dropped. Answer: user must indicate they would not use the injection device or get a new device.

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/

TIANYI ZHANG
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ARIANE O CONRAD
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JASON A FLINT
07/16/2024 12:02:09 PM

**PRODUCT QUALITY MICROBIOLOGY/FACILITY
ASSESSMENT****Memorandum of Review to the File**

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Extract

Application ID	BLA 761061 – SUPPL - 021
Submission Type	PAS: Efficacy Supplement with CMC information: Introduction of three drug product presentations: 200 mg final vial product (FVP) for short-term IV induction administration; 200 mg PFS for SC maintenance administration: 2mL PFS-U (UltraSafe Plus) and 2mL PFS-Y (YpsoMate autoinjector)
Drug Product Name	guselkumab
Strengths	IV 10mg/mL / Injection of 200 mg/2.0 mL
Dosage Form	Solution for Infusion / Solution for injection
Administration Route	Intravenous / Subcutaneous
Indication	Treatment of adult patients with moderately to severely active ulcerative colitis
Applicant Name	Janssen Biotech, Inc.
US License Number	1864
Application Type	351 (a)
Primary Reviewer	Bingchen (Ben) Du, PhD, OPQ/OPMA/DPMavi
Secondary Reviewer	Micro: Maxwell Van Tassell, PhD, SPQA, OPQ/OPMA/DPMavi Facility: Zhong Li, PhD, SPQA, OPQ/OPMA/DPMavi
Goal Date	9/11/2024

Recommendation for Approvability:

- This BLA was reviewed from a sterility assurance perspective and is recommended for Approval with the following post-marketing commitment(s):

○

(b) (4)

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
0700	3/11/2024
0810	8/23/2024

List of DMFs Assessed (Table):

DMF #	Item Referenced	Date Reviewed	Finding	Document Reference
(b) (4)				

Application Submission Background

Reviewer's Comment: For Information

In this current submission, the supplement contains three new drug product presentations for the proposed ulcerative colitis (UC) indication.

- 200 mg final vial product for short-term IV induction administration
- 200 mg prefilled syringe (PFS) presentations for SC maintenance administration:
 - 200 mg PFS assembled with the UltraSafe Plus needle safety guard (2 mL PFS-U)
 - 200 mg PFS assembled with the YpsoMate autoinjector (2 mL PFS-Y)

Under this BLA, previously, 100 mg PFS was approved (1 mL).

MODULE 1

1.14 LABELING

Reconstitution and Dilution Instructions

TREMFYA 200 mg/20 mL (10 mg/mL) Vial for Intravenous Infusion needs to be diluted into a 250 mL intravenous infusion bag of 0.9% Sodium Chloride Injection USP. Noted that 20 mL of the 0.9% sodium chloride injection needs to be withdrawn to allow 20 mL of the vial content from the drug product to be transferred into.

The diluted infusion solution could be kept at room temperature, i.e, 77°F or 25°C for up to 10 hours, or in a refrigerator between 36-46°F (2-8°C) for up to 24 hours.

Reviewer's Comment: For Information

The FVP (vial) drug product will be diluted into 0.9% Sodium Chloride Injection USP prior to infusion administration. The dilution could be stored at room temperature for up to 10 hours, or in the refrigerator for up to 24 hours. The refrigerated dilution needs to be administered and completed within 10 hours out of refrigeration. This storage condition is supported by the microbial challenge data provided in 3.2.P.2.6 Compatibility (FVP).

MODULE 3.2.P

Module 3.2.P Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

P.1 Description and Composition of the Drug Product

FVP (Vial)

The 200 mg/20 mL (10 mg/mL) guselkumab (JNJ-54160366) final vial product (FVP) is supplied as a sterile liquid in vial presentation for intravenous (IV) administration. It is referred to as the 10 mg/mL drug product (DP) throughout the dossier. (b) (4)

(b) (4)

Reviewer's Comment: For Information

(b) (4)

P.2 Pharmaceutical Development

(b) (4)



Ben
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Maxwell
Van Tassell

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Date: 9/05/2024 12:36:40PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA761061Orig1s021

OTHER REVIEW(s)

LABELS AND LABELING ASSESSMENT

Date of Assessment:	September 4, 2024
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Yun Wu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761061 S-21
Applicant:	Janssen Biotech, Inc.
Submission Date:	March 11, 2024
Product:	Tremfya (guselkumab)
Dosage form(s):	injection
Strength and Container-Closure:	100 mg/mL single-dose prefilled syringe 100 mg/mL single-dose One-Press patient-controlled injector 200 mg/2 mL (100 mg/mL) single-dose prefilled pen autoinjector (proposed) 200 mg/2 mL (100 mg/mL) single-dose prefilled syringe (proposed) 200 mg/20 mL (10 mg/mL) single-dose vial (proposed)
Purpose of assessment:	The Applicant submitted an efficacy supplement for the treatment of adult patients with moderately to severely active ulcerative colitis and proposes three product presentations (200 mg/20 mL vial for short-term intravenous induction and 200 mg/2 mL prefilled syringe or autoinjector).
Recommendations:	The prescribing information and medication guide (submitted on August 22, 2024), instructions for use (submitted on August 30, 2024), container labels and carton labeling (submitted on August 23, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information and medication guide (submitted on August 22, 2024), instructions for use (submitted on August 30, 2024), container labels and carton labeling (submitted on August 23, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on March 11, 2024

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Instructions for Use (submitted on March 11, 2024

<\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-y.pdf>,
<\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-u.pdf>)

(b) (4)

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Proper Name (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i), 21 CFR 600.3(k)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: For all proposed container labels, revise your manufacturer information to match your 100 mg/mL single-dose prefilled syringe: "Janssen Biotech, Inc. (b) (4) Historical practice has been to include the U.S license number with the manufacturer's information, even for container capable of only bearing a partial label to accommodate the addition of the US license number, consider removing the qualifying phrase "Manufactured by". *The Applicant revised as requested*

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Lot number or other lot identification (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	☒ Yes ☐ No ☐ N/A

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Note that the entire contents of the 200 mg/2 mL prefilled syringe and prefilled pen are administered for a dose thus the expression of strength is provided as the strength per total volume (total drug content supplied in container) and does not include a parenthetical for the strength/mL.

Multiple-dose containers (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 <i>(recommended individual dose)</i>	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Medication Guide (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	Acceptable
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

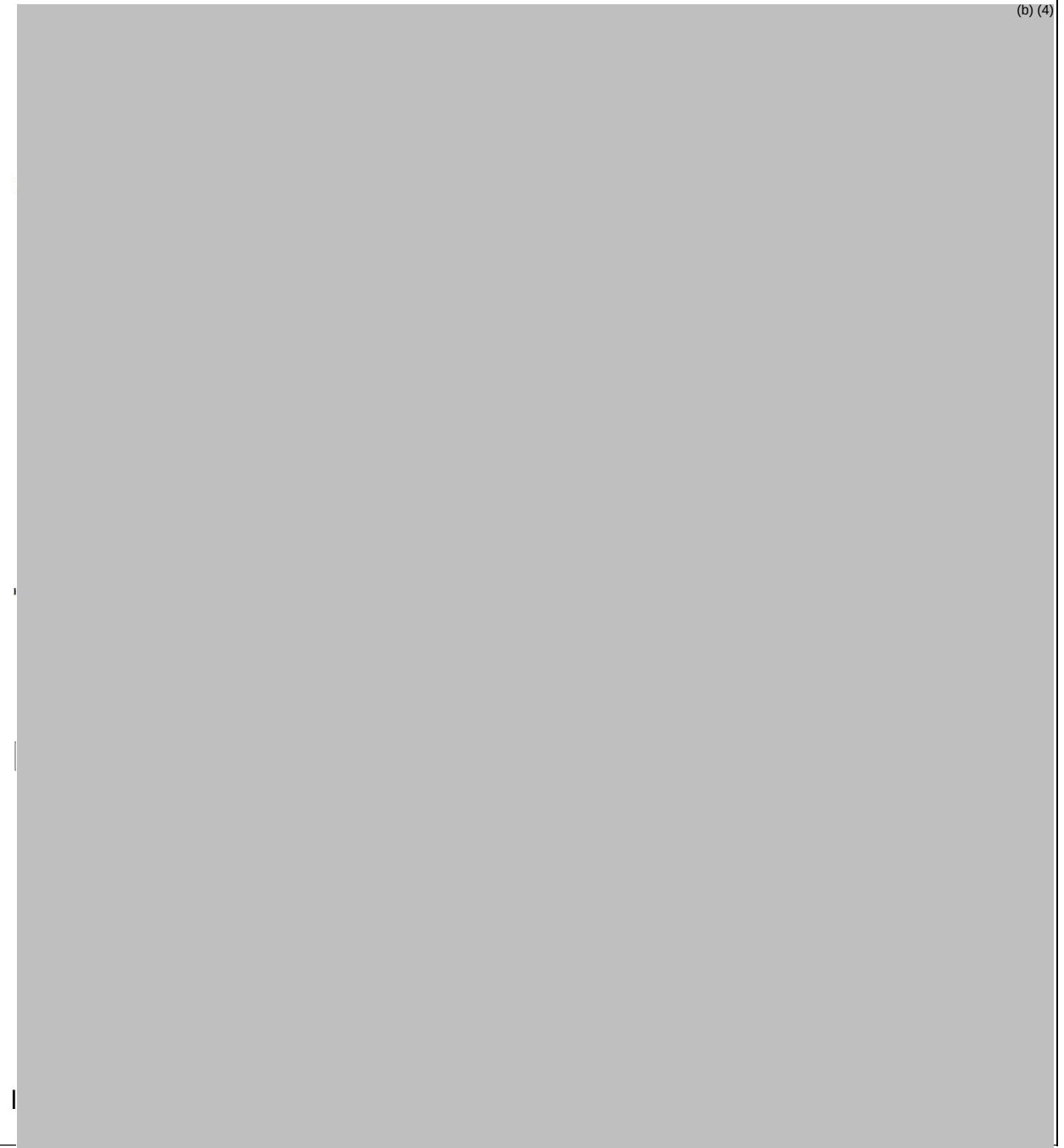
Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vial presentation. *Applicant response: The Sponsor would like to note that the batch name will be printed on the ferrule. The Sponsor confirms that there is no text on the cap or overseal of the vial.*

Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: For all presentations, confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

(b) (4)



<u>Route of administration (container label)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

<u>NDC numbers (container label)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

<u>Preparation instructions (container label)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☐ Yes ☐ No ☒ N/A

<u>Package type term (container label)</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

No misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	Acceptable
Regulation: 21 CFR 201.20	☒ Yes ☐ No ☐ N/A

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Bar Code Label Requirements Questions and Answers (August 2011)</i> <i>Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Space considerations for PFP and PFS partial label.

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: partial label

Storage requirements (container label)	Acceptable
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Space considerations for PFP and PFS partial label.

Dispensing container (container label)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package⁶ Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	☒ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
<i>Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	Acceptable

⁶ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Regulation: 21 CFR 610.61(e)	☒ Yes ☐ No ☐ N/A

Number of containers (package labeling)	Acceptable
Regulation: 21 CFR 610.61(f)	☒ Yes ☐ No ☐ N/A

Product Strength (package labeling)	Acceptable
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Note that the entire contents of the 200 mg/2 mL prefilled syringe and prefilled pen are administered for a dose thus the expression of strength is provided as the strength per total volume (total drug content supplied in container) and does not include a parenthetical for the strength/mL.

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	Acceptable

Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Labeled to state "Not made with natural rubber latex" product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for guselkumab products (i.e., there is no specific test method described in regulation for guselkumab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Tremfya because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes

	☐ No ☒ N/A

<u>NDC numbers (package labeling)</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A

<u>Preparation instructions (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

<u>Package type term (package labeling)</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

<u>No misleading statements (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.6	☒ Yes ☐ No ☐ N/A

<u>Prominence of required label statements (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

<u>Spanish-language (Drugs) (package labeling)</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☒ Yes ☐ No ☐ N/A

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☒ Yes ☐ No

	☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
<u>PRODUCT TITLE</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
<u>DOSAGE AND ADMINISTRATION</u>	<u>Acceptable</u>
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
<u>DOSAGE FORMS AND STRENGTHS</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter <659> Packaging and Storage Requirements USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
<u>2 DOSAGE AND ADMINISTRATION</u>	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(3)(iv) <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter</i>	☒ Yes ☐ No ☐ N/A

<i>and discoloration prior to administration, whenever solution and container permit."</i>	
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised for readability from "for single use" to read as "Each vial is for one time use in one patient only." <i>The Applicant revised as requested.</i> Revise the proposed storage condition for the diluted solution accordingly per your IR Response # 3, sequence 0786 (dated 07/23/2024). <i>The Applicant removed the alternative storage condition from the labeling.</i>

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	<u>Acceptable</u>
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised for readability and to reduce redundancy of tradename and container closure in this section. We note that the particle description has been provide in section 2.7. <i>The Applicant revised as requested</i>

Full Prescribing Information	
11 DESCRIPTION	<u>Acceptable</u>
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised for readability. Add the molecular weight. <i>The Applicant revised as requested</i> Added subsections for readability. <i>The Applicant revised as requested</i> Relocated this information regarding the syringes to the how supplied section. <i>The Applicant revised as requested</i> Condensed the information for readability <i>The Applicant revised as requested</i> We note that the particle description has been provide in section 2.7. <i>The Applicant revised as requested</i>

Full Prescribing Information	
15 & 16 Hazardous Drug	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures. ¹	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Revised for readability by creating subsections and reducing redundancy. <i>The Applicant revised as requested</i>

Full Prescribing Information	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
<u>TITLE (NAMES AND DOSAGE FORM)</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
<u>INGREDIENTS</u>	<u>Acceptable</u>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☒ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
<u>TITLE (NAMES AND DOSAGE FORM)</u>	<u>Acceptable</u>
<i>Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022)). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).</i>	☒ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
<i>Recommended labeling practices for IFU: Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised the color and clarity to match your prescribing information *The Applicant revised as requested*

INSTRUCTIONS FOR USE	
<u>INGREDIENTS</u>	<u>Acceptable</u>
<i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)</i>	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
21 CFR 201.1, 19 CFR 134.11	☒ Yes ☐ No ☐ N/A
<i>Guidance for Industry Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products – Content and Format (July 2022). 21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Include the manufacturer information

Manufactured by:

Janssen Biotech, Inc.

Horsham, PA 19044, USA

US License No. 1864

The Applicant revised as requested

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

Prescribing Information (submitted on August 22, 2024

<\\CDSESUB1\EVSPROD\bla761061\0806\m1\us\114-labeling\draft\labeling\uspi-clean-uc-indication.pdf>)

Medication Guide (submitted on August 22, 2024

<\\CDSESUB1\EVSPROD\bla761061\0806\m1\us\114-labeling\draft\labeling\medication-guide-clean-uc-indication.pdf>)

Instructions for Use (submitted on August 30, 2024

<\\CDSESUB1\EVSPROD\bla761061\0818\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-y-clean.pdf> and <\\CDSESUB1\EVSPROD\bla761061\0818\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-u-clean.pdf>)

(b) (4)



Vicky
Borders-Hemphill

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Yun
Wu

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Memorandum of Assessment:

Submission Tracking Number (STN):	BLA 761061/S-21 eCTD 0700, 0786, 0817 (SDN 1228, 1261, 1292)
Subject:	Efficacy PAS: Treatment of adult patients with moderately to severely active ulcerative colitis (UC), with 3 new drug presentations for the proposed indication: 200 mg/20 mL final vial product for short-term intravenous induction administration 200 mg prefilled syringe (PFS) assembled with UltraSafe Plus needle safety guard (2 mL PFS-U) for subcutaneous (SC) administration 200 mg PFS assembled with YpsoMate autoinjector (2 mL PFS-Y) for SC administration
Date Received:	03/11/2024
Assessment/Revision Date:	09/05/2024
Primary Assessor:	Yun Wu, PhD, DVM CDER/OPQ/OPQA-III/DPQA XIII
Secondary Assessor:	Willie Wilson III, PhD, CDER/OPQ/OPQA-III/DPQA XIII
Tertiary Assessor:	Qing (Joanna) Zhou, PhD, CDER/OPQ/OPQA-III/DPQA XIII
RBPM:	Melinda Bauerlien, MS, CDER/OPQ/OPRO/DRBPM I
Consults:	CDRH: ICCR# 00979891
Applicant:	Janssen Biotech, Inc.
Product:	TREMFYA® (guselkumab, CNTO 1959)
Indication:	Treatment of adults with moderate to severe plaque psoriasis and active psoriatic arthritis
Filing Action Date:	05/11/2024
Action Due Date:	09/11/2024

1. Summary Basis of Recommendation:

- a. Recommendation:** I recommend Approval of this supplement.
- b. Justification:** Sufficient information and data were provided to support the manufacture and control of the proposed 200 mg/20 mL FVP, 200 mg PFS-U, and 200 mg PFS-Y Tremfya drug product presentations from an OPQAIII product quality-perspective. An inspection of the proposed drug product manufacturing and device assembly facility, (b) (4) was waived based on recent acceptable inspection history and facility's experiences in manufacturing biologics products (b) (4).
(b) (4).
- Review of all other facilities and sterility assurance control strategies is deferred to the OPMA assessment team.

2. Assessment:

Note: Assessor comments are indicated in italics. Figures and tables are adopted or copied directly from the applicant's submission unless noted otherwise.

BACKGROUND/PRODUCT DESCRIPTION:

TREMFYA (guselkumab, CNT01959) is a fully human IgG1 λ monoclonal antibody (mAb) that binds to the p19 subunit of extracellular human interleukin 23 (IL-23). TREMFYA is currently approved for the treatment of Plaque Psoriasis (original BLA) and active Psoriatic Arthritis (Suppl-7). The currently approved DP is supplied as a single-dose, 100 mg/1 mL solution in a pre-filled syringe (PFS) assembled with an UltraSafe Plus needle safety guard (1 mL PFS-U) or a One-Press patient-controlled injector (PFS-S, Suppl-1) for subcutaneous administration. (b) (4)

(b) (4)

(b) (4)

To support the proposed indication of Ulcerative Colitis (UC), the following 3 new presentations are introduced:

- 200 mg/20 mL final vial product (FVP): for short-term induction via IV administration
- 200 mg/2 mL PFS presentations for maintenance via SC administration

(b) (4)

All new DP presentations use the same currently approved DS. A new formulation was developed for the FVP presentation, while the 200 mg/2 mL PFS shares the same formulation with the 100 mg/1 mL PFS.

MODULE 1 Administrative Information and Prescribing Information

1.12.14 Environmental Analysis

A claim for categorical exclusion from environmental assessment (EA) was provided. The Applicant certifies that no extraordinary circumstances exist that would require the preparation of an EA as per 21 CFR 25.21.

MODULE 3.2.P Drug Product [active] [all presentations] [all]

P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

FVP

The FVP presentation, also referred to as the 10 mg/mL DP, for IV administration is provided as a sterile liquid containing 200 mg guselkumab in a 20 mL nominal fill volume (b) (4). It is formulated in (b) (4) L-histidine, (b) (4) sucrose, (b) (4) (b) (4) polysorbate 80 (b) (4) L-methionine, and (b) (4) EDTA sodium 2H₂O, pH 5.8. The container closure system consists of a (b) (4) (b) (4) vial (b) (4) stopper (b) (4) and (b) (4) (b) (4) seal with a flip-off cap (b) (4)

PFS 200 mg

The 200 mg/2 mL PFS, also referred to as the 200 mg PFS to be distinguished from the approved 100 mg PFS, is filled in a (b) (4) PFS with a 27G needle covered with a needle shield. The formulation is the same as that for the 100 mg PFS. The fill volume is (b) (4) to deliver a nominal 200 mg in 2.0 mL per syringe.

P.2 PHARMACEUTICAL DEVELOPMENT

Assessor's comment: Documents under this Section are reviewed in the order of 100 mg PFS, FVP, and 200 mg PFS.

PFS (100 MG/1 ML PFS)

Minor changes were made to the following sub-sections:

- P.2.1.1 Components of the Drug Product – Drug Substance: Add explanation to *q.s.*
- P.2.2.2 Overages: Remove deliverable volume for the DP
- P.2.2.3 Physicochemical and Biological Properties: Correct glass transition Temperature midpoint of frozen DS in Table 1 to -26°C

Assessor's comment: There is no actual changes in content. The editorial changes are acceptable.

FVP

P.2.1 Components of the Drug Product

(b) (4)

P.2.2 Drug Product

(b) (4)



Yun
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Zhou

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COA Tracking ID: C2024079

BLA Number: 761061/S-21 (Referenced IND for BLA: 140330)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024079
BLA# (Referenced IND for BLA):	761061/S-21 (140330)
Applicant:	Janssen Biotech, Inc
Established Name/Trade Name:	Guselkumab/TREMFYA
Indication:	Treatment of adult patients with moderately to severely active ulcerative colitis Please check all that apply: ☐ Rare Disease/Orphan Designation ☐ Pediatrics
PDUFA Goal Date:	September 11, 2024
Review Division:	Division of Gastroenterology
Clinical Reviewer:	Jaime Wolf
Clinical Team Leader (TL)	Suruchi Batra
Regulatory Project Manager:	Andrew Chi
COA Reviewer:	Susan Pretko, PharmD, MPH
COA TL:	Onyeka Illoh, OD, MPH
Instruments reviewed:	☒ Patient-reported outcome (PRO) • Patient-Reported Outcomes Measurement Information System[®] (PROMIS[®])-Fatigue Short Form (SF)-7a

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1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Gastroenterology regarding BLA 761061 for guselkumab (TREMIFYA®). The Applicant submitted an efficacy supplement (S-21) for TREMIFYA seeking an indication for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). The indication was supported by data from a phase 2b dose-ranging Induction Study 1 (IS-1) and from two pivotal studies: a phase 3 Induction Study 2 (IS-2) and a phase 3 Maintenance Study (MS).

The Applicant proposes COA-related labeling claims based on the following ranked secondary efficacy patient-reported outcome (PRO) endpoints in the IS-2 and MS studies as assessed by the Patient-Reported Outcomes Measurement Information System (PROMIS®)-Fatigue Short Form (SF) 7a:

- Fatigue response (defined as a ≥ 7 -point improvement from baseline) at Week I-12 in IS-2
- Fatigue response at Week M-44 in MS

Data from IS-2 demonstrated that TREMIFYA treatment resulted in statistically significant improvement in the PROMIS-Fatigue SF 7a scores compared with placebo. Data from MS also demonstrated a statistically significant results for the PROMIS-Fatigue SF 7a scores in favor of TREMIFYA compared to placebo. However, the review team determined that interpretability of the results of the “fatigue response” from MS is limited by the high number of placebo subjects who experienced an intercurrent event (ICE) in MS and the prespecified handling of ICEs in the efficacy analysis.

As such, the primary objective of this COA review is to evaluate the adequacy of the PROMIS-Fatigue SF 7a and its corresponding endpoint data from IS-2 to support labeling claims. To support the PROMIS-Fatigue SF 7a claims, the Applicant submitted a COA evidence dossier.^{1,2}

This review concludes that the evidence submitted by the Applicant is sufficient to demonstrate that the PROMIS-Fatigue SF 7a data from IS-2 is fit-for-purpose³ for the context of use of this drug development program to support labeling claims.

(b) (4)

2 REVIEW SUMMARY AND CONCLUSIONS

The PROMIS-Fatigue SF 7a was reviewed for content validity, quantitative measurement properties, and meaningful within-patient score change.

Data from the literature and qualitative research in subjects with UC demonstrated that the PROMIS®-Fatigue SF-7a is content valid for the context of use. (b) (4)

(b) (4) Similarly, psychometric analysis demonstrated reasonable quantitative measurement properties for the PROMIS®-Fatigue SF-7a.

Based on results of anchor-based analyses for the interpretation of score change, the clinical meaningfulness of the statistically significant results of the analysis of “fatigue response” at Week I-12 in IS-2 (defined as a ≥ 7 -point improvement from induction baseline as measured by the PROMIS®-Fatigue SF-7a) (b) (4)

3 BACKGROUND

Regulatory Background:

- TREMFYA was initially approved by FDA in 2017 for the treatment of plaque psoriasis and the indication was later expanded for the treatment of active psoriatic arthritis.⁴
- COA-labeling claims currently in TREMFYA USPI are based on the Psoriasis Area and Severity Index (PASI) composite score, Psoriasis Area and Severity Index (IGA), Psoriasis Symptoms and Signs Diary (PSSD), Pain Visual Analog Scale (VAS), patient global assessment, Disability Index of the Health Assessment Questionnaire (HAQ-DI), Short Form health survey (SF-36), and Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F).

⁴ BLA 761061. TREMFYA U.S. Prescribing Information (USPI). https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761061s007lbl.pdf

Previous COA Reviews:

There are no previous COA reviews for this BLA/referenced IND 140330 for the UC indication. However, research to support the PROMIS[®]-Fatigue SF-7a in patients with UC or Crohn's disease (CD) was reviewed by DCOA under IND 133845 regarding guselkumab for the treatment of moderately to severely active CD, as referenced below.

- C2023024_IND 133845_Li (DARRTS Reference ID: [5221365](#))
- C2020540_IND 133845_Chung (DARRTS Reference ID: [4759139](#))

Disease Background:

UC is a chronic relapsing/remitting bowel disorder of unknown etiology characterized by chronic inflammation of the gastrointestinal (GI) tract. Clinical manifestations of active disease include diarrhea, rectal bleeding (RB), weight loss, abdominal pain, bowel urgency, fatigue, fever, and possibly extraintestinal manifestations (e.g., arthritis).

Investigational Product:

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody that selectively binds to interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

Materials reviewed:

To support the efficacy labeling supplement to expand the indication statement to treat adults with UC and patient-reported outcome (PRO)-based labeling claims supported by the PROMIS[®]-Fatigue SF-7a, the Applicant submitted TREMFYA annotated labeling, pivotal clinical trial information (e.g., protocols, statistical analyses, study reports), and a PRO Evidence Dossier with supporting qualitative and quantitative evidence.^{1,2}

4 CLINICAL OUTCOME ASSESSMENT REVIEW

4.1 Clinical Trial Populations

In the phase 3 induction study (IS-2), a total of 736 adult subjects aged ≥ 18 years were randomized across 32 countries/territories and 701 subjects were included in the Full Analysis Set (FAS) (includes all randomized participants with a modified Mayo score (mMS) of 5 to 9 who received at least 1 (partial or complete) dose of study intervention). For subjects in the FAS, the majority were male (n=399, 56.9%) and White (n=508, 72.5%), and the mean age was 40.5 years (standard deviation (SD): 13.72; range 18 to 79). At Induction Baseline, the mean mMS was 6.9 (SD: 1.10).

In the phase 3 maintenance study (MS), a total of 805 subjects who completed the phase 2 and phase 3 induction studies (IS-1 and IS-2, respectively) and were in clinical response (defined as a decrease from induction baseline in the mMS by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 -point decrease from baseline in the RB subscore or a RB subscore of 0 or 1) to induction study intervention were included in the FAS for the phase 3 MS. For subjects in the FAS, the majority were male (n=445, 55.3%) and White (n=586, 72.8%) and the mean age was 40.7 years (SD: 13.68; range 18 to 79). At Maintenance Baseline, the mean mMS was 2.7 (SD: 1.55; range 0 to 7) and 34.2% of subjects were in clinical remission (defined as a stool frequency (SF) subscore

of 0 or 1, an RB subscore of 0, and an endoscopy subscore (ES) of 0 or 1 with no friability present on the endoscopy, where the SF subscore has not increased from induction baseline.)

4.2 Clinical Trial Design and Trial Endpoints

The Phase 2b/3 clinical development program for guselkumab in UC was conducted under a single protocol (CNT01959UCO3001) consisting of 3 separate studies, Induction Study (IS)-1 (phase 2b induction dose-ranging study), a phase 3 IS-2, and a phase 3 Maintenance Study (MS). The IS-2 and MS were the pivotal studies submitted to support this efficacy supplement. The PROMIS®-Fatigue SF-7a was administered electronically (no skip logic was used) in the pivotal trials for use as a key secondary endpoint measure.

4.2.1 Phase 3 Induction Study (IS-2)

Study IS-2 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, phase 3 IS that evaluated the safety and efficacy of guselkumab in participants with moderately to severely active UC. The primary and multiplicity-adjusted PRO secondary endpoint definitions and study endpoint results are in **Table 1**.

Table 1. Study IS-2: Primary and PRO-based secondary endpoint definitions and study results

Endpoint definition	Study results
Primary endpoint	
Clinical remission ¹ at week 12 of the induction study (I-12)	A significantly greater proportion of subjects treated with guselkumab were in clinical remission at Week I-12 (22.6%) compared with placebo (7.9%; adjusted treatment difference: 14.9% [p-value < 0.001])
Patient-Reported Outcome-based secondary endpoint (numbered by testing order)	
5. Fatigue response ² at Week I-12	A significantly greater proportion of subjects in the guselkumab 200 mg IV group achieved a fatigue response at Week I-12 (b) (4)

¹ Clinical remission is defined as a Mayo SF subscore of 0 or 1, a Mayo RB subscore of 0, and a Mayo ES of 0 or 1 with no friability present on the endoscopy, where the SF subscore has not increased from induction baseline.

² Fatigue response is defined as ≥ 7-point improvement in the PROMIS®-Fatigue SF-7a score.

The cumulative distribution function (CDF) curves by treatment group for change in PROMIS®-Fatigue SF-70 T-score at Week I-12 is in [Appendix 1](#).

(b) (4)

4.2.2 Phase 3 Maintenance Study (MS)

Study MS was a randomized withdrawal phase 3 study in subjects with moderately to severely active UC who demonstrated a clinical response to guselkumab treatment in either study IS-1 or IS-2. Subjects who met the definition of clinical response in the 12-week IS received an additional 44 weeks of guselkumab treatment. Efficacy was assessed at Week 44 after a total of 56 weeks of guselkumab treatment. The primary and multiplicity-adjusted PRO secondary endpoint definitions and study endpoint results are in **Table 2**.

Table 2. Study MS: Primary and COA-based secondary endpoint definitions and study results

Endpoint definition	Study results
Primary endpoint	
Clinical remission ¹ at Week 44 of the maintenance study (M-44) ¹	A significantly greater proportions of subjects in the guselkumab 200 mg (50.0%) and 100 mg (45.2%) groups were in clinical remission at Week M-44 compared with the placebo group (18.9%; p-value < 0.001 for both guselkumab groups)
Patient-reported outcome-based secondary endpoint (numbered by testing order)	
7. Fatigue response at Week M-44	(b) (4)

¹ Clinical remission is defined as a Mayo SF subscore of 0 or 1, a Mayo RB subscore of 0, and a Mayo ES of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.

[Reviewer's Comment: The improvement from induction baseline in the PROMIS®-Fatigue SF-7a appears to be maintained through Week M-44 ([Appendix 2](#)).]

(b) (4)

COA Tracking ID: C2024079

BLA Number: 761061/S-21 (Referenced IND for BLA: 140330)

(b) (5), (b) (4)



(b) (4)



⁵ SKYRIZI (risankizumab), BLA 761262. USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761105s029,761262s007lbl.pdf

⁶ RINVOQ (upadacitinib), NDA 211675. USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/211675s021s022lbl.pdf

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: August 9, 2024

To: Andrew Chi
Regulatory Health Project Manager
Division of Gastroenterology (DG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD, LCSW, BCD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Montherson L. Saint Juste, PharmD, MS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route: TREMFYA (guselkumab) injection, for subcutaneous use
TREMFYA PEN (guselkumab) injection, for subcutaneous use
TREMFYA (guselkumab) injection, for intravenous use

Application Type/Number: BLA 761061

Supplement Number: S-021

Applicant: Janssen Biotech, Inc.

1 INTRODUCTION

On March 11, 2024, Janssen Biotech, Inc. submitted for the Agency's review a supplement to the original Biologics License Application (BLA 761061) for TREMFYA (guselkumab). The purpose of this supplement (as stated by the Applicant) is as follows:

Janssen Research & Development, LLC (Janssen), on behalf of Janssen Biotech, Inc. (JBI), is hereby submitting a supplement to BLA 761061 with an accompanying Rare Pediatric Disease Priority Review Voucher, for the approval of TREMFYA for the treatment of adult patients with moderately to severely active UC.

In addition, this supplement contains three new drug product presentations for the proposed UC indication:

- *200 mg final vial product for short-term IV induction administration*
- *200 mg prefilled syringe (PFS) presentations for SC maintenance administration:*
 - *200 mg PFS assembled with the UltraSafe Plus needle safety guard (2 mL PFS-U)*
 - *200 mg PFS assembled with the Ypsomate autoinjector (2 mL PFS-Y)*

Reference is made to BLA 760161 for TREMFYA® (guselkumab), IND 140330 for guselkumab for the treatment of moderately to severely active ulcerative colitis (UC), and the Pre-sBLA Meeting with the Agency on March 22, 2023.

This review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Gastroenterology (DG) on March 13, 2024, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TREMFYA (guselkumab).

2 MATERIAL REVIEWED

- Draft TREMFYA (guselkumab) MG and IFU received on March 11, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2024.
- Draft TREMFYA (guselkumab) Prescribing Information (PI) received on March 11, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 2, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB)

published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We reformatted the IFU documents using the Arial font, size 11.

In our collaborative review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Review

Date: 07/26/2024

Dates consulted: 03/20/2024 and 06/26/2024

From: Sarah Sheikh, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health

To: Andrew Chi, Regulatory Project Manager (RPM)
Division of Gastroenterology (DG)

Drug: Tremfya (guselkumab)

BLA: 761061/s-21/s-24

Applicant: Janssen Biotech, Inc

Subject: Pregnancy and Lactation Labeling

Indications: Ulcerative colitis (UC) and Crohn's Disease (CD)

Materials Reviewed:

- DPMH consult request dated 03/20/24, DARRTS Reference ID 5350126
- DPMH consult request dated 06/26/24, DARRTS Reference ID 5404150
- Applicant submitted background package and proposed labeling for BLA 761061/s-21
- Applicant submitted background package and proposed labeling for BLA 761061/s-24

- Prior DPMH PLLR Review of Guselkumab for injection; BLA 761061 by Leyla Sahin, MD dated 04/12/17, DARRTS reference ID 4083650¹
- Information request (IR), sent 04/08/24
- Applicant's response to IR submitted on 05/01/24
- IR #2 sent 6/13/24
- Applicant's response IR#2 submitted on 06/17/24
- IR #3 sent 6/24/24
- Applicant's response to IR#3 submitted on 06/26/24

Consult Question:

DG received efficacy supplements in which the Applicant is proposing to expand both UC and CD as indications for treatment in adults. DG is requesting review of the submitted PI and the proposed changes to ensure compliance with the PLLR.

INTRODUCTION

On March 11, 2024, Janssen Biotech, Inc., submitted a priority review efficacy supplement for guselkumab injection to add UC as an indication for treatment in adults. Subsequently on June 20, 2024, Jansen Biotech, Inc. submitted an efficacy supplement to the existing BLA for the approval of guselkumab for the treatment of CD in adults.

DG consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Regulatory History

In 2017, guselkumab was initially approved by the FDA for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In 2020, guselkumab was approved for the treatment of adult patients with psoriatic arthritis (PsA) by the Agency.

The applicant is proposing a new indication for treatment of adult patients with moderately to severely active UC and CD.

Drug Characteristics²

- Description: human monoclonal IgG1 λ antibody
- Dosage and administration

For UC:

- Induction dosage: 200 mg intravenous (IV) infusion over at least one hour at Week 0, Week 4 and Week 8.

¹ DPMH did not rely on data in the guselkumab injection BLA or the Agency's finding of safety and effectiveness for guselkumab injection BLA to support labeling sections of this TREMFYA BLA. Rather, the cross-reference to the above-mentioned DPMH consult is included to avoid duplicating background information relevant to this class of products.

² Tremfya currently approved labeling. Drugs@FDA. Revised 07/2020.

- Maintenance dosage: 200 mg subcutaneous (SC) injection at Week 12, and every 4 weeks. For some patients, a dosage of 100 mg administered by SC injection at Week 16, and every 8 weeks thereafter, may be used.

For CD:

- Induction: 200 mg administered by IV infusion over at least one hour at Week 0, Week 4, and Week 8 or 400 mg administered by SC injection at Week 0, Week 4, and Week 8.
- Maintenance: 200 mg administered by SC injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by SC injection at Week 16, and every 8 weeks thereafter, may be used.
- Mechanism of action: selectively binds to interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor, blocking release of inflammatory cytokines
- Drug class: Monoclonal antibody (mAb)
- Molecular weight; 143,600 Daltons
 - Mean half-life: 15-18 days with plaque psoriasis, 17 days with UC and CD
 - % bioavailability: 49%

Current State of Labeling²

Currently approved labeling is in the Pregnancy and Lactation Labeling Rule (PLLR) format. Details of labeling content are listed below:

- There is no boxed warning regarding embryo-fetotoxicity
- There is no contraindication for use in pregnancy or during lactation
- Serious adverse reactions include:
 - Hypersensitivity Reactions, including anaphylaxis.
 - Increased risk of infection
 - Tuberculosis (TB) infection: evaluation for TB prior initiation of treatment
- There are no pregnancy testing or contraception recommendations
- There are no known drug-drug interactions with hormonal contraceptives
- Labeling excerpt:



(b) (4)

REVIEW

PREGNANCY

Ulcerative colitis and Pregnancy³

Crohn's Disease and Pregnancy³

UC and CD are both subtypes of inflammatory bowel disease (IBD) characterized by diffuse inflammation of the digestive tract. Many patients with IBD, whether UC or CD, are of reproductive age. In approximately 80% of female patients with IBD who conceive while their disease is still in remission, the IBD tends to remain in remission throughout the pregnancy and in the postpartum period. Of the patients who conceive when their disease is active, 66% continue to have active disease or worsening of their IBD. In up to 45% of patients with UC who conceive while their disease is active, the colitis worsens during pregnancy; in 24%, the colitis continues to be active but stable, and in the remainder of patients, the disease goes into

³ Hashash JG, Kane S. Pregnancy and Inflammatory Bowel Disease. Gastroenterol Hepatol (N Y). 2015 Feb;11(2):96-102. PMID: 27099578; PMCID: PMC4836574

remission. Among patients with CD who conceive while their disease is active, the disease goes into remission in one-third, remains stably active in one-third, and worsens in one-third.³ In addition, studies have shown IBD flare are similar in pregnant and nonpregnant patients with IBD, both UC and CD. Disease flares tend to be more frequent in the first 6 months of pregnancy and the first 3 months of the postpartum period. The goal of therapy is to induce and maintain remission with medical management, whether at conception or throughout pregnancy and the postpartum period. Active IBD itself is associated with poor pregnancy outcomes, including preterm birth, low-birth weight, and fetal loss. Medications given in pregnancy and lactation include aspirin, antibiotics, sulfasalazine, 5-aminosalicylic acid (5-ASA), and anti-tumor necrosis factor agents (anti-TNF).⁴

Nonclinical Experience

In a combined embryofetal development and prenatal and postnatal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab from the beginning of organogenesis to parturition at a dose (50 mg/kg) resulting in exposures (AUC) 18 times the exposure in humans administered 200 mg intravenously and 32 times the human exposure at 200 mg given subcutaneously. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (4 times the exposure (AUC) in humans administered 200 mg intravenously and 7 times the exposure (AUC) at 200 mg given subcutaneously) and three monkeys administered guselkumab at 50 mg/kg/week (18 times the exposure (AUC) in humans administered 200 mg intravenously and 32 times the exposure (AUC) following a 200 mg subcutaneous dose). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

The reader is referred to the full Pharmacology/Toxicology review by Dr. Blessy George.

Review of Pharmacovigilance Database

The applicant performed a search of the Global Medical Safety (GMS) global safety database was performed through March 31, 2024. A total of 951 cases involving guselkumab maternal exposure during pregnancy and lactation were identified, of which 656 cases were excluded. Refer to Appendix A for listing of pregnancy case disposition, including reasons for excluded cases, i.e. ongoing pregnancies and cases without in utero exposure, etc.

The applicant reported 270 pregnancy outcomes (267 pregnancies) by trimester with maternal exposure; 34 cases were spontaneous reports, 43 cases were from interventional clinical trials, and 190 cases were from noninterventional clinical studies. Refer to Appendix B for the complete listing of pregnancy outcomes and timing of maternal guselkumab exposure.

The pregnancy outcomes are as follows:

- 169 resulted in a live birth,
 - 161 in a normal live birth
 - 6 in a live birth with Adverse Event (AE)
 - 2 in a live birth with congenital anomalies
- 60 in spontaneous abortion,

⁴ Peppercorn, et al, UpToDate. Fertility, pregnancy, and nursing in inflammatory bowel disease. Nov 30, 2023.

- 25 in pregnancy termination (including 1 case also reporting congenital anomaly and 1 case also reporting baby AE,
- 9 in ectopic pregnancy,
- 3 in intrauterine death/still birth/fetal/neonatal demise,
- 1 in missed abortion,
- 3 in unknown outcomes

The applicant noted 10 cases of Neonatal Adverse Events (AEs) and congenital anomalies from maternal exposure to guselkumab listed below:

- Two major congenital malformations (MCM)-one case reported congenital heart disease and one case with esophageal atresia
- Pregnancy termination in the first trimester due to genetic malformation unspecified.
- Pregnancy termination at 11 weeks for unspecified fetal abnormality. Patient previously on methotrexate then switched to guselkumab. Patient had a smoking history.
- Preterm labor and delivery at 35 weeks with low birth weight. Neonatal course reported as normal.
- Fetal distress and emergency cesarean delivery at 37 weeks. 20-week scan revealed fetus was “small”.
- Gestational diabetes, along with fetal distress and emergency cesarean delivery at unspecified gestation.
- Neonatal demise 2 weeks after birth. Unknown if autopsy performed.
- Infant readmitted for jaundice 6 days after birth at 39 weeks. Baby discharged home on the same day.
- Failure to progress and fetal distress and emergency cesarean delivery at 40 weeks

The applicant concluded, “The review of the cases retrieved from the Sponsor’s global safety database is consistent with the known safety profile of guselkumab and no new safety concerns were identified which impact the benefit/risk profile in relation to pregnancy.”

Reviewer’s comment: This reviewer did not identify any pattern to the AEs reported. No new safety signals were identified. There are many limitations to the pharmacovigilance reports, including co-medications, as well as timing and duration of treatment, making interpretation challenging. The reason for the pregnancy terminations and the etiology of the neonatal demise are unknown.

There is a large amount of missing pregnancy outcome data, which makes interpretation of the adverse pregnancy outcomes difficult. The pharmacovigilance data of maternal guselkumab exposed pregnancies are missing outcome data in almost two-thirds of cases(489 out of 756). Of note, the spontaneous abortion rate (60 out of 270) among the pharmacovigilance cases with known outcomes is at the upper limit of the background miscarriage risk in the US. Continued monitoring of these cases will be needed to determine the true prevalence of miscarriage with guselkumab exposure.

Within the Medical Dictionary for Regulatory Activities (MedDRA), the applicant identified 10 events of interest (10 cases) reporting AEs related to perinatal complications from guselkumab exposure. These events are reported as follows:

- Gestational diabetes- 6 events
- Hypertension- 1 events
- Gestational hypertension-1 event
- Postpartum hemorrhage- 1 event
- Pre-eclampsia- 1 event

Reviewer's comment: The most frequent event was Gestational diabetes. Continued monitoring of future cases would be needed to note any trend with gestational diabetes and maternal exposure to guselkumab.

Review of Literature

Applicant's Review of Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS, MEDLINE, Derwent Drug File, and Embase;
- Search terms: Guselkumab, Tremfya AND pregnancy, pregnant woman, birth outcome, pregnancy outcome, prenatal drug exposure, prenatal exposure delayed effects, fetus outcome, reproductive toxicity, spontaneous abortion, teratogenicity, pregnan\$, gravid?, obstetric\$, (expos\$ adj2 (maternal or paternal or transplacenta? or f?etal or f?etus or gestation\$ or trimester? or intrauterine or intrauterine or antenatal or ante-natal or prenatal\$ or pre-natal\$ or perinatal\$ or peri-natal\$ or postnatal or post-natal\$ or pre-conception or preconception or periconception\$ or periconception\$ or prepregnan\$ or pre-pregnan\$ or postpartum or post-partum or pre-partum or prepartum or peripartum or peri-partum or pre-birth or preterm or pre-term or parturient?)), ((infant\$ or neo-nat\$ or neonat\$ or newborn\$ or new-born\$ or baby or babies or f?etus\$ or f?etal or embryo\$ or unborn) adj3 (harm\$ or impair\$ or risk\$ or abnormal\$ or anomal\$ or malform\$ or deform\$ or birth defect? or injur\$)), abort\$, miscarr\$, (congenital adj2 (abnormalit\$ or defect\$ or deform\$ or anomal\$)), embryopath\$, embryolethal\$, embryotox\$, f?etotox\$, (reproductive adj (risk\$ or toxic\$ or dysfunction or outcome? or safe\$)), reprotox\$, terat\$, (birth? or pregnanc\$ or f?etus\$ or f?etal or neonatal) adj3 outcome?)
- Limits: from 01 July 2017 to 31 December 2023.

A total of 105 publications were retrieved, of which 2 articles were relevant and discussed below. One article will be discussed under *Lactation*. Refer to Table 1 in Appendix B for a tabular summary of both publications.

- *Sánchez-García et al.*⁵ conducted a literature meta-analysis and systematic review of 51 observational studies, which included 739 pregnancies exposed to approved biologics for treatment of psoriasis. Thirteen pregnancies (1.8%) were exposed to guselkumab during the first trimester and then discontinued. No congenital malformations were reported. The outcome of these 13 guselkumab-exposed pregnancies were reported as follows:

⁵ Sánchez-García V, Hernández-Quiles R, de-Miguel-Balsa E, Giménez-Richarte Á, Ramos-Rincón JM, Belinchón-Romero I. Exposure to biologic therapy before and during pregnancy in patients with psoriasis: Systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2023 Oct;37(10):1971-1990. doi: 10.1111/jdv.19238. Epub 2023 Jun 13. PMID: 37262303.

- 8 live births
- 2 miscarriages
- 2 elective abortions,
- 1 unspecified abortion

Reviewer comment: The sample size for guselkumab-exposed pregnancies is too small in this study to make any generalizable conclusion. IgG are not transferred to the fetus in large quantities in the first trimester, therefore not expected to increase the risk of congenital malformations.

DPMH Review of Literature

This Reviewer performed a published literature search in PubMed, Embase, Micromedex⁶, TERIS⁷, and Reprotox⁸ to find relevant articles not cited by the applicant.

Search terms included “guselkumab” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” OR “miscarriage.”

No other relevant published literature was identified.

TREMFYA Pregnancy Exposure Registry

The TREMFYA (guselkumab) Pregnancy Exposure Registry is a North American based, observational pregnancy registry designed to monitor planned or unplanned pregnancies exposed to guselkumab for an approved indication (psoriasis or PsA), and to collect follow-up health status information on exposed infants through approximately 1 year of age.⁹

The collected information will include any adverse pregnancy outcomes, such as small birth size, preterm delivery, spontaneous or therapeutic abortion, and stillbirth. In live born infants, an evaluation of the potential effects of exposure on growth and development, serious or opportunistic infections, and malignancies will be reported through the first year of life.

The registry is conducted by the Organization of Teratology Information Specialists (OTIS) and public information service is provided by MotherToBaby.

The registry started enrolling patients in August 2018. As of May 31, 2023, seven patients have been enrolled. No MCMs were reported.

Pregnancy outcomes include:

- 3 live born infants
- 1 spontaneous abortion
- 3 pending pregnancy outcomes

Reviewer comment: Although no MCMs have been reported thus far, more patients need to be enrolled in the existing registry to perform a more meaningful assessment on the safety of guselkumab exposure in pregnancy. There is a complementary claims database pregnancy safety study (PMR 3225-3) for the psoriasis indication for which study completion is expected December 2024¹⁰. For the UC and CD indications, a similar pregnancy exposure registry and complementary study should also be conducted. Based on the animal study findings of neonatal

⁶ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 06/11/24.

⁷ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 06/11/24.

⁸ Reprotox Website: www.Reprotox.org. Accessed 06/11/24.

⁹ Final Protocol for pregnancy exposure registry submitted to FDA on Jan 31, 2018 [IND 105004 (SN0279)].

¹⁰ Final Protocol for complementary claims database pregnancy safety study submitted to FDA on Mar 26, 2019 [IND 105004 (SN0327)].

death, the limited available human data with guselkumab during pregnancy, and the need to treat during pregnancy to control active IBD and adverse pregnancy outcomes, post-approval studies are still needed to characterize guselkumab's potential serious safety concern in pregnancy (see Discussion and Conclusions below).

LACTATION

Nonclinical Experience

Guselkumab was not detected in the milk of lactating cynomolgus monkeys. Please refer to the full Nonclinical review by Dr. Blessy George.

Review of Pharmacovigilance Database

The applicant reviewed cases from their Global Medical Safety (GMS) database cumulatively through 31 March 2024 and found 55 cases of exposure to guselkumab during lactation. Of these cases, only 1 case reported a non-serious neonatal adverse event (AE) of infant thrush following guselkumab exposure during lactation at an unspecified time frame. The mother was receiving guselkumab for psoriasis. The infant's symptoms resolved after 12 days including treatment with nystatin. The remaining 54 cases did not report any infant AE or congenital anomaly after lactation exposure. None of the cases reported any fatal outcomes.

Reviewer comment: No conclusion on the causality of infant thrush and guselkumab exposure during lactation can be made with one case. Confounding factors, such as other maternal medical conditions or concomitant medications, could also have caused oral thrush in the infant.

Review of Literature

Applicant's Review of Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS, MEDLINE, Derwent Drug File, and Embase;
- Search terms: Guselkumab, Tremfya AND breastfed\$ or breast f?ed\$ or breastmilk or breast milk or colostrum or milk or lactation or lactating or lacteal, nurs\$ adj3 (baby or babies or infant? or newborn?, breast milk, colostrum, drug milk level, exp breast feeding, exp lactation disorders, exp lactation, milk, human

One relevant article was identified and discussed below:

- **Thatiparthi et al.**¹¹ discuss the use of biologics for psoriasis in pregnant and breastfeeding women. The authors state that the research on the use of IL-23 inhibitors in pregnancy is limited, and guselkumab can cross the placenta and be transported into human milk during lactation. The authors conclude, "preliminary data indicate that safety and adverse event profiles are similar to those of older biologic agents".¹²
After noting the above, the applicant concludes, "Therefore, this information is considered unassessable/unclassifiable".

¹¹ Thatiparthi A, Martin A, Liu J, Egeberg A, Wu JJ. Biologic Treatment Algorithms for Moderate-to-Severe Psoriasis with Comorbid Conditions and Special Populations: A Review. Am J Clin Dermatol. 2021 Jul;22(4):425-442. doi: 10.1007/s40257-021-00603-w. Epub 2021 Apr 16. PMID: 33861409; PMCID: PMC8051287.

¹² Abrouk M, Beroukhim K, Nakamura M, Zhu TH, Farahnik B, Singh R, et al. Considerations on biologic agents in psoriasis with the new pregnancy lactation labeling rule. Int J Womens Dermatol. 2016;2(2):62-4.

*Reviewer comment: The **Thatiparti et al.** article does not specifically discuss any new safety concerns regarding guselkumab use in lactation. The article does not cite any specific studies to support the presence of guselkumab in human milk, nor provide any details on how the authors arrive at this conclusion, other than cross-reference the United States Prescribing Information (USPI) for guselkumab. Thus, no conclusion can be drawn from the article on the safety of guselkumab exposure in lactation.*

DPMH Review of Literature

DPMH conducted an updated search of literature in PubMed and Embase, Micromedex¹³, Hale's Medications and Mothers' Milk¹⁴, Reprotox, the Drugs and Lactation Database (LactMed)¹⁵, and Briggs Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk¹⁶, using the search terms "guselkumab" and "lactation" or "breastfeeding." No new literature was found other than the literature presented by the applicant.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 25 mg/kg weekly (26 times the exposure (AUC) in humans administered a 200 mg dose intravenously and 45 times the exposure (AUC) at the 200 mg subcutaneous dose).

No effects on fertility parameters were observed after female guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly (12 times the exposure (AUC) in humans administered 200 mg intravenously and 21 times the exposure (AUC) at the 200 mg subcutaneous dose).

Review of Pharmacovigilance Database

The applicant reviewed cases from their Global Medical Safety (GMS) database cumulatively through 31 March 2024 and identified 27 cases of fertility disorders with guselkumab use; 2 were serious and 25 were non-serious. The two serious cases were related to polycystic ovarian syndrome.

Review of Literature

Applicant's Review of Literature

The applicant performed a cumulative literature search with the following strategy:

- Databases: BIOSIS, MEDLINE, Derwent Drug File, and Embase;
- Search terms: Guselkumab, Tremfya AND fertility, infertility, female fertility, female infertility, female sterility, male fertility, male infertility, male sterility, thermosensitive genic male sterility, sterility or fertile or infertile, reproductive potential, gravidity, fecundity

¹³ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 6/12/24.

¹⁴ Hale, Thomas W. Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

¹⁵ Drugs and Lactation Database (LactMed). Accessed 6/12/24

¹⁶ Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

No relevant published literature was found.

DPMH Review of Literature

This Reviewer performed a search in PubMed, Embase, Reprotox¹⁷ to find relevant articles related to the use of guselkumab and effects on fertility. Search terms included “guselkumab” AND “fertility,” “infertility,” “contraception,” and “oral contraceptives.” No published literature was identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

Ulcerative colitis and Crohn’s disease are common in females of reproductive potential, and therefore, unintended and intended exposures to guselkumab in pregnancy are likely to occur. For the pregnant individual with active IBD, treatment is imperative to control IBD symptoms and decrease complications, and to lessen disease-associated adverse pregnancy outcomes. While pregnant women were actively excluded from enrollment in clinical trials with guselkumab during the drug development program, 43 pregnancies occurred during interventional clinical trials and 190 pregnancies occurred during noninterventional clinical studies with guselkumab exposure.

The available published literature and limited pharmacovigilance are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. However, neonatal death in cynomolgus monkeys was shown to occur at exposures as low as 4 times the exposure (AUC) in humans administered 200 mg intravenously. These findings have unknown clinical relevance.

Therefore, post-approval studies are needed to characterize guselkumab’s potential serious safety concern in pregnancy. DPMH recommends a Post-Marketing Requirement (PMR) that requires the applicant to perform a pregnancy exposure registry study and a complementary study (i.e., a claims database study with chart review) to assess the safety of guselkumab in pregnant women. A claims database study with chart review is recommended to correlate with findings in the ongoing pregnancy exposure registry and because of the nonclinical findings in cynomolgus monkeys. A pregnancy exposure registry and complementary study currently exists for TREMFYA’s plaque psoriasis and psoriatic arthritis indications. A similar approach is recommended for the UC and CD populations.

We recommend using the following language for (b) (4) :

(b) (4)

¹⁷ Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 6/11/24

In comparison to other IL-23 inhibitors approved by the Agency in the past for treatment of IBD, DPMH does not propose to include a *Fetal/Neonatal Adverse Reactions* subheading under Clinical Considerations in section 8.1, recommending withholding live virus immunizations. The rationale to not include this recommendation was based upon recent discussion with expert panelists at an FDA Public workshop held on July 11-12, 2024, titled *Evaluating Immunosuppressive Effects of in Utero Exposure to Drugs and Biologic Products*. At the workshop, Dr. Uma Mahadevan, a distinguished research gastroenterologist in the area of IBD and pregnancy, advised not to delay live attenuated vaccines, such as Rotavirus, to infants exposed to immunosuppressive biologics in utero, as there is no published data of serious adverse events that support withholding live attenuated vaccines.¹⁸ She emphasized the lack of protection from withholding vaccination could cause more harm than good during a time when the infant's immune system is highly vulnerable.

Lactation

There are limited pharmacovigilance cases of guselkumab use during lactation, with one report of thrush in an infant following exposure to guselkumab via breast milk. There remains no new published data on guselkumab use in lactation. DPMH thinking regarding lactation studies for mAb drug products has evolved since 2017. A lactation study to confirm that presence/absence of the guselkumab in milk would be helpful for both patients and providers. In addition, data are needed regarding potential adverse events in breastfed infants whose mothers are receiving guselkumab therapeutically.

Guselkumab is indicated for a condition that would be expected to be seen in females of reproductive potential (including during lactation). There are no available data currently to inform women regarding guselkumab use during lactation. Therefore, DPMH recommends issuing a PMR for the applicant to conduct a clinical lactation study with guselkumab to inform labeling.

Refer to the FDA draft Guidance for Industry Clinical Lactation Studies: Considerations for Study Design published May 2019.

¹⁸ Fitzpatrick T, Alsager K, Sadarangani M, Pham-Huy A, Murguía-Favela L, Morris SK, Seow CH, Piché-Renaud PP, Jadavji T, Vanderkooi OG, Top KA, Constantinescu C; Special Immunization Clinic Network investigators. Immunological effects and safety of live rotavirus vaccination after antenatal exposure to immunomodulatory biologic agents: a prospective cohort study from the Canadian Immunization Research Network. *Lancet Child Adolesc Health*. 2023 Sep;7(9):648-656. doi: 10.1016/S2352-4642(23)00136-0. Epub 2023 Jun 27. PMID: 37390832.

We recommend using the following language for PMR lactation study:

Clinical Lactation Study:

Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received guselkumab, regardless of indication, to measure concentrations of guselkumab in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on the study population.

Females and Males of Reproductive Potential

There are no available human data on the effects of guselkumab on male or female fertility. Animal fertility studies do not indicate any adverse effects. In addition, animal reproduction studies do not indicate an increased risk for embryo-fetal toxicity. Therefore, DPMH recommends omitting subsection 8.3 from labeling for TREMFYA.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and section 17 of labeling for compliance with the PLLR and to reflect current labeling practices (see below). DPMH discussed our labeling recommendations with DG on 07/01/24. DPMH recommendations are below and reflect the discussions with DG. DPMH refers to the final BLA action for final labeling.

**DPMH Proposed Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION**



APPENDIX A

Pharmacovigilance (PV) Data in Pregnancy and Lactation from the Applicant

Table 1: Disposition of Cases Reporting Guselkumab Maternal Exposure During Pregnancy and/or Lactation Received Cumulatively Through 31 March 2024 (n=951)

Case Status	Number of Cases
Total Number of Cases With Maternal Exposure Retrieved	951
Total Number of Cases Excluded from Analysis	656
Unique pregnancy cases with ongoing or unknown pregnancy outcome, without reported perinatal complications	489
No in utero exposure	90
Linked baby cases	23
Multiple unidentifiable patients	8
Guselkumab exposure prior to pregnancy (prolonged latency >3 months)	15
Blinded cases	18
Duplicate cases	6
Suspected pregnancy	5
No guselkumab administration/exposure	2

Table 1: Disposition of Cases Reporting Guselkumab Maternal Exposure During Pregnancy and/or Lactation Received Cumulatively Through 31 March 2024 (n=951)

Case Status	Number of Cases
Total Number of Cases Included for Analysis	295
Unique Pregnancy Cases With Maternal Exposure	267^{a,b}
Clinical study (noninterventional)	190 ^c
Clinical trial (interventional)	43
Spontaneous	34 ^d
Unique Cases With Lactation Exposure Only	28
Clinical study (noninterventional)	18
Spontaneous	10

Key: n=Number of Cases

a: Included cases which also reported lactation (n=14) along with maternal exposure.

b: Count included 3 unique pregnancies with ongoing or unknown pregnancy outcome, with reported perinatal complications.

c: Count included 1 unique pregnancy from literature source.

d: Count included 3 unique pregnancies from literature source.

Appendix B

PV Data in Pregnancy from Applicant

Table 1: Overview of Outcomes of Unique Pregnancy Cases by Source and Trimester of Maternal Exposure Reported With Guselkumab: Cumulatively Through 31 March 2024 (Cases=267^a; Outcomes=270^a)

Pregnancy Outcomes	Spontaneous (34 Pregnancy Cases; 34 Outcomes)						Clinical Study (233 Pregnancy Cases; 236 Outcomes)						Total
	Timing of Exposure in Pregnancy						Timing of Exposure in Pregnancy						
	Before Conception ^a	First Trimester ^a	After First Trimester ^a	During All Pregnancy ^b	NR	Total ^a	Before Conception ^b	First Trimester ^b	After First Trimester ^b	During All Pregnancy ^b	NR	Total ^a	
Live birth	0	6	2	1	11	20	15	49	1	8	76	149	169
Normal live birth	0	6	2	1	9	18	14	48	1	7	73	143	161 ^c
Live birth with AE	0	0	0	0	1 ^d	1	1 ^e	1 ^f	0	1 ^g	2 ^h	5	6
Live birth with congenital anomaly	0	0	0	0	1 ⁱ	1	0	0	0	0	1 ^j	1	2
Interrupted pregnancies	0	3	0	0	9	12	6	35	0	0	33	74	86
Spontaneous abortion	0	2	0	0	8	10	5	20	0	0	25	50	60
Congenital anomaly	0	0	0	0	0	0	0	0	0	0	0	0	0
Elective/Induced abortion	0	1 ^k	0	0	1	2	1	14	0	0	8	23	25
Congenital anomaly	0	0	0	0	0	0	0	1 ^l	0	0	0	1	1
Fetal AE	0	0	0	0	0	0	0	0	0	0	0	0	0
Missed abortion	0	0	0	0	0	0	0	1	0	0	0	1	1
Ectopic pregnancy	0	1	0	0	0	1	1	1	0	0	6	8	9
Intrauterine death/Still birth/Neonatal demise	0	0	0	0	0	0	0	2	0	0	1	3	3
NR/Continuing co-reported with Perinatal complication	0	1	0	0	0	1	0	0	0	0	2	2	3 ^m
Total	0	11	2	1	20	34	22	87	1	8	117	236	270

Note: A missed abortion refers to when there was vaginal bleeding and perhaps some passage of tissue or products of conception. Induced abortion is a deliberate surgical or medical termination of pregnancy that has not reached viability and includes both safe and unsafe abortions.

Key: AE=Adverse Event; kg=Kilogram; lb=Pounds; NR=Not Reported

a: Each pregnancy was assigned an index case, which uniquely identified the pregnancy. In this table, an index pregnancy case is based on the maternal case. The case count and total outcome count may differ as it may include the count of twin or triplet pregnancy, which were counted more than once. One case (b) (6) reported twin pregnancy and one case (b) (6) reported triplet pregnancy. The total counts of the pregnancy outcome included 267 known pregnancy outcomes and 3 unknown pregnancy outcomes co-reported with perinatal complications.

Table 1: Overview of Outcomes of Unique Pregnancy Cases by Source and Trimester of Maternal Exposure Reported With Guselkumab: Cumulatively Through 31 March 2024 (Cases=267^a; Outcomes=270^a)

Pregnancy Outcomes	Spontaneous (34 Pregnancy Cases; 34 Outcomes)						Clinical Study (233 Pregnancy Cases; 236 Outcomes)						Total
	Timing of Exposure in Pregnancy						Timing of Exposure in Pregnancy						
	Before Conception ^a	First Trimester ^a	After First Trimester ^a	During All Pregnancy ^b	NR	Total ^a	Before Conception ^b	First Trimester ^b	After First Trimester ^b	During All Pregnancy ^b	NR	Total ^a	

b: Cases reporting exposure to guselkumab in all 3 trimesters have been counted only once under 'During All Pregnancy' category. Cases reporting either second or third trimester exposure along with first trimester exposure have been counted only once under 'First Trimester' category.

c: Six cases (b) (6) reported premature birth. The reported timing of trimester exposure was NR (2); Before conception, First trimester, After First trimester, During all pregnancy (1 each). Four cases (b) (6) reported delivery of normal/healthy babies with low birth weights of < 2.5 kg (5.5 lbs). Six cases (b) (6) reported perinatal complications including gestational diabetes

(4); postpartum haemorrhage, and pre-eclampsia (1 of each).

d: Case (b) (6) reported baby AE of foetal heart rate abnormal.

e: One case (b) (6) reported baby AEs of foetal distress syndrome and foetus measurement small.

f: One case (b) (6) reported baby AE of jaundice.

g: Case (b) (6) reported death neonatal.

h: Case (b) (6) reported baby AE of foetal heart rate decreased and perinatal complication of gestational diabetes. Case (b) (6) reported baby AE of premature baby (low birth weight [5 lbs]).

i: Case (b) (6) reported congenital anomaly of oesophageal atresia and fetal AE of tracheomalacia.

j: Case (b) (6) reported congenital anomalies of heart disease congenital.

k: Case (b) (6) reported baby AE of foetal disorder.

l: Case (b) (6) reported congenital anomaly of foetal malformation and elective abortion.

m: The reported perinatal complications for these 3 cases included gestational diabetes, gestational hypertension, and hypertension (1 of each)

Appendix C

Tabular listing of published literature^{19,20} results from applicant

Table 1: Tabular listing of publications and results.

Author (Year)	Study Design	Number Exposed / Unexposed	Endpoint	Point Estimates	Confidence Interval ^a	p Value
Sanchez-Garcia (2023)	Systematic literature review and meta-analysis of prevalence, following the PRISMA guidelines	739 ^b / 0	Spontaneous abortions	15.3%	12.7, 18.0	0.98
			Elective abortions	10.8%	7.7, 14.3	0.38
			Total abortions	23.7%	18.8, 29.0	0.99
			Congenital malformations in live births	3.0%	1.6, 4.8	0.074
		13 ^c / 0	Live births	61.5% (8/13)	N/A	0.11 ^d
			Miscarriage	15.4% (2/13)	N/A	0.15 ^d
			Elective abortion	15.4% (2/13)	N/A	0.04 ^d
			Unspecified abortion	7.7% (1/13)	N/A	0.00 ^d
Thatiparthi (2021) ^e	Review of current evidence	N/A	N/A	N/A	N/A	N/A

^a 95% Confidence Interval

^b Subjects exposed to a biologic.

^c Subjects exposed to guselkumab compared to all other biologics.

^d p value for combined biologic exposure (not limited to guselkumab).

^e There are no details regarding how the authors arrived at this conclusion and no secondary references to studies pertinent to this observation were provided. Therefore, this information is considered unassessable / unclassifiable.

¹⁹ Sánchez-García V, Hernández-Quiles R, de-Miguel-Balsa E, Giménez-Richarte Á, Ramos-Rincón JM, Belinchón-Romero I. Exposure to biologic therapy before and during pregnancy in patients with psoriasis: Systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2023 Oct;37(10):1971-1990. doi: 10.1111/jdv.19238. Epub 2023 Jun 13. PMID: 37262303.

²⁰ Thatiparthi A, Martin A, Liu J, Egeberg A, Wu JJ. Biologic Treatment Algorithms for Moderate-to-Severe Psoriasis with Comorbid Conditions and Special Populations: A Review. *Am J Clin Dermatol*. 2021 Jul;22(4):425-442. doi: 10.1007/s40257-021-00603-w. Epub 2021 Apr 16. PMID: 33861409; PMCID: PMC8051287.

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/s/

TAMARA N JOHNSON

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Signing for self and as proxy for primary author Dr. Sarah Sheikh.

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Division of Hepatology and Nutrition (DHN) Consultation

Drug-induced Liver Injury (DILI) Team

BLA/IND	761061 S-21 IND 133845(CD), 140330 (UC)
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Guselkumab
Indication	Ulcerative Colitis (UC)
Applicant	Janssen Research and Development, LLC
Requesting Division, contact	Andrew Chi, RPM, Jaime Folk, MO, Suruchi Batra TL, Blessy George, Nonclinical Reviewer
Primary Reviewer	Eileen Navarro Almario, MD, DILI Team Lead, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Clinical Data Scientist	Aaron Waddell, PhD
Nonclinical pharmacology, DHN	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	George Makar MD, Associate Director for Therapeutic Review; Signing for Frank Anania, Director (Acting), OND/DHN
Assessment Date	July 17, 2024

Context: Guselkumab (GSL), a human monoclonal IgG1 λ antibody that selectively binds the p19 subunit of interleukin 23 (IL-23) thereby inhibiting IL-23 induced inflammation. It is approved for adults with plaque psoriasis (PSO) and psoriatic arthritis (PSA). GSL is under BLA 761061, supplemental review (S-21) for adults with moderately to severely active ulcerative colitis (UC). An application for Crohn's disease (CD) (BLA 761061, S-24; IND 133845) came in Jun 20, 2024. GSL has no hepatotoxicity language in Section 5 of the label for PSO and PSA, but the dose used is lower at 100 mg every four to eight weeks. The proposed dose for UC and CD is 200 mg given intravenously (IV) every four weeks, times three, followed by 200 mg subcutaneously (SC) every four to eight weeks. A case of DILI meeting Hy's Law in the CD IND and hepatotoxicity seen with other anti-p19 IL-23 monoclonals prompted the Division of Gastroenterology (DG) to consult the Division of Hepatology and Nutrition (DHN) DILI Team for opinion on liver injury risk and input on DILI related labeling language, and post-market requirements or commitments.

Executive Summary: We found no convincing DILI in the UC program that presents an approvability concern. Non-clinical and study level data did not suggest a liver injury risk. Case level data analyses did not yield any cases meeting Hy's Law or having cholestatic DILI with jaundice. While the safety data were underpowered to provide 95% confidence in detecting a Hy's Law case, the number of UC subjects exposed to GSL was over 700, and the lack of significant imbalances in Temple's Corollary between GSL and placebo

treatment arms is encouraging. Our review of case level data from the IND for CD, which was sent with this supplemental BLA for UC, confirmed one case meeting Hy's Law, but this subject was in a phase 2 study taking a 1200 mg dose which is six times higher than the labeled dose for UC (200 mg). The 1200 mg dose was discontinued in the CD development program. At the time of this consult, we have not analyzed the CD study level data (e.g., eDISH, enzyme shift tables) in the supplemental BLA for CD, and therefore, we do not have a study level context for this Hy's Law case.

Overall, we support approval for UC if benefit is established, but the incomplete analysis on DILI risk in CD creates some challenges on how best to label for hepatotoxicity in UC. The UC data alone, supports hepatotoxicity language in Section 6 only. Elevating such language to Section 5 of the label may be warranted based on a drug class effect and description of the case meeting Hy's Law in the CD development program. The label may need later modification pending full analyses of the supplemental BLA for CD. We do not see a need for DILI related post market requirements for the UC indication. Our complete assessment and recommendations are below.

Consultation Sections:

Section 1.0 Target Disease and Rationale

Section 2.0 ADME and DDI pertinent to DILI risk

Section 3.0 Non-clinical data pertinent to DILI.

Section 4.0 Clinical data

Section 5.0 Assessment & Recommendations

Appendix: Additional tables and figures

Abbreviations:

ADA: anti-drug antibody

ADME: absorption, distribution, metabolism, excretion

ALP or AP: alkaline phosphatase

ALT: alanine aminotransferase

AP: alkaline phosphatase

AST: aspartate aminotransferase

AT: aminotransferase (ALT and/or AST)

BMI: body mass index

CD: Crohn's disease

CPK or CK: creatine phosphokinase

CYP: cytochrome P450

DB: direct bilirubin

DDI: drug-drug interaction

DILI: drug-induced liver injury

FAERS: FDA Adverse Events Reporting System

GGT: gamma-glutamyl transferase

GSL: guselkumab

HBV: hepatitis B virus

HCV: hepatitis C virus

HDS: herbal and dietary supplements

IP: investigational product

IV: intravenous

mAb: monoclonal antibody
MMS: Modified Mayo Score for UC disease activity
MRI: magnetic resonance imaging
PSA: psoriatic arthritis
PSC: primary sclerosing cholangitis
PSO: psoriasis
R-value: ALT/ULN ÷ ALP/ULN
sBLA: supplemental BLA
SC: subcutaneous
TB: total bilirubin
UC: ulcerative colitis
US: ultrasound
ULN: upper limit of normal

1.0 Target Disease and Rationale

1.1 Ulcerative Colitis: Ulcerative colitis (UC) is a chronic disease of unknown etiology. It is characterized by recurring episodes of inflammation limited to the mucosal layer of the colon. It commonly involves the rectum and may extend in a proximal and continuous fashion to involve the entire colon. Per 100,000 persons, 140 to 286 in North America, 2.4 to 505 in Europe, and 4.6 to 57.3 in Asia may have UC.¹ Approximately 67% of patients have at least one relapse within ten years after diagnosis. Approximately 40% to 50% of patients with moderately to severely active UC fail treatment with current biologic or small-molecule therapies in the first year of treatment.

Treatment of UC includes induction medications for initial remission, followed by maintenance medications that prevent a relapse of the disease.² First-line induction therapy options include biologic agents or glucocorticoids. Maintenance medications for UC treatment include glucocorticoids (budesonide, prednisone), and immunosuppressive agents (azathioprine, methotrexate, cyclosporine). FDA approved small molecules include two Janus kinase (JAK) inhibitors (tofacitinib and upadacitinib) and ozanimod; biologic therapies for UC include TNF α -inhibitors (adalimumab, golimumab, infliximab), an IL-12/23 inhibitor (ustekinumab), an anti-Integrin agent (vedolizumab), and recently approved IL-23 inhibitors (risankizumab, mirikizumab).

Approximately 2.5% of UC patients have primary sclerosing cholangitis (PSC)³ compared to a prevalence in CD of 0.96%. PSC is a chronic progressive disorder arising from inflammation of the biliary system. The inflammation can cause biliary strictures, both diffuse and focal, that ultimately lead to cirrhosis and need for liver transplantation. Acutely, PSC strictures can cause intermittent and unpredictable cholangitis with acute rises in liver analytes including aminotransferases (AT) and total bilirubin (TB) that may confound a diagnosis of DILI.

¹ Ng SC, et al. [Lancet, 2017 Dec 23;390\(10114\):2769-2778](#)

² UptoDate, https://www.uptodate.com/contents/management-of-moderate-to-severe-ulcerative-colitis-in-adults?topicRef=4068&source=see_link, accessed Sep 18, 2022.

³ Barberio B, et al. Prevalence of Primary Sclerosing Cholangitis in Patients with Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Gastroenterology*. 2021; 61:1865–1877

1.2 Rationale (Drug mechanism of action): Guselkumab (GSL) is a human immunoglobulin G1 lamda monoclonal antibody (mAb) against the p19 protein of human interleukin 23 (IL-23); it blocks binding to the IL-23 receptor, inhibiting IL-23's immune response cascade (**Figure 1**).⁴ Genetic polymorphisms involving the IL-23/IL-23 receptor interaction are considered risk factors for IBD.⁵ This BLA is for the treatment of adults with moderate to severely active UC. Labeling dose includes an intravenous (IV) induction of 200 mg once monthly for two months followed by maintenance of 200 mg subcutaneous (SC) monthly from week 12 onward.⁶ The BLA for Crohn's Disease (CD) is expected by mid-2024. GSL is approved for the treatment of adults with moderate to severe plaque psoriasis (2017) and for psoriasis arthritis (2020).⁷

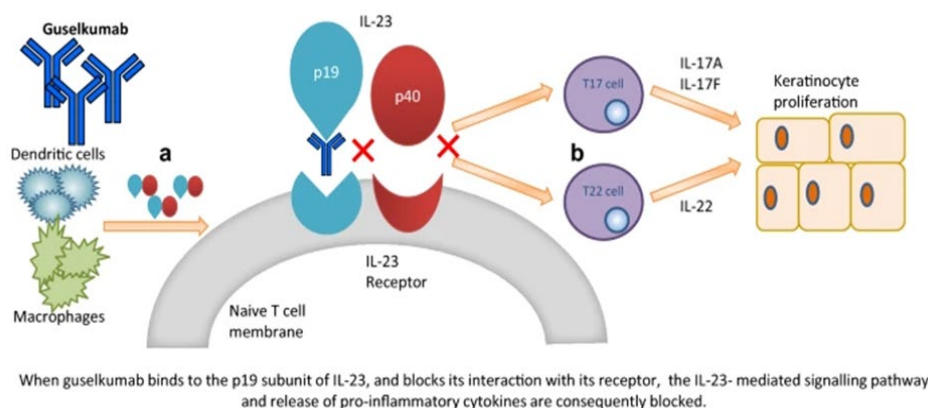


Figure 1: Guselkumab mechanism of action⁸

2.0 Human ADME and DDI pertinent to DILI risk

mAbs are generally taken up in a variety of tissues and metabolized intracellularly to short peptides and amino acids, so metabolism specific to the liver is not expected unless they specifically target liver antigens. Metabolic pathways used by small molecules (e.g., cytochromes, glucuronidation) and DDI based on cytochrome inhibition are not pertinent. Nevertheless, downstream perturbations in the immune system can also lead to liver injury. The DILI from monoclonals acting as immune check point inhibitors and those targeting tumor necrosis factor are examples of such downstream immune mediated liver injury. Also, neoantigen formation from the antibody breakdown and anti-drug antibodies are theoretical pathways for liver injury.

2.1 Structure: See **Figure 2**.

⁴ [BLA761061 \(761061 - 0700 - \(1172\) - 2024-03-11 - SUPPL-21 \(Efficacy\) /Multiple Categories/Subcategories\) - Nonclinical Overview \(#15\)](#)

⁵ [BLA761061 \(761061 - 0723 - \(1198\) - 2024-04-11 - MARKETING-979 /Marketing/2253 Professional\) - Introduction \(#2\)](#)

⁶ [BLA761061 \(761061 - 0700 - \(1172\) - 2024-03-11 - SUPPL-21 \(Efficacy\) /Multiple Categories/Subcategories\) - Introduction \(#2\)](#)

⁷ [Tremfya \(guselkumab\) | CenterWatch](#)

⁸ Al-Salama, Z.T and Scott, L.J. Guselkumab: A Review in Moderate to Severe Plaque Psoriasis. *Am J Clin Dermatol* 2018; **19**: 907–918. <https://doi.org/10.1007/s40257-018-0406-1>

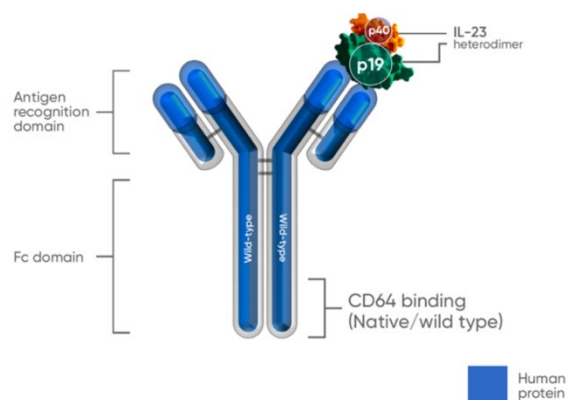


Figure 2: Schematic structure of Guselkumab.⁹

2.2 Absorption: There was slow absorption of GSL into the systemic circulation. Following single SC dose of 100 mg in healthy individuals, T_{max} was 5.0 to 5.5 days with a bioavailability from 48 to 55%. Lymphatic circulation is likely the main route of GSL absorption. There was no evidence of GSL accumulation through week 44. Hence,

GSL was slowly absorbed into the lymphatic system and there was a moderate bioavailability.

2.3 Distribution: GSL is confined to the circulatory system with limited tissue distribution. It distributes to 10 to 12.3% of body weight in healthy subjects.

2.4 Metabolism: Like other endogenous IgGs, GSL is expected to be metabolized into small peptides and amino acids in the peripheral vascular and lymphatic system as well as other tissues. Reactive metabolites that covalently bind proteins are not expected.

2.5 Excretion (elimination): GSL's mean terminal $T_{1/2}$ was about 17 days following a single IV or SC 100 mg dose in healthy subjects. One in 30 subjects (3.3%) receiving IV GSL tested positive to anti-drug antibody (ADA) resulting in a slightly higher clearance and shorter $T_{1/2}$ of 11.5 days. None of the 6 given SC GSL developed ADAs. Thus, GSL is eliminated via degradation to amino acids and small peptides with relatively long half-life of over two weeks when ADAs are not present, falling to under two weeks with ADA formation.

ADME highlights are in **Table 1**.

Table 1: ADME summary table

Item	Finding
Absorption	Slow, primarily via lymphatic system
Distribution	Mostly confined in the circulatory system.
Metabolism	Catabolism into small peptides and amino acids peripherally
Elimination	Peripheral/systemic catabolism and $T_{1/2}$ estimate: 16.7 to 17.2 days

Table made by DILI Team

2.6 Drug-Drug Interactions (DDI): We do not expect GLS to be a victim of CYP inhibitors or inducers. There was no effect on GSL clearance in DDI studies assessing SC GSL and four of the most frequently reported concomitant medications (ibuprofen, acetylsalicylic acid, paracetamol, and isoniazid). In cryopreserved human hepatocytes, IL-23 does not alter the expression or effect CYPs commonly involved in drug metabolism (1A2, 2B6, 2C9, 2C19, 2D6, and 3A4); thus its inhibition by GSL is not expected to perpetrate DDIs.

⁹ <https://www.tremfyahcp.com/psoriatic-arthritis/moa/molecular-structure/>

3.0 Non-clinical data pertinent to DILI

3.1 In vitro data: We found no in vitro data related to DILI.

3.2 Animal data: NOAEL was 100 mg/kg twice weekly in SC dosing in guinea pigs. In monkey, following IV weekly dosing for five weeks and SC weekly dosing for five and 24 weeks, NOAEL was 50 mg/kg/week. For an average adult US male weighing 91 kg and female weighing 78 kg, GSLs maximum labeled dose is 200 mg/month, or 2.2 and 2.6 mg/kg/month, respectively.¹⁰

Following a three-week SC dosing in guinea pigs at doses up to 100 mg/kg twice weekly, there were fatty liver changes in one animal on day one, and it died on day three. The cause of death was unknown per sponsor.

During a 5-week IV and SC and 24-week SC toxicity in monkeys, there were no significant changes in transaminases (TA), alkaline phosphatase (ALP), and total bilirubin (TB) up to 50 mg/kg. There were no histopathologic changes clearly associated with GSL. There were no GSL related effects on hematology, immunophenotyping, histopathology of immune tissues, or T- and B-cell distribution in monkeys and their off-spring.

Overall, non-clinical data do not predict hepatotoxicity from GSL. There were no liver analyte increases in serum and no liver histopathology. No immunotoxicity occurred. There was some GSL accumulation in guinea pigs. Some monkeys as well as some of their offspring were ADA positive but without significant changes in GSL exposures, suggesting that non-neutralizing ADA could be more abundant compared to neutralizing ADA.

Section 4.0 Clinical Data

4.1 In class or near class data: Labelling information and LiverTox® assessments for marketed anti-IL23 mAbs are in **Table 2**.

Table 2: Five approved anti-IL23 mAbs with DILI information by label and LiverTox®.¹¹ mAbs are prioritized by p19 target specificity and then by year of first approval.

Drug (Brand), Target Disease(s)	Mechanism of action	Approval year (s)	Labeling regarding DILI in - Box Warning (BW) - Warnings/Precautions, Highlights (W/P, HL) - Adverse Reactions, Highlights (AR, HL) - Sections 5 & 6 (S5 & S6)	LiverTox® category ¹²
Guselkumab (Tremfya®) PSO, PSA	Human monoclonal IL-23	2017 (PSO) 2020 (PSA)	BW: No - W/P, HL: No. - AR, HL: No - S5: No	E: suspected but unproven cause of clinically apparent liver injury, but experience

¹⁰ <https://www.cdc.gov/nchs/fastats/body-measurements.htm>

¹¹ LiverTox® <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

¹² LiverTox® <https://www.ncbi.nlm.nih.gov/books/NBK547852/>

	inhibitor via <i>p19 subunit</i>		• S6: Yes, describes liver mild to moderate enzyme elevations without need for stopping drug.	with its use has been limited
Risankizumab (SKYRIZI®) PSO, PSA, CD	Humanized monoclonal IL-23 inhibitor via <i>p19 subunit</i>	2019 (PSO) 2022 (PSA) 2022 (CD)	• BW: No • W/P, HL: Yes, liver analyte monitoring recommended. • AR, HL: No • S5: Yes, describes DILI case meeting Hy's Law. • S6: Yes, references S5.	E: unlikely cause of clinically apparent liver injury (updated as of 2021)
Mirikizumab (Omvoh®), UC	Humanized monoclonal IL-23 inhibitor via <i>p19 subunit</i>	2023 (UC)	• BW: No • W/P (HL): Yes; Liver analyte monitoring recommended. • AR (HL): No • S5: Yes, describes DILI case meeting Hy's Law. • S6: Yes, references S5.	NA
Ustekinumab (STELARA®), PSO, PSA, CD, UC	Human monoclonal IL-12, IL-23 inhibitor	2009 (PSO) 2013 (PSA) 2016 (CD) 2019 (UC)	• BW: No • W/P, HL: No. • AR, HL: No • S5: No • S6: No	E: unproven but suspected rare cause of clinically apparent liver injury, possible reactivation of HBV.
Tildrakizumab (Ilumya) PSO	Humanized monoclonal IL-23 inhibitor	2018 (PSO)	• BW: No • W/P, HL: No. • AR, HL: No • S5: No • S6: No	E: unlikely cause of clinically apparent liver injury but experience with its use has been limited
AR = Adverse Reactions; BW = box warning; HL = highlighted (page 1 of label); NA = not available; S5 = Label Section 5; S6 = Label Section 6; W/P = Warnings and Precautions CD= Crohn's disease, PSA: psoriatic arthritis, UC: Ulcerative colitis, CD: Crohn's disease, PSO: plaque psoriasis. Table developed by DILI Team				

Table 3 shows the number of reports in the FDA Adverse Events Reporting System (FAERS), an estimated rate per patient prescribed drug, and hepatotoxicity cases published for the five marketed anti-IL23 mAbs. Ustekinumab served as an active comparator in the CD program, so it has pertinence to that expected CD BLA for GSL. Ustekinumab's product label does not mention liver enzymes elevations or DILI, but hepatobiliary adverse events ranging from mild enzyme elevations and piecemeal necrosis

and hepatotoxicity are reported in FAERS and PubMed.^{13, 14}

Table 3: FAERS and PubMed searches related to DILI for five marketed anti-IL23 monoclonal antibodies ranked by year of first approval.

Drug (Initial approval year)	FAERS Total hepatobiliary reports (DILI, hepatotoxicity) ^	Rate of total FAERS reports per patient prescribed drug (%) ^{^^ 15}	PubMed Search for DILI Search syntax: (Drug Name) AND ((hepatotoxicity) or (liver injury) or (DILI))
Ustekinumab (2009)	2694 (260, 59)	0.72	8 cases
Guselkumab (2017)	139 (5, 2)	0.08	0 cases
Tildrakizumab (2018)	15 (0, 0)	0.20	0 cases
Risankizumab (2019)	543 (6, 2)	0.24	0 cases
Mirikizumab (2023)	0 (0, 0)	0.00	0 cases
[^] DILI and hepatotoxicity reports are included in the total hepatobiliary report count.			
^{^^} Number of patients based on Metys® estimations extending through 2010. Table made by DILI team			

4.2 Drug Development Program^{16,17}

Overview of three safety studies supporting this BLA are shown in **Figure 3**. Two were induction studies (IS) and are boxed in **blue**. IS 3001q1 (hereafter IS q1) was a phase 2 study while IS 3001q2 (hereafter IS q2) was a phase 3. IS q1 was a dose ranging study that randomized subjects (1:1:1) to 400 mg, 200 mg, and placebo dosed IV on day 1, week 4 and week 8 followed by primary efficacy assessment at week twelve. IS q2 compared the proposed label dose of 200 mg IV to placebo, followed by assessment at week twelve. Both IS q1 and q2 had repeat twelve-week induction phases for non-responders. The third study (Study 3001qm) boxed in **green** was a phase 3 with re-randomized withdrawal maintenance for twelve-week responders and non-randomized arms for 24-week responders. 3001qm enrolled only from IS q1 and q2; there were no de novo subjects entering 3001qm. The target enrollment population for IS q1 and q2 was

¹³ Lovero R, et al. A Case of Severe Transaminase Elevation Following a Single Ustekinumab Dose with Remission After Drug Withdrawal. *Curr Drug Saf.* 2018; 13:221-223

¹⁴ Llamas-Valasco M, et al. Liver Injury in Psoriasis Patients Receiving Ustekinumab: A Retrospective Study of 44 Patients Treated in the Clinical Practice Setting. *Actas Dermosifiliogr.* 2015; 106:470-476.

¹⁵ Metys® used to estimate patients prescribed drug

<https://metys.symphonyhealth.com/metys/#/home/prescriptionQuery>

¹⁶ BLA761061 (761061 - 0700 - (1172) - 2024-03-11 - SUPPL-21 (Efficacy) /Multiple Categories/Subcategories) - Tabular Listing of All Clinical Studies - UC Indication

¹⁷ NDA219195 (219195 - 0001 - (1) - 2023-12-28 - ORIG-1 /Multiple Categories/Subcategories) - Summary of Clinical Safety

1000 subjects, 95% with a Modified Mayo Score (MMS) of five to nine and 5% with MMS of four. Actual total enrollment numbers are shown in red in **Figure 3**.



Figure 3: Studies supporting the UC indication and populations screened for DILI.

Flow of subjects from IS q1 and q2 to 3001qm depended on when and whether a clinical response occurred (**Figure 4, below**). Responders to GSL at week twelve and placebo cross over

subjects in IS q1 & q2 who responded at week 24 were re-randomized in study in 3001qm. Thus, only those who responded in their first twelve weeks of GSL exposure were re-randomized in 3001qm with one third going to placebo (withdrawal arm). Subjects who responded only after an additional twelve weeks of GSL stayed on GSL 200 mg dosing in 3001qm (non-randomized). Subjects who responded to placebo at 12 weeks remained on placebo in the maintenance 3001qm (non-randomized).

Accordingly, we had CDS provide two DILI related analyses for each study.

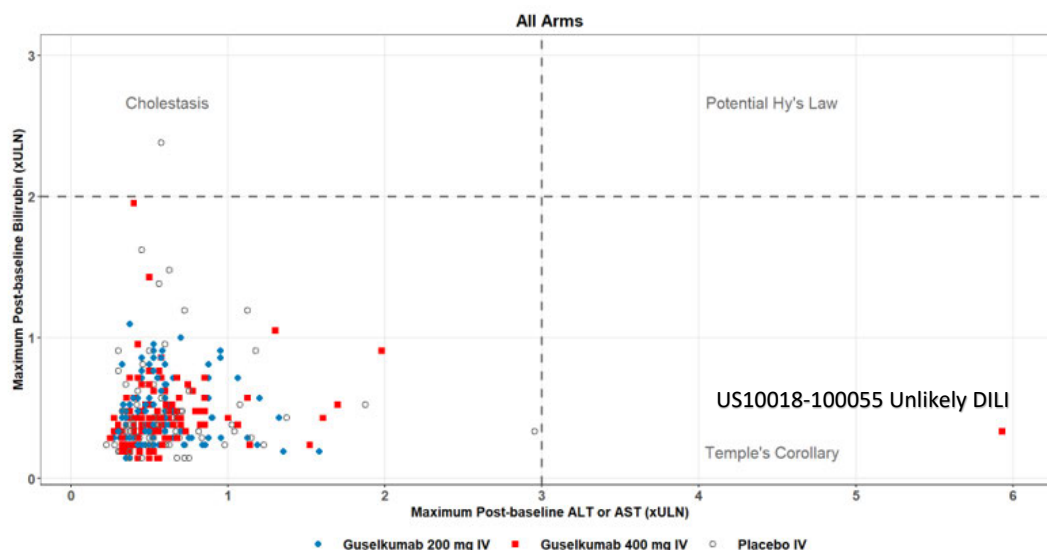
- IS q1
 - All subjects, randomized, placebo controlled, first twelve weeks.
 - Non-responders at week twelve receiving additional twelve weeks.
- IS q2
 - All subjects, randomized, placebo controlled, first twelve weeks.
 - Non-responders at week twelve receiving additional twelve weeks
- 3001qm
 - Randomized subjects (responders to twelve weeks of GSL in q1 & q2
 - Non-randomized subjects (24 week GSL & 12 week responders)

4.3 Study level data:

4.3.1 *Change in Liver Analytes:* The OND Clinical Data Scientists (CDS) provided analyses for IS q1, IS q2 and 3001qm (**Figure 4**). Each study had two CDS analyses. IS q1 and q2 each had twelve-week responder and non-responder analyses, the latter subjects receiving an additional twelve-weeks of GSL induction. Study 3001qm had randomized and non-randomized analyses (**Figure 4**).

4.3.1.1 **Induction Study, IS q1:**

- *Twelve-week responders:* For the twelve-week responders in IS q1, only one subject on GSL plotted to Temple's Corollary quadrant. No other subjects on GSL plotted outside the left lower quadrant (**Figure 5**). Cholestatic DILI screening plot had just one subject on GSL in the right lower quadrant with an ALP just over twice ULN, and no others outside the left lower quadrant (plot not shown). Thus, there were no subjects on GSL with jaundice and therefore, no subjects meeting AT and TB criteria for Hy's Law or cholestatic jaundice. As reflected in the eDISH plot, the numbers and rates of subjects with liver analyte increases by xULN cut-offs in all three arms were nearly zero (**Appendix, Table A**).



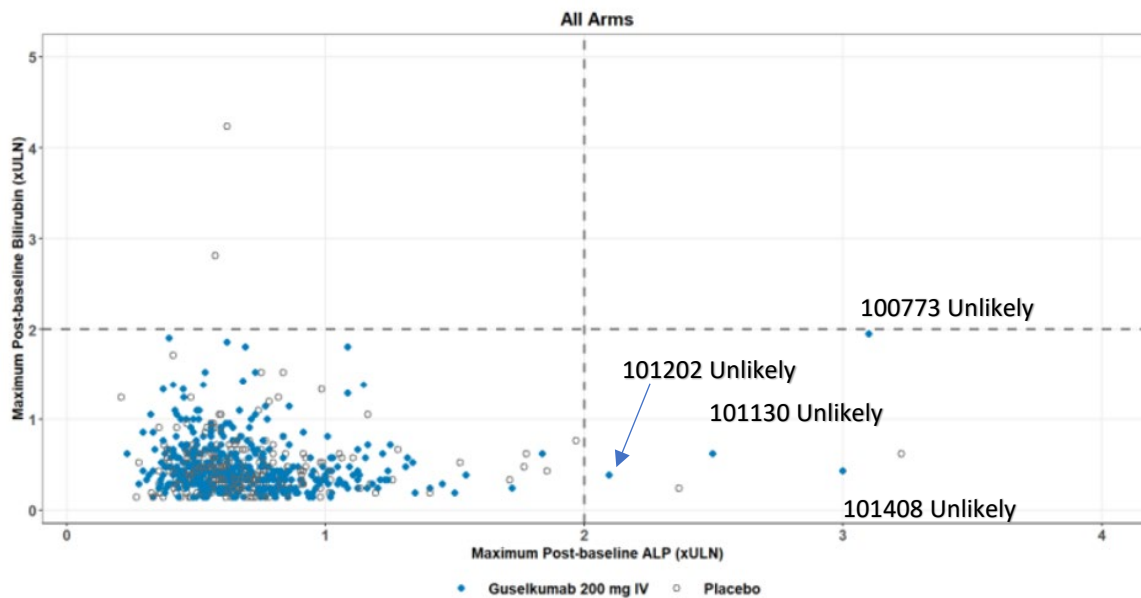
Made by CDS.

Figure 5: Hepatocellular DILI (eDISH) screening plot for [IS q1](#) twelve-week responders. The DILI Team assessed the case in Temple's Corollary as unlikely DILI due to GSL.

- *Twelve-week non-responders:* For the twelve-week *non*-reponders in [IS q1](#), the liver analyte data were similarly negative for DILI. Two subjects on placebo for the first twelve weeks and then GSL 200 mg IV for weeks 12 to 24 plotted to the cholestasis quadrant in eDISH. Otherwise, no subjects were outside the left lower quadrant. These two jaundiced subjects stayed in the left upper quadrant on the Cholestatic screening plot meaning they had jaundice without substantial elevation in ALP or ATs, and making DILI unlikely (**Appendix, Figure A**). No significant differences in liver analytes were seen between arms with all enzyme elevations occurring in the 1x to 3x ULN only (**Appendix, Table B**).

4.3.1.2 Induction Study, [IS q2](#):

- *Twelve-week responders:* For the twelve-week responders in [IS q2](#), no subject on GSL plotted outside the left lower quadrant on eDISH (plot not shown). The cholestatic screening plot had four subjects on GSL compared to two on placebo in the right lower quadrant (ALP >2x ULN without jaundice). There were no subjects in the right upper quadrant (**Figure 6**). While numerically, there were more subjects on GSL with ALP >2x ULN, the rates were similar (**Table 4**).



Made by CDS.

Figure 6: Cholestatic DILI screening plot (max. TB vs. max. ALP) for IS q2 twelve-week non-responders. We assessed all four subjects in the right lower quadrant (ALP >2x ULN) as unlikely DILI due to GSL.

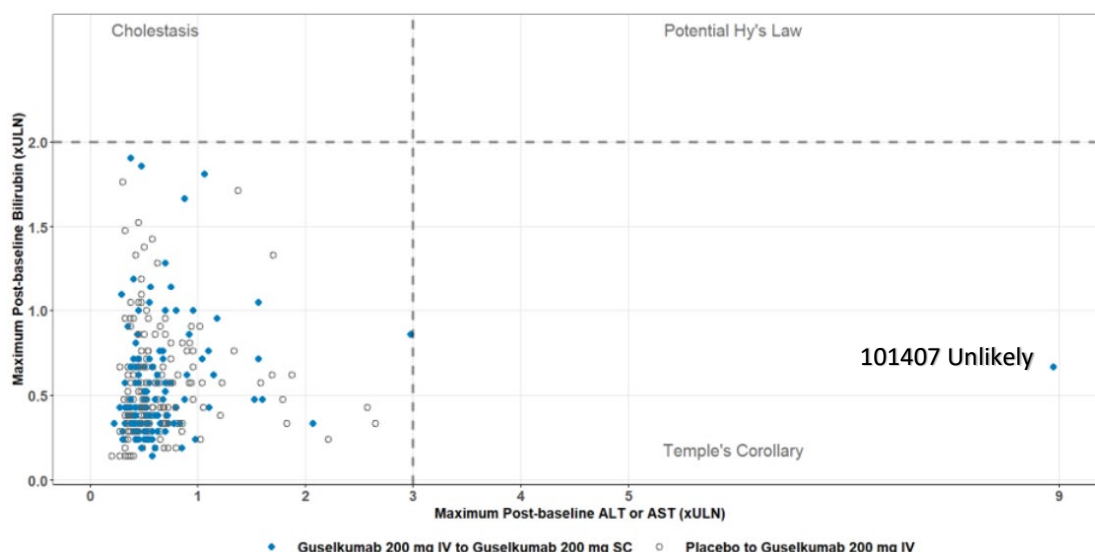
Table 4: Number and rates of ALP elevations by xULN cut-offs by study arm in IS q2 twelve-week responders.

Laboratory Abnormality	Guselkumab 200 mg IV N=440 n (%)	Placebo N=295 n (%)	Risk Difference (%) (95% CI)
ALP			
>=2X ULN	4/433 (0.9)	2/287 (0.7)	0.2 (-1.7, 1.8)
>=3X ULN	2/433 (0.5)	1/287 (0.3)	0.1 (-1.5, 1.4)

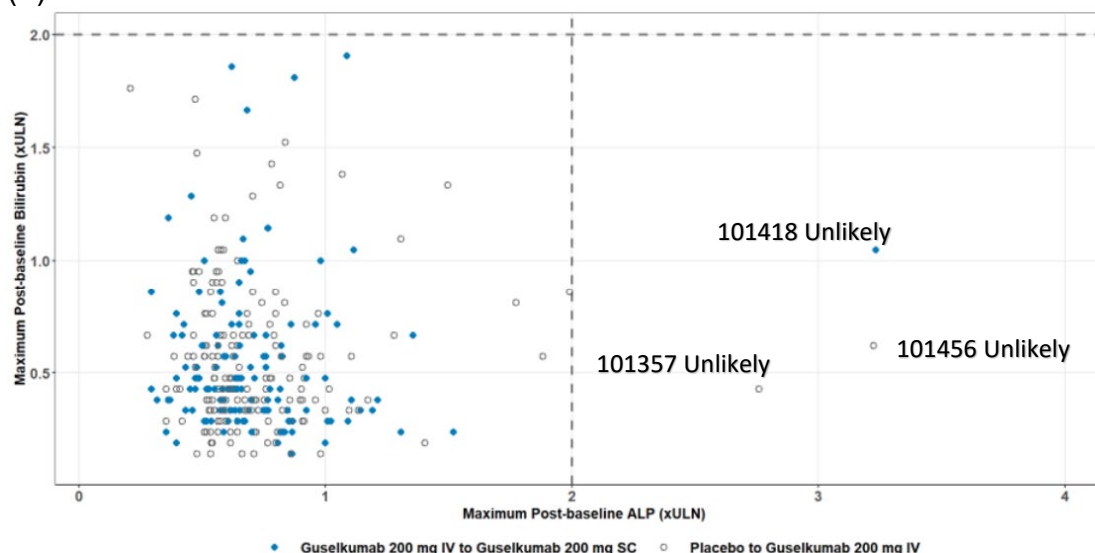
Table made by CDS

- *Twelve-week non-responders:* For the twelve-week *non*-responders in [IS q2](#), only one subject plotted outside the left lower quadrant on eDISH and that subject assessed as unlikely DILI (**Figure 7a**). Three subjects were in the left lower quadrant on cholestatic DILI screening plot and none were attributable to DILI (**Figure 7b**).

(a)



(b)



Made by CDS.

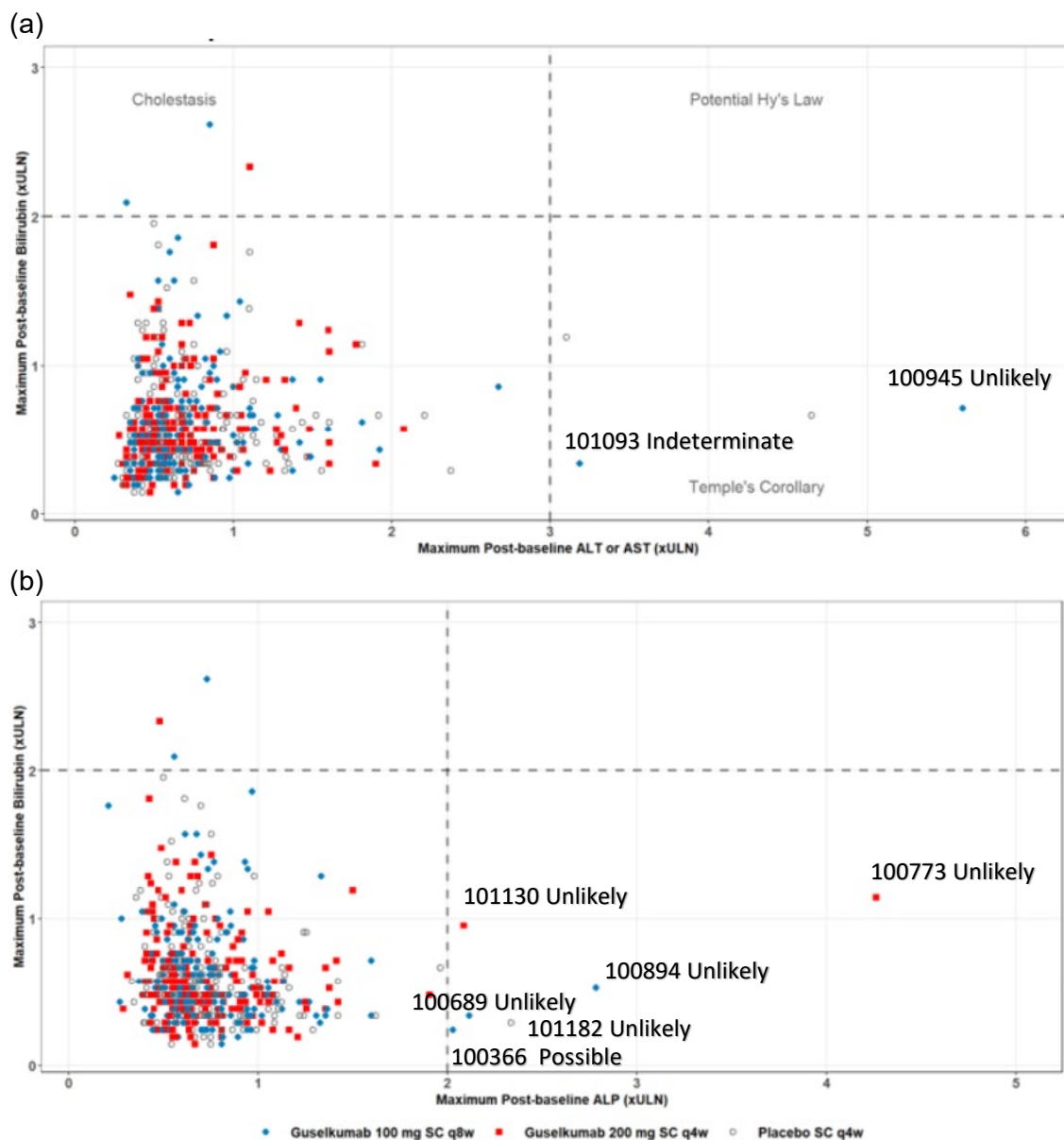
Figure 7: Hepatocellular DILI (dDISH) screening plot for IS q2 for twelve-week non-responders given an additional twelve weeks of induction.

No significant differences in liver analyte elevations were seen between arms with most enzyme elevations occurring in the 1x to 3x ULN only (**Appendix, Table C**).

4.3.1.3 **Maintenance Study, 3001qm:** CDS split these data by the randomized and the non-randomized portions.

For the randomized portion of **3001qm**, two subjects randomized to GSL plotted to Temple's and three to the Cholestasis quadrants (**Figure 8a**). On subject (Subject 101093) lacked detailed narrative data and was considered indeterminant, but the ATs were just over 3x ULN without hyperbilirubinemia, and the study drug continued making clinically important DILI unlikely. There were no subjects in potential Hy's Law quadrant.

These three jaundiced subjects in the Cholestasis quadrant stayed in the left upper quadrant on cholestatic screening plot meaning they had jaundice without substantial elevation in ALP or ATs, making DILI unlikely (**Figure 8b**). There were numerically more subjects on GSL with ALP >2x ULN in the GSL arm, but the proportionate differences between arms at >3x ULN was small and none of the cases had jaundice (**Table 5**).



Made by CDS.

Figure 8: Hepatocellular (eDISH) and cholestatic DILI screening plots for 3001qm, randomized portion.

Table 5: Number and rates of liver analyte elevations by xULN cut-offs by study arm in 3001qm randomized portion.

Laboratory Parameter	Guselkumab 100 mg SC Q8W N=186 n/N _w (%)	Guselkumab 200 mg SC Q4W N=190 n/N _w (%)	Placebo SC Q4W N=192 n/N _w (%)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	5/186 (2.7)	3/189 (1.6)	3/191 (1.6)
Level 2 (>2X ULN)	3/186 (1.6)	2/189 (1.1)	1/191 (0.5)
Level 3 (>3X ULN)	0/186 (0)	1/189 (0.5)	0/191 (0)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	2/186 (1.1)	0/189 (0)	1/191 (0.5)
Level 2 (>5X ULN)	1/186 (0.5)	0/189 (0)	0/191 (0)
Level 3 (>10X ULN)	0/186 (0)	0/189 (0)	0/191 (0)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	0/186 (0)	0/189 (0)	1/191 (0.5)
Level 2 (>5X ULN)	0/186 (0)	0/189 (0)	0/191 (0)
Level 3 (>10X ULN)	0/186 (0)	0/189 (0)	0/191 (0)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	6/186 (3.2)	2/189 (1.1)	5/191 (2.6)
Level 2 (>2X ULN)	2/186 (1.1)	1/189 (0.5)	0/191 (0)
Level 3 (>3X ULN)	0/186 (0)	0/189 (0)	0/191 (0)

Source: adlb.xpt; Software: R

Made by primary statistical review team.

For the non-randomized portion of 3001qm, there were again no cases in the right upper quadrants of the hepatocellular (eDISH) and cholestatic DILI screening plots suggesting no Hy's Law cases or cholestatic DILI with jaundice (**Appendix, Figure B**). There were no imbalances in liver analyte elevations between arms by varying cut-off levels in xULN (**Appendix, Table D**).

4.3.2 Adverse Event Analysis: We assessed deaths, severe adverse events (SAE) and AEs related to liver related liver analytes for IS q1 and q2 during their initial twelve-week randomized placebo-controlled portions. We did the same for 3001qm, randomized portion. There were no GSL associated deaths across the UC program. There were no liver related SAEs or AEs leading to discontinuation in the maintenance phase through week 44.

Hepatobiliary disorders FMQ and Drug Induced Liver Injury AESI were numerically more frequent with guselkumab in IS q1 and q2 (**Table 6**). However, none of these events led to death, transplantation, or treatment discontinuation.

Table 6: Patients with Adverse Events by System Organ, FDA Medical Query and AESI Safety Population Trial, Studies [IS q1](#) and [q2](#).

System Organ Class or AE FMQ or AE term	Guselkumab 200 mg N=101 n (%)	Guselkumab 400 mg N=107 n (%)	Placebo N=105 n (%)	Guselkumab 200 mg vs. Placebo Risk Difference % (95% CI)	Guselkumab 400 mg vs. Placebo Risk Difference % (95% CI)
3001q1 (12 weeks)					
Hepatobiliary disorders*					
Hepatic injury (Narrow)	3 (3.0)	2 (1.9)	1 (1.0)	2.0 (-2.5, 7.6)	0.9 (-3.5, 5.7)
Hepatic injury (Broad)	3 (3.0)	4 (3.7)	1 (1.0)	2.0 (-2.5, 7.6)	2.8 (-1.9, 8.4)
Drug-Induced Liver Injury AESI					
AE grouping related to AESI	3 (3.0)	2 (1.9)	1 (1.0)	2.0 (-2.5, 7.6)	0.9 (-3.5, 5.7)
ALT increased	2 (2.0)	2 (1.9)	1 (1.0)	1.0 (-3.4, 6.1)	0.9 (-3.5, 5.7)
AST increased	2 (2.0)	1 (0.9)	0	2.0 (-1.6, 7.0)	0.9 (-2.6, 5.1)
Cholestasis	1 (1.0)	0	0	1.0 (-2.6, 5.4)	0.0 (-3.5, 3.5)
3001q2 (12 weeks)					
Hepatobiliary disorders*					
Hepatic injury (Narrow)					
Hepatic injury (Broad)	10 (2.4)		2 (0.7)	1.7 (-0.4, 3.7)	
Drug-Induced Liver Injury AESI					
AE grouping related to AESI	3 (0.7)		0	0.7 (-0.6, 2.1)	
ALT increased	2 (0.5)		0	0.5 (-0.9, 1.7)	
AST increased	2 (0.5)		0	0.5 (-0.9, 1.7)	
Cholestasis	1 (0.2)		0	0.2 (-1.1, 1.3)	

Made by CDS.

For the randomized portion of [3001qm](#), there were numerically and proportionately more subjects with the FMQ broad term of “Hepatic failure” (**Table 7**), but none resulted in death, transplantation, or discontinuation. While the FMQ broad terms included “Hepatic failure” cases, we found no “acute liver failure” or “liver failure” entries in the “AETERM” columns of the adam (adae.xpt) or stdm (ae.xpt) files for [IS q1](#), [IS q2](#) or [3001qm](#). On reconciliation for liver related AEs with DILI narratives, there were no convincing hepatic failures (**Appendix, Table E**). We found no cases of liver transplant or liver related deaths.

Table 7. Patients with Adverse Events by System Organ Class and FDA Medical Query (Broad), Showing Terms Occurring in at Least 2% of Subjects in Any Arm, Safety Population Trial [3001qm](#)

SOC or AE	Guselkumab 100 mg SC Q8W N=186 n (%)	Guselkumab 200 mg SC Q4W N=190 n (%)	Placebo SC Q4W N=192 n (%)	Guselkumab 200 mg SC Q4W vs. Placebo 100 mg SC Q8W Risk Difference % (95% CI)	Guselkumab 100 mg SC Q8W vs. Placebo SC Q4W Risk Difference % (95% CI)	Guselkumab 200 mg SC Q4W vs. Placebo SC Q4W Risk Difference % (95% CI)
FMQ broad						
Hepatic failure	4 (2.2)	1 (0.5)	1 (0.5)	-1.6 (-4.9, 1.0)	1.6 (-1.0, 4.9)	0.0 (-2.4, 2.4)
Hepatic injury	10 (5.4)	4 (2.1)	5 (2.6)	-3.3 (-7.8, 0.6)	2.8 (-1.3, 7.3)	-0.5 (-4.1, 3.0)
Preferred term	5 (2.7)	2 (1.1)	1 (0.5)	-1.6 (-5.2, 1.4)	2.2 (-0.5, 5.7)	0.5 (-1.9, 3.3)
AESI grouping	1 (0.5)	2 (1.1)	1 (0.5)	0.5 (-2.0, 3.3)	0.0 (-2.4, 2.5)	0.5 (-1.9, 3.3)
ALT increased	1 (0.5)	1 (0.5)	0	-0.0 (-2.5, 2.4)	0.5 (-1.4, 3.0)	0.5 (-1.4, 2.9)
AST increased	0	1 (0.5)	1 (0.5)	0.5 (-1.5, 2.9)	-0.5 (-2.9, 1.5)	0.0 (-2.4, 2.4)
Hepatomegaly	0	1 (0.5)	0	0.5 (-1.5, 2.9)	0.0 (-2.0, 2.0)	0.5 (-1.4, 2.9)

Made by CDS.

4.4 Case level analyses

4.4.1 Ulcerative Colitis: We assessed 15 subjects with elevation in liver analytes for GSL hepatotoxicity across the UC drug development program. These 15 covered nearly all subjects outside the left lower quadrants of the DILI screening scatterplots. A few cases with modest enzyme elevations (ALP 2x to 3x ULN or AT 3x to 5x UL) without hyperbilirubinemia were not reviewed in detail. We considered only one case as possible liver injury from GSL, and it was cholestatic and mild with only modest ALP elevation. We considered the remaining cases as unlikely DILI due to GSL with primary sclerosing cholangitis being the most common alternate diagnosis (Table 8).

Table 8: Fourteen subjects with liver analyte elevations assessed for DILI across the GSL ulcerative colitis development program.

#	ID	Causality Score*	Alternate diagnosis	Study	Age (y)	Sex	Race	Hy's Law	Latency from start drug (d)~	Latency from stop drug (d)~	ALT peak (U/L)^	AST peak (U/L)^	ALP peak (U/L)^	Bilirubin peak (mg/dL)	R value peak
1	(b) (6)	4	Unknown	CNT01959UCO3001	24	F	White	No	349	[26]	34	NA	211	0.23	0.49
2		5	PSC diagnosed	CNT01959UCO3001	34	M	White	No	28	[308]	73	60	417	1.29	0.54
3		5	PSC diagnosed	CNT01959UCO3001	31	M	White	No	53	[310]	58	37	550	2.4	0.32
4		5	PSC diagnosed	CNT01959UCO3001	35	F	White	No	[23]	[79]	53	47	287	0.53	0.56
5		5	PSC diagnosed	CNT01959UCO3001	24	M	White	No	[27]	[90]	34	34	416	0.76	0.25
6		5	PSC diagnosed	CNT01959UCO3001	22	F	White	No	0	[64]	102	45	243	0.18	1.28
7		5	Non-liver AP	CNT01959UCO3001	56	M	Asian	No	28	[28]	34	34	322	0.53	0.32
8		5	Non-liver AP	CNT01959UCO3001	56	M	Asian	No	28	[340]	34	34	322	0.53	0.32
9		5	Non-liver AP	CNT01959UCO3001	20	F	White	No	225	[138]	34	34	220	0.23	0.47
10		5	Mesalazine	CNT01959UCO3001	76	F	White	No	0	[54]	255	93	104	0.41	7.50
11		5	Myopathy	CNT01959UCO3001	19	M	White	No	140	0	88	358	358	0.53	0.75
12		5	AM/CL	CNT01959UCO3001	45	M	White	No	141	[223]	269	71	206	0.41	3.99
13		5	Unknown	CNT01959UCO3001	76	M	Asian	No	0	[56]	47	83	953	0.41	0.15
14		5	Unknown	CNT01959UCO3001	39	F	White	No	0	[56]	NA	55	218	0.47	NA
15		5	Unknown	CNT01959UCO3001	45	M	Asian	No	85	[224]	34	34	257	0.41	0.29

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [] day values mean the the injury started before study drug given or continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

AM/CL = amoxicillin/clavulanate; PSC = primary sclerosing cholangitis

Made by DILI Team.

The 90-day safety update reported one more case potentially fulfilling Hy's Law AT and TB criteria (Subject (b) (6)).¹⁸ We considered this case as unlikely liver injury from GSL, favoring PSC as the source of liver enzyme and TB elevations.

¹⁸ [\\CDSESUB1\evsprod\BLA761061\0771](#)

4.4.2 Safety Data from Crohn's Disease (CD) Development Program: The Sponsor is developing GSL for treating CD, and that BLA is expected this year. The Sponsor implemented a unilateral pause in the CD development program due to three cases of liver injury, one of which was concerning for potentially meeting Hy's Law. This latter case was on the highest dose of 1200 mg. The CD program resumed with elimination of this 1200 mg dosing.

The UC BLA under review for this consult included a Clinical Study Report (CSR) and data from one phase 2 CD study, Galaxi1. No phase 3 aggregate data are available, but the Sponsor identified 17 subjects with liver injury from across the CD development program. Thirteen of the 17 had detailed case level data provided via an information request, and the DILI Team reviewed these 13 which included the three cases that prompted the prior pause in development (Subjects (b) (6)). The DILI Team considered Subject (b) (6) as having probable DILI due to GSL (dose = 1200 mg) and meeting Hy's Law. This case is detailed below. We concluded that the two other subjects that prompted the prior pause as unlikely DILI due to GSL but identified two possible DILI cases amongst the remaining nine cases (**Table 9**); both subjects had identified completing causes (COVID-19 vaccination and isoniazid). Overall, ten cases were considered unlikely DILI due to GSL with gallstone disease as the most common competing diagnosis.

Table 9: Thirteen subjects with liver injury from the GSL Crohn's disease development program.

#	ID	Causality Score*	Alternate diagnosis	Study	Age (y)	Sex	Race	Hy's Law	Latency from start drug (d)	Latency from stop drug (d)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak^
1	(b) (6)	3	NA	CNT01959CRD3001	44	F	White	Yes	86	0	601	372	123	2.9	14.9
2		4	COVID-19 vaccine	CNT01959CRD3001	24	M	White	No	229	0	324	140	104	0.9	9.5
3		4	Isoniazid	CNT01959CRD3001	67	M	White	No	54	0	553	288	288	1.3	5.9
4		5	Gallstone disease	CNT01959CRD3004	19	F	White	No	342	0	101	272	104	0.7	3.0
5		5	Gallstone disease	CNT01959CRD3001	40	M	White	No	138	[167]	221	133	470	0.8	1.4
6		5	Gallstone disease	CNT01959CRD3001	55	M	White	No	113	[168]	262	245	104	0.5	7.7
7		5	Gallstone disease	CNT01959CRD3001	42	M	White	No	166	[113]	93	181	104	0.4	2.7
8		5	Myopathy/PSC	CNT01959CRD3001	26	M	White	No	81	[196]	95	128	104	3.0	2.8
9		5	Infection	CNT01959CRD3001	27	M	White	No	143	11	281	167	112	3.8	7.7
10		5	Dengue fever	CNT01959CRD3004	29	M	Unknown	No	336	0	245	167	104	0.9	7.2
11		5	Unknown	CNT01959CRD3004	22	F	White	No	0	[1]	372	131	312	0.7	3.6
12		5	Unknown	CNT01959CRD3001	49	F	Unknown	No	93	[103]	181	64	104	0.5	5.3
13		5	Unknown	CNT01959CRD3001	31	F	White	No	28	[84]	232	122	167	0.4	4.2

NA = not applicable; PSC = primary sclerosing cholangitis

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

Made by DILI Team

Case of Interest: We highlight the one subject with probable DILI due to GLS in the CD program.

- Subject [REDACTED] (b) (6) Probable DILI due to GSL and meets Hy's Law.

Summary: This is a 44-year-old female of unknown or unstated race, with CD, who developed elevated aminotransferases and jaundice approximately 86 days after starting GSL. Initial dose was 1200 mg IV q 30 days.

At baseline, the subject's BMI was 21.5 kg/m². Relevant medical history included just the targeted disease. The narrative says, "negative history of chronic liver disease." Alcohol history was "negative," but not otherwise specified. Concurrent medications were irrelevant to DILI risk. The subject's ALT, AST, AP, and TB were 11 U/L, 17 U/L, 50 U/L, and 0.35 mg/dL, respectively.

The subject started GSL at 1200 mg IV q 30 days x 3 on June 26, 2019 (Day 1). On Sep 6, 2019 (Day 72), she had an enterovirus infection that was treated with bismuth. On September 20, 2019 (Day 86), ALT, AST, AP, and TB were 519 U/L, 347 U/L, 118 U/L and 1.52 mg/dL, respectively. No symptoms were mentioned. There was no mention of study drug change. Per protocol, she moved on to the maintenance dosing and received her first SC 200 mg dose that same day (Day 86). However, on September 24, 2019 (Day 90), ALT, AST, AP, and TB were 601 U/L, 372 U/L, 123 U/L and 2.92 mg/dL, respectively. She was hospitalized on Sep 30, 2020 (Day 97) for "toxic hepatitis," and by this time, she had rash, weakness, pruritus, and jaundice. The study drug was stopped, the last dose being on September 20, 2019 (Day 86). She was given several medications for her "toxic hepatitis" including prednisolone (Oct 1 to Nov 8, Days 98-136; dose not given), ademetonine (SAME), glutathione, and Silybum marianum. Liver analytes improved and she was discharged on October 8, 2019 (Day 104), ALT, AST, and TB were 90 U/L, 36 U/L, and 1.8 mg/dL, respectively. Thereafter, liver analytes returned to baseline values within 36-90 days after peak (**Figure 9**).

Evaluation testing included negative serologies for HAV, HBV, HCV, HEV, and CMV. HCV RNA testing was negative. Autoimmune markers were negative for ANA; no ASMA was done. IgG level was not provided. Liver imaging by ultrasound showed no obvious etiology for liver injury. No liver biopsy was done.

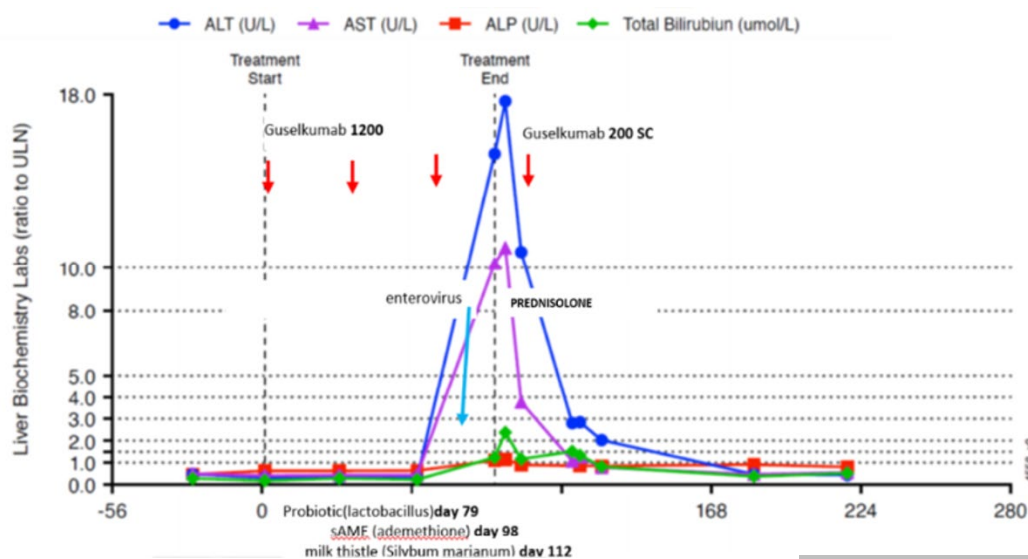


Figure 9: Liver analytes and events by Study Day for Subject (b) (6)

(b) (6)

Assessment: We considered this case as probable liver injury due to GSL. The timing and dechallenge washout are consistent with DILI. The injury was hepatocellular (R-value > 13) with jaundice (TB >2x ULN) thus fulfilling Hy's Law. Enteroviral infection confounds the diagnosis mildly. Enteroviral infection with jaundice would be atypical, and onset of symptoms (fever, rash) came over three weeks after the infection was diagnosed. Evaluation for other causes was reasonably complete. EBV testing was not done, but CMV serologies were negative. It is unclear whether this injury was predominantly immune mediated. Her ALT was already down from 601 U/L to 354 U/L by the time the prednisolone was started so response to this therapy is unclear.

5.0 Assessment & Recommendations

5.1 Assessment: Guselkumab (GSL) is a human monoclonal, IgG1 λ antibody that binds the p19 subunit of IL-23, thereby inhibiting downstream inflammatory effects. It is delivered IV or SC. It is already marketed for psoriasis and psoriatic arthritis but is dosed lower (100 mg per dose) than that proposed for UC (200 mg per dose).

Non-clinical data do not suggest a risk of DILI, but being a monoclonal antibody, standard reactive metabolite experiments to predict hepatotoxicity are not as applicable and are likely less sensitive at detecting liver injury risk. While anti-drug antibodies did develop, there were no substantial liver enzyme elevations or histopathologic changes associated with GSL in the animal studies.

Clinical data does not suggest a substantial liver injury risk either. GLS was marketed in 2017 for psoriasis (PSO) and 2020 for psoriatic arthritis (PSA). There is no liver risk language in the label's Section 5 (Warnings and Precautions), and our search for liver

¹⁹ Modified from [BLA761061 \(761061 - 0750 - \(1225\) - 2024-05-22 - SUPPL-21 \(Efficacy\) /Clinical/Response To Information Request\) - Response to 16 May 2024 IR - CD Hepatic Events \(#32\)](#)

related FAERS reports and case reports in the published literature did not suggest a substantial DILI risk (**See Section 4.1**). Nevertheless, other anti-p19 IL-23 monoclonals approved for inflammatory bowel disease are labeled for hepatotoxicity in Section 5.

The pivotal clinical trials in this UC supplemental BLA (sBLA) did not show a substantial DILI risk. No subjects met Hy's Law or had cholestatic DILI with jaundice. The total enrolled was just over 1000 subjects with around 640 initially randomizing to GSL and at least 200 more eventually crossing over to GSL in the longer-term study. Therefore, study level data was not powered to give a 95% confidence in detecting a Hy's Law case, but the lack of DILI leading to jaundice is encouraging. Moreover, eDISH and cholestatic DILI screening plots did not have substantial imbalances in quadrant categories (e.g., Temple's Corollary, potential Hy's Law). While there were mild imbalances in specific liver enzyme elevations in the randomized placebo-controlled portions of the data, the imbalances were modest and/or inconsistent across studies (e.g., higher rates in the placebo arms versus active arm for ALT but the opposite for AST; imbalance only at ALT cut-off of 1x to 3x ULN). Case level analyses were remarkable for the lack of DILI. We assessed only one subject with possible DILI and the others as unlikely (**Section 4.4.1, Table 8**). Primary sclerosing cholangitis (PSC) was a common confounder. We also reviewed liver related adverse events (AE) rates, with particular focus on those under the broad FMQ of "hepatic failure." We found no specific acute liver failure terms when drilling down to the specific AE terms. We found no cases of acute liver failure, liver transplant or liver related deaths across the development program.

The low risk of hepatotoxicity in UC patients contrasts with our case level analyses in the Crohn's disease (CD) sBLA. Of 13 reviewed, we assessed one case as probable DILI meeting Hy's Law, and two others as possible DILI. However, we do not have full study level analyses yet (e.g., eDISH, enzyme shift tables) for the CD sBLA to provide context for the case level findings. Also, the subject meeting Hy's Law got 1200 mg dosing in a phase 2 study. The 1200 mg dose is six times higher than the labeled dose for UC (200 mg) and was stopped in the CD program for liver injury concerns. Besides dose, UC patients could have a lower risk of DILI compared to CD patients. More substantial loss of colonic mucosal integrity in UC may allow higher antigen presentation to the liver which may lead to more tolerance of neoantigens, ADAs, and IL-23 effects from GSL.²⁰ The gut microbiome may also be different between UC and CD, and microbiomes may have a role in idiosyncratic DILI.^{21,22} But such differential risk is speculative. The DILI Team is not aware of data that confirms a higher DILI risk in CD patients over those with UC.

Therefore, we support approval for UC if benefit is established, but the incomplete analysis of DILI risk in CD creates some challenges on how best to label for hepatotoxicity in UC. The DILI Team does not see strong data in the UC sBLA alone that supports

²⁰ Amos GCA, et al. Exploring how microbiome signatures change across inflammatory bowel disease conditions and disease locations. *Scientific Rep.* 2021; 11:18699 [microbiome differences between UC and CD and their location in the gut](#)

²¹ Losurdo G. et al. Liver involvement in inflammatory bowel disease: What should the clinician know? *World J Hepatol.* 2021; 13:1534-51. [hepatotoxicity in UC vs CD](#)

²² Li G, et al. Interplay Between Drug-Induced Liver Injury and Gut Microbiota: A Comprehensive Overview. *Cell Mol Gastro Hep.* 2024. 18: <https://doi.org/10.1016/j.jcmgh.2024.05.003>

hepatotoxicity language in Warnings and Precautions or recommendations for regular monitoring. However, such labeling could stand on (a) drug-class risk and (b) the *potential* for DILI in CD patients, particularly if GSL could be given to CD patients misdiagnosed as UC or as off-label use. If hepatotoxicity language is included in the label's Section 5, then description of the CD subject meeting Hy's Law is recommended with mention that the dose was several-fold higher than the labeled dose.

5.2 Recommendations

- 1) No serious DILI emerged in UC subjects to preclude approval if efficacy is established.
- 2) Labeling for hepatotoxicity should GSL be approved:
 - a. Description of liver enzyme elevations observed in Section 6
 - b. Higher level of hepatotoxicity risk language (i.e., Section 5) would need to be supported by drug-class risk and discussion of the CD patient with hepatocellular DILI meeting Hy's Law. The CD patient may also be discussed in the context of overuse or overdosing GSL.
- 3) We do not recommend post market requirements for DILI risk. Standard pharmacovigilance should suffice.

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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.

/s/

PAUL H HAYASHI
07/18/2024 05:55:33 PM

HUMAN FACTORS STUDY REPORTS REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 15, 2024
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761061/S-021
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form, and Strength:	Tremfya (guselkumab) Injection, 200 mg/2 mL
Device Constituent:	Autoinjector and prefilled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Research & Development, LLC (Janssen)
Submission Date:	March 11, 2024
TTT ID #:	2024-8736
DMEPA 1 Safety Evaluator:	Tianyi Zhang, PhD, MS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results submitted under prior approval supplement BLA 761061/S-021 for Tremfya (guselkumab) Autoinjector (AI) and prefilled syringe (PFS). The HF validation study included Ulcerative Colitis (UC) and Crohn's Disease (CD) participants. However, for this supplement, Janssen is only proposing to expand the indication of Tremfya to include the treatment of adult patients with UC. Tremfya is currently approved for the indications listed in Table 2 below.

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	Section 1.2
Human Factors Study Reports	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C
Detailed List of Use Errors, Use Difficulties, And Close Calls for Section 3.1	Appendix D

1.1 PRODUCT DESCRIPTION

Table 2 presents relevant product information for Tremfya that Janssen submitted on March 11, 2024.

Table 2. Relevant Product Information for Tremfya	
Initial Approval Date	July 13, 2017
Application Number	BLA 761061
Active Ingredient	guselkumab
Indication	Approved: For the treatment of adult patients with: • moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • active psoriatic arthritis Proposed: • Treatment of adult patients with Ulcerative Colitis (UC)
Route of Administration	Subcutaneous and intravenous infusion
Dosage Form	Injection
Strength	<u>Approved:</u> 100 mg/mL

	<u>Proposed:</u> 200 mg/mL
Dose and Frequency	<u>Approved:</u> <u>Plaque Psoriasis:</u> 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. <u>Psoriatic Arthritis:</u> 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. Tremfya can be used alone or in combination with a conventional DMARD (e.g., methotrexate). <u>Proposed:</u> <u>Ulcerative Colitis:</u> - Induction: 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8. - Maintenance: 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.
How Supplied	<u>Approved:</u> - Subcutaneous injection: Single-dose 100 mg/mL prefilled syringe (PFS) assembled with the UltraSafe Plus needle safety guard - Subcutaneous injection: Single-dose 100 mg/mL PFS assembled with the One-Press patient-controlled injector <u>Proposed:</u> - Subcutaneous injection: single-dose 200 mg/2 mL PFS assembled with the UltraSafe Plus needle safety guard - Subcutaneous injection: single-dose 200 mg/2 mL AI - Intravenous infusion: single-dose 200 mg/20 mL (10 mg/mL) solution vial
Storage	The entire carton should be stored in the refrigerator (36°–46°F; 2°–8°C) and protected from light. Keep out of reach of children Do not freeze Do not shake
Container Closure/Device Constituent	<u>AI:</u> - Available in cartons containing one AI <u>PFS:</u> - Available in cartons containing one PFS

	<table border="1"> <thead> <tr> <th>AI</th><th>PFS</th></tr> </thead> <tbody> <tr> <td></td><td></td></tr> </tbody> </table>	AI	PFS		
AI	PFS				
					
Intended Users	Healthcare professionals (HCPs), patients, caregivers				
Intended Use Environment	Hospital/clinic, home				

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On May 3, 2024, we searched previous DMEPA reviews and FDA/Janssen interactions relevant to this current review using the terms, “Tremfya” and “BLA 761061”. See details below.

- On November 16, 2016, Janssen submitted Biologics License Application (BLA) 761061 for the indication of moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This submission included two HF study reports to support Tremfya (guselkumab) injection 100 mg/mL. We reviewed the two HF validation study results reports and did not have any recommendations.¹
- On July 13, 2017, the Agency approved Tremfya (guselkumab) injection 100 mg/mL PFS under BLA 761061.²
- On February 21, 2019, Janssen submitted a Type C meeting request to discuss the development of guselkumab injection 200 mg/2 mL in PFS and AI presentations for the treatment of CD under IND 133845.

¹ Mena-Grillasca, CM. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. OSE RCM No.: 2016-2621 and 2016-2649.

² Beitz, J. Approval letter for Tremfya (guselkumab) injection 100 mg/mL (BLA 761061). Silver Spring (MD): FDA, CDER, OND, OII, DDD (US); 2017 JUL 13. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8044a998>.

- We met with Janssen on May 9, 2019. In the meeting minutes dated May 24, 2019, we recommended that Janssen submit a comprehensive use-related risk analysis (URRA) and their justification that the proposed product and platforms can be used safely in the proposed investigational studies.³
- On April 21, 2020, Janssen submitted a URRA and their justification that the proposed product and platforms can be used safely in the proposed investigational studies under IND 133845.
 - On June 16, 2020, we reviewed the URRA and Janssen’s justification that the information provided is sufficient to *“support safe clinical use of the subcutaneous injection devices in the proposed investigational studies.”* We agreed with Janssen’s determination and noted that we did not have any specific concerns that would warrant Janssen to submit results from a HF study to the Agency prior to the introduction of the proposed devices into the clinical study/studies.⁴
- On November 2, 2022, Janssen submitted HF validation study protocols for guselkumab injection 200 mg/2 mL PFS and AI for the treatment of CD and UC under IND 133845. We reviewed the protocol and provided recommendations.⁵
- On March 11, 2024, Janssen submitted BLA 761061/S-021 for Tremfya 200 mg/2 mL PFS and AI for the treatment of UC. This submission included HF validation study result reports, which are the subjects of the review.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 3 presents a summary of the HF validation study designs. See Appendix A for more details on the study designs.

Table 3. Study Methodology for the Human Factors (HF) Validation Studies	
Study Design Elements	Details provided by Applicant
User Groups	PFS HF Validation Study ● Adult (≥ 18 years of age, n=15) patients diagnosed with and treating UC and/or CD ● Adult (≥ 18 years of age, n=15) caregivers of patients diagnosed with and treating UC and/or CD (half injection-naïve and half injection-experienced).

³ Allan, LW. Meeting Minutes for Guselkumab (IND 133845). Silver Spring (MD): FDA, CDER, OND, OII, DG (US); 2019 MAY 24. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804f74f2>.

⁴ Barlow M. Use-Related Risk Analysis (URRA) Review for guselkumab injection (IND 133845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 16. TTT ID No.: 2020-837.

⁵ Fung M. Guselkumab HF Protocol Review (IND 133845). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2023 OCT 5. TTT ID No.: 2022-2716.

	- Adult (≥ 18 years of age, n=15) nurses specializing in gastroenterology or primary care AI HF Validation Study - Adult (≥ 18 years of age, n=15) patients diagnosed with and treating UC and/or CD - Adult (≥ 18 years of age, n=15) caregivers of patients diagnosed with and treating UC and/or CD (half injection-naïve and half injection-experienced). - Adult (≥ 18 years of age, n=15) nurses specializing in gastroenterology or primary care																																
Training	No training was provided																																
Test Environment and Materials	<table border="1"> <tr> <th colspan="2">Simulated Use Environment for Hospital and Clinic Environments</th></tr> <tr> <td>Environment Variables</td><td>Simulated Use Environment</td></tr> <tr> <td>Noise and Distraction</td><td>Standard variable background noise and activity level typical of a hospital/clinic setting</td></tr> <tr> <td>Storage</td><td>Product should be refrigerated at 36°F to 46°F (2° to 8°C)</td></tr> <tr> <td>Conditions of Visibility</td><td>Standard variable lighting conditions found in a hospital/clinic environment</td></tr> <tr> <td>Physical</td><td>Standard temperature and humidity ranges found in a hospital or clinic environment</td></tr> <tr> <td>Mobility</td><td>Table surface was provided to prepare and administer the injection.</td></tr> <tr> <td>Disposal</td><td>A sharps container was provided</td></tr> </table> <table border="1"> <tr> <th colspan="2">Simulated Use Environment for Home Environments</th></tr> <tr> <td>Environment Variables</td><td>Simulated Use Environment</td></tr> <tr> <td>Noise and Distraction</td><td>Standard variable background noise and activity level typical of a home setting</td></tr> <tr> <td>Storage</td><td>Product should be refrigerated at 36°F to 46°F (2° to 8°C)</td></tr> <tr> <td>Conditions of Visibility</td><td>Standard variable lighting conditions found in a home environment</td></tr> <tr> <td>Physical</td><td>Standard temperature and humidity ranges found in a home environment</td></tr> <tr> <td>Mobility</td><td>Table surface was provided to prepare and administer the injection.</td></tr> <tr> <td>Disposal</td><td>A sharps container was provided</td></tr> </table>	Simulated Use Environment for Hospital and Clinic Environments		Environment Variables	Simulated Use Environment	Noise and Distraction	Standard variable background noise and activity level typical of a hospital/clinic setting	Storage	Product should be refrigerated at 36°F to 46°F (2° to 8°C)	Conditions of Visibility	Standard variable lighting conditions found in a hospital/clinic environment	Physical	Standard temperature and humidity ranges found in a hospital or clinic environment	Mobility	Table surface was provided to prepare and administer the injection.	Disposal	A sharps container was provided	Simulated Use Environment for Home Environments		Environment Variables	Simulated Use Environment	Noise and Distraction	Standard variable background noise and activity level typical of a home setting	Storage	Product should be refrigerated at 36°F to 46°F (2° to 8°C)	Conditions of Visibility	Standard variable lighting conditions found in a home environment	Physical	Standard temperature and humidity ranges found in a home environment	Mobility	Table surface was provided to prepare and administer the injection.	Disposal	A sharps container was provided
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	• Tremfya 200 mg/2 mL PFS/AI pack - o Carton - o Tray - o Tremfya 200 mg/2 mL PFS/AI containing active medication - o IFU - o Mock PI • Tremfya One-Press packaging and device (for HCP product-differentiation task only) • Tremfya 2 mL Autoinjector packaging and device (for HCP product differentiation task only) • Mock prescription • Alcohol wipes • Mock sink/hand sanitizer • Gloves • Band-aids • Gauze pads/cotton balls • Injection pad • Manikin (for HCP and caregiver participants only) • Sharps container • Trash bin (to capture potential use errors) • Mock Refrigerator (for HCP participants only)
Sequence of Study	1. Differentiation/Confirmation Tasks - o HCP only: Product and dose differentiation (packaged product) - o HCP only: Product and dose differentiation (device only) - o Patient and caregiver only: product and dose confirmation (packaged product) - o Root cause probing 2. Simulated-Use Scenarios - o Trial 1 (IFU optional) - o Trial 2 (IFU mandatory) - o Root cause probing - o Knowledge tasks (IFU optional and IFU mandatory) - o Root cause probing - o Subjective feedback

3 RESULTS AND ANALYSES

In this section, we have carefully reviewed each reported issue (i.e., use error, close calls, use difficulty), Janssen's URRAs, the participants' subjective feedback, Janssen's root cause analysis, Janssen's post HF validation study mitigations and Janssen's comments to

determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. We provide a discussion of the identified use tasks below where we agree with Janssen's conclusions and have no further recommendation or comment.

3.1 ANALYSIS OF THE IDENTIFIED ISSUES

The HF validation study reports showed issues with the tasks evaluated by simulated use and knowledge task assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), Janssen's root cause analysis, Janssen's post-HF validation study mitigations, and our evaluation of the residual risks, we find the proposed user interface has been appropriately designed. The labels and labeling include information that is prominent, and we did not identify recommendations to address the identified issues with the tasks in Appendix D.

Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under a separate cover⁶.

4 CONCLUSIONS

The results of the HF validation study demonstrated several use errors with critical tasks that may result in harm. However, based on our review of the available participants' and subjective feedback, and root cause analysis from the HF validation study, and Janssen's post-HF validation study mitigations, we did not identify additional risk mitigations to address the use errors. We find that the risks have been mitigated to an acceptable level and no further changes to the user interface are likely to further mitigate these risks. As such, we have no recommendations for this prior approval supplement.

⁶ Abraham, S. Label and Labeling Packaging Review for Tremfya (guselkumab) BLA 761061/S-021. Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 July 2. TTT ID #: 2024-8735.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

Prefilled syringe: <\\CDSESUB1\EVSPROD\bla761061\0700\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uc\5354-other-stud-rep\pfs-u-2ml\pfs-u-2ml-study-report-2.pdf>

Autoinjector: <\\CDSESUB1\EVSPROD\bla761061\0700\m5\53-clin-stud-rep\535-rep-effic-safety-stud\uc\5354-other-stud-rep\pfs-y-2ml\pfs-y-2ml-study-report-2.pdf>

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Tremfya labels and labeling submitted by Janssen.

Autoinjector container label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-y-label.pdf
Autoinjector carton label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-y-carton.pdf
Autoinjector instructions for use (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-y.pdf
Prefilled syringe container label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-u-label.pdf
Prefilled syringe carton label (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0733\m1\us\114-labeling\draft\carton-and-container\2-ml-pfs-u-carton.pdf
Prefilled Syringe instructions for use (Image not shown)	\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\labeling\ifu-2-ml-pfs-u.pdf

⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3.1

- Autoinjector simulated use tasks:
 - Inspect liquid in window to see that it is clear to slightly yellow
 - Choose an injection site
 - Wash hands
 - Clean injection site
 - Remove cap
 - Inject medication: there were 5 use errors, 1 close call, 1 use difficulty observed for this task. The root cause analysis indicated these use errors, close call, and use difficulty were due to:
 - Negative transfer:
 - A participant initially looked for an activation button but subsequently successfully completed the injection after referring to the IFU images
 - A participant removed the AI before the second click due to their previous experience with AIs that are quick and only click once
 - Mistaking the first click as the second click
 - Mental model
 - A participant expected the device to dispense the medication faster and removed the AI before the second click
 - A participant didn't position the AI with the viewing window facing them
 - A participant removed the AI before the second click because they were trying to inspect the viewing window during injection, but the viewing window was not visible to them
 - Inconspicuous instruction
 - The instructions for use (IFU) does not saliently instruct users regarding what to do if two injections are required
 - Study artifact (participants did not think the needle would activate since it was a simulation).

We note that Janssen stated that the injection completion time ranges from 4 seconds to 5.2 seconds with the mean of 4.6 seconds. Two of the five participants in Trial 1 (IFU optional) who experienced use difficulty or use errors with this task had an injection time (i.e., 10 seconds and 5 seconds, respectively) of more than 4.6 seconds. Two participants in Trial 2 (IFU mandatory) who experienced close call or use error with this task had an injection time (i.e., 12 seconds and 8 seconds, respectively) of more than 4.6 seconds. Based on this information, we note that these participants would have received the full dose. Based on the errors observed and the root cause analysis, Janssen added (b) (4)

” to IFU Step 3e, in red font to remind users to follow the same steps for the second device, if required. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close call, and use difficulty, and have no recommendations at this time.

- o Remove injection device: there was 1 use difficulty observed for this task. The root cause analysis indicated that the user failed to notice the second click but was still able to complete the injection. Based on our review of the user interface, we did not identify any additional mitigations to address this use difficulty and have no recommendations at this time.
 - o Check injection site
 - o Dispose of the device
- Autoinjector study knowledge task assessment:
 - o When, if ever, should you shake the injection device? Answer: user must indicate do not shake/never.
 - o If your prescribed dose requires two injection devices, where, if anywhere, should the second injection be given? Answer: user must indicate not to inject into the same injection site or different acceptable site or at least 2 inches way from first injection site.
 - o Into which area or areas on the body can you inject with this injection device? Answer: upper thigh, lower abdomen, and/or back of arms. There was 1 use error observed for this question. The root cause analysis indicated the use error was due to the misleading IFU image (the participant thought the image of the appropriate injection locations showed the side of the arm instead of the back of the upper arm). Based on the errors and root cause analysis, Janssen changed the blue area on the arm to be smaller, so it looks more like the back of the upper arm rather than the side of upper arm. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
 - o What, if anything, should you do with the injection device if it is dropped? Answer: user must indicate they would not use the injection device or get a new device.
 - o What, if anything, should you not do while the medication is being injected into the skin? Answer: do not lift the device during the injection. There was 1 use error observed for this question. The root cause analysis was incomplete because Janssen did not investigate why the participant gave the answer “*they should not shake or move the device*”. However, based on our review of the user

interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.

- PFS simulated use tasks:
 - Inspect liquid in window
 - Choose an injection site
 - Wash hands
 - Clean injection site
 - Remove needle cover
 - Pinch skin and insert needle: there were 42 use errors. The root cause analysis indicated these use errors were due to negative transfer (Participants recalled previous experience seeing/performing an injection or using autoinjectors and determined inserting at 90 degrees was correct or no pinching was necessary.), study artifact (participants did not pinch the skin because it was not their skin), and inconspicuous image depicting pinching the skin (the image of the appropriate technique with pinching did not look like pinching). Based on the use errors and root cause analysis, Janssen changed the image to depict a larger amount of skin being pinched and increased font size of “45” in the IFU Step 3b image. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
 - Inject medication: there were 7 use errors, 1 close call and 4 use difficulties, observed for this task. The root cause analysis indicated that the use errors, close call and use difficulties were due to negative transfer (A participant relied on their previous experience with injections leading them to prime the device. Another participant stated they typically draw back on the syringe to ensure there’s no blood for all injections and performed a draw to ensure there’s no blood in the study) and the confusing order of steps in the IFU (instruction “If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second prefilled syringe” was after Step 4b – *Dispose of your prefilled syringe*). Based on the use errors and root cause analysis, Janssen moved the text “*If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second prefilled syringe*” to the Step 3d. We acknowledge Janssen’s mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close call and use difficulties, and have no recommendations at this time.
 - Check injection site
 - Dispose of the device

- PFS study knowledge task assessment:
 - o When, if ever, should you shake the injection device? Answer: user must indicate do not shake/never.
 - o Into which area or areas on the body can you inject with this injection device? Answer: upper thigh, lower abdomen, and/or back of arms. There was 1 use error observed for this question. The root cause analysis indicated the use error was due to the inconspicuous IFU Step 2 image (the image of the appropriate injection location does not sufficiently depict the back of the upper arm). Based on the error and root cause analysis, Janssen made the image of the blue area of the arm smaller so it looks more like the back of upper arms. We acknowledge Janssen's mitigation strategy and, based on our review of the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
 - o What, if anything, should you do with the injection device if it is dropped. Answer: user must indicate they would not use the injection device or get a new device.

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/

TIANYI ZHANG
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OLUWAMUREWA OGUNTIMEIN
07/15/2024 05:14:50 PM

ARIANE O CONRAD
07/16/2024 09:51:19 AM

JASON A FLINT
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PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 24, 2024
Application Type and Number:	BLA 761061/S-021
Product Name, Dosage Form, and Strength:	Tremfya (guselkumab) injection Prefilled syringe: 200 mg/2mL Vial: 200 mg/20mL (10 mg/mL) Tremfya Pen (guselkumab) injection Prefilled Pen: 200 mg/2 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Research & Development, LLC (Janssen)
PNR ID #:	2024-1044725726 (Tremfya) 2024-1044725729 (Tremfya Pen)
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, Pharm.D.

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1 INTRODUCTION

This review evaluates the proposed proprietary names, Tremfya and Tremfya Pen, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary names are outlined in the Reference section and Appendix A, respectively. Janssen did not submit an external name study for these proposed proprietary names.

1.1 REGULATORY HISTORY

The proprietary name Tremfya was approved on July 13, 2017, for guselkumab 100 mg/mL subcutaneous injection for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.^a

On March 11, 2024, Janssen submitted an Efficacy Supplement for Tremfya (guselkumab) single-dose vial for intravenous infusion, Tremfya (guselkumab) prefilled syringe for subcutaneous injection, and Tremfya Pen (guselkumab) prefilled pen for subcutaneous injection for treatment of adult patients with moderately to severely active ulcerative colitis. On April 3, 2024, we issued an information request (IR) to clarify Janssen's intention to utilize the proprietary name, Tremfya, for the new presentations. Specifically, we instructed Janssen *"If you intend to utilize the same proprietary name Tremfya for your proposed drug product presentations, we recommend you submit a REQUEST FOR A PROPOSED PROPRIETARY NAME REVIEW as soon as possible. Additionally, we note that carton labeling and container labels of your proposed autoinjector states 'Tremfya Pen'. If you intend to use this proposed proprietary name + modifier for your proposed autoinjector presentation, we recommend you submit a REQUEST FOR PROPRIETARY NAME REVIEW as soon as possible."*^b

Thus, on April 10, 2024, Janssen submitted a request for proprietary name review under BLA 761061/S-021 for the proposed proprietary names, Tremfya and Tremfya Pen, for intravenous injection [single-dose vial 200 mg/20 mL (100 mg/mL)], subcutaneous prefilled syringe (200 mg/2 mL), and subcutaneous prefilled pen (200 mg/2 mL).

^a Tremfya [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. July 2018. [cited 2024 MAY 15]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761061s000lbl.pdf

^b Chi, A. FDA Communication: BLA 761061/s-21 | Information Request 4-3-24 for Tremfya (guselkumab). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 APR 03. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80737476>

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission received on April 10, 2024^c and the prescribing information received on March 11, 2024.^d

Table 1. Relevant Product Information for Tremfya (guselkumab) and Tremfya Pen (guselkumab)			
Product Name	Tremfya ^e BLA 761061	Tremfya BLA 761061/S-021 (Proposed)	Tremfya Pen BLA 761061/S-021 (Proposed)
Initial Approval Date	July 13, 2017	N/A	N/A
Active Ingredient	guselkumab		
Intended Pronunciation	trem fye' ah		trem fye' ah pen
Indication	indicated for the treatment of adult patients with: • moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • active psoriatic arthritis. • Proposed: moderately to severely active ulcerative colitis		
Route of Administration	subcutaneous	subcutaneous and intravenous	subcutaneous
Dosage Form	injection		
Strength	100 mg/mL	200 mg/2 mL	200 mg/2 mL

^c Request for Proprietary Name Review for Tremfya and Tremfya Pen BLA 761061/S-021. Horsham (PA): Janssen Research & Development, LLC; 2024 APR 10 Available from: <\\CDSESUB1\EVSPROD\bla761061\0721\m1\us\118-proprietary-names\request-for-proprietary-name-review-20-ml-fvp.pdf>, <\\CDSESUB1\EVSPROD\bla761061\0721\m1\us\118-proprietary-names\request-for-proprietary-name-review-2-ml-pfs-u.pdf>, and <\\CDSESUB1\EVSPROD\bla761061\0721\m1\us\118-proprietary-names\request-for-proprietary-name-review-2-ml-pfs-y.pdf>

^d Proposed prescribing information for Tremfya. Horsham (PA): Janssen Research & Development, LLC; 2024 MAR 11. Available from: <\\CDSESUB1\EVSPROD\bla761061\0700\m1\us\114-labeling\draft\annotated\annotated-uspi-uc-indication-word.doc>

^e Tremfya [Prescribing Information]. DailyMed. U.S. National Library of Medicine. November 2023. [cited 2024 MAY 15]. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=1e6dc9ae-1c4c-42d9-87aa-c315ecc51b56>

Table 1. Relevant Product Information for Tremfya (guselkumab) and Tremfya Pen (guselkumab)			
Product Name	Tremfya ^e BLA 761061	Tremfya BLA 761061/S-021 (Proposed)	Tremfya Pen BLA 761061/S-021 (Proposed)
		200 mg/20 mL (10 mg/mL)	
Dose and Frequency	<u>Plaque Psoriasis:</u> 100 mg by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. <u>Psoriatic Arthritis:</u> 100 mg by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. <u>Ulcerative Colitis (Proposed)</u> <u>Induction:</u> 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8. <u>Maintenance:</u> 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.		
How Supplied	100 mg/mL in a single-dose One-Press patient-controlled injector per carton 100 mg/mL in a single-dose prefilled syringe per carton	<u>Subcutaneous Injection</u> 200 mg/2 mL in a single-dose prefilled syringe per carton <u>Intravenous Infusion</u> 200 mg/20 mL (10 mg/mL) solution in a single-dose vial per carton	200 mg/2 mL in a single-dose prefilled pen per carton
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Store in original carton until time of use. Protect from light until use. Do not freeze. Do not shake.		

2 DISCUSSION

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary names, Tremfya and Tremfya Pen.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Tremfya and Tremfya Pen would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Tremfya and Tremfya Pen. The Division of Gastroenterology (DG) concurred with the findings of OPDP's assessment for Tremfya and Tremfya Pen.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary names, Tremfya and Tremfya Pen.

2.2.1 UNITED STATES ADOPTED NAMES (USAN) SEARCH

There is no USAN stem present in the proposed proprietary names.^f

2.2.2 COMPONENTS OF THE PROPOSED PROPRIETARY NAME

Janssen did not provide a derivation or intended meaning for the proposed proprietary names, Tremfya and Tremfya Pen, in their submission. Tremfya is comprised of a single word and Tremfya Pen is composed of two words; both names contain the letters 'Tr' which is the abbreviation for 'time release'. Additionally, we note the proprietary name Tremfya Pen contains the letters 'Pe' which is the abbreviation for Phenylephrine. As the letter strings "Tr-" and "Pe-" are located at the beginning of the name and modifier, respectively, we evaluated the potential risk of misinterpreting the proposed proprietary names as "TR [drug similar to emfya]", "TR [drug similar to emfya Pen]", and "Tremfya PE [n]" and did not identify any concerns.^g Therefore, in this case, we do not object to the proposed proprietary names based on the inclusion of these medical abbreviations.

2.2.3 COMMENTS FROM OTHER REVIEW DISCIPLINES AT INITIAL REVIEW

On May 21, 2024, the Division of Gastroenterology (DG) did not forward any comments or concerns relating to Tremfya or Tremfya Pen at the initial phase of the review.

2.2.4 FDA PRESCRIPTION SIMULATION STUDIES

Eighty-seven (n=87) practitioners participated in DMEPA's prescription studies for Tremfya. Eighty-four (n=84) practitioners participated in DMEPA's prescription studies for Tremfya Pen. One respondent in the Computerized Prescription Order Entry (CPOE) study incorrectly selected the name Trymex. However, the participant entered an incorrect sequence of letters, 'Trym' when searching for the study name. As a result, the CPOE generated picklist did not contain Tremfya Pen as a choice. The participant proceeded to incorrectly select Trymex as their response after 14 seconds in order to proceed with the FDA prescription stimulation study. Thus, in this case, the study response is unlikely to be representative of a plausible CPOE based

^f USAN stem search conducted on April 19, 2024.

^g POCA search for "emfya" conducted on June 4, 2024, in version 5.9.

risk. Despite this, we further evaluated the name pair and determined that this name pair has sufficient orthographic and phonetic differences.

Additionally, eight inpatient participants and three outpatient participants misinterpreted 'Tremfya Pen' as 'Tremfya'. We acknowledge that omission and oversight of a modifier is cited in literature as a common cause of medication error.^h We further evaluate the use of the modifier, Pen, in section 2.2.5 below.

The remaining responses did not overlap with any currently marketed products, nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the prescription simulation studies.

2.2.5 SAFETY ANALYSIS OF THE PROPOSED MODIFIER, "PEN"

The proposed proprietary name, Tremfya Pen, is comprised of the root name, "Tremfya" and the modifier, "Pen". Janssen proposes the modifier "Pen" to differentiate the proposed prefilled pen from the currently marketed (one-press patient-controlled injector (100 mg/mL), prefilled syringe (100 mg/mL)), the proposed prefilled syringe (200 mg/2 mL), and single-dose vial [200 mg/20mL (10 mg/mL)] Tremfya products. As such, we evaluated the following: (1) evaluation of the use of the same root name, (2) use of a modifier to differentiate the product, and (3) evaluation of the proposed modifier, "Pen".

1. Evaluation of the use of the same root name "Tremfya"

Our routine postmarket surveillance has not identified name confusion medication errors associated with the root name, "Tremfya". We note that the currently marketed Tremfya One-Press patient-controlled injector and prefilled syringe; the proposed Tremfya prefilled syringe and single-dose vial; and the proposed Tremfya Pen prefilled pen share the same active ingredient (guselkumab), with differences in the presentation, indication, and intended route of administration. See Table 1 for a comparison of product characteristics.

We note the currently approved 100 mg products are intended for the currently approved indications of plaque psoriasis and psoriatic arthritis, where the recommended dosing is 100 mg at weeks 0 and 4 and then every 8 weeks thereafter. The proposed 200 mg products are intended for the proposed indication of ulcerative colitis; that is, the 200 mg/20 mL (10 mg/mL) vial is intended to be used for intravenous induction dosing (200 mg intravenously at weeks 0, 4, and 8) and the 200 mg prefilled syringe and pen products are intended to be used for maintenance dosing (200 mg every 4 weeks starting at week 12). We note that the 100 mg products may be appropriate in select ulcerative colitis patients who may receive maintenance doses of 100 mg every 8 weeks starting at week 16.

Additionally, we note the Applicant states that they have *"incorporated visual differentiators in the carton and vial labeling for the proposed Final Vial Product (FVP) presentation, including a descriptor for 'injection' and 'for intravenous infusion only'". These differentiators, in addition to the clear differences in the sizes of the carton and vial between the IV and SC presentations, are intended to reduce the potential for confusion or*

^h Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587.

medication errors by distributors, pharmacists, physicians, and other healthcare professionals. Furthermore, the FVP vials are intended to be distributed directly to physicians, infusion centers and hospital pharmacies; since patients will not be handling the FVP vials directly, the Sponsor does not anticipate issues with confusion or errors at the patient level."^c We find the Applicant's rationale acceptable at this time.

II. Evaluation of the use of a modifier to differentiate the product

The use of a modifier to differentiate product characteristics between products, such as a different product presentation, is a common naming practice as part of a product line extension. The addition of a modifier to Tremfya may help differentiate the proposed prefilled pen from the currently marketed one-press patient-controlled injector (100 mg/mL), prefilled syringe (100 mg/mL), the proposed prefilled syringe (200 mg/2 mL), and single-dose vial [200 mg/20mL (10 mg/mL)].

We note that omission and oversight of modifiers is cited in literature as a common cause of medication errors. Postmarket experience shows that family branding may result in medication errors if the modifier is omitted, and the product characteristics are similar or overlap. We considered the risk of name confusion if the modifier is dropped. Omission of the proposed modifier "Pen" was observed in the FDA Prescription Simulation Study, in which eight participants in the inpatient study and three participants in the outpatient study did not record the modifier as part of their response (See Section 2.2.4 above). If the modifier "Pen" was to be omitted, we note that the strength and intended dose to be administered with the prefilled pen differs from that of the currently marketed Tremfya One-Press patient-controlled injector and prefilled syringe (200 mg/2 mL versus 100 mg/mL). Additionally, if the modifier 'Pen' were to be omitted or overlooked and the patient were to receive the currently proposed prefilled syringe (200 mg/2 mL) instead, it would be the same strength and dose, but a different presentation. In an instance where the intended product is the prefilled pen presentation and the modifier 'Pen' is omitted or overlooked on a prescription, it is unlikely that the intravenous formulation would be inadvertently prepared and administered subcutaneously, given the large volume of the intravenous formulation needed to administer a dose of 200 mg subcutaneously. Thus, we do not object to the use of modifiers to distinguish the products.

An alternative to using a modifier to distinguish this product from the currently marketed products is to use a different root name. However, marketing the new product under a unique proprietary name also carries a risk of medication errors, such as therapeutic duplication and overdoses.

Although the proposed naming strategy is not devoid of risk because modifiers may be omitted, in this case, we agree that using a modifier may assist in differentiating the current and proposed products.

III. Evaluation of the proposed modifier "Pen"

The Applicant proposes the modifier "Pen" to denote the product is a prefilled pen presentation. Based on the Institute for Safe Medication Practices (ISMP) List of Products

with Drug Name Suffixesⁱ, the modifier “Pen” is typically used to convey the meaning “prefilled pen”. As the proposed product is a prefilled pen, the use of the modifier “Pen” is consistent with its existing meaning and is appropriate in this case. In summary, we find the use of the proposed naming strategy (the use of the same root name, Tremfya, with a distinguishing modifier) acceptable. Additionally, we find the proposed modifier, “Pen”, sufficiently differentiates the proposed product from the currently marketed and proposed Tremfya products. Therefore, based on the totality of information considered above, we do not object to the proposed name, Tremfya Pen, for the proposed product.

In summary, we find the use of the proposed naming strategy (the use of the same root name, Tremfya, with a distinguishing modifier) acceptable. Additionally, we find the proposed modifier, “Pen”, sufficiently differentiates the proposed product from the currently marketed and proposed Tremfya products. Therefore, based on the totality of information considered above, we do not object to the proposed name, Tremfya Pen, for the proposed prefilled pen product.

2.2.6 COMMUNICATION OF DMEPA'S DETERMINATION

On June 24, 2024, DMEPA 1 communicated our determination to the Division of Gastroenterology (DG).

3 CONCLUSION

The proposed proprietary names, Tremfya and Tremfya Pen, are conditionally acceptable.

If you have any questions or need clarifications, please contact Alvis Dunson, OSE project manager, at 301-796-6400.

3.1 COMMENTS TO JANSSEN RESEARCH & DEVELOPMENT, LLC

We have completed our review of the proposed proprietary names, Tremfya and Tremfya Pen, and have concluded that these proprietary names are conditionally acceptable.

If any of the proposed product characteristics as stated in your submission, received on April 10, 2024, are altered prior to approval of the marketing application, the proprietary names must be resubmitted for review.

ⁱ ISMP's List of Products with Drug Name Suffixes [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2010. Available from: <https://www.ismp.org/sites/default/files/attachments/2018-04/drugnamesuffixes.pdf>

REFERENCES

1. *United States Adopted Names (USAN) Stems*

USAN Stems List contains all the recognized USAN stems, available at <https://www.ama-assn.org/about/united-states-adopted-names/united-states-adopted-names-approved-stems>.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved brand name and generic drugs; therapeutic biological products, prescription and over-the-counter human drugs; and discontinued drugs (see Drugs@FDA Glossary of Terms, available at <https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms>).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html>).

Purple Book

The Purple Book is an online database that contains information about biological products, including biosimilar and interchangeable biological products, licensed (approved) by the FDA under the Public Health Service (PHS) Act. See Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, available at <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or>.

Division of Medication Errors Prevention and Analysis pending proprietary name requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis.

4 APPENDICES

APPENDIX A. FDA'S PROPRIETARY NAME RISK ASSESSMENT EVALUATES PROPOSED PROPRIETARY NAMES FOR MISBRANDING AND SAFETY CONCERNS

1. **Misbranding Assessment:** For prescription drug products, the Office of Prescription Drug Promotion (OPDP) assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by the Office of Non-Prescription Drugs (ONPD). OPDP or ONPD evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or ONPD provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. **Preliminary Assessment:** We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 3*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.^j

*Table 3. Prescreening Checklist for Proposed Proprietary Name	
Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.	
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.

^j National Coordinating Council for Medication Error Reporting and Prevention. <https://www.nccmerp.org/about-medication-errors>. Last accessed 10/05/2020.

*Table 3. Prescreening Checklist for Proposed Proprietary Name	
Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.	
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@FDA, Cerner RxNorm, Purple Book, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score $\geq 70\%$.
- Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.
- Low similarity: combined match percentage score $\leq 54\%$.

Using the criteria outlined in the check list (Table 4-6) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 4).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
 - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in

the confusion of drug names^k. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.

- o Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 5).
 - Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 6) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.
- c. FDA Prescription Simulation Studies: DMEPA also conducts prescription simulation studies using FDA health care professionals.

Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.
- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND), Office of Generic Drugs (OGD), and/or Office of Pharmaceutical Quality (OPQ) for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-

^k Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the Safety Evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

Additionally, other review disciplines opinions such as OPQ may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary Safety Evaluator assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 4. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq$ 70%).			
Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 5: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 55\%$ to $\leq 69\%$).		
Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e., drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg	
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names with overlapping or similar strengths or doses.	
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? • Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? • *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as z and f), is there a different number or	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 55\%$ to $\leq 69\%$).

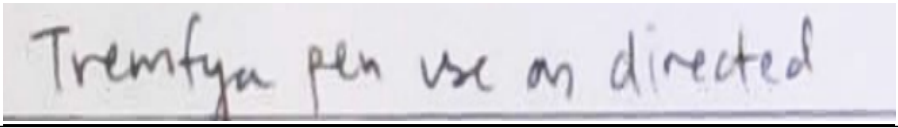
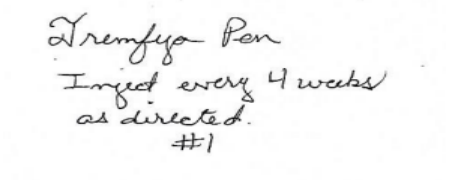
	placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	

Table 6. Low Similarity Name Pair Checklist (i.e., combined score is $\leq 54\%$).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

APPENDIX B. PRESCRIPTION SIMULATION SAMPLES AND RESULTS

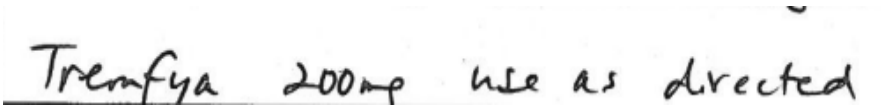
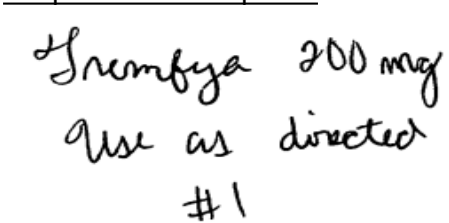
Figure 1. Tremfya Pen Study (Conducted on 4/26/2024)

Handwritten Medication Order Prescription	Verbal Prescription
<u>Medication Order:</u> 	Tremfya Pen Inject every 4 weeks as directed #1
<u>Outpatient Prescription:</u> 	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font) Tremfya Pen	

FDA Prescription Simulation Responses (Aggregate Report)					
Study Name: Tremfya Pen					
People Received Study: 190					
People Responded: 84					
Total	23	25	14	22	84
INTERPRETATION	INPATIENT	OUTPATIENT	VOICE	CPOE	TOTAL
CREMFIA PEN	0	0	1	0	1
CREMVIA PEN	0	0	1	0	1
GRENFYA PEN	0	1	0	0	1
JREMFYA PEN	0	1	0	0	1
PREMFIYA PEN	0	0	1	0	1
PREMFYA PEN	0	0	1	0	1
PREMVIA PEN	0	0	1	0	1
TRAMFYA PEN	0	0	1	0	1
TREMFAYA PEN	0	0	1	0	1
TREMFAYAPAN	0	0	1	0	1
TREMFIAPEN	0	0	1	0	1
TREMFIIYA PEN	0	1	0	0	1
TREMFUA PEN	1	0	0	0	1

TREMFYA	8	3	0	0	11
TREMFYA PEN	13	16	4	21	54
TREMFYO PEN	0	3	0	0	3
TREMFYU	1	0	0	0	1
TREMVIA PEN	0	0	1	0	1
TRYMEX	0	0	0	1	1

Figure 2. Tremfya Study (Conducted on 4/30/2024)

Handwritten Medication Order Prescription	Verbal Prescription
<u>Medication Order:</u> 	Tremfya 200 mg Use as directed #1
<u>Outpatient Prescription:</u> 	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Tremfya	

FDA Prescription Simulation Responses (Aggregate Report)					
Study Name: Tremfya					
People Received Study: 197					
People Responded: 87					
INTERPRETATION	INPATIENT	OUTPATIENT	VOICE	CPOE	TOTAL
Total	24	24	17	22	87
JNEMFYA	0	1	0	0	1
TREMBAYA	0	0	1	0	1
TREMFIA	0	0	5	0	5
TREMFIIYA	1	0	5	0	6
TREMFYA	22	22	4	22	70
TREMFYZA	0	1	0	0	1
TREMVIA	0	0	2	0	2
TRENFYA	1	0	0	0	1

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Memorandum

Date: 06/28/2024

Reviewer: Suraj Rajasimhan, PharmD, BCPS, BCCCP
Division of Pharmacovigilance I (DPV-I)

Team Leader: Michelle Hines, PharmD, BCPS
DPV-I

Deputy Division Director: Lisa Wolf, PharmD, BCCCP
DPV-I

Product Name: Tremfya (guselkumab)

Subject: All adverse events

Application Type/Number: BLA 761061/S-21

Applicant/Sponsor: Janssen Biotech, Inc.

TTT Record ID: 2024-8826

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EXECUTIVE SUMMARY

This pharmacovigilance review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), contains an analysis of postmarketing adverse events associated with Tremfya (guselkumab) from the FDA Adverse Event Reporting System (FAERS) database, the medical literature, and the Applicant's periodic safety reports (PSRs). This review will inform DG's review of supplement 21 (S-021) for BLA 761061, which proposes a new indication of ulcerative colitis (UC) in adults. Specifically, DPV-I evaluated reports for liver injury reported with guselkumab injection. In addition, DPV-I evaluated all adverse events with guselkumab injection to identify reports of adverse events with the potential for serious outcomes or serious labeled events with an increase in severity that are not described in the Applicant's proposed labeling for BLA 761061/S-021.

Of 4,588 FAERS reports with guselkumab with a serious outcome, the majority (n=3,128; 68 percent) were coded with psoriasis or psoriatic arthropathy as the reason for use; only 76 reports (1.7 percent) were coded with CD or UC as the reason for use. Therefore, the FAERS reports evaluated in this review predominantly reflect the postmarketing safety profile of guselkumab for psoriasis and psoriatic arthritis. It is possible that the postmarketing safety profile of guselkumab in patients with CD and UC is different from that which is described in this review.

The proposed dosing regimen for guselkumab use in UC is 200 mg intravenously (IV) at Week 0, Week 4, and Week 8, followed by 200 mg SC at Week 12 and every 4 weeks thereafter. In the clinical development program of guselkumab for Crohn's disease (CD), a case of toxic hepatitis with severe elevation of liver function tests meeting Hy's Law criteria occurred in a subject who was randomized to guselkumab 1,200 mg intravenous at weeks 0, 4 and 8 followed by 200 mg subcutaneous every 4 weeks. Two additional possible cases of drug-induced liver injury (DILI) have been reported in the guselkumab CD development program in subjects exposed to the 200 mg dose. Elevated liver enzymes is currently described under Section 6.1 *Clinical Trials Experience* of guselkumab label. In this review, DPV-I did not identify additional postmarketing cases of DILI meeting Hy's Law criteria in the FAERS database or medical literature. However, the majority of FAERS reports described guselkumab use in psoriasis at a lower dose than that proposed for use in UC labeling.

In addition, we identified postmarketing cases of the unlabeled events of death, major adverse cardiovascular outcomes, device malfunctions, malignancies, and neurologic adverse events that had a temporal association to guselkumab use. However, the cases generally contained limited clinical details necessary to assess the causal association to guselkumab.

DPV-I did not identify any new safety signals to inform labeling changes for guselkumab at this time. DPV-I will continue routine pharmacovigilance monitoring for guselkumab.

1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology (DG), evaluates the FDA Adverse Event Reporting System (FAERS) and medical literature for all adverse events reported with guselkumab injection from January 25, 2019 (i.e., the data-lock date of DPV-I's 2019 postmarket surveillance summary), to April 23, 2024. This review will inform DG's review of supplement 21 (S-021) for BLA 761061, which proposes a new indication of ulcerative colitis (UC) in adults.

1.1 BACKGROUND AND REGULATORY HISTORY

Guselkumab is a human immunoglobulin G1 lambda monoclonal antibody (mAb) that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor, inhibiting the release of proinflammatory cytokines and chemokines (Tremfya Prescribing Information (PI)). The FDA approved guselkumab on July 13, 2017, for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (Tremfya BLA 761061).

On April 4, 2019, and June 1, 2020, the FDA approved labeling supplements adding serious hypersensitivity reactions and anaphylaxis, respectively, to the guselkumab labeling (Tremfya BLA 761061/S-002).

On July 13, 2020, the FDA approved guselkumab for treatment of adult patients with active psoriatic arthritis (Tremfya BLA 761061/S-007).

The recommended dosing of guselkumab for psoriatic arthritis and psoriasis is 100 mg subcutaneously (SC) at Week 0, Week 4, and every 8 weeks thereafter. Guselkumab can be administered alone or in combination with a conventional disease-modifying antirheumatic drug (DMARD), such as methotrexate (Tremfya PI).

On March 11, 2024, the Applicant submitted BLA 761061/S-021, which proposes a new indication of UC in adults. The proposed dosing regimen for guselkumab use in UC is 200 mg intravenously (IV) at Week 0, Week 4, and Week 8, followed by 200 mg SC at Week 12 and every 4 weeks thereafter. For some patients, a dosage of 100 mg SC at Week 16 and then every 8 weeks is proposed. In the clinical development program of guselkumab for Crohn's disease (CD), a case of toxic hepatitis with severe elevation of liver function tests meeting Hy's Law criteria occurred in a subject participating in Study CNTO1959CRD3001 (NCT 03466411), who was randomized to guselkumab 1,200 mg IV at Weeks 0, 4 and 8 followed by 200 mg SC every 4 weeks (PBRER - 9). This event resulted in the removal of the 1,200 mg IV dose from all relevant clinical trials. Two additional possible cases of drug-induced liver injury (DILI) have occurred in the guselkumab CD development program:

- one subject was exposed to 200 mg IV at Weeks 0, 4, and 8; transitioned to 100 mg SC every 8 weeks at Week 12; and DILI was identified at Week 17
- one subject was exposed to 200 mg IV at Weeks 0, 4, and 8; and DILI was identified at Week 12

In psoriasis patients, mild liver transaminase elevations (<3 times the Upper Limit of Normal (ULN)) were seen at guselkumab dosages of 100 mg every 4 weeks or higher. More significant elevations (alanine aminotransferase (ALT) >5x ULN) or cases satisfying the biochemical criteria for Hy's Law were confounded by concomitant medications, alcohol use, and/or concurrent diagnoses or medical history (PBRER - 9). Of note, the proposed dosing regimen for the UC indication is higher than that currently approved for the psoriatic indications.

On March 25, 2024, DG consulted DPV-I to search FAERS for cases of adverse events with guselkumab to inform DG's review of BLA 761061/S-021. The consult specifically requested that DPV-I evaluate events concerning for DILI possibly associated with guselkumab. Moreover, a signal identification analyses (TreeScan) for guselkumab is ongoing utilizing the Sentinel Distributed Database (SDD). See **Appendix A** for additional information on TreeScan and SSD.

1.2 SUMMARY OF PRIOR POSTMARKETING SAFETY REVIEWS AND PREVIOUSLY IDENTIFIED SAFETY SIGNALS FOR GUSELKUMAB

- On December 6, 2018, and April 27, 2020, DPV-I completed consult reviews of guselkumab and hypersensitivity reactions to inform the Division of Dermatology and Dentistry's (DDD) review of labeling supplements (Weintraub and Grenade 2018; Weintraub and Reyes 2020). DPV-I's reviews described cases of hypersensitivity reactions, including anaphylaxis (the 2020 review), that informed the description of hypersensitivity reactions in WARNINGS AND PRECAUTIONS.
- On March 13, 2019, DPV-I completed a postmarket drug safety surveillance summary for guselkumab. DPV-I reviewed FAERS reports with guselkumab received by FDA from guselkumab approval to January 24, 2019, and did not identify any new safety signals (Weintraub 2019).
- On August 25, 2021, DDD consulted DPV-I to search the FAERS database for adverse events of toxic hepatitis, DILI, transaminitis, acute liver injury, and hepatitis with guselkumab use in response to the case reporting "toxic hepatitis" meeting Hy's Law in NCT 03466411 described in **Section 1.1**. In this review, DPV-I did not identify a signal for DILI in FAERS or the medical literature for guselkumab used at the doses approved for psoriasis and psoriatic arthritis (Weintraub and Reyes 2021).
- **Device issues (SSID 1004143):** On March 17, 2021, DPV-I identified the safety signal for device-related issues (e.g., *Syringe issue*, *Drug delivery system malfunction*, *Device malfunction*, *Needle issue*, *Product leakage*) with the Tremfya prefilled syringe UltraSafe Plus (PFS-U) and One-Press presentations. Subsequent evaluations performed by the Applicant, the Division of Medication Error Prevention and Analysis (DMEPA), the Office of Medication Error Prevention and Risk Management (OMEPRM), and the Center for Devices and Radiologic Health (CDRH) concluded the device-related issues with both the Tremfya One-Press and PFS-U are likely use-related. The Applicant submitted a Use Related Risk Analysis report and labeling supplement to revise the carton labeling and Instructions for Use (IFU) for Tremfya One-Press. CDRH noted most of the PFS-U cases are likely caused by incorrectly using the plunger rod to handle the PFS-U during removal from the carton or administration; therefore, CDRH recommended

adding a warning to the inner carton flap that is immediately visible when the user opens the carton (Wyeth J and Patel M 2021).

- **Skin reaction (SSID 1005298):** On March 4, 2024, DPV-I opened pre-evaluation NISS 1005298 after identifying medical literature reports of skin reactions with guselkumab. DPV-I conducted a pre-evaluation for the NISS and determined it as an indeterminate safety signal. During the pre-evaluation phase, DPV-I reviewed data from FAERS, medical literature, and data mining results. A FAERS search on March 4, 2024, identified reports of the following PTs with guselkumab: *Pustular psoriasis* (n=24), *Pemphigoid* (n=13), and *Lentigo* (n=1). A literature search identified one additional case report of bullous pemphigoid with guselkumab. The reports of skin reactions were largely confounded by indication or other concomitant medications. Therefore, DPV-I concluded that there is insufficient information to warrant further evaluation of the NISS and recommended closing SSID 1005298 in the pre-evaluation phase (Pedretti Z 2024).

1.3 RELEVANT PRODUCT LABELING

Portions of the proposed guselkumab labeling^a relevant to this review are provided below:

5. WARNINGS AND PRECAUTIONS

- *Hypersensitivity Reactions:* Serious hypersensitivity reactions, including anaphylaxis, may occur. (5.1)
- *Infections:* TREMFYA may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue TREMFYA until the infection resolves. (5.2)
- *Tuberculosis (TB):* Evaluate for TB prior to initiating treatment with TREMFYA. (5.3)

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Specific Adverse Reactions

Elevated Liver Enzymes

Elevated liver enzymes were reported more frequently in the TREMFYA group (2.6%) than in the placebo group (1.9%). Of the 21 patients who were reported to have elevated liver enzymes in the TREMFYA group, all events except one were mild to moderate in severity and none of the events led to discontinuation of TREMFYA.

2 METHODS AND MATERIALS

2.1 FAERS DATABASE SEARCHES

We aimed to identify reports of unlabeled adverse events with guselkumab, including liver injury. DPV-I searched the FAERS database with the search strategy described in **Table 1**.

^a Proposed labeling for Tremfya, submitted by the Applicant to BLA 761061 S-021 on March 11, 2024

Table 1. FAERS Search Strategy*		
	Query 1	Query 2
Date of search	April 10, 2024	April 23, 2024
Time period of search	September 2, 2021 [†] – April 10, 2024	January 25, 2019 [‡] – April 22, 2024
Search type	RxLogix - Quick Query	RxLogix - Quick Query
Product terms	Product Active Ingredient: Guselkumab	Product Active Ingredient: Guselkumab
MedDRA search terms	Standardised MedDRA Query: <i>Drug related hepatic disorders - comprehensive search (Broad)</i>	
Outcomes [§]	All outcomes	All serious outcomes
*See Appendix A for a description of the FAERS database [†] Data-lock date of the FAERS search for the 2021 review of liver injury with guselkumab [‡] Data-lock date of the FAERS search for the 2019 guselkumab surveillance summary [§] We limited Query 2 to reports with a serious outcome because of the large number of reports. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities		

2.2 DATA MINING SEARCH STRATEGY

DPV-I conducted a disproportionality analysis of FAERS data using Empirica Signal with the strategy described in **Table 2**.

Table 2. Data Mining Search Strategy*	
Data refresh date	May 8, 2024
Product term	Guselkumab
Empirica Signal run name	PAM (S), serious only
MedDRA search strategy	All adverse events, retrieved at the MedDRA PT level
MedDRA version	26.1
Seriousness	Serious only
*See Appendix A for description of Data Mining of FAERS using Empirica Signal. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAM = Product Active Moiety, PT=Preferred Term	

2.3 MEDICAL LITERATURE

DPV-I searched the medical literature with the strategy described in **Table 3**.

Table 3. Literature Search Strategy		
	Search 1	Search 2
Date of search	May 1, 2024	May 1, 2024
Time period of search	January 25, 2019*, to May 1, 2024	September 2, 2021†, to May 1, 2024
Database	Embase	Embase
Search terms	'guselkumab'/exp/dd_ae	('guselkumab'/exp OR guselkumab) AND ('drug-induced liver injury' OR 'hepatobiliary disease' OR 'hepatitis' OR 'liver disease' OR 'liver injury') AND [humans]/lim AND [02-09-2021]/sd NOT [02-05-2024]/sd
Filters	[humans]/lim	[humans, case reports]/lim
*Data-lock date of the literature search for the 2019 guselkumab surveillance summary		
†Data-lock date of the literature search for the 2021 review of liver injury with guselkumab		

2.4 PERIODIC SAFETY REPORTS

DPV-I screened the following periodic safety reports (PSRs) for guselkumab:

- PBRER #14 - Reporting period July 13, 2022, to July 12, 2023
- PBRER #13 - Reporting period July 13, 2021, to July 12, 2022
- PBRER #12 - Reporting period July 12, 2020, to July 12, 2021

2.5 CASE DEFINITION AND CATEGORIZATION OF LIVER INJURY

2.5.1 Case Definition of Liver Injury

We used a case definition adapted from the Drug-Induced Liver Injury Network and the Office of Surveillance and Epidemiology (OSE) DILI case definition (Fontana RJ et al. 2009). If the upper limit of normal (ULN) was not provided in the case, we used an ULN of ALT of 33 international units (IU)/liter (L) in males and 25 IU/L in females, aspartate aminotransferase (AST) of 40 IU/L, and alkaline phosphatase (AP) of 120 IU/L. Any of the following satisfies the case definition of liver injury:

- Serum ALT or AST >5x ULN or AP >2x ULN
- (Serum total bilirubin >2.5 mg/dL OR international normalized ratio (INR) >1.5) AND elevated AST, ALT, or AP
- Healthcare provider-reported or confirmed liver injury (e.g., toxic hepatitis, DILI, transaminitis, acute liver injury, hepatitis) with or without reported symptoms (e.g., nausea, vomiting, jaundice) or diagnostic information

We excluded reports meeting one or more of the following criteria:

- Liver injury without diagnostic information reported by non-healthcare provider without medical confirmation
- The only liver-related adverse event reported was hepatic malignancy
- Duplicates

2.5.2 Categorization of Liver Injury

We categorized cases by severity using the definitions in **Table 4** below (Fontana RJ et al. 2009). Severity scores of 4 and 5 are considered liver failure.

Table 4. Drug-Induced Liver Injury Severity Index Definitions		
Severity Score	Grade	Definition
0	Insufficient data	Case describes liver injury but does not provide information needed to determine the severity
1	Mild	Patient has elevation in ALT and/or AP levels but total serum bilirubin is <2.5 mg/dL AND INR is <1.5
2	Moderate	Patient has elevation in ALT and/or AP levels AND total serum bilirubin >2.5 mg/dL OR INR is >1.5
3	Moderate-Severe	Patient has elevation in ALT, AP, bilirubin and/or INR levels AND patient is hospitalized, or an ongoing hospitalization is prolonged because of DILI
4	Severe	Patient has elevation in ALT and/or AP levels AND total serum bilirubin is >2.5 mg/dL AND there is at least one of the following: 1) hepatic failure (INR >1.5, ascites, or encephalopathy); 2) other organ failure believed to be due to DILI event
5	Transplantation-Fatal	Patient dies or undergoes liver transplantation because of DILI event

Hy's Law cases are typically categorized as meeting both criteria below. Based on the limited information provided in some FAERS cases to rule out other causes of liver injury, we categorized cases meeting the biochemical criterion in the first bullet as potential Hy's Law cases:

- ALT or AST >3x ULN, total bilirubin $\geq$ 2x ULN, and AP <2x ULN
- No other reason found to explain the combination of increased aminotransferase and bilirubin (e.g., viral hepatitis A, B, or C; preexisting or acute liver disease; another drug capable of causing the observed injury)

We classified the pattern of liver injury as follows based on the R ratio $((\text{ALT}/\text{ULN})/(\text{AP}/\text{ULN}))$ calculated on the first available values after onset:

- Hepatocellular: $R > 5$
- Cholestatic: $R < 2$
- Mixed: $R = 2-5$

2.6 CAUSALITY CRITERIA

We used a modification of the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality System in **Table 5** to assess the relationship of the liver injury to guselkumab use. We excluded cases categorized as “unassessable” or “unlikely.”

Table 5. WHO Causality Assessment Scale	
Causality Term	Assessment Criteria
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or another drug • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

3 RESULTS

3.1 FAERS DATA SUMMARY

Our search of the FAERS database for all adverse events with guselkumab described in **Table 1** yielded 4,588 reports with a serious outcome.

To identify new safety signals for guselkumab, we compared the adverse events listed in the Applicant’s proposed labeling for BLA 761061 S-021 to the following groups of Preferred Terms (PTs): 1) the 50 most frequently reported PTs, and 2) a list of Designated Medical Events^b (DMEs) with a serious outcome. Because of the large number of reports with serious outcomes, we did not perform a case-level analysis of every report. Report counts may include duplicate reports, miscoded reports, or unrelated reports. See **Section 3.1.1** for our analysis of these reports.

Table 6 provides an overview of descriptive characteristics for reports of all serious adverse events with guselkumab since the data-lock date of the 2019 surveillance summary.

^b DMEs are adverse events that are considered serious and, from a pharmacovigilance perspective, may be caused by exposure to drugs from many pharmacological or therapeutic classes. DMEs are not intended to include events with a high prevalence in the general population. See **Appendix B** for a list of the OSE DMEs.

Table 6. Descriptive Characteristics of Serious Reports With Guselkumab, Received by FDA to the FAERS Database From January 25, 2019, to April 22, 2024	
Data Element	Number of Reports (N=4,588*)
Sex/gender	
Female	2,198
Male	1,814
Not reported	576
Age	
1 to <3 years	1
7 to <17 years	2
17 to <65 years	1,983
≥65 years	804
Not reported	1798
Country	
United States	2,243
Foreign	2,342
Unknown	3
Guselkumab indication for use [†]	
Psoriasis/psoriatic arthropathy	3,224
Crohn's disease/ulcerative colitis	67
Other	222
Not reported	2,286
Report type	
Expedited	4,043
Periodic	262
Direct	269
Serious outcomes [‡]	
Other serious outcome	3,198
Hospitalization	1,357
Death	242
Disability	50
Life-threatening	110
Congenital anomaly	1
Required intervention	21
*May include duplicates †A report can have one or more indications for use. "Other" indications included palmoplantar pustulosis, rheumatoid arthritis, hidradenitis eczema, ankylosing spondylitis etc. ‡Serious adverse drug experience includes outcomes of congenital anomaly, death, disability, hospitalization, life-threatening, or other serious important medical events. A report can have one or more outcomes.	

3.1.1 Most Frequently Reported PTs for Serious Reports With Guselkumab

Table 7 contains the 50 most frequently reported PTs for serious reports with guselkumab. The bolded PTs in **Table 7** are further discussed in **Section 3.5**.

Table 7. Top 50 Most Frequently Reported PTs for Serious Reports With Guselkumab, Received by FDA From January 25, 2019, to April 22, 2024, Sorted by Decreasing Number of FAERS Reports per PT

	MedDRA PT	Number of Reports* (N=4,588)	Labeled (Yes/No), Location [†] /Comment
1	Pneumonia	439	No; Increase risk of infections labeled under W/P
2	Psoriatic arthropathy	338	No; Alt Ex
3	Psoriasis	313	No; Alt Ex
4	Drug ineffective	261	No; U
5	Product dose omission issue	233	No; U
6	Off label use	211	No; U
7	Death	164	No; See Section 3.5.2
8	COVID-19	159	No; Alt Ex [‡]
9	Lower respiratory tract infection	139	No; Increased risk of infections labeled under W/P
10	Arthralgia	88	No; Alt Ex
11	Cellulitis	83	No; Increased risk of infections labeled under W/P [§]
12	Headache	77	Yes; AR
13	Infection	69	Yes; W/P
14	Dyspnoea	65	No; U
15	Product use issue	65	No; U
16	Accidental exposure to product	63	No; U
17	Hospitalisation	63	No; U
18	Pain	63	Yes; AR, relates to injection site reaction
19	Rash	58	Yes; AR
20	Myocardial infarction	56	No; See Section 3.5.3
21	Pyrexia	55	No; U
22	Fall	54	No; U
23	Diarrhoea	53	Yes; AR
24	Product use in unapproved indication	53	No; U
25	Pruritus	52	Yes; AR
26	Cerebrovascular accident	51	No; See Section 3.5.3
27	Fatigue	51	No; Alt Ex
28	Breast cancer	50	No; See Section 3.5.5
29	Inappropriate schedule of product administration	50	No; U
30	Neoplasm malignant	50	No; See Section 3.5.5
31	Urinary tract infection	47	No; Increased risk of infections labeled under W/P
32	Condition aggravated	46	No; U
33	Influenza	43	No; Increased risk of infections labeled under W/P
34	Surgery	43	No; U
35	Hypertension	42	No; U

Table 7. Top 50 Most Frequently Reported PTs for Serious Reports With Guselkumab, Received by FDA From January 25, 2019, to April 22, 2024, Sorted by Decreasing Number of FAERS Reports per PT

	MedDRA PT	Number of Reports* (N=4,588)	Labeled (Yes/No), Location [†] /Comment
36	Tuberculosis	40	Yes; W/P
37	Arthritis	39	No; Alt Ex
38	Nausea	39	No; U
39	Sepsis	39	No; Increased risk of infections labeled under W/P
40	Nasopharyngitis	38	Yes; AR
41	Depression	35	No; See Section 3.4
42	Dizziness	35	No; U
43	Hypersensitivity	35	Yes; W/P
44	Bronchitis	34	Yes; AR
45	Device malfunction	34	No; See Section 3.5.4
46	Therapeutic product effect decreased	34	No; U
47	Kidney infection	33	No; Increased risk of infections labeled under W/P
48	Nephrolithiasis	33	No; U**
49	Chest pain	32	No; U
50	Cough	32	No; U

*A report can contain more than one MedDRA PT. Report counts may include duplicates.

[†]If the event is included in multiple sections of labeling, only the section of highest importance is listed.

[‡]Reports with the PT *COVID-19* reflect diagnosis of COVID-19 during the pandemic while receiving guselkumab

[§]We conducted hands-on review of 25 reports with the PT *Cellulitis*; these contained limited information for assessment or were related to underlying psoriasis flare.

^{||}We conducted hands-on review of 20 reports with the PT *Dyspnoea*; these contained limited information for assessment or were more likely related to underlying disease such as chronic obstructive pulmonary disease than guselkumab.

[¶]We reviewed 20 reports with the PT *Pyrexia*; these contained limited information for assessment or described pyrexia associated with infection or hypersensitivity reaction.

^{**}We reviewed 20 reports with the PT *Nephrolithiasis*; these contained limited information for assessment or reported previous history of kidney stones.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, W/P =

Warnings/Precautions, AR = Adverse Reactions, Alt Ex = alternative explanation (e.g., disease-related, indication-related, concomitant medication-related), U = uninformative

3.1.2 Designated Medical Events With Guselkumab

Table 8 lists the reported DMEs from all serious reports for guselkumab received to the FAERS database since the data-lock date of DPV-I's 2019 surveillance summary and the location within the Applicant's proposed labeling for BLA 761061 S-021. The bolded PTs in **Table 8** are further discussed in **Sections 3.4** or **3.5**.

Table 8. Reported DMEs With Guselkumab, Received by FDA From January 25, 2019, to April 22, 2024, Sorted by Decreasing Number of Total FAERS Reports per PT			
	DME MedDRA PT	Number of Reports (N=4,588)*	Labeled (Yes/No), Location†/Comment
1	Seizure	19	No; See section 3.56
2	Acute kidney injury	15	No; U
3	Hepatic failure	10	No; See Section 3.5.1
4	Anaphylactic reaction	9	Yes; W/P
5	Pancytopenia	6	No; See Section 3.4
6	Acute generalised exanthematous pustulosis	5	No; U
7	Deafness	5	No; U
8	Drug-induced liver injury	5	No; See Section 3.5.1
9	Anaphylactoid reaction	4	Yes; W/P
10	Blindness	4	No; U
11	Thrombotic microangiopathy	4	No; Alt Ex
12	Anaphylactic shock	3	Yes; W/P
13	Blindness unilateral	3	No; U
14	Agranulocytosis	2	No; Alt Ex
15	Blindness transient	2	No; U
16	Completed suicide	2	No; See Section 3.4
17	Generalised tonic-clonic seizure	2	No; See Section 3.56
18	Rhabdomyolysis	2	No; Alt Ex
19	Sudden hearing loss	2	No; U
20	Deafness neurosensory	1	No; U
21	Drug reaction with eosinophilia and systemic symptoms	1	No; U
22	Liver transplant	1	No; See Section 3.5.1
23	Product contamination	1	No; U
24	Sudden cardiac death	1	No; U
25	Sudden death	1	No; See Section 3.5.2
26	Thrombotic thrombocytopenic purpura	1	No; U
27	Toxic epidermal necrolysis	1	No; U
*A report can contain more than one MedDRA PT. Report counts may include duplicates. †If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term, W/P = Warnings/Precautions, AR = Adverse Reactions, Alt Ex = alternative explanation (e.g., disease-related, indication-related, concomitant medication-related), U = uninformative			

Reviewer's Comment: After performing this high-level overview of FAERS reports associated with the 50 most frequently reported PTs (Table 7) and DME PTs (Table 8) we noted the following:

- *The majority of serious reports with guselkumab retrieved in FAERS were coded with PTs related to infections (Pneumonia, COVID-19, Lower respiratory tract infection, Cellulitis, Infection, and Sepsis) or other medical conditions. Guselkumab is labeled for infections in WARNINGS AND PRECAUTIONS (Infections (5.2)).*

- *The reports coded with DMEs generally had limited information for causality assessment or reported alternative disease or drug etiologies. Several reports showed a temporal relation to guselkumab however the reports did not include sufficient details for assessment or included possible alternate etiologies for the event and therefore were deemed uninformative.*
- *We conducted a narrative text search for all reports coded with the PTs Drug ineffective or Therapeutic product effect decreased for the terms "immunogenicity", "antibodies", "antibody", or "neutralizing" to identify reports describing antidrug antibodies. Our search identified one report (FAERS# 22542065) attributing decreased guselkumab efficacy to antidrug antibodies by a patient with a history of antidrug antibodies to adalimumab.*

3.2 DATA MINING

DPV-I used Empirica Signal Software to perform disproportionality analysis of FAERS data and to identify patterns of associations or unexpected occurrences (i.e., potential signals). If a drug-event combination has an $EB05 \geq 2$, this indicates with 95% confidence that the drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining results do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation.

Data mining results for PTs with $EB05 \geq 2$ from serious reports with guselkumab are provided in **Appendix C**. DPV-I screened the data mining results for adverse events of potential interest that are not labeled for guselkumab, do not describe a symptom of a labeled event, and are not disease-related. A summary of relevant PTs is provided below:

- *Cellulitis: No trends noted; all reports screened were either unassessable because of limited clinical details within the reports or had unknown temporal association. Guselkumab is labeled for increased risk of infections in WARNINGS AND PRECAUTIONS (Infections (5.2)).*
- *Sweat gland disorder: No trends noted; all reports screened were duplicate reports of one primary report unrelated to guselkumab.*
- *Malignancy: Multiple PTs with $EB05 \geq 2$ described malignancies, including Malignant melanoma, Endometrial cancer, and Hodgkin's disease. Although several reported positive temporal relations, the reports contained limited details regarding alternate risk factors for the events. See **Section 3.5.5** for further analysis of this safety issue.*
- *Pemphigoid: In a previous NISS pre-evaluation described in **Section 1.2**, eight reports of pemphigoid were identified from FAERS and medical literature through March 4, 2024. In our current search, which overlapped the dates covered by the previous DPV-I search, we identified 11 reports of pemphigoid reported with guselkumab, including 1 literature report identified in the previous DPV-I NISS pre-evaluation (Burlando et al. 2022). Of these 11 reports, 7 described a positive temporal association; however, these 7 reports*

contained limited information for assessment (n=3) or could be attributed to underlying psoriasis (n=1) or concomitant medications (n=3). The remaining four reports did not report a clear temporal relation to guselkumab. Patients with psoriasis are at a higher risk for development of bullous pemphigoid. No serious outcomes relating to pemphigoid were identified in the reports. DPV-I will continue routine pharmacovigilance for skin reactions associated with guselkumab.

3.3 LITERATURE CASES

DPV-I screened the medical literature using the search strategy described in **Table 3** and identified two publications describing axonal sensorimotor polyneuropathy and alopecia areata; these safety findings are discussed below:

- **Axonal sensorimotor polyneuropathy:** We identified one published case report describing axonal sensorimotor polyneuropathy after starting guselkumab in a 20-year-old male (Hamadah and Chisti 2022). See **Section 3.56** for DPV-I's analysis of neurologic adverse events.
- **Alopecia areata:** We identified one published case report describing alopecia areata after guselkumab treatment (Şentürk and Çetin 2023). This case described a 26-year-old male patient diagnosed with psoriasis 6 years previously with a childhood history of alopecia areata. Previous treatments for psoriasis included topical steroids, methotrexate, and cyclosporine. Following second dose of guselkumab, the patient experienced lesions of alopecia areata on the scalp. The lesions increased after the third dose of guselkumab; because of the worsening alopecia, the patient's therapy was switched to secukinumab. Alopecia areata was treated with intralesional corticosteroids. After three sessions of corticosteroid injections and switching to secukinumab, full regrowth of hair on the vertex was recorded.

Our FAERS search described in **Table 1** retrieved 21 reports coded with the following PTs related to hair loss: *Alopecia*, *Androgenetic alopecia*, *Alopecia areata*, and *Madarosis*. We conducted a hands-on review of all 21 reports and excluded 20 from further review (unassessable, n=13^c; unlikely casual association to guselkumab, n=7^d). The remaining one report (FAERS # 2127282) described a 59-year-old female with palmoplantar psoriasis on guselkumab 100 mg every 8 weeks. Concomitant medications included cholecalciferol and levothyroxine. One year after initiating guselkumab, the patient experienced hair loss. The guselkumab dose was not changed for the reported event. No further information was available.

^c Reports provided limited clinical details necessary for causality assessment (e.g., medical history, concomitant medications).

^d Three reports described hair loss due to underlying psoriasis flare.

3.4 PERIODIC SAFETY REPORTS

DPV-I screened the PSRs for guselkumab listed in **Section 2.4** and identified the following relevant new safety findings listed in **Table 9**.

Table 9. Relevant New Safety Findings From the Applicant's Periodic Safety Reports (PSRs)	
Reporting Periods	Safety Finding Summary
13 July 2021 to 12 July 2022	Suicidal Ideation and Behavior (SIB): The Pharmacovigilance Risk Assessment Committee (PRAC) and Health Canada's Marketed Health Products Directorate (MHPD) requested the Applicant to evaluate the risk of suicidal ideation and behaviors (SIB) with guselkumab. The Applicant performed a cumulative review of reports of SIB from the Applicant's global safety database coded with the MedDRA SMQ <i>Suicide/self-injury (narrow)</i> and identified 39 reports. The most frequently reported MedDRA PTs of interest were <i>Suicidal ideation</i> (n=17), <i>Completed suicide</i> (n=10) and <i>Suicide attempt</i> (n=5). A total of 74 percent (29/39) of reports were from clinical study sources (including reports from interventional clinical trials (n=9) and solicited reports (n=20)). The Applicant concluded that of the 39 reports reviewed, 26 had risk factors/confounders for the event and 13 provided insufficient information for a meaningful medical assessment. Based on the review of the data, no new safety information was identified by the Applicant. <i>Reviewer's comment: The FAERS search strategy described in Table 1 retrieved 18 reports coded with the PTs Suicidal ideation, Intentional self-injury, Completed suicide, or Suicide attempt. DPV-I reviewed all 18 reports; 15 were unassessable (n=11) or had an unlikely causal association to guselkumab (n=3); the remaining three reports (i.e., FAERS# 20331667, 18273725, 22112911) described a temporal association to guselkumab but had concurrent medical conditions that could plausibly have a contributory role in the event (i.e., depression, anxiety, alcoholism). In addition, the top 50 most frequently reported PTs described in Table 7 included 35 reports with the PT Depression, including 26 spontaneous reports. We reviewed all 26 spontaneous reports and identified 5 reports with a temporal relation that are possibly related to guselkumab (FAERS# 17111461, 20331667, 21601488, 18330809, 17159056); among the 5 reports, an underlying past medical history of depression was reported in 3 reports, and the remaining 2 reports did not report the patient's past medical history or concomitant medications. DPV-I will continue routine pharmacovigilance for SIB.</i>
13 July 2022 - 12 July 2023	Drug-Induced Liver Injury (DILI): The PRAC requested the Applicant to continue to monitor potential cases of DILI. Additionally, Health Canada requested to discuss all cases of elevated liver enzymes meeting biochemical Hy's Law criteria and all potential adverse events of hepatotoxicity. The Applicant performed a cumulative search of reports of DILI from the Applicant's global safety database and clinical trial data coded with the MedDRA SMQ <i>Drug related hepatic disorders-comprehensive search (narrow)</i> and identified 210 reports for evaluation. The Applicant noted that compared with the previous PSUR, exposure increased for clinical trials by 1.23x and postmarketing by 1.7x, while the number of reported postmarketing DILI cases increased 3x. The Applicant requested to present in the next PSUR an explanation for this 3x increase and possible measures for risk

	minimization. Of the 210 reports, most (70 percent (147/210)) were reported from clinical study (noninterventional) source. The most frequently reported indication was psoriasis (71.2 percent (121/170)). The most frequently reported MedDRA PT of interest was <i>Hepatic enzyme increased</i> (27 percent (60/222)). The majority of reports (n=186) did not report LFTs. Of the 24 reports that reported LFT values, none met Hy's Law criteria. The Applicant concluded that the reports did not provide sufficient evidence to support DILI as an ADR for guselkumab. <i>Reviewer's comment: See Section 3.5.1 for DPV-I's analysis of liver injury.</i>
13 July 2022 - 12 July 2023	<u>Neutropenia</u>: The PRAC requested the Applicant to continue to review all reports of serious and nonserious neutropenia associated with infection based on clinical studies and postmarketing sources. In the most recent PBRER #14, the Applicant provided their analysis of 10 reports of neutropenia-related events received during the reporting period. The most frequently reported MedDRA PT of interest was <i>Neutropenia</i> (n=4); two events were associated with infection. Of the 10 total reports, 1 was confounded by the patient's medical history (included stem cell transplant, plasma cell myeloma, and concomitant pomalidomide use); the remaining 9 reports provided limited information regarding the patient's medical history and concomitant medications to conduct a meaningful assessment. The Applicant concluded that no new safety information was identified during the reporting interval for neutropenia. <i>Reviewer's comment: The FAERS search strategy described in Table 1 retrieved 25 spontaneous reports coded with the PTs Neutropenia (n=10), White blood cell count decreased (n=8), Neutrophil count decreased (1), and Pancytopenia (n=6). All reports contained limited information, which precluded a comprehensive assessment. DPV-I will continue routine pharmacovigilance for neutropenia.</i>
13 July 2022 – 12 July 2023	<u>Venous Thromboembolism</u>: A safety signal for venous thrombosis was identified from the Applicant's Development Safety Update Report covering July 13, 2020, to July 12, 2021. In this report, the Applicant concluded that based on the currently available evidence, the benefit-risk profile of guselkumab continues to be favorable. During the most recent PSR reporting interval, the Applicant identified 37 reports describing events related to VTE from the Applicant's global safety database. Review of these reports did not identify new safety concerns by the Applicant. <i>Reviewer's comment: The FAERS search described in Table 1 identified 37 spontaneous reports with the PTs Thrombosis, Deep vein thrombosis, Pulmonary embolism, Pulmonary thrombosis, Portal vein thrombosis, Cardiac ventricular thrombosis, or Peripheral artery thrombosis. We conducted a hands-on review of all 37 reports. After eliminating duplicate reports (n=1), reports with limited information for assessment (n=26), and reports assessed as unlikely to be related to guselkumab (n=5), we identified 5 reports (FAERS #20535749, 23220178, 15868544, 16696841, 19621524) with a temporal association to guselkumab, including 1 report of mortality due to pulmonary thrombosis. All five reports were considered possibly related to guselkumab because the patients had concomitant medical conditions that increased the underlying risk of thrombosis. DPV-I will continue routine pharmacovigilance for VTE.</i>

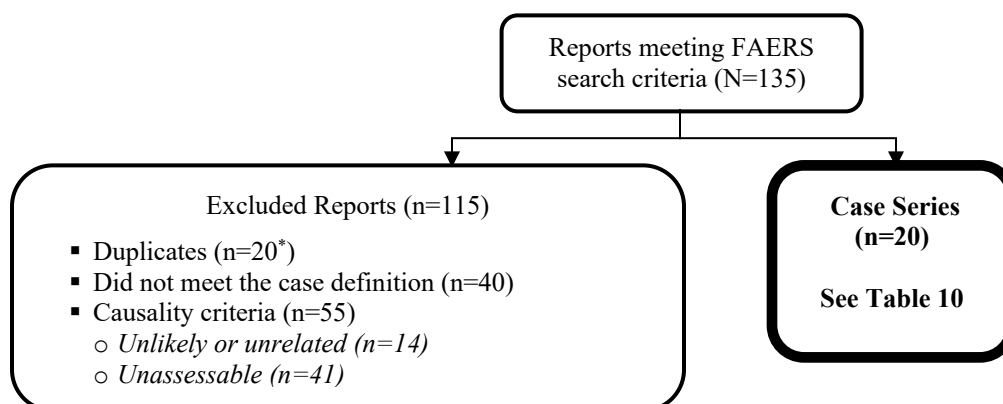
13 July 2022 – 12 July 2023	Device Malfunction: In the most recent PRBER#14, the Applicant provided a summary of device-related issues including device malfunction, needle issue, drug delivery system malfunction and other device related issues. The Applicant concluded that the review of medical device related issues did not identify any specific patterns or trends. <i>Reviewer’s comment: See Section 3.5.4 for DPV-I’s analysis of device malfunction.</i>
13 July 2022 – 12 July 2023	Malignancy: The Applicant’s core risk management plan includes malignancy as an important potential risk associated with the use of guselkumab. In the most recent PRBER #14, the Applicant provided an analysis of 335 reports related to malignancy with the use of guselkumab. No new safety information was identified in this review by the Applicant. <i>Reviewer’s comment: See Section 3.5.5 for DPV-I’s analysis of malignancy.</i>
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, SMQ=Standardized MedDRA Query, LFT=liver function test, ADR=adverse drug reaction, VTE=venous thromboembolism	

3.5 SUMMARY OF SELECT ADVERSE EVENTS WITH GUSELKUMAB

3.5.1 Drug-Induced Liver Injury

The FAERS search for liver injury described in **Table 1** retrieved 135 reports. A case-level analysis was conducted for all 135 reports. The literature search described in **Table 6** retrieved no additional unique reports. After applying the case definition in **Section 2.5.1**, the causality criteria in **Section 2.6**, and accounting for duplicate reports, 20 cases were included in the case series of liver injury with guselkumab use (see **Figure 1**).^e

Figure 1. FAERS Case Selection – Liver Injury



*Includes FAERS#23305219, which was the index case in the previous 2021 DPV-I review of liver injury with guselkumab.

Table 10 summarizes the 20 FAERS cases of liver injury with guselkumab for this case series. **Appendix D** contains a line listing of the 20 cases in this case series.

^e The Applicant’s assessment of this safety issue from the periodic safety report is described in **Section 3.4**.

Table 10. Descriptive FAERS Case Characteristics of Liver Injury With Guselkumab Received by FDA From September 2, 2021, Through April 10, 2024 (N=20)	
Age, years (n=13)	
Mean	48
Median	50
Range	31-72
Sex/gender (n=18)	
Female	5
Male	13
Report type	
Expedited	12
Periodic	8
Initial FDA received year	
2021	1
2022	10
2023	8
2024	1
Country	
United States	9
Foreign	11
Reported outcome	
Death	1
Hospitalization	4
Other serious*	11
Nonserious	4
Reason for guselkumab use (n=18)	
Psoriasis	15
Ankylosing spondylitis	1
Palmoplantar pustulosis	1
Psoriatic arthropathy	1
Guselkumab dosage (n=12)	
100 mg every 4-8 weeks	2
100 mg every 8 weeks	6
100 mg every 6 weeks	1
100 mg (dosing interval not specified)	3
Not reported	8
Time of onset from starting guselkumab (n=16)	
<1 month	1
1 month-<3 months	2
3 months-<6 months	5
6 months-<9 months	2
9 months-<1 year	0
≥1 year	6
Causality assessment	
Possible	20

Table 10. Descriptive FAERS Case Characteristics of Liver Injury With Guselkumab Received by FDA From September 2, 2021, Through April 10, 2024 (N=20)	
Action taken for guselkumab (n=15)	
Continued	4
Liver injury improved	1
No follow-up information	3
Stopped	11
Liver injury improved	4
Liver injury ongoing	2
No follow-up information	5
Not reported	5
* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. A case can have more than one serious outcome. Abbreviation: mg=milligrams	

Table 11 provides information on diagnostic information, risk factors, and treatment of liver injury with guselkumab.

Table 11. Diagnostic Information, Risk Factors, and Treatment for FAERS Cases of Liver Injury With Guselkumab Received by FDA From September 2, 2021, Through April 10, 2024 (N=20)	
Maximum total bilirubin (n=2)	
Total bilirubin >2x ULN	0
Total bilirubin <1 mg/dL or 17.1 umol/L	2
Maximum ALT ULN (n=7)	
>5-20x ULN	3
>3-5x ULN	2
>ULN-≤3x ULN	2
Maximum AST ULN (n=5)	
>5-20x ULN	1
>ULN-≤3x ULN	4
ALT or AST >3x ULN, total bilirubin ≥2x ULN, and AP<2x ULN (Potential Hy's Law case)	0
AST/ALT ratio (n=5)	
AST/ALT ratio <1	2
AST/ALT ratio=1-2	3
AST/ALT ratio >2	0
Pattern of liver injury (R ratio; n=1)	
Mixed (R=2-5)	1
DILI severity (n=20)	
Insufficient data	19
Fatal (Grade 5)*	1
Liver biopsy (n=1)	
“Steatohepatitis” alcoholic or nonalcoholic steatohepatitis with differential diagnosis of DILI with NASH pattern	1

Table 11. Diagnostic Information, Risk Factors, and Treatment for FAERS Cases of Liver Injury With Guselkumab Received by FDA From September 2, 2021, Through April 10, 2024 (N=20)	
Risk factors for liver injury (n=9)	
Alcohol use reported	5
Concomitant medications	4
Suspected infection	2
Treatment for liver injury (n=2)	
Ursodeoxycholic acid	1
Decrease alcohol use	1
*One fatal case of DILI (FAERS # 21563531) describes a 58-year-old male with end stage liver disease 16 months after initiating guselkumab 100 mg every 8 weeks; patient had a history of concomitant alcohol use. The case did not provide laboratory details, previous medical history, or concomitant medications. Abbreviations: ALT=alanine aminotransferase, AP=alkaline phosphatase, AST=aspartate aminotransferase, DILI=drug-induced liver injury, L=liter, NASH=nonalcoholic steatohepatitis, ULN=upper limit of normal, umol=micromoles, mg=milligrams	

Of the 20 cases of liver injury with guselkumab, most (n=19) did not provide sufficient information to determine the severity of liver injury (see **Table 4**). All 20 cases were assessed as possibly due to guselkumab. Concomitant alcohol use and/or medications were considered alternative causes in nine cases. Eleven cases reported discontinuation of guselkumab following liver injury; of these, four reported improvements in liver damage after guselkumab discontinuation, including two that either received treatment (ursodeoxycholic acid, n=1) or mitigated concomitant risk factor for liver injury (decreased ethanol use, n=1). None of the 20 cases met Hy's Law criteria for liver injury. One case (FAERS#21563531) described death from end stage liver damage; however, this case lacked necessary laboratory details for further assessment.

3.5.2 Death

The FAERS search described in **Table 1** retrieved 242 reports with guselkumab that had an outcome of death; we conducted hands-on review of 120 death reports. Overall, the fatal reports generally lacked clinical details necessary for causality assessment (e.g., medical history, concomitant medications, events preceding death). Of the 120 reports, the cause of death was not reported in 74 and was reported as unknown in 42 reports. The remaining four reports described the cause of deaths as septic shock, malignant cardiac arrhythmia, natural cause, or renal failure; these four reports in general contained limited clinical information and did not provide details that support a clear association between guselkumab and the fatal events.

3.5.3 Major Adverse Cardiovascular Events (MACE)

The European Union Risk Management Plan includes MACE as an important potential risk associated with the use of guselkumab. In the most recent PBRER #14 (reporting period July 13, 2022, to July 12, 2023), the Applicant analyzed 151 reports of MACE from their global safety database, literature, and clinical studies. The most frequently reported PTs included *Cerebrovascular accident* and *Myocardial infraction*. The Applicant did not identify any new trend or significant safety information regarding the risk of MACE.

The FAERS search described in **Table 1** identified 168 reports (spontaneous, n=131; solicited, n=37) that were coded with PTs within the *Haemorrhagic central nervous system vascular conditions (SMQ) Narrow search*, *Ischaemic central nervous system vascular conditions (SMQ) Narrow search*, or *Myocardial infarction (SMQ) Narrow search* or that were coded with the PTs *Sudden death*, *Cardiac death*, or *Sudden cardiac death*. We conducted hands-on review of all 131 reports derived from spontaneous reporting sources; of these, we excluded 107 from further review (unassessable, n=93^f; unlikely causal association to guselkumab, n=5; did not describe MACE, n=4; duplicates, n=5). The remaining 24 cases had a possible causal association (e.g., temporal association to guselkumab initiation) to guselkumab and are summarized below. A line listing of the 24 cases can be found in **Appendix E**.

- All 24 cases had a guselkumab indication of psoriasis
- The most commonly reported MACE was myocardial infarction (n=14), followed by cerebrovascular events including cerebrovascular accident, cerebral haemorrhage, cerebral infarction or subarachnoid haemorrhage (n=9) and acute coronary syndrome (n=1)
- Age ranged from 40 to 84 years with a mean age of 59 years
- All 24 cases reported at least 1 cardiovascular risk factor (e.g., age, diabetes mellitus, hyperlipidemia, hypertension, obesity, tobacco use)
- Time from guselkumab initiation to myocardial infarction ranged from 3 days to 13 months

3.5.4 Device Malfunction

The Applicant provided a summary of device-related issues in the most recent PBRER #14 (reporting period July 13, 2022, to July 12, 2023). This summary included reports describing device malfunction (n=454), needle issue (n=776), drug delivery system malfunction (n=297), and other device issues; which included syringe issue (n=189), product label issue (n=78), product packaging issue (n=20), drug delivery system issue (n=14), and device difficult to use (n=4). The One-Press injector device represented >90 percent of all reports. The Applicant concluded that their review of all cases reporting device-related issues did not identify any unusual patterns.

DPV-I conducted hands-on review of 34 serious reports from the FAERS search strategy described in **Table 1** with the PT *Device malfunction*.^g Of the 34 reports, 24 involved the One-Press injector device, and the remaining 10 reports described events involving prefilled syringe or prefilled pen. Overall, the reports lacked sufficient information to assess whether the described device malfunctions occurred because of device defect or use error. Of the 24 reports that described a root cause in the case narrative, 23 reported that the root cause was either not manufacturing-related or that a manufacturing-related root cause could not be identified; the remaining 1 report (FAERS#23389448) described the root cause as manufacturing-related and is described below.^h

^f Reports provided limited clinical details necessary for causality assessment (e.g., medical history, concomitant medications).

^g See **Section 1.2** for a summary of FDA's prior investigation of Tremfya device issues (SSID 1004143).

^h FAERS 23389448 describing manufacturing-related root cause was shared with CDRH

FAERS #23389448; Other serious outcome; Spontaneous; United States; 2024: This report describes a 51-year-old female with a history of psoriasis and arthritis who reported a device malfunction with the guselkumab One-Press injector. During administration of the drug, the patient noted that the device was “locked,” preventing her from pressing it down; the needle did not deploy, and medication was left in the device. She observed a circular mark on her abdomen from the device, but there was no puncture mark from the needle. The patient has prior experience using this device and has been on guselkumab for 2 years. The report narrative described the root cause as manufacturing-related, stating, “needle shield not removed with cap.”

3.5.5 Malignancies

The Applicant identified malignancy as an important potential risk for guselkumab in the most recent PBRER #14 (reporting period July 13, 2022, to July 12, 2023). The Applicant conducted a search in the global safety database with MedDRA SMQ: *Malignant tumors (Broad)* and identified 335 cases reporting events related to malignancy with the use of guselkumab during this reporting period. Of the 335 cases, the majority were reported from noninterventional clinical studies (n=245), and the most frequently reported indication was psoriasis (n=213). The most frequently reported MedDRA PT of interest was *Neoplasm malignant* (n=45). After eliminating reports with short latency (n=35), limited information for assessment (n=250), and reports confounded by medical history or concurrent medications (n=48), the Applicant identified 2 cases with no potential confounders. The Applicant stated that the reporting rate of malignancy in patients treated with guselkumab in the postmarket setting is consistent with the expected rate for the general population except for nonmelanoma skin cancer (NMSC) and melanoma based on data from the GLOBOCAN database, which is consistent with published data showing higher background rates in psoriasis patients (Reddy SP et al. 2017, Wang X et al. 2020). The two cases identified by the Applicant are described below.

FAERS# 21125098; Manufacturer Case ID 20220743507 (Gastric cancer stage III); Japan:

This spontaneous serious case concerned an elderly male in the eighth decade of life who received treatment with guselkumab (100 mg SC, frequency unspecified) for psoriasis. The patient’s past medical history included benign neoplasm of bladder and bladder neoplasm surgery. Concomitant medications included amlodipine and esomeprazole. Prior to guselkumab treatment, the patient was treated with risankizumab. After approximately 1 year of guselkumab therapy, the patient was switched to secukinumab. Approximately 1.3 years after initiating treatment with guselkumab and approximately 4 months from the last dose of guselkumab, the patient experienced gastric discomfort; gastroscopy was performed, and the patient was diagnosed with gastric cancer (Stage 3B). Approximately 1 month later, the patient was referred to the gastrointestinal surgery department and surgery was performed for gastric cancer. No pathological examination was performed. Approximately 1 month after the surgery, the event of gastric cancer resolved, and the patient was discharged. The Applicant considered the patient’s advanced age and concomitant proton pump inhibitor use as possible risk factors for the event.

Manufacturer Case ID 20230223027 (Malignant melanoma); United States: This nonserious noninterventional case concerned a male of unspecified age who received treatment with guselkumab (100 mg, route and frequency unspecified) for psoriasis. Concomitant medications included topical corticosteroids. The patient was previously treated with secukinumab. Approximately 4 years and 3 months after initiating treatment with guselkumab, the patient was

diagnosed with melanoma in situ. Biopsy on left forehead was performed, which revealed melanoma in situ (lentigo malignant type). The patient underwent excisional biopsies and the event of malignant melanoma resolved. The dose of guselkumab was not changed.

The Empirica Signal analysis described in **Section 3.2** identified multiple MedDRA PTs for malignancies with an EB05 ≥ 2.0 , including *Endometrial cancer* (n=9), *Malignant melanoma* (n=22), and *Hodgkin's disease* (n=9) (see **Appendix C**); these reports contained limited details regarding alternate risk factors for the events. The top 50 MedDRA PTs described in **Table 7** included 77 reports of malignancies from spontaneous sources coded with the PTs *Malignant neoplasm* (n=30) or *Breast cancer* (n=47). We conducted a hands-on review of all 77 spontaneous reports and excluded 73 reports for the following: unassessable because of limited information within the reports (n=63ⁱ), short latency period of < 6 months after guselkumab initiation (n=5), and duplicate reports (n=5). The remaining four FAERS cases described the PT *Breast cancer* (FAERS# 22228270, 23734389, 16485806, 22089810). All four reports described a temporal relation to guselkumab initiation ranging from 15 months to 3 years in female patients with a median age of 48 years (range 37 to 71 years). Concomitant methotrexate use was described in two reports. Guselkumab was withdrawn in one report while patient was receiving chemotherapy.

The four cases of breast cancer reported with guselkumab are described below.

FAERS #22228270; Other serious outcome; Spontaneous; France; 2023: A pharmacist reported that a 71-year-old female was diagnosed with breast adenocarcinoma 4 months after discontinuing guselkumab. The patient was previously treated with methotrexate (duration of therapy not reported) for psoriasis, then received guselkumab (dosage not reported) for 2 years, and was subsequently transitioned to risankizumab. Concomitant medications included betamethasone dipropionate/calcipotriol monohydrate, bisoprolol fumarate, hydrochlorothiazide, pravastatin sodium, and ramipril. No further information was available.

FAERS #23734389; Other serious outcome; Spontaneous; United States; 2024: This report was received from a physician and describes a 42-year-old female who was treated with guselkumab (dosage not reported) for psoriasis and concomitant dupilumab injection for atopic dermatitis. Approximately 3 years after starting guselkumab and dupilumab, the patient was diagnosed with breast cancer. During the patient's course of guselkumab therapy, the dose was reduced because of gastrointestinal symptoms. No further information was available.

FAERS #16485806; Other serious outcome; Spontaneous; United States; 2019: This report was received from a physician and describes a 55-year-old female with psoriasis being treated with guselkumab 100 mg every 8 weeks; she was previously treated with etanercept, infliximab, and ustekinumab. Concomitant medications included citalopram, clobetasol, flupirtine, and pimecrolimus for unreported indications. Nineteen months after guselkumab therapy initiation, the patient was diagnosed with left breast cancer stage IIB/IIA. The patient underwent surgery and chemotherapy, and the guselkumab dose was not changed. The reporter considered the causality between guselkumab and left breast carcinoma as doubtful.

ⁱ Reports provided limited clinical details necessary for causality assessment (e.g., medical history, concomitant medications).

FAERS #22089810; Hospitalization, Life Threatening; Spontaneous; Germany; 2023: A report from a physician describes a 37-year-old female with a history of smoking who was treated with guselkumab (dosage not specified) for psoriasis; the patient was previously treated with methotrexate. Approximately 2 years 6 months after guselkumab initiation, the patient was diagnosed with breast cancer and was hospitalized. Guselkumab was discontinued during chemotherapy. The outcome of the patient's breast cancer was not reported.

3.5.6 Neurologic Adverse Events

We identified reports of neurologic adverse events (e.g., axonal sensorimotor polyneuropathy, peripheral neuropathy, seizures) among the most commonly reported DME PTs and in the medical literature search.

A published case report by Hamadah and Chisti described a 20-year-old male with 10-year history of chronic plaque psoriasis uncontrolled by topical treatments who was initiated on guselkumab. The patient was not taking any other prescription or over the counter medications. One month after the third dose of guselkumab (dosage not reported), the patient developed tremors, which were diagnosed by neurology as enhanced physiologic tremor. Guselkumab was continued for approximately 6 months; during this time, the patient developed numbness in the lower extremities, and he was referred back to the neurology clinic. He was diagnosed with peripheral axonal polyneuropathy and guselkumab was discontinued. The patient's neurologic symptoms improved significantly after drug discontinuation without additional interventions. The reporters considered the possibility of drug induced peripheral neuropathy due to guselkumab (Hamadah and Chisti 2022).

The FAERS search described in **Table 1** retrieved 23 reports coded with the following PTs related to neuropathy: *Peripheral sensorimotor neuropathy*, *Neuropathy peripheral*, *Polyneuropathy*, and *Optic neuropathy*. We conducted a hands-on review of all 23 reports. FAERS #19172343 described the above identified literature report. Of the remaining 22 reports, we excluded 20 from further review (unassessable, n=15^j; unlikely casual association to guselkumab, n=5). The remaining two reports (FAERS# 23448632, 16705896) describing peripheral neuropathy after the second guselkumab dose are summarized below.

FAERS #23448632; Other serious outcome; Spontaneous; United States; 2024: This case was reported by a non-healthcare provider describing a 60-year-old female who initiated guselkumab 100 mg (frequency not reported) for psoriatic arthritis. No concomitant medications were reported. Shortly after the second loading dose of guselkumab, the patient started to feel neuropathy in her hands and feet. The doctor discontinued guselkumab and recommended reporting the adverse event to the Applicant. The neuropathy lasted 5 to 6 weeks after drug discontinuation and "faded away".

FAERS #16705896; Other serious outcome; Spontaneous; Egypt; 2019: A physician described a 35-year-old male patient with severe plaque psoriasis with joint involvement, hypertension, and obesity who received guselkumab pre-filled pen. Concomitant medications included cyclosporin. Two weeks after the 2nd dose of guselkumab, the patient experienced

^j Reports provided limited clinical details necessary for causality assessment (e.g., medical history, concomitant medications).

peripheral neuritis and lack of efficacy. Guselkumab was discontinued due to lack of improvement in skin patches and peripheral neuritis. The physician reported that guselkumab did not work at all on his psoriasis. Peripheral neuritis was reported as recovering.

The PT *Seizure* was the most commonly reported DME PT identified in **Section 3.1.2**. The FAERS search described in **Table 1** retrieved 28 reports coded with the following seizure-related PTs: *Generalised tonic-clonic seizure*, *Epilepsy*, *Seizure*, and *Partial seizures*. We conducted a hands-on review of all 28 reports and excluded 22 from further review (unassessable, n=15; unlikely or unknown causal association, n=7). The remaining six reports described a temporal relation to guselkumab administration; however, the reports contained limited information regarding patient's medical history, concomitant medications, and outcomes for a comprehensive assessment.

4 DISCUSSION

DPV-I evaluated postmarketing adverse events associated with guselkumab using data from the FAERS database, the medical literature, and the Applicant's PSRs. The analysis did not identify any new signals that warrant a change in the labeling for guselkumab at this time. The results of the ongoing Signal Identification (TreeScan) analysis of guselkumab using the SDD will be described in a future review.

Of 4,588 FAERS reports with a serious outcome, the majority (n=3,128; 68 percent) were coded with psoriasis or psoriatic arthropathy as the reason for use; only 76 reports (1.7 percent) were coded with CD or UC as the reason for use. Therefore, the FAERS reports evaluated in this review predominantly reflect the postmarketing safety profile of guselkumab for psoriasis and psoriatic arthritis. It is possible that the postmarketing safety profile of guselkumab in patients with CD and UC is different from that which is described in this review. Moreover, because of the large number of FAERS reports with guselkumab, we focused our review on reports with a serious outcome; the ongoing TreeScan analysis of guselkumab using SSD will evaluate both serious and nonserious adverse events.

Drug-Induced Liver Injury

The 2021 DPV-I review of DILI with guselkumab described 29 FAERS cases of elevations in liver enzymes; the cases in the case series had other risk factors for liver injury or lacked clinical information (e.g., concomitant medication use) needed for assessment of the cases (Weintraub and Reyes 2021).

In this review, we performed a hands-on review of 135 FAERS reports of liver injury with guselkumab use and identified 20 cases that met our case definition and case selection criteria. Most cases reported elevations in liver enzymes or liver toxicity by a healthcare provider but provided limited laboratory values necessary to determine the severity of liver injury. Among the 18 cases that reported guselkumab indication, most (n=15) reported psoriasis, and none reported an indication of inflammatory bowel disease. All cases were assessed as possibly related to guselkumab because they described a temporal relationship between guselkumab initiation and the event but had limited information to assess possible alternate etiologies for liver injury (e.g., alcohol use, concomitant medications, medical history). We identified one fatal case of

DILI with guselkumab (FAERS # 21563531); the case describes a 58-year-old male with concomitant alcohol use who, 16 months after guselkumab initiation, was hospitalized because of end stage liver disease and died. The case provided limited laboratory details and did not provide the indication for guselkumab use.

Guselkumab is currently labeled for elevated liver enzymes in ADVERSE REACTIONS, *Clinical Trials Experience*. In the clinical development program for plaque psoriasis, mild liver enzyme elevations occurred more frequently in the guselkumab group (2.6 percent) than in the placebo group (1.9 percent). In the clinical development program for CD, two possible Hy's Law cases of DILI occurred among patients who received guselkumab at dosages proposed for use in UC. DPV-I will continue to monitor for postmarket reports of hepatic adverse events with guselkumab.

Death

We conducted hands-on review of 120 reports with an outcome of death; the cause of death was unknown or unreported in 116 reports. The four reports that provided a cause of death contained limited information and did not provide details that support a clear association with guselkumab use and the fatal events.

MACE

In our review, *Myocardial infraction* and *Cerebrovascular accident* were the among the most frequently reported PTs with a serious outcome; we identified 24 cases of MACE that described a temporal relation to guselkumab use in psoriasis. The cases described a time to onset ranging from 3 days to 13 months from guselkumab initiation. All 24 cases had one or more underlying cardiovascular risk factors.

Psoriasis may increase risk for MACE in patients with severe disease (Mehta et al. 2011, Li et al. 2012). Moreover, in a Danish nationwide cohort, systemic therapies including biologics and methotrexate have been associated with reduced risk of cardiovascular events in patients with psoriasis (Ahlehoff et al. 2015); both cutaneous and systemic inflammation from uncontrolled psoriasis can increase the risk of MACE in psoriasis patients (Garshick et al. 2021). Because of the inherent elevated risk for MACE in patients with psoriatic disease and the presence of underlying cardiovascular risk factors, we were unable to determine whether guselkumab had a contributory role in the events of MACE described among the 24 cases. Furthermore, postmarketing reports have limited utility to establish a causal relationship with MACE because of the increased underlying risk in this patient population. DPV-I will continue routine pharmacovigilance for MACE.

Device Malfunctions

Device malfunction was among the most frequently reported PTs with guselkumab. Previous analyses of device malfunction with the One-Press and PFS-U devices by CDRH and DMEPA concluded that device-related issues are likely use-related and recommended changes to the

Tremfya labeling and IFU. In our review, we did not identify reports describing device malfunction leading to adverse events with a serious outcome.

Malignancies

In our review, we identified four FAERS reports of breast cancer temporally associated to guselkumab use that had limited information for assessment. In addition, the Applicant's analysis in PSR #14 identified one report of gastric cancer and one report of malignant melanoma in guselkumab-treated patients; the Applicant concluded that, with the exception of NMSC and melanoma, the rates of malignancy were consistent with the expected rate for general population. Of note, patients with psoriasis may be at a higher risk of developing NMSC compared to patients without psoriasis (Wang et al. 2020).

In Phase III clinical studies of guselkumab for the treatment of psoriasis, 18 patients with a history of malignancy (>5 years) excluding NMSC were included. In the 5-year follow-up period, no concerning patterns were identified in the observed incidence of new or recurrent malignancies (Blauvelt A et al. 2023). Guselkumab is not currently labeled for malignancy. Postmarketing reports have limited utility to establish a causal relationship with malignancy because of the long latency period of many malignancies, high background incidence of certain malignancies in the general population, and lack of clinical information regarding the underlying risks within the reports. DPV-I will continue routine pharmacovigilance for malignancies reported with guselkumab.

Neurologic Adverse Events

In our review, we identified reports of neurologic adverse events (i.e., seizure, neuropathy) with a temporal association to guselkumab use. The six reports of seizures had limited information regarding the patient's medical history, concomitant medications, and outcome of the event. We identified two FAERS reports describing peripheral neuropathy occurring after the second dose of guselkumab; of these, one case suggested inadequate psoriasis control leading to discontinuation of guselkumab. Further, a literature case describing axonal sensorimotor polyneuropathy with guselkumab in a 20-year-old male reported worsening of disease while on guselkumab with positive dechallenge following guselkumab discontinuation (Hamadah and Chisti 2022).

In general, the reports of neurological adverse events identified in this review contained insufficient information regarding patients' medical histories, concomitant medications, and outcomes for a comprehensive assessment. These available postmarketing reports do not support updating guselkumab labeling to include seizures or neuropathy at this time. Additionally, autoimmune mechanisms can be a potential risk factor for epilepsy (Ong et al. 2014). DPV-I will open and close a pre-evaluation NISS to document the cases of neuropathy identified in this review and will continue routine pharmacovigilance for reports of neurologic adverse events with guselkumab.

5 CONCLUSION

DPV-I reviewed multiple data sources to identify safety signals for guselkumab, including FAERS reports from January 25, 2019, the medical literature, and the Applicant's periodic safety reports. In this review, DPV-I did not identify any new safety signals warranting a change in labeling for guselkumab at this time. DPV-I will continue routine pharmacovigilance monitoring for guselkumab.

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7 APPENDICES

7.1 APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS Using Empirica Signal

Empirica Signal refers to the software that the Office of Surveillance and Epidemiology (OSE) uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. “Data mining” refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., “potential signals”) in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

Sentinel Distributed Database

The Sentinel Distributed Database (SDD) is a national distributed data network of electronic healthcare databases used by FDA for active surveillance of medical product safety. The SDD includes individuals covered by commercial health plans, integrated delivery systems, and beneficiaries of Medicare and Medicaid. Each Sentinel Data Partner collects person-level information on beneficiaries’ enrollment, demographics, drug dispensing, drug prescribing, and medical encounters, diagnoses and procedures associated with outpatient visits and inpatient

stays, among other variables. The self-controlled risk interval (SCRI) study used data from 13 Sentinel Data Partners. The active comparator study used data from six Sentinel Data Partners where the propensity score models converged. The study period for SCRI and active comparator studies included data from April 23, 2019, through September 30, 2023.

TreeScan and Sentinel Signal Identification

The United States Food and Drug Administration Amendments Act of 2007 mandated the development of signal identification methods in the Sentinel System (Federal Food, Drug, and Cosmetic Act Section 505(k)(3)I(i)(3)(cc) (21 U.S.C. 355(k)(3)I(i)(III)(cc))). This mandate required FDA to create a system to identify safety signals in drugs and therapeutic biologics over their lifetime. Tree-based scan statistic (TreeScan) is a statistical data-mining method, compatible with multiple study designs that can be used to identify potential safety signals from administrative claims and electronic health records databases. The method uses a hierarchical outcome tree to group clinically related diagnostic codes together and applies scan statistics to adjust for multiple testing of correlated hypotheses when screening thousands of outcomes. SDD data included in these studies was evaluated via the Treescan™ software (v.2.1.1) to determine whether there were imbalances in outcome occurrence between an exposure and reference group that rose to the level of statistical significance. Statistical alerts do not, by themselves, constitute a safety signal.

7.2 APPENDIX B. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 26.1)
Blood and lymphatic system disorders	Agranulocytosis Aplastic anaemia Bone marrow failure Coombs negative haemolytic anaemia Coombs positive haemolytic anaemia Haemolytic anaemia Haemolytic uraemic syndrome Microangiopathic haemolytic anaemia Pancytopenia Thrombotic microangiopathy Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes Ventricular fibrillation
Ear and labyrinth disorders	Deafness Deafness bilateral Deafness neurosensory Deafness permanent Deafness transitory Deafness unilateral Ototoxicity Sudden hearing loss
Eye disorders	Blindness Blindness transient Blindness unilateral Optic ischaemic neuropathy Sudden visual loss Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis Pancreatitis haemorrhagic Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death Sudden death
Hepatobiliary disorders	Acute hepatic failure Drug-induced liver injury Hepatic failure Hepatic necrosis Hepatitis fulminant
Immune system disorders	Anaphylactic reaction Anaphylactic shock Anaphylactoid reaction Anaphylactoid shock Immunotoxicity
Infections and infestations	Progressive multifocal leukoencephalopathy Suspected transmission of an infectious agent via product Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure New onset refractory status epilepticus Seizure Serotonin syndrome

System Organ Class	Preferred Terms (MedDRA version 26.1)
	Status epilepticus
Product issues	Product compounding quality issue Product contamination Product contamination chemical Product contamination microbial Product contamination physical Product sterility issue
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalized exanthematous pustulosis AGEP-DRESS overlap Drug reaction with eosinophilia and systemic symptoms Generalised bullous fixed drug eruption Severe cutaneous adverse reaction SJS-TEN overlap Stevens-Johnson syndrome Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

7.3 APPENDIX C. DATA MINING RESULTS FOR GUSELKUMAB

Data Mining Results Using Empirica Signal for Events With EB05 $\geq$ 2.0 Reported With Guselkumab Use, Sorted by Descending EB05 Score					
	MedDRA PT	N	EB05*	EBGM	EB95
1	Drug delivery system malfunction†	29	38.842	53.355	71.859
2	Psoriatic arthropathy	349	16.077	17.59	19.208
3	Psoriasis	331	11.469	12.602	13.83
4	Accidental exposure to product	62	10.835	14.044	17.932
5	Erythrodermic psoriasis	9	8.099	27.87	54.1
6	Lower respiratory tract infection	161	7.454	8.502	9.666
7	Syringe issue†	16	5.627	9.143	16.389
8	Tuberculosis	43	5.029	6.501	8.297
9	Pustular psoriasis	13	4.901	8.298	15.602
10	Device malfunction†	35	4.568	6.075	7.952
11	Needle issue†	27	4.397	6.089	8.264
12	Paternal exposure during pregnancy	9	4.381	9.68	27.555
13	Cellulitis	99	4.314	5.102	6
14	Product label issue	12	4.092	6.78	10.977
15	Dermatitis exfoliative generalised	15	3.777	5.865	8.8
16	Respiratory tract infection	45	3.711	4.768	6.049
17	Product storage error	31	3.592	4.863	6.467
18	Pneumonia	474	3.41	3.679	3.965
19	Sweat gland disorder	4	3.228	36.412	147.457
20	Infective pneumonia (SMQ) [narrow]	585	3.151	3.374	3.61
21	Endometrial cancer	9	3.074	5.454	9.177
22	Kidney infection	36	2.89	3.826	4.987
23	Product leakage†	8	2.883	5.303	9.201
24	Product dose omission issue	244	2.806	3.12	3.463
25	Diverticular perforation	7	2.656	5.104	9.185
26	Injection site reaction	20	2.596	3.79	5.384
27	Therapeutic response decreased	33	2.461	3.299	4.349
28	Immune-mediated/autoimmune disorders (SMQ) [narrow]	778	2.357	2.501	2.652
29	Device issue†	32	2.337	3.148	4.167
30	Malignant melanoma	22	2.275	3.262	4.563
31	Pemphigoid	13	2.173	3.481	5.349
32	Latent tuberculosis	7	2.16	4.121	7.3
33	Hodgkin's disease	9	2.065	3.646	6.065

*An EB05 $\geq$ 2 indicates with 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."

†Medications with drug device combinations are compared against all other drugs, with or without a device, in the database. Hence, a high EB05 score for PTs related to device issues may not represent disproportional reporting of device-related issues.

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred Term

7.4 APPENDIX D. FAERS LINE LISTING OF DRUG-INDUCED LIVER INJURY CASE SERIES (N=20)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) *
1	05-OCT-2021	19920529	2	US-JNJFOC- 20210953643	PERIODI C	31	Male	USA	OT
2	25-JUL-2023	22746955	2	FR-JNJFOC- 20230749467	15-DAY	34	Male	FRA	OT
3	25-MAR-2022	20637817	2	US-JNJFOC- 20220324350	PERIODI C	39	Male	USA	OT
4	21-NOV-2023	23208397	2	CA-JNJFOC- 20231134301	15-DAY	42	Male	CAN	HO
5	07-AUG-2023	22791325	1	FR-JNJFOC- 20230811169	15-DAY	43	Female	FRA	OT
6	30-NOV-2023	23246771	1	US-JNJFOC- 20231159720	PERIODI C	44	Male	USA	OT
7	03-MAR-2023	22058216	1	CA-JNJFOC- 20200123078	15-DAY	50	Female	CAN	OT, HO
8	26-APR-2023	22253472	1	US-JNJFOC- 20230449438	15-DAY	50	Male	USA	HO
9	12-MAY-2022	20820104	7	JP-JNJFOC- 20220523128	15-DAY	54	Male	JPN	OT
10	24-MAY-2022	20865353	1	CH-JNJFOC- 20220526316	15-DAY	57	Male	CHE	OT
11	08-NOV-2022	21563531	1	CA-JNJFOC- 20220935861	15-DAY	58	Male	CAN	HO, DE
12	02-MAR-2022	20536648	1	JP-JNJFOC- 20210941383	15-DAY	60	Male	JPN	OT
13	04-MAY-2022	20782157	3	JP-JNJFOC- 20220330093	15-DAY	72	Male	JPN	HO
14	15-FEB-2024	23527213	1	US-JNJFOC- 20240208031	PERIODI C			USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
15	23-AUG-2022	21242922	1	US-JNJFOC- 20220820864	PERIODI C			USA	
16	28-JUN-2022	21018601	2	BR-JNJFOC- 20220645104	15-DAY		Female	BRA	OT
17	25-MAY-2023	22366933	2	US-JNJFOC- 20230550823	PERIODI C		Female	USA	OT
18	25-JUL-2023	22745211	2	US-JNJFOC- 20230742784	PERIODI C		Female	USA	
19	22-DEC-2022	21765843	4	JP-JNJFOC- 20221245514	15-DAY		Male	JPN	OT
20	27-APR-2022	20755306	1	US-JNJFOC- 20220431018	PERIODI C	31	Male	USA	OT
*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter, and are coded as nonserious. A case can have more than one serious outcome. Abbreviations: DE=death, HO=hospitalization, OT=other medically significant									

7.5 APPENDIX E. FAERS LINE LISTING OF MAJOR ADVERSE CARDIOVASCULAR EVENTS CASE SERIES (N=24)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) *
1	12-SEP-2023	22932393	4	TR-JNJFOC- 20230917596	Expedited (15-Day)	40	Female	TUR	LT
2	12-JUN-2020	17890379	3	JP-JNJFOC- 20200609324	Expedited (15-Day)	41	Female	JPN	HO
3	14-OCT-2020	18384010	4	FR-JNJFOC- 20201019680	Expedited (15-Day)	41	Male	FRA	OT, HO
4	28-FEB-2022	20525815	1	BG-JNJFOC- 20211152893	Expedited (15-Day)	48	Male	BGR	HO
5	14-MAY-2020	17788287	2	BE-JNJFOC- 20190616517	Expedited (15-Day)	49	Male	BEL	OT
6	19-SEP-2023	22955815	2	FR-JNJFOC- 20230932591	Expedited (15-Day)	49	Male	FRA	HO
7	25-FEB-2020	17458312	5	ES-JNJFOC- 20200220031	Expedited (15-Day)	50	Female	ESP	HO, OT
8	03-DEC-2019	17107542	3	FI-JNJFOC- 20191143933	Expedited (15-Day)	53	Female	FIN	HO
9	06-FEB-2022	20435393	5	AR-JNJFOC- 20211054665	Expedited (15-Day)	54	Male	ARG	HO
10	02-NOV-2023	23136290	3	FR-JNJFOC- 20231076866	Expedited (15-Day)	56	Female	FRA	HO
11	22-DEC-2021	20219945	2	CN-JNJFOC- 20211244910	Expedited (15-Day)	57	Female	CHN	DE, LT
12	23-SEP-2019	16840716	2	ES-JNJFOC- 20190921199	Expedited (15-Day)	59		ESP	HO
13	25-MAY-2020	17820579	3	FR-ABBVIE- 20K-056- 3410387-00	Expedited (15-Day)	62	Female	FRA	HO
14	04-JUN-2019	16390222	2	IT-JNJFOC- 20190541854	Expedited (15-Day)	64	Male	ITA	HO, LT
15	03-APR-2019	16153453	2	PL-JNJFOC- 20160620991	Expedited (15-Day)	65	Female	POL	HO

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
16	29-NOV-2023	23238161	2	SK-JNJFOC- 20231162151	Expedited (15-Day)	67	Female	SVK	OT, HO
17	02-FEB-2021	18819951	3	US-JNJFOC- 20210143530	Expedited (15-Day)	71	Male	USA	DE
18	18-JUN-2021	19433349	4	JP-JNJFOC- 20210632608	Expedited (15-Day)	73	Male	JPN	HO
19	03-DEC-2019	17108103	3	JP-JNJFOC- 20191146804	Expedited (15-Day)	81	Male	JPN	HO
20	13-AUG-2019	16697842	1	GB-JNJFOC- 20190810176	Expedited (15-Day)	82	Male	GBR	OT
21	06-SEP-2019	16780820	3	JP-JNJFOC- 20190836894	Expedited (15-Day)	84	Male	JPN	HO
22	08-FEB-2024	23499306	2	CA-JNJFOC- 20240186137	Expedited (15-Day)			CAN	OT
23	01-FEB-2022	20408032	2	US-JNJFOC- 20220157234	Expedited (15-Day)		Female	USA	LT
24	15-APR-2024	23743634	2	US-JNJFOC- 20240423739	Expedited (15-Day)		Female	USA	LT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those that are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: DE=death, HO=hospitalization, LT=life threatening, OT=other medically significant

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STATISTICAL REVIEW AND EVALUATION

FILING REVIEW OF A BLA

NDA/BLA #: BLA 761061
Supplement #: 21
Related IND #: 140330
Product Name: Tremfya (guselkumab); 200 mg IV q4W (induction), 100 mg SC q8w (maintenance), 200 mg q4W (maintenance)
Indication(s): Ulcerative Colitis
Applicant: Janssen Research and Development
Dates: Received: 3/11/24
PDUFA: 9/11/24
Review Priority: Priority
Biometrics Division: DB3
Statistical Reviewer: Joshua Sampson
Concurring Reviewers: Paul Imbriano
Medical Division: Gastroenterology
Clinical Team: Jaime Wolfe
Suruchi Batra
Project Manager: Andrew Chi

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

The efficacy for guselkumab is based on two Phase 3 studies (Induction Study 2 and Maintenance Study) and a Phase 2b induction dose-ranging study (Induction Study 1) conducted under a single protocol, CNTO1959UCO3001 (QUASAR). For the two induction studies, subjects were randomized to either treatment with guselkumab or placebo with the primary endpoint evaluated at Week 12. For the maintenance study, clinical responders who received guselkumab during the induction studies were randomized to either treatment with guselkumab or placebo with the primary endpoint evaluated at Week 44. Currently, Induction Study 2 and Maintenance Study are positioned as the primary trials for providing substantial evidence of efficacy. Details about the trials are provided in the tables below.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size**	Endpoint/Analysis	Preliminary Findings
CNTO1959UCO3001 Induction Study 1	MC, R, DB, PG, PC trial	Guselkumab 200 mg/101	Primary: Clinical Response at Week	Primary: Placebo: 27.6%

(IS-1)	(12 wks)	Guselkumab 400 mg/107	12 Key Secondary: Clinical Remission at Week 12	200 mg: 61.4% 400 mg: 60.7%
		Placebo/105		Secondary: Placebo: 9.5% 200 mg: 25.7% 400 mg: 25.2%
CNT01959UCO3001 Induction Study 2 (IS-2)	MC, R, DB, PG, PC trial (12 wks)	Guselkumab 200 mg/421	Primary: Clinical Remission at Week 12	Placebo: 7.9% 200 mg: 22.6%
		Placebo/280		
CNT01959UCO3001 Maintenance Study	MC, R, DB, PG, PC trial (44 wks)	Guselkumab 200 mg/190	Primary: Clinical Remission at Week 44	Placebo: 18.9% 100 mg: 45.2% 200 mg: 50.0%
		Guselkumab 100 mg/188		
		Placebo/190		

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

** Full Analysis Set

Table 2: Secondary Endpoint for Study CNT01959UCO3001 Induction Study 1 (Full Analysis Set)

	Placebo IV	Guselkumab 200 mg IV	Guselkumab 400 mg IV
N	105	101	107
Subjects in clinical remission at Week 12	10 (9.5%)	26 (25.7%)	27 (25.2%)
Adjusted treatment difference ^a (95% CI)		16.3 (6.3, 26.3)	15.7 (6.0, 25.4)
p-value ^{b, c}		0.002	0.002

Source: Clinical Study Report Table 6 (page 86)

^a The adjusted treatment difference is the common risk differences with Cochran-Mantel-Haenszel (CMH) weights for ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No).

^b The p-values were based on the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by ADT-failure status (Yes/No)

and concomitant use of corticosteroids at baseline (Yes/No).

^c The protocol did not define a multiplicity controlling procedure for the secondary endpoints.

Table 3: Primary Endpoint for Study CNT01959UCO3001 Induction Study 2 (Full Analysis Set)

	Placebo IV	Guselkumab 200 mg IV
N	280	421
Subjects in clinical remission at Week 12	22 (7.9%)	95 (22.6%)
Adjusted treatment difference ^a (95% CI)		14.9 (9.9, 19.9)
p-value ^b		<0.001

Source: Clinical Study Report Table 5 (page 92)

^a The adjusted treatment difference is the common risk differences with Cochran-Mantel-Haenszel (CMH) weights for ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No).

^b The p-values were based on the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No).

Table 4: Primary Endpoint for Study CNTO1959UCO3001 Maintenance Study (Full Analysis Set)

	Placebo SC	Guselkumab 100 mg SC	Guselkumab 200 mg SC
N	190	188	190
Subjects in clinical remission at Week 44	36 (18.9%)	85 (45.2%)	95 (50.0%)
Adjusted treatment difference ^a (95% CI)		25.2 (16.4, 33.9)	29.5 (20.9, 38.1)
p-value ^b		<0.001	<0.001

Source: Clinical Study Report Table 7 (page 85)

^a The adjusted treatment difference is the common risk differences with Cochran-Mantel-Haenszel (CMH) weights for ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No).

^b The p-values were based on the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by ADT-failure status (Yes/No) and concomitant use of corticosteroids at baseline (Yes/No).

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Yes
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	Yes
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes

3. Electronic Data Assessment

[Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.]

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\EVSPROD\bla761061\0700\m5\datasets\
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM, ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADEFF
Are the <i>analysis datasets</i> sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			
Safety and efficacy were investigated for gender, racial, ethnic, and geriatric subgroups.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application appears to be free from any other deficiency that render the application unreviewable,	X			

Content Parameter	Yes	No	NA	Comments
administratively incomplete, or inconsistent with regulatory requirements.				

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

5.2. Information Requests/Review Issues

The Sponsor's original submission did not include subgroup analyses for the primary endpoint with subgroups defined by ethnicity, age (< 65, ≥ 65), and race. An Information Request (IR) was sent to the Sponsor on March 29, 2024 and the Sponsor provided the requested subgroup analyses in their IR response dated April 3, 2024.

6. Advisory Committee

	Response/Comments
If the Advisory Committee Decision Aid (ACDA) is required for this application (it is required for a new molecular entity or original BLA), do you have any comments relevant to the completion of this document?	No
Has the review division determined that an Advisory Committee (AC) meeting is needed?	☐ Yes ☒ No ☐ To be Determined
If an AC meeting may be held for this application, are there any areas of expertise that may be important for AC statistician(s) to have?	No

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/s/

JOSHUA N SAMPSON
04/10/2024 04:05:10 PM

PAUL M IMBRIANO
04/11/2024 08:54:11 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
BLA761061Orig1s021

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: August 8, 2024

To: Andrew Chi, Regulatory Project Manager,
Division of Gastroenterology (DG)

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TREMFYA®(guselkumab) injection, for subcutaneous use; TREMFYA PEN®(guselkumab) injection, for subcutaneous use; TREMFYA®(guselkumab) injection, for intravenous use

BLA: 761061, S-21

Background:

In response to DG's consult request dated March 13, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for supplement 21 for TREMFYA® (guselkumab). This supplement seeks the approval of TREMFYA for the treatment of adult patients with moderately to severely active UC and contains three new drug product presentations for the proposed UC indication.

PI/Medication Guide/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 2, 2024, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on August 6, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

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/s/

MONTHERSON L SAINT JUSTE
08/08/2024 04:20:59 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 27, 2024
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761061/S-021
Product Name, Dosage Form, and Strength:	Tremfya (guselkumab) injection Prefilled syringe: 200 mg/2mL (proposed) Vial: 200 mg/20 mL (10 mg/mL) (proposed) Tremfya Pen (guselkumab) injection Prefilled Pen: 200 mg/2 mL (proposed)
Applicant Name:	Janssen Research & Development, LLC (Janssen)
FDA Received Date:	August 23, 2024
TTT ID #:	2024-8735-1
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Janssen submitted revised container labels and carton labeling received on August 23, 2024 for Tremfya and Tremfya Pen. The Division of Gastroenterology (DG) requested that we review the revised container labels and carton labeling for Tremfya and Tremfya Pen (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Janssen implemented all our container label and carton labeling recommendations and we have no additional recommendations at this time.

^a Abraham, S. Label and Labeling Review for Tremfya and Tremfya Pen (BLA 761061/S-021). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 2. TTT ID: 2024-8735.

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/s/

SHERLY ABRAHAM
08/27/2024 04:25:56 PM



BLA 761061/S-021

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

ATTENTION: Jenna Giacchi, MS
Associate Director, Global Regulatory Affairs

Dear Jenna Giacchi:

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

We also refer to your correspondence dated and received April 10, 2024, requesting review of your proposed proprietary name, Tremfya.

We have completed our review of the proposed proprietary name, Tremfya and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 10, 2024, submission are altered prior to approval of the supplemental marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*¹
- *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027*²

¹ 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>.

² <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm>

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Alvis Dunson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-6400. For any other information regarding this application, contact Andrew Chi, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8597.

Sincerely,

{See appended electronic signature page}

Mishale Mistry, PharmD, MPH
Division Director
Division of Medication Error Prevention and Analysis I
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MISHALE P MISTRY
07/08/2024 12:19:47 PM