CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761061Orig1s007

Trade Name:	TREMFYA
Generic or Proper Name:	guselkumab
Sponsor:	Janssen Biotech, Inc.
Approval Date:	July 13, 2020
Indication:	This Prior Approval supplemental biologics application provides for the treatment of adult patients with active psoriatic arthritis.

CENTER FOR DRUG EVALUATION AND RESEARCH

761061Orig1s007

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

BLA 761061/S-007

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
800/850 Ridgeview Drive
Horsham, PA, 19044

Attention: Manomi Tennakoon, PhD
Director, Global Regulatory Affairs, Immunology

Dear Dr. Tennakoon:

Please refer to your supplemental biologics license application (sBLA), dated September 13, 2019, received September 13, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tremfya (guselkumab) Injection.

This Prior Approval supplemental biologics application provides for the new indication: Treatment of adult patients with active psoriatic arthritis.

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.

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 (text for the Prescribing Information, Instructions 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.

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

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 5 years of age because necessary studies are impossible or highly impracticable due to the rarity of the diagnosis in this age group.

We are deferring submission of your pediatric study for ages 5 years to 17 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act is required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3899-1 Provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age.

Study/Trial Completion: 10/2023
Final Report Submission: 04/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit the protocol(s) to your IND 124177, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. 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.

PROMOTIONAL MATERIALS

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

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

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

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).

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

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov, MD
Director (Acting)
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

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/

NIKOLAY P NIKOLOV
07/13/2020 05:18:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	07/2020
Dosage and Administration (2.2)	07/2020
Warnings and Precautions, Hypersensitivity (5.1)	06/2020
Warnings and Precautions, Infections (5.2)	07/2020
Warnings and Precautions, Pre-treatment Evaluation for TB (5.3)	07/2020

----------INDICATIONS AND USAGE----------

TREMFYA is an interleukin-23 blocker 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)

----------DOSAGE AND ADMINISTRATION----------

Plaque Psoriasis
100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. (2.1)

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). (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/mL in a single-dose prefilled syringe or single-dose One-Press patient-controlled injector. (3)

----------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. 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)

----------ADVERSE REACTIONS----------

Most common (≥1%) adverse reactions associated with TREMFYA include upper respiratory infections, headache, injection site reactions, arthralgia, bronchitis, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (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: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

TREMFYA® is indicated for the treatment of adults 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.

2 DOSAGE AND ADMINISTRATION

2.1 Plaque Psoriasis

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

2.2 Psoriatic Arthritis

TREMFYA is administered by subcutaneous injection. The recommended dose 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).

2.3 Important Administration Instructions

Administer TREMFYA subcutaneously. Each prefilled syringe or One-Press injector is for single-dose only. Instruct patients to inject the full amount (1 mL), which provides 100 mg of TREMFYA.

Do not inject TREMFYA into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis *[see Instructions for Use]*.

TREMFYA is intended for use under the guidance and supervision of a physician. TREMFYA may be administered by a health care professional, or a patient may self-inject after proper training in subcutaneous injection technique.

The TREMFYA *Instructions for Use* contains more detailed patient instructions on the preparation and administration of TREMFYA *[see Instructions for Use]*.

2.4 Preparation for Use of TREMFYA Prefilled Syringe or One-Press Injector

Before injection, remove TREMFYA prefilled syringe or One-Press injector from the refrigerator and allow TREMFYA to reach room temperature (30 minutes) without removing the needle cap.

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 cloudy. TREMFYA does not contain preservatives; therefore, discard any unused product remaining in the prefilled syringe or One-Press injector.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/mL in a single-dose prefilled syringe or single-dose One-Press patient-controlled injector.

TREMFYA is a clear and colorless to light yellow solution that may contain small translucent particles.

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 postmarket 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 ≤ 0.2%. A similar risk of infection was seen in placebo-controlled trials in subjects with psoriatic arthritis. 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 and 71 subjects with psoriatic arthritis 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

Prior to initiating therapy with TREMFYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA. 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:

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

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 ≥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 (≥ 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.

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with TREMFYA. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to guselkumab across indications or with the incidences of antibodies to other products may be misleading.

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 subject 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.

6.3 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, TNFα, 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 by calling 1-877-311-8972.

Risk Summary

There are no available data on TREMFYA use in pregnant women to inform a drug associated risk of adverse developmental 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 30 times the maximum recommended human dose (MRHD). Neonatal deaths were observed at 6- to 30-times the MRHD *(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 estimated 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.

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 up to 50 mg/kg (30 times the MRHD based on a mg/kg comparison) from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (6 times the MRHD based on a mg/kg comparison) and three monkeys administered guselkumab at 50 mg/kg/week (30 times the MRHD based on a mg/kg comparison). 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. Maternal IgG is known to be present in human milk. 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.

8.3 Pediatric Use

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

8.4 Geriatric Use

Of the 3406 subjects with plaque psoriasis or psoriatic arthritis exposed to TREMFYA, a total of 185 subjects were 65 years or older, and 13 subjects were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger subjects who received TREMFYA. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

11 DESCRIPTION

Guselkumab, an interleukin-23 blocker, is a human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody. Guselkumab is produced in a mammalian cell line using recombinant DNA technology.

TREMFYA (guselkumab) injection is a sterile, preservative free, clear, colorless to light yellow solution that may contain small translucent particles. TREMFYA is supplied as a single-dose solution in a 1 mL glass syringe with a 27G, half inch fixed needle assembled in a passive needle guard delivery system or One-Press patient-controlled injector for subcutaneous use.

Each TREMFYA 1 mL prefilled syringe or One-Press patient-controlled injector contains 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guselkumab is a human monoclonal IgG1λ 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.

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± 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.

Distribution

In subjects with plaque psoriasis, apparent volume of distribution was 13.5 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.

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, 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)]*.

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 (15 times the MRHD based on a mg/kg comparison).

No effects on fertility parameters were observed after female guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly (60 times the MRHD based on a mg/kg comparison).

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

Table 2: Efficacy Results at Week 16 in Adults with Plaque Psoriasis (NRI[a])

	PsO1		PsO2	
Endpoint	**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 3 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 3: Efficacy Results in Adults with Plaque Psoriasis (NRI[a])

	PsO1		PsO2	
Endpoint	**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]). Patients 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-TNFα) agents whereas in PsA2 all subjects were biologic naïve. Approximately 58% of subjects from both trials had concomitant methotrexate (MTX) use. Patients 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 ≥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 4 and 5). Similar responses

were seen regardless of prior anti-TNFα 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 4: Percent of Subjects with ACR Responses in PsA1

	Placebo (N=126)	TREMFYA 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.

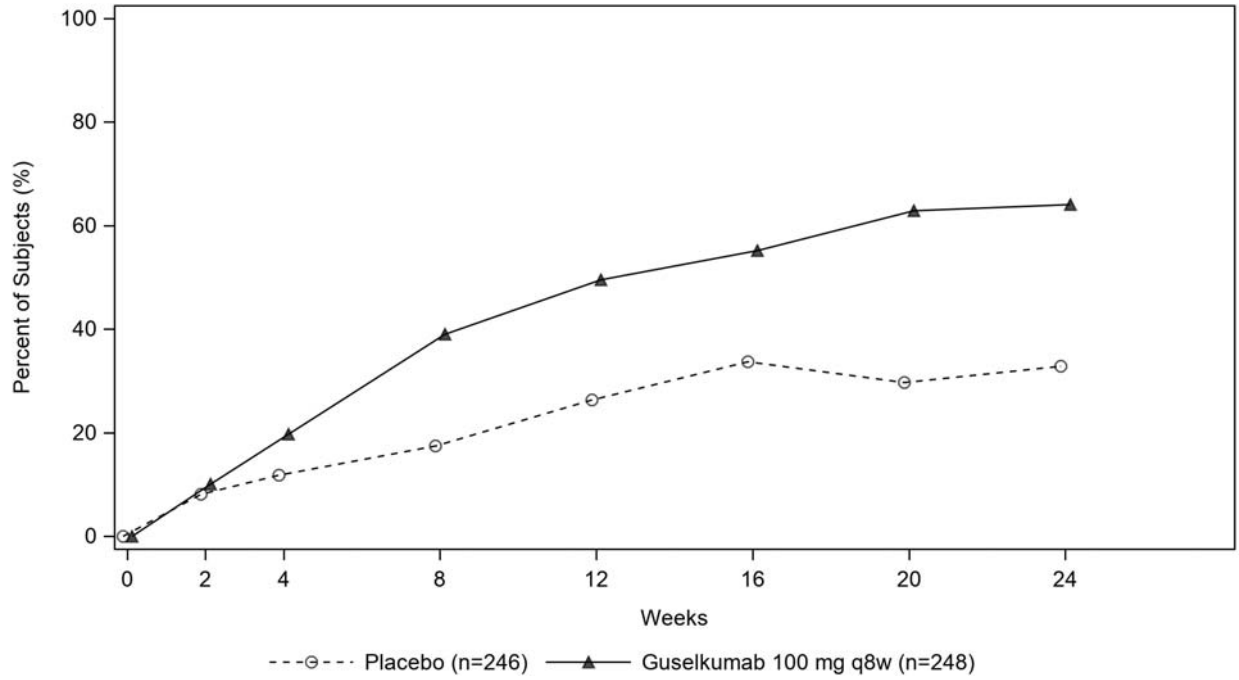
Table 5: Percent of Subjects with ACR Responses in PsA2

	Placebo (N=246)	TREMFYA 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 6.

Table 6: 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 patients 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TREMFYA (guselkumab) Injection is a clear and colorless to light yellow solution that may contain small translucent particles. TREMFYA is supplied as:

- Single-dose 100 mg/mL prefilled syringe (NDC: 57894-640-01)
- Single-dose 100 mg/mL One-Press patient-controlled injector (NDC: 57894-640-11)

16.2 Storage and Handling

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

- Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF).
- 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.

Keep out of reach of children.

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)]*.

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 *[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 to inject their dose as soon as they remember. They should then take their next dose at the appropriate scheduled time.

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

Medication Guide
TREMFYA® (trem fye´ ah)
(guselkumab)
injection, for subcutaneous 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).

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.
- 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?

See the detailed "Instructions for Use" that comes with TREMFYA for information on how to prepare and inject a dose of TREMFYA, and how to properly throw away (dispose of) used TREMFYA prefilled syringes or One-Press injectors.

- 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.

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:

- upper respiratory infections
- joint pain (arthralgia)
- fungal skin infections
- headache
- diarrhea
- herpes simplex infections
- injection site reactions
- stomach flu (gastroenteritis)
- 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.

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: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection

Not made with natural rubber latex.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, U.S. License Number 1864
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: 07/2020

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.

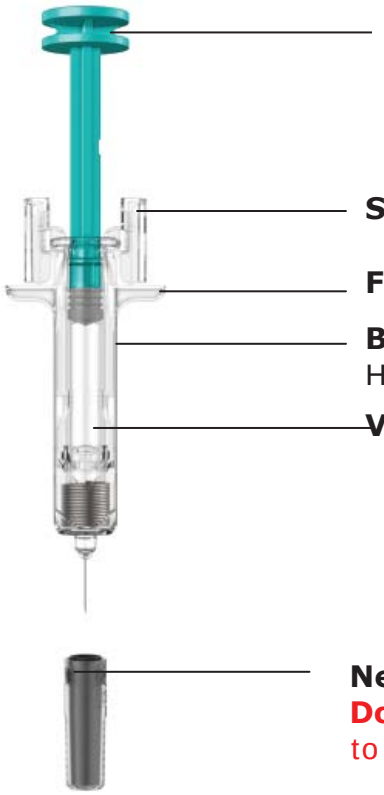
Keep TREMFYA prefilled syringe and all medicines out of reach of children.

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



Plunger
Do not hold or pull plunger at any time.

Safety guard

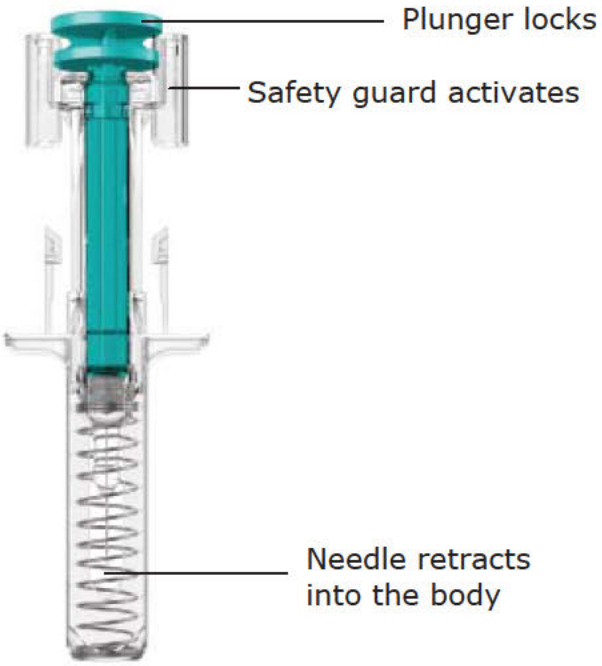
Finger flange

Body
Hold syringe body **below** finger flange.

Viewing window

Needle cover
Do not remove until you are ready to inject TREMFYA (See Step 2).

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

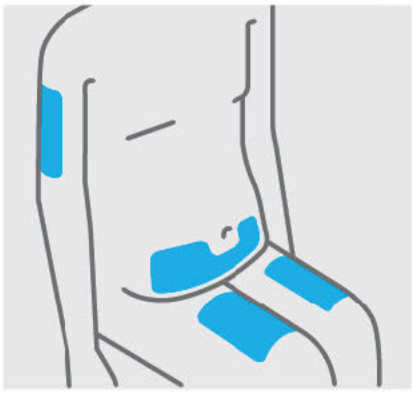
Remove your TREMFYA prefilled syringe carton from the refrigerator.
Keep the prefilled syringe in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

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.

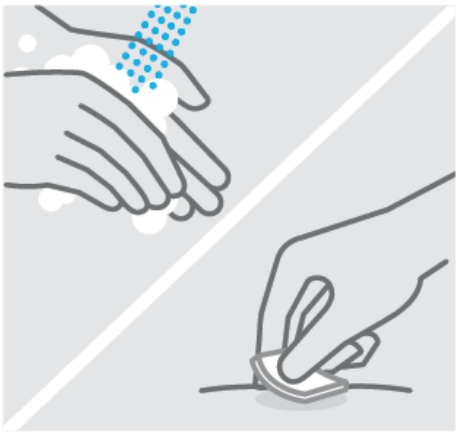


Choose injection site

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.

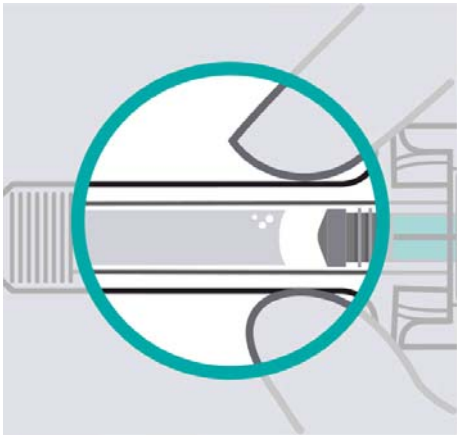


Clean injection site

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.



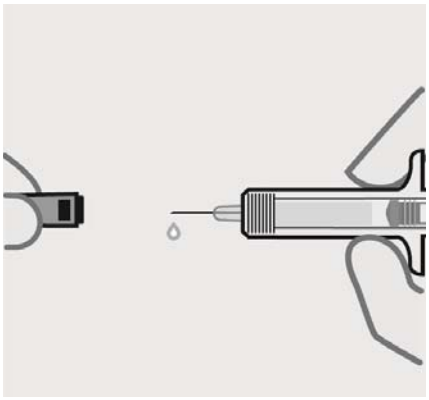
Inspect liquid

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

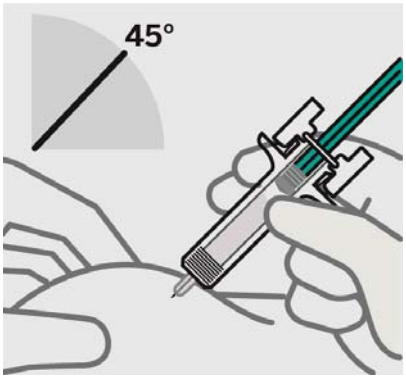
Hold your prefilled syringe by the body and pull needle cover straight off.
It is normal to see a drop of liquid.

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.

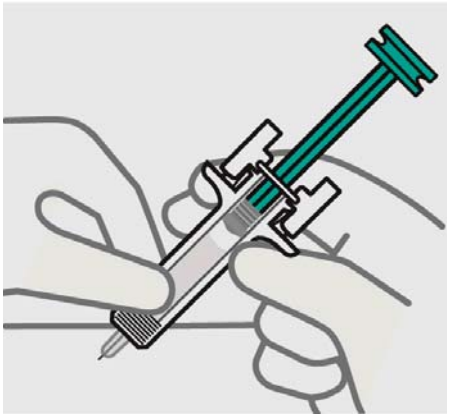
Do not touch plunger or area above finger flange as this may cause the needle safety device to activate.

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**

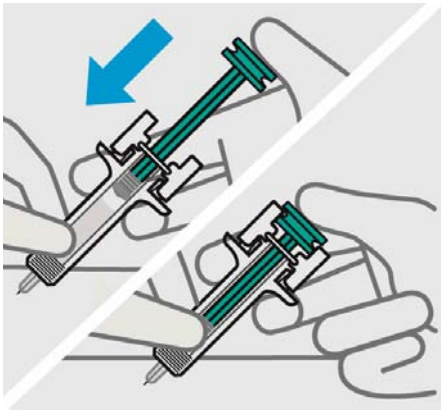
the skin and not into the muscle.

Insert needle with a quick, dart-like motion.



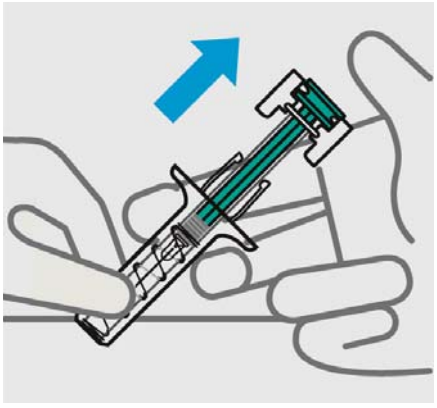
Release pinch and reposition hand

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

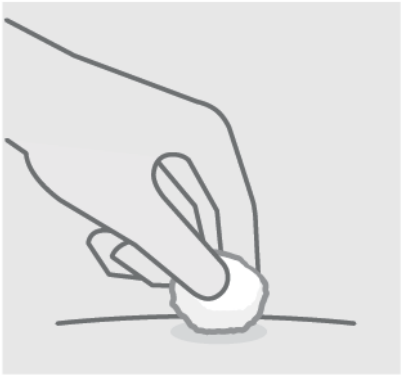
Dispose of your prefilled syringe

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

janssen

Instructions for Use
TREMFYA®
(trem fye' ah)
(guselkumab)
One-Press Patient-Controlled Injector

SINGLE-DOSE

Important

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

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

Do not shake your One-Press injector.

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

Reference ID: 4640103

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

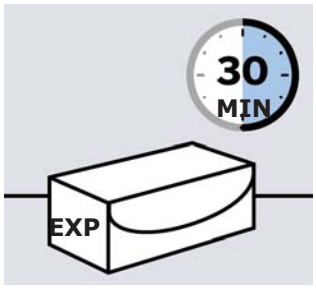
You will need:

- **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. Prepare for your injection



Inspect carton

Remove your One-Press injector carton from the refrigerator.

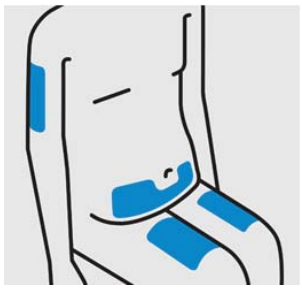
Keep your One-Press injector in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

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 perforations on the carton are broken. Call your healthcare provider or pharmacist for a new One-Press injector.

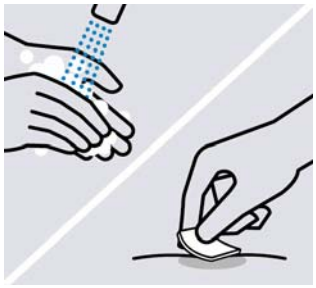


Choose injection site

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.

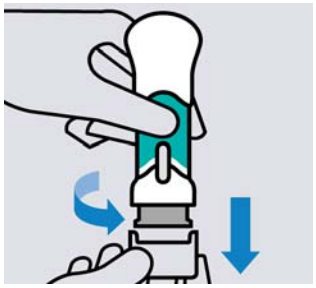
Inspect liquid in window

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 or discolored, or has large particles. Call your healthcare provider or pharmacist for a new One-Press injector.

2. Inject TREMFYA using the One-Press injector



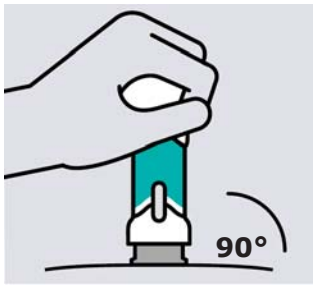
Twist and pull off bottom cap

Keep hands away from the needle guard after the cap is removed.

Inject TREMFYA within 5 minutes of removing the cap.

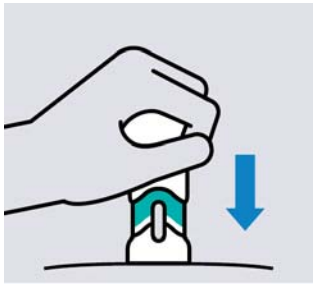
Do not put the cap back on, this could damage the needle.

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 on skin

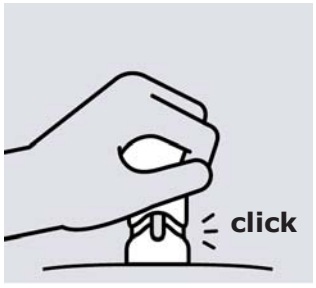
Position the One-Press injector straight onto the skin (about 90 degrees relative to injection site).



Push handle straight down

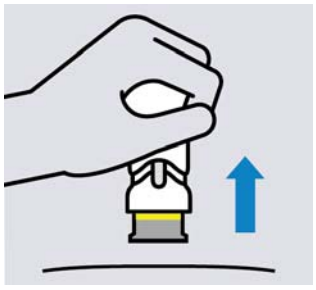
Medication injects as you push. Do this at a speed that is comfortable for you.

Do not lift the One-Press injector during the injection. The needle guard will lock and the full dose will not be delivered.



Complete injection

Injection is complete when the handle is pushed all the way down, you hear a click, and the teal body is no longer visible.



Lift straight up

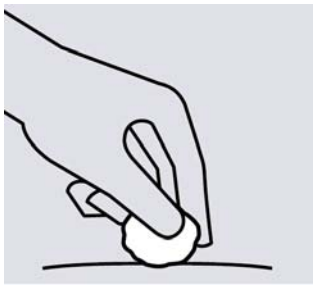
The yellow band indicates that the needle guard is locked.

3. After your injection

Dispose of your One-Press injector

Put your used One-Press injector in an FDA-cleared 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 "How should I dispose of the used 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.

How should I dispose of the used 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

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: January 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761061Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	761061 S007; S(b) (4)
Priority or Standard	Standard
Submit Date(s)	09/13/2019
Received Date(s)	09/13/2019
PDUFA Goal Date	07/13/2020
Division/Office	DRTM/ OII
Review Completion Date	See electronic stamp date
Established/Proper Name	Guselkumab
(Proposed) Trade Name	Tremfya
Pharmacologic Class	Interleukin-23 blocker
Code name	L04AC16
Applicant	Janssen Biotech, Inc.
Doseage form	Subcutaneous injection
Applicant proposed Dosing Regimen	S007: 100 mg at Week 0, Week 4 and every 8 weeks thereafter, or (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with active psoriatic arthritis
Recommendation on Regulatory Action	Approval of supplement 007 Supplement (b) (4) was withdrawn prior to action
Recommended Indication(s)/Population(s)	Adult patients with active psoriatic arthritis
Recommended Dosing Regimen	100 mg at Week 0, Week 4 and every 8 weeks thereafter

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sadaf Nabavian, PharmD
Nonclinical Reviewer	Carol Galvis, PhD
Nonclinical Team Leader	Carol Galvis, PhD
Office of Clinical Pharmacology Reviewer(s)	Dipak Pisal, PhD, MS
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, MD, PhD
Clinical Reviewer	Nadia Habal, MD
Clinical Team Leader	Rachel Glaser, MD
Statistical Reviewer	Kyunghee Song, PhD
Statistical Team Leader	Rebecca Rothwell, PhD
Cross-Disciplinary Team Leader	Rachel Glaser, MD
Division Director (OCP)	Chandrahas Sahajwalla, PhD
Deputy Division Director (OB)	Gregory Levin, PhD
Division Director (DRTM)	Nikolay Nikolov, MD

Additional Reviewers of Application

OBP	Kelly Ballard, MS (SRBPM)/Cindy Osborn, PhD (reviewer)/Willie Wilson, PhD (TL)
Deputy Director for Safety (DRTM)	Ozlem Belen, MD, MPH (DD) June Germain, MS, MT (ASCP), RAC (Safety RPM)
OPDP	Adewale Adeleye, PharmD, MBA
OSI	Tina Chang Suyoung, MD (reviewer)/Lu Min, MD, MPH (TL)/Kasssa Ayalew, MD, MPH (Branch Chief)
SRPM	Saharat Patanavanich, PharmD, BCACP (SRPM)/Nichelle Rashid (SRPM TL)
OSE/DMEPA	Sarah Vee, PharmD (reviewer)/Ashlee Lowery, PharmD, BCCCP (TL)
CDRH	Suzanne Hudak, PhD (reviewer)/Rumi Young, PhD (TL)
PLT/DMPP	Sharon Williams, MSN, BSN, RN (reviewer)/Marcia Williams, PhD (TL)

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dipak Pisal, MS. PhD.	OCP/DIIP	Section:6	Select one: _X__ Authored ___ Approved
	Signature: Dipak Pisal -S Digitally signed by Dipak Pisal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dipak Pisal -S, 0.9.2342.19200300.100.1.1=2001808716 Date: 2020.07.12 18:58:12 -04'00'			
Clinical Pharmacology Team Leader	Jianmeng Chen, MD, PhD	OCP/DIIP	Section:6	Select one: ___ Authored _X__ Approved
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Pharmacometrics Reviewer	Junshan Qiu,PhD	OCP/DPM	Section: Appendix 15.3	Select one: __X_ Authored ___ Approved
	Signature: Junshan Qiu -S Digitally signed by Junshan Qiu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Junshan Qiu -S, 0.9.2342.19200300.100.1.1=2000348577 Date: 2020.07.13 08:55:13 -04'00'			
Pharmacometrics Team Leader	Jingyu Yu, PhD	OCP/DPM	Section:Appendix 15.3	Select one: ___ Authored _X__ Approved
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Clinical Reviewer	Nadia Habal	OII/DRTM	Sections: 1.1, 2, 3, 7, 8.1, 8.4, 9-13	Select one: _X_ Authored ___ Approved
	Signature: Nadia Habal -S Digitally signed by Nadia Habal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nadia Habal -S, 0.9.2342.19200300.100.1.1=0014318202 Date: 2020.07.13 09:41:01 -04'00'			
Clinical Team Leader	Rachel Glaser	OII/DRTM	Sections: All	Select one: _X__ Authored: 1 _X__ Approved
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Division Director (Clinical)/Division Signatory	Nikolay Nikolov	OII/DRTM	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2020.07.12 18:25:20 -04'00'			
Statistical Reviewer	Kyunghee Song	OB/DB2	Sections: 7, 8.1-8.3, 8.5-8.6	**Select one:** _X__ Authored ___ Approved
	Signature: Kyunghee K. Song Digitally signed by Kyunghee K. Song DN: cn=Kyunghee K. Song, o, ou, email=kyunghee.song@fda.hhs.gov, c=US Date: 2020.07.13 07:09:24 -04'00'			
Statistical Team Leader	Rebecca Rothwell	OB/DB3	Sections: 1.2-1.3, 7, 8.1-8.3, 8.5-8.6, 14	**Select one:** ___ Authored _X__ Approved
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Deputy Division Director (OB)	Gregory Levin	OB/DB3	Sections: 1.2-1.3, 8.6	**Select one:** ___ Authored _X__ Approved
	Signature: Gregory P. Levin -S Digitally signed by Gregory P. Levin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001127703, cn=Gregory P. Levin -S Date: 2020.07.13 07:52:20 -04'00'			

Glossary

ACR	American College of Rheumatology
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BLA	Biologics license application
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Crohn's disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CI	Confidence interval
CMC	Chemistry, manufacturing, and controls
CMH	Cochran–Mantel–Haenszel
COA	Clinical outcomes assessment
CRP	C-reactive protein
CSR	Clinical study report
DB	Double blind
D/C	Discontinuation
DDI	Drug drug interaction
dL	Deciliter
DMARDS	Disease modifying antirheumatic drugs
DMC	Data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DMPP	Division of Medical Policy Programs
DRTM	Division of Rheumatology and Transplant Medicine
ECLIA	Electrochemiluminescence immunoassay analyzer
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EE	Early escape
FACIT	Functional Assessment of Chronic Illness Therapy
FCS	Full Conditional Specification
FDA	Food and Drug Administration
GLMM	Generalized linear mixed model

GUS	Guselkumab
HAQ-DI	Health assessment questionnaire disability index
HCQ	Hydroxychloroquine
HCP	Health care professional
HS	Hidradenitis Suppurativa
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IL	Interleukin
iPSP	Initial pediatric study plan
ISR	Injection site reaction
IV	Intravenous
JAK	Janus kinase
jPsA	Juvenile psoriatic arthritis
Kg	Kilogram
L	Liter
LEF	Leflunomide
LOCF	Last Observation Carried Forward
MACE	Major adverse cardiovascular event
MAR	Missing at random
MC	Multicenter
mCPDAI	Modified Composite Psoriatic Disease Activity Index
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MI	Multiple imputation
MMRM	Mixed-model repeated measures
MPD	Major protocol deviations
MSD	Meso Scale Discovery
MTX	Methotrexate
NPF	National Psoriasis Foundation
NSAIDS	Non-steroidal anti-inflammatory drugs
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSM	Oral small molecule
OSI	Office of Scientific Investigations
PASI	Psoriasis Area and Severity Index
PBRER	Periodic Benefit Risk Evaluation Report
PFS	Prefilled syringe
PC	Placebo-controlled
PD	Pharmacodynamics
PDE4	Phosphodiesterase 4
PeRC	Pediatric Review Committee

PK	Pharmacokinetics
PMR	Postmarketing requirement
PO	By mouth
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PsA	Psoriatic arthritis
PsO	Psoriasis
PT	Preferred term
Q4w	Every four weeks
Q8w	Every eight weeks
R	Randomized
RA	Rheumatoid arthritis
RBC	Red blood cell
REMS	Risk evaluation and mitigation strategy
RF	Rheumatoid factor
RPM	Regulatory Project Manager
RTI	Respiratory tract infection
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36 MCS	36-item Short Form Health Survey Mental Component
SF-36 PCS	36-item Short Form Health Survey Physical Component
SOC	Standard of care
SOC	System Organ Class
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TF	Treatment failure
TNFα	Tumor necrosis factor alpha inhibitors
TRT	Treatment
µg	Microgram
µL	Microliter
US	United States
USPI	United States Prescribing Information
vdHS	Van der Heijde-Sharp
WBC	White blood cell
XR	Extended release

1 Executive Summary

1.1. Product Introduction

Guselkumab (Tremfya®) is a recombinant human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 protein subunit of human interleukin-23 (IL-23). IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 mediated intracellular signaling and release of proinflammatory cytokines and chemokines. It is approved in the United States for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dosage is 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter and comes in a single-dose prefilled syringe or single-dose One-Press patient-controlled injector.

Janssen Biotech, Inc. has submitted supplement 7 to Biological Licensing Application (BLA) 761061 for the treatment of adult patients with active psoriatic arthritis. The proposed doses are 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter (b) (4). Supplement 7 was subsequently administratively split following Agency policy as follows: Supplement 7 for the treatment of adult patients with active psoriatic arthritis in adult patients at doses of 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter, and Supplement (b) (4). Refer to Section 14 for additional discussion. No changes to the currently marketed presentations are being proposed in this supplemental BLA (sBLA).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The primary data to support this application are derived from two phase 3 studies: study CNTO1959PSA3001 (referred to as PSA3001 in the document) and study CNTO1959PSA3002 (referred to as PSA3002 in this document). Both studies were multicenter, randomized, double-blind, placebo-controlled, 3-arm studies of guselkumab in subjects with active PsA who had an inadequate response to standard therapies. Subjects with an inadequate response to prior TNFα-inhibitors, as well as other non-biologic therapies, were enrolled in study PSA3001, while study PSA3002 enrolled subjects naïve to biologic disease-modifying anti-rheumatic drug (DMARD) therapy. In both studies, the primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24. A greater proportion of subjects on guselkumab q4w (59% and 64%) and q8w (52% and 64%) compared to placebo (22% and 33%) achieved an ACR20 response at Week 24 in studies PSA3001 and 3002, respectively. Efficacy of guselkumab over placebo was further supported by secondary endpoints at Week 24 including HAQ-DI, IGA response, and DAS28(CRP). Similar responses for

the primary and secondary endpoints were observed in the guselkumab q4w and q8w treatment groups for assessments of signs and symptoms and physical function.

Assessment of radiographic progression, based on modified vdH-S score at Week 24 was evaluated in study PSA3002 only. A statistically significant change in vdH-S at Week 24 was observed with the guselkumab q4w regimen, but not with the q8w regimen. The interpretation of the results for vdH-S score, a biomarker, in the absence of dose dependent differences on clinical outcomes, is uncertain. Further, the effect of guselkumab on vdH-S scores was not confirmed by an additional study, nor is there additional supportive information from other sources, such as an effect in a related indication or an effect observed in other members of the drug class.

In conclusion, studies PSA3001 and PSA3002 provide substantial evidence on the efficacy of guselkumab q8w dosing regimen for the treatment of adult patients with active psoriatic arthritis. (b) (4)

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis that may result in pain, disability, and permanent joint damage. Although multiple therapies are approved for PsA in the United States, there still remains an unmet need for additional therapeutic options in this population.

Guselkumab is an interleukin-23 blocker approved in the United States for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dose in psoriasis is guselkumab 100 mg SC at Weeks 0, 4, and every 8 weeks thereafter. In this supplemental BLA, Janssen Biotech, Inc. submitted the results of two phase 3 studies in adult subjects with active PsA, studies PSA3001 and PSA3002. Both studies were multicenter, randomized, double-blind, placebo-controlled, 3-arm studies of guselkumab in patients with active PsA who had an inadequate response to standard therapies, who were randomized to treatment with guselkumab at Weeks 0, 4, and then every 4 weeks thereafter (q4w), guselkumab at Weeks 0, 4, and then every 8 weeks thereafter (q8w), or placebo. These studies provide substantial evidence for the effectiveness of both dosing regimens compared to placebo to improve signs and symptoms, as measured by American College of Rheumatology (ACR) 20% response criteria. The efficacy of guselkumab over placebo was further supported by secondary endpoints at Week 24 including HAQ-DI, IGA response, and DAS28(CRP).

In general, the efficacy results for key endpoints assessing signs and symptoms and physical function were largely similar for the two studied dosing regimens of guselkumab. There were no statistical differences between the two dose levels for ACR20 response at Week 24 for both studies (p=0.22 in PSA3001 and p=0.92 on PSA3002). Furthermore, for some secondary endpoints (IGA response, 36-SF PCS and enthesitis (from pooled data)) in PSA3002, less numerical improvement was obtained in guselkumab q4w compared to guselkumab q8w. Study PSA3002 assessed the effect of guselkumab on radiographic progression, based on change from baseline in vdH-S score at Week 24. A statistically significant effect on vdH-S at Week 24 was observed with the guselkumab q4w regimen, but not with the q8w regimen. However, there is a lot of uncertainty around the comparison between the doses with respect to this endpoint. In addition, the interpretation of the results for vdH-S score, a biomarker, in the absence of dose dependent differences on clinical outcomes, is uncertain. Further, the effect of guselkumab on vdH-S scores has not been confirmed by assessment of this endpoint in an additional study, nor is there additional supportive information from other sources, such as an effect in a related indication or an effect observed with other members of the drug class. (b) (4)

More adverse events (AEs) occurred in the guselkumab-treated subjects compared to the PBO-treated subjects during the double-blind period

of the phase 3 studies. However, the number of serious adverse events (SAEs) and AEs leading to discontinuation were low and similar across the treatment groups. No deaths occurred in the guselkumab groups and there was one death in the placebo group in study PSA3001 during the placebo-controlled period. Overall, the safety profile of guselkumab in the treatment of PsA is consistent with the previous experience with guselkumab. However, the q4w dosing regimen was not studied in the previously approved indication of psoriasis, limiting the controlled safety information for this dose to 24 weeks.

In conclusion, supplement 007 has provided adequate data to inform the benefit-risk assessment of guselkumab for the treatment of adult patients with active psoriatic arthritis. The benefit-risk profile is favorable to support the q8w chronic dosing regimen for the proposed indication. (b) (4) . The safety of guselkumab q8w was consistent with the known safety of guselkumab and offered an acceptable risk for the therapeutic benefits. Guselkumab provides an additional treatment option in the US for adult patients with active psoriatic arthritis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PsA arthritis is a chronic progressive inflammatory arthritis associated with psoriasis. The clinical manifestations of PsA may include peripheral and axial inflammatory arthritis, dactylitis and enthesitis • Patients with PsA can develop destructive disease characterized by radiographic progression of structural damage • Psoriatic arthritis (PsA) is a clinical diagnosis and is typically based on the CASPAR criteria. To fulfill the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following five categories: o Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis o Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination o A negative test result for the presence of rheumatoid factor	• PsA is an inflammatory arthritis associated with psoriasis that may result in pain, disability, and permanent joint damage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Either current dactylitis or a history of dactylitis recorded by a rheumatologist ○ Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot • The goals of PsA treatment are to improve signs and symptoms, physical function, and inhibit long-term structural damage	
Current Treatment Options	• The management of patients with PsA includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), systemic and/or intra-articular glucocorticoids, and small molecule and biologic disease modifying antirheumatic drugs (DMARDs) • FDA approved drugs for the treatment of PsA include TNFα-inhibitors; apremilast, an oral small molecule inhibitor of phosphodiesterase 4; ustekinumab, an IL-12/23 inhibitor; secukinumab, an IL-17A inhibitor; abatacept, a T-cell costimulation modulator; ixekizumab, an IL-17A inhibitor; and tofacitinib, a janus kinase (JAK) inhibitor. Other non-biologic DMARDs may be used off label for treatment of PsA.	Although many patients with PsA may respond to the current treatment options, there are patients who may have contraindications to or continued disease despite these available therapies; thus, an unmet need remains for additional therapeutic options for this population.
Benefit	• The Applicant submitted two randomized and well-controlled phase 3 studies, PSA3001 and PSA3002., Both studies were multicenter, randomized, double-blind, placebo-controlled studies of guselkumab in patients with active PsA who had an inadequate response to standard therapies, who were randomized to treatment with guselkumab at Weeks 0, 4, and then every 4 weeks thereafter (q4w) or every 8 weeks thereafter (q8w) or placebo. Study PSA3001 assessed 381 subjects with an inadequate response to non-biologic therapies and previous TNFα-inhibitors (up to 30% of study population), while study PSA3002 enrolled 739 subjects naïve to biologic DMARD therapy. • The primary endpoint was the proportion of subjects who achieved an ACR 20 response at Week 24	The Applicant has submitted two adequate and well-controlled studies, PSA3001 and PSA3002, that demonstrate substantial evidence of efficacy of guselkumab for the treatment of PsA in adults. The studies used validated and well-established primary and secondary endpoints that were designed to capture clinically meaningful changes in disease activity. The submitted studies demonstrate the benefit of guselkumab treatment on the signs and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In studies PSA3001 and 3002, a greater proportion of subjects on guselkumab q4w (59% and 64%) and q8w (52% and 64%) compared to placebo (22% and 33%) achieved an ACR20 response at Week 24, respectively. The primary endpoint was significant when comparing both guselkumab doses to placebo. There were no statistical differences between the two dose levels for ACR20 response at Week 24 • Results for key secondary endpoints assessed at Week 24, such as IGA response, change from baseline in HAQ-DI, and change from baseline in SF-36 PCS, provided additional support for the efficacy of both guselkumab doses, without consistent evidence of a dose dependent effect • Radiographic progression based on change from baseline in vdH-S score at Week 24 was assessed in Study PSA3002. A statistically significant change in vdH-S at Week 24 was observed with the guselkumab q4w regimen, but not with the q8w regimen, although there is a lot of uncertainty around the comparison between doses for this endpoint.	symptoms and physical function in adults with active PsA. There were no consistent differences in clinical response on measures of signs and symptoms or physical function between the two guselkumab dosing regimens. A statistically significant change in vdH-S at Week 24 was observed with the guselkumab q4w regimen, but not with the q8w regimen. The interpretation of the results for vdH-S score, a biomarker, in the absence of dose dependent differences on clinical outcomes, is uncertain. Further, there is a lack of independent confirmatory data from another study or other supportive information, such as an effect observed in a related indication or an effect observed in other members of the drug class. (b) (4) (b) (4)
Risk and Risk Management	• Studies PSA3001 and PSA3002 provided the data for the safety assessment. • The overall number of safety events were low. No deaths occurred in the guselkumab groups. SAEs and AEs leading to discontinuation were low and similar across treatment arms. • A similar safety profile was observed for the two doses without apparently clinically meaningful differences between them. • The safety profile was generally consistent with the known safety	The safety data from guselkumab in the PsA studies were similar between guselkumab groups and consistent with the known safety profile of guselkumab in psoriasis. There were no new safety signals. (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	profile of guselkumab in psoriasis. • (b) (4) • There were no new safety signals.	No new safety signals were identified to require further risk management.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data		**Section 8.3:** • ACR20 • HAQ-DI • SF-36 • FACIT-fatigue • IGA response
		X	Patient reported outcome (PRO)	**Section 8.3:** • SF-36 • FACIT-fatigue
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Psoriatic arthritis (PsA) is a chronic progressive inflammatory arthritis associated with psoriasis that may result in permanent joint damage and disability.[1] The prevalence of PsA is approximately 0.3-1% of the population. PsA affects women and men equally, and the mean age of onset of PsA is around 40 years. Approximately 80% of patients with PsA have skin involvement with psoriasis prior to or at the time of diagnosis with PsA. Because of its tendency to involve the spine (occurring in up to 40% of PsA patients) and lack rheumatoid factor (RF), PsA is considered one of the seronegative spondyloarthropathies.

The clinical manifestations of PsA include peripheral and axial inflammatory arthritis. The peripheral arthritis may present as an asymmetric oligoarthritis, a symmetric polyarthritis of the small joints of the hands and feet, arthritis mutilans, or other patterns. Patients with PsA can also have involvement of the tendons, dactylitis and enthesitis, as well as spondyloarthritis. Some patients have only one clinical manifestation, while others have overlapping manifestations. Patients with PsA can develop destructive disease characterized by radiographic progression of structural damage.

The Classification Criteria for Psoriatic Arthritis (CASPAR)[2] criteria published in 2006 has been used for the diagnosis of psoriatic arthritis. A patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following five categories: evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis; typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination; a negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range; either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist; radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

[1] Gladman DD, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 suppl 2:ii14-17.
[2] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006; 54(8): 2665-2673.

2.2. Analysis of Current Treatment Options

The goals of PsA treatment are to improve signs and symptoms, improve physical function, and prevent radiographic progression. The treatment should also consider concomitant psoriatic skin involvement, enthesitis/dactylitis, and axial involvement. According to the 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) Guideline for the Treatment of Psoriatic Arthritis,[3] the management of patients with PsA includes treatments with non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular and/or systemic glucocorticoids, and small molecule and biologic disease modifying anti-rheumatic drugs. FDA approved drugs for the treatment of PsA include tumor necrosis factor alpha inhibitors (TNFα), an interleukin-17 inhibitor (IL-17), an IL-17A inhibitor, an IL-12/23 inhibitor, a phosphodiesterase 4 (PDE4) inhibitor, a T-cell costimulation modulator, and a janus kinase (JAK) inhibitor as shown in Table 1. Among the approved drugs, the TNFα-inhibitors, secukinumab, and ixekizumab, have been shown to reduce the radiographic progression of peripheral arthritis in PsA.

Table 1 Drugs Approved for the Treatment of Psoriatic Arthritis (PsA)

Drug	Mechanism of Action	Date of Approval for PsA	Dosage and Administration
Etanercept (Enbrel)	TNFα-Inhibitor	1/15/2002	50 mg SC once weekly with or without methotrexate
Infliximab (Remicade)	TNFα-Inhibitor	5/18/2005	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks
Adalimumab (Humira)	TNFα-Inhibitor	10/3/2005	40 mg SC every other week
Golimumab (SC) (Simponi)	TNFα-Inhibitor	4/24/2009	50 mg SC once per month
Ustekinumab (Stelara)	IL-12/23 Inhibitor	9/20/2013	45 mg SC initially and 4 weeks later, followed by 45 mg every 12 weeks
Certolizumab (Cimzia)	TNFα-Inhibitor	9/27/2013	400 mg SC initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered
Apremilast (Otezla)	PDE4 Inhibitor	3/21/2014	30 mg PO twice daily after a 6 day titration schedule

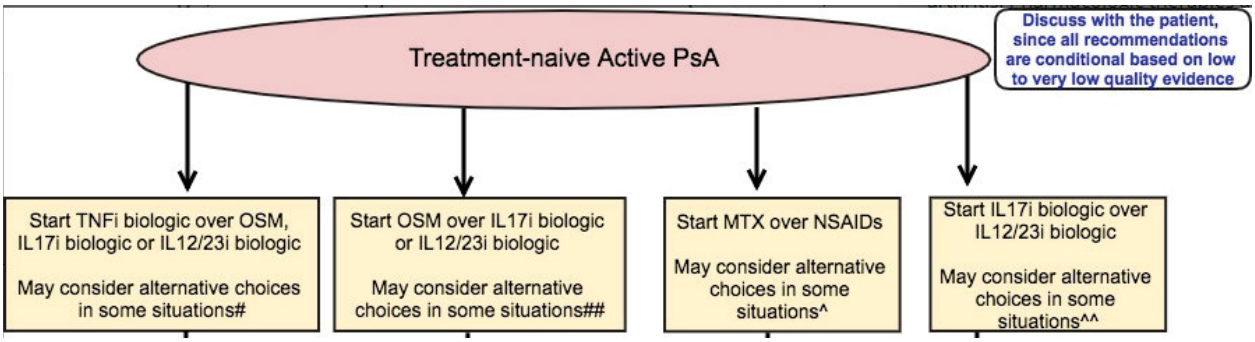
[3] Jasvinder A. Singh, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32.

Secukinumab (Cosentyx)	IL-17 Inhibitor	1/15/2016	• With a loading dose: 150 mg SC at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter • Without a loading dose150 mg every 4 weeks • If a patient continues to have active psoriatic arthritis, consider a dose of 300 mg
Abatacept (Orencia)	T-Cell Costimulation Modulator	6/1/2017	• 500-1000 mg IV at 0, 2, and 4 weeks, then every 4 weeks • 125 mg SC once weekly
Golimumab (IV) (Simponi Aria)	TNFα-Inhibitor	10/20/2017	2 mg/kg IV over 30 minutes at weeks 0 and 4, then every 8 weeks
Ixekizumab (Taltz)	IL-17A Inhibitor	12/1/2017	160 mg SC at Week 0, followed by 80 mg every 4 weeks
Tofacitinib (Xeljanz)	JAK-Inhibitor	12/14/2017	• 5 mg PO twice daily • XR: 11 mg PO once daily

Abbreviations: TNF=tumor necrosis factor; PDE4=phosphodiesterase 4; IL=interleukin; JAK=janus kinase; SC=subcutaneous; IV=intravenous; PO=by mouth; mg=milligram; kg=kilogram; XR=extended release

The ACR/NPF Guideline[3] provides recommendations for the treatment of patients with active psoriatic arthritis who are treatment-naive (no exposure to oral small molecules (OSMs) or other treatments) as seen in Figure 1. Note that all recommendations are conditional based on low- to very-low-quality evidence. In treatment-naive patients with active PsA, a TNFα-inhibitor is recommended over an OSM as a first-line option. However, OSMs may be used instead of a TNFα-inhibitor in certain circumstances, such as in patients without severe PsA and without severe psoriasis, those who prefer an oral drug instead of parenteral therapy, or those with contraindications to TNFα treatment. For treatment-naive patients with active PsA, the use of a TNFα-inhibitor or OSM is recommended over an interleukin-17 inhibitor (IL-17) or IL-12/23 inhibitor. However, an IL-17 inhibitor or IL-12/23 inhibitor may be used instead of TNFα-inhibitor in patients with severe psoriasis or contraindications to TNFα-inhibitors, and may be used instead of OSMs in patients with severe psoriasis or severe PsA. While an IL-17 inhibitor is recommended over an IL-12/23 inhibitor, IL-12/23 inhibitors may be preferred in patients who have concomitant inflammatory bowel disease.[3] MTX is recommended over NSAIDs in treatment-naive patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and side effect profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity. For patients with an inadequate response to OSM, TNFα-inhibitor, or other bDMARD therapy, change to an alternative treatment in the same or a different therapeutic class is recommended, with similar considerations of disease severity, comorbid conditions, and patient preference.

Figure 1 Recommendations for the treatment of patients with active psoriatic arthritis (PsA) who are treatment-naive (no exposure to oral small molecules [OSMs] or other treatments)



Source: Adapted from Figure 3 from Jasvinder A. Singh, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Guselkumab was first approved in the United States on July 13, 2017 for the treatment of adult patients with moderate to severe plaque psoriasis.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Agency had several regulatory interactions with the Applicant regarding the development of guselkumab for the treatment of PsA. Key discussion points are summarized below:
07/15/2016, Type C written responses only

- The Agency, noting only a single dose assessed in the phase 2 study, advised dose ranging for PsA
- The use of a loading regimen with greater exposure than the maintenance regimen may confound assessment of efficacy, and use of loading dose was not recommended. If loading dose to be used, include direct comparison of regimens with and without loading doses in phase 3
- The Agency suggested that the Applicant should consider including an active comparator arm in at least one of the phase 3 trials to provide long-term (e.g., at least one year) randomized, controlled, double-blind comparisons against standard-of-care
- The Agency suggested that the Applicant should consider evaluating endpoints at Week 16, prior to the time point of rescue
- If the study includes guselkumab without a loading dose, then the Agency wrote that it was reasonable to evaluate X-ray data at Week 24 in study CNTO1959PSA3002
- The Agency recommended an active comparator arm since all subjects on placebo would cross over to guselkumab at Week 24. Evaluations beyond Week 24 would be uncontrolled and limit conclusions about long-term safety and efficacy.

1/12/2017, Initial pediatric study plan (iPSP) Agreement

The Agency agreed with the Applicant's request for a full waiver of requirement to submit pediatric assessments of guselkumab in juvenile PsA for all pediatric age groups because studies would be impossible or highly impracticable

4/24/2019, pre-sBLA teleconference

- General agreement on content and format of planned sBLA
- The Agency agreed with the strategy for an integrated analysis of safety including pooling of safety data from studies CNTO1959PSA3001 and CNTO1959PSA3002
- Agency recommended submission of updated risk analysis to include any differences in risk with new indication and include why specifications/acceptance criteria for intended user and patient populations
- Regarding FACIT-Fatigue and (b) (4), the Agency stated that the Sponsor's rationale for why these outcome measures should be included in labeling should address the issues of redundancy and clinical meaningfulness. In addition, these endpoints are not included in the studies' multiplicity control procedures, and the rationale should address this issue as well.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division of Clinical Compliance from the Office of Scientific Investigations (OSI) was consulted to conduct clinical site inspections of three facilities:

- Dr. Ince Akgun: Site# US10005; Saint Louis, MO
- Dr. Marek Krogulec: Site# PL10013; Mazowieckie, Poland
- Dr. Wiland Piotr: Site# PL10010 for Study CNTO1959PSA3001, and Site# PL10016 for Study CNTO1959PSA3002; Dolnoslaskie, Poland

The clinical sites were selected using risk ranking from the clinical site selection tool for the phase 3 studies based on high enrollment, high response rate, and participation in both phase 3 studies.

Upon completion of study site inspections, OSI Investigations concluded that the data generated by these clinical investigators' sites submitted by the Applicant appear acceptable and in support of this BLA. For complete details, refer to the review by OSI Medical Officer, Tina Chang, MD, dated March 24, 2020.

4.2. Product Quality

No new CMC information was submitted and was not required for the regulatory decision for this supplement. The relevant information was reviewed in the original BLA. The CMC review team has reviewed submitted data to support the suitability of cut-points determined during the validation of assays to analyze the PsA clinical samples. The CMC reviewer recommends approval of this supplement from the product quality perspective. For additional details, refer to the review by Cindy Osborn, PhD dated June 2, 2020.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

CDRH reviewed the guselkumab UltraSafe Plus and guselkumab SelfDose drug-device combination products for use in the new indication of PsA. The development of the combination product of the guselkumab PFS assembled with the UltraSafe Plus (PFS-U) and guselkumab PFS assembled with the SelfDose (PFS-S) included consideration that the combination product (b) (4) may be used by patient populations with varying abilities of handling injection. The performance specifications, and verification and validation testing, have taken into account all (b) (4) indications for use for the drug product and (b) (4) user populations. The CDRH review team has concluded that there are no approvability issues related to the device constituent parts of the combination product. For additional details, refer to the review by Suzanne Hudak, dated July 6, 2020.

5 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology and toxicology studies were conducted or required to support the regulatory decision for this supplement. The relevant information was previously reviewed in the original BLA.

6 Clinical Pharmacology

6.1. Summary of Clinical Pharmacology Assessment

The Applicant is seeking the approval of TREMFYA® (guselkumab) for the treatment of active psoriatic arthritis (PsA). The clinical pharmacology information in this sBLA consists of pharmacokinetic (PK), pharmacodynamic (PD), and exposure response (ER) data from a global Phase 2 study (CNTO1959PSA2001 [hereafter referred to as PSA2001]) and 2 global Phase 3 studies (CNTO1959PSA3001 [hereafter referred to as PSA3001] and CNTO1959PSA3002 [hereafter referred to as PSA3002]).

The proposed dosing regimen is 100 mg by subcutaneous (SC) injection at Week 0, Week 4 and every 8 weeks (b) (4). The recommended dosing regimen for psoriatic arthritis 100 mg administered by SC injection at week 0, week 4, and every 8 weeks (q8w) thereafter is acceptable (see section 6.2.2, section 7, and section 8).

The following are the major clinical pharmacology findings of the current review:

- There was no clear dose/exposure response observed, as efficacy (ACR 20) appears to reach a plateau with both the dosing regimens of guselkumab (100 mg doses given by SC injections q8w or q4w,). In the E-R analysis for safety, the incidence of the safety parameters of interest (ie, adverse events [AEs], serious adverse events, AEs leading to study agent discontinuation, infections, and serious infections) were not associated with observed steady-state trough serum guselkumab concentrations or model-predicted PK exposure parameters (ie, maximum plasma concentration [Cmax], average steady-state serum concentration [Cave,ss], and area under the concentration-time curve to Week 24 [AUC0-24w]). See Section 8 and Pharmacometrics review in appendix 15.3.

- Population PK analysis was performed using pooled data through Week 24 from the 2 Phase 3 studies in subjects with PsA (PSA3001 and PSA3002). Guselkumab PK in subjects with PsA is generally comparable to subjects with PsO following SC administration of guselkumab 100 mg q8w.

- No dose adjustment is recommended for any intrinsic or extrinsic factors.

- In the Phase 3 studies, 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.

- The incidence of treatment-emergent antidrug antibodies (ADA) was generally low (2.0%, 15 of 744 subjects). The incidence of antibodies to guselkumab through Week 24 was similar between the 100 mg q8w (1.6%, 6 of 373 subjects) and 100 mg q4w (2.4%, 9 of 371 subjects) dose regimens.

Recommendations

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under sBLA 761067 and finds the sBLA approvable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings of the current review:

Dose/Exposure-Response

- There was no clear dose/exposure response observed, as efficacy (ACR 20) appears to reach a plateau with both the dosing regimens of guselkumab(100 mg doses given by SC injections q8w or q4w, Figure 12).

- In the E-R analysis for safety, the incidence of the safety parameters of interest (ie, adverse events [AEs], serious adverse events, AEs leading to study agent discontinuation, infections, and serious infections) was not associated with observed steady-state trough serum guselkumab concentrations or model-predicted PK exposure parameters (ie, maximum plasma concentration [C_{max}], average steady-state serum concentration [$C_{ave,ss}$], and area under the concentration-time curve to Week 24 [AUC_{0-24w}]). See Section 8 and Pharmacometrics review in appendix 15.3.

Pharmacokinetics

- Following SC administration of guselkumab, trough serum guselkumab concentrations reached steady state by Week 20 for the 100 mg dose at Weeks 0 and 4 then every 8 weeks (100 mg q8w group) and by Week 12 for the 100 mg every 4 weeks (q4w) group.

- Across the Phase 3 PsA studies, the median steady-state trough serum guselkumab concentrations following SC administration of guselkumab were 1.01 µg/mL (mean±standard deviation [SD]: 1.18±0.87 µg/mL) in the 100 mg q8w group and 3.50

µg/mL (mean±SD: 3.83±1.92 µg/mL) in the 100 mg q4w group. The median steady-state trough serum guselkumab concentrations were approximately 3- to 5-fold higher in the 100 mg q4w group compared with those in the guselkumab 100 mg q8w group.

- Serum guselkumab concentrations were generally comparable between subjects with PsA and psoriasis following SC administration of guselkumab 100 mg q8w. The median steadystate trough serum guselkumab concentrations were 1.01 µg/mL (mean±SD: 1.18 ± 0.87 µg/mL) in subjects with PsA and 1.06 µg/mL (mean±SD: 1.18 ± 0.77 µg/mL) in subjects with psoriasis. The q4w regimen was not studied in psoriasis program hence that data was not available for comparison.

- Population PK data analyses indicated that the clearance of guselkumab was not impacted by concomitant administration of oral corticosteroids, methotrexate (MTX), non-biologic disease-modifying antirheumatic drugs (DMARDs), or nonsteroidal anti-inflammatory drugs. Therefore, no dose adjustment is recommended.

- The effect of guselkumab on the PK of other drugs was not evaluated in subjects with PsA.

- In population PK analysis, body weight and comorbid diabetes were found to be significant covariates on clearance and volume terms in the PsA PK model. However, consistent efficacy was observed for both the guselkumab 100 mg q8w and the 100 mg q4w dose regimens in different weight groups, and in subjects with and without diabetes (Table 2, Table 3). Therefore, no dose adjustment is recommended with respect to these PK covariates.

Immunogenicity

- The incidence of treatment-emergent antidrug antibodies (ADA) was generally low (2.0%, 15 of 744 subjects) in subjects with PsA treated with guselkumab for up to 24 weeks. Only 1 of 15 subjects (6.7%) who were positive for antibodies to guselkumab was positive for neutralizing antibodies (NAbs) to guselkumab, which equated an overall incidence of NAbs to guselkumab of 0.1%. The incidence of antibodies to guselkumab through Week 24 was similar between the 100 mg q8w (1.6%, 6 of 373 subjects) and 100 mg q4w (2.4%, 9 of 371 subjects) dose regimens.

- The small number of subjects who were positive for antibodies to guselkumab (n=15) limits a definitive conclusion of the effect of immunogenicity on guselkumab PK, efficacy and safety (see section 6.3.2 & section 8).

6.2.1.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of Guselkumab in adult subjects with PsA is 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks (b) (4).

The clinical efficacy of the (b) (4) 100 mg q8w and q4w dosing regimen was demonstrated in two pivotal phase 3 studies PSA3001 and PSA3002, (see Sections 8.1 and 8.2). There was no clear dose/exposure response observed as efficacy appears to reach a plateau with both the dosing regimens of guselkumab (100 mg doses given by SC injections Q8W or Q4W). Overall, guselkumab 100 mg q8w and 100 mg q4w dose regimens achieved comparable clinical efficacy in improving signs and symptoms of PsA, as measured by the proportion of subjects achieving ACR 20. Results of the PK/PD analyses are consistent with the efficacy evaluation in subjects with PsA. Refer to the pharmacometrics review in Appendix 15.3 for details on the population PK and ER analysis.

Therapeutic Individualization

Intrinsic factors were not found to have a clinically meaningful effect on guselkumab PK in adult subjects with PsA. Therefore, no dose adjustment is necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Characteristics of guselkumab in Adult Subjects with PsA following SC Administration

Guselkumab PK has been assessed in healthy subjects, adult subjects with PSO and PsA. For details, see archived unireview & clinical pharmacology review. (Reference ID: 4123785 Reference ID: 4519469, respectively).

Serum guselkumab concentrations were generally comparable between subjects with PsA and psoriasis following SC administration of guselkumab 100 mg Q8W. The median steadystate trough serum guselkumab concentrations were 1.01 µg/mL (mean±SD: 1.18±0.87 µg/mL) in subjects with PsA and 1.06 µg/mL (mean±SD: 1.18±0.77 µg/mL) in subjects with psoriasis.

Across the phase 3 PsA studies, the median steady-state trough serum guselkumab concentrations following SC administration of guselkumab were 1.01 µg/mL (mean±standard deviation [SD]: 1.18±0.87 µg/mL) in the 100 mg q8w group and 3.50 µg/mL (mean±SD: 3.83±1.92 µg/mL) in the 100 mg q4w group. The median steady-state trough serum guselkumab

concentrations were approximately 3- to 5-fold higher in the 100 mg q4w group compared with those in the guselkumab 100 mg q8w group.

A Population PK analysis was conducted using pooled data through Week 24 from the 2 phase 3 studies in subjects with PsA (PSA3001 and PSA3002)to determine guselkumab PK parameters in adult subjects with PsA and assess the effect of intrinsic and extrinsic factors on guselkumab PK in the intended patient population.

The typical population estimates for apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.596 L/day and 15.5 L, respectively, with a median body weight of 84 kg. The model-derived elimination half-life was approximately 18.1 days, which is consistent with that in subjects with psoriasis.

Population PK data analyses indicated that the clearance of guselkumab was not impacted by concomitant administration of oral corticosteroids, methotrexate (MTX), non-biologic disease-modifying antirheumatic drugs (DMARDs), or nonsteroidal anti-inflammatory drugs.

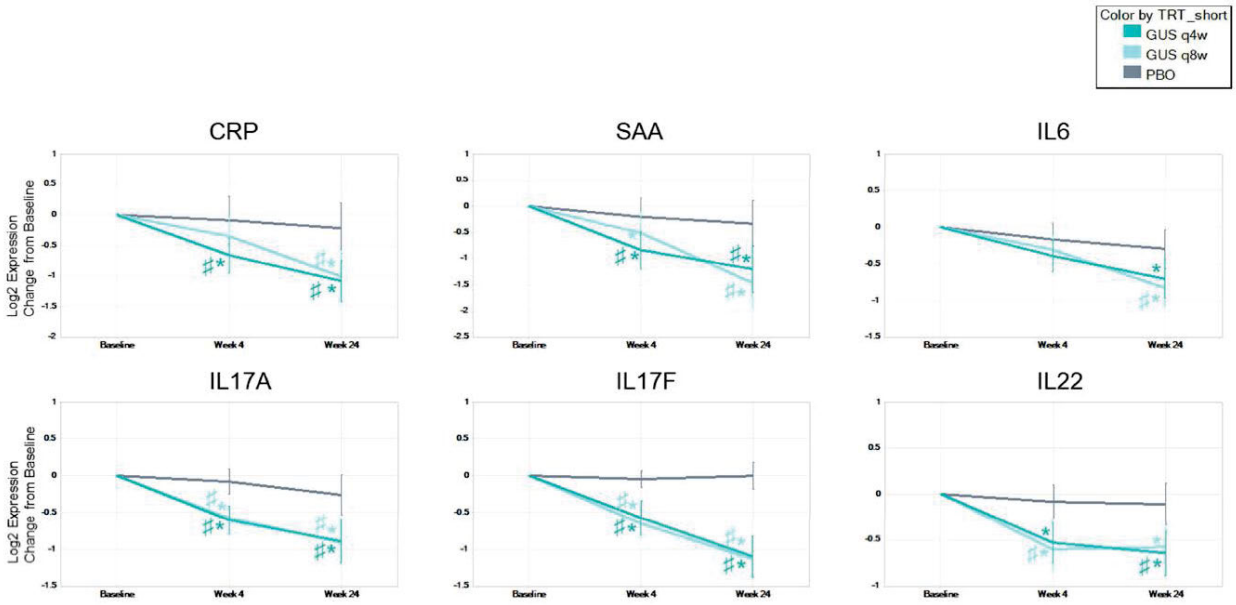
Pharmacodynamic (PD) Biomarker Characteristics of guselkumab in Adult Subjects with PsA following SC Administration:

In PSA3001 and PSA3002, 21 serum proteins were measured from a subpopulation of 50 subjects per treatment group per study (n=300 subjects in total) at Weeks 0 (pretreatment), 4, and 24.

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 (Figure 2 below).

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

Figure 2 Change from Baseline in Serum Proteins After Guselkumab Treatment



Note: Error bars represented 2 SEM (approximately 95% CI); * indicates statistical significance change from baseline defined by p<.05 and |fold difference| ≥ 1.4; ♯ indicates statistical significance vs Placebo defined by p <.05 and |fold difference| ≥ 1.4.
CI=confidence interval; CRP=C-reactive protein; IL=interleukin; PBO=placebo; q4w=every 4 weeks; q8w=every 8 weeks; SAA=serum amyloid A; SEM=standard error of the mean; TRT=treatment
(Source: Summary of Clinical Pharmacology, figure 14, page 62)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

This sBLA for PsA is supported by placebo-controlled pharmacokinetics (PK), safety and efficacy data from studies PSA2001, PSA3001 and PSA3002. Refer to Section 8.1 for assessment of the primary and secondary endpoints in the pivotal studies.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen is 100 mg by subcutaneous (SC) injection at Week 0, Week 4 and every 8 weeks (b) (4). The recommended dosing regimen for psoriatic arthritis is 100 mg administered by SC injection at week 0, week 4, and every 8 weeks (q8w) thereafter (see Section 6.2.2, Section 7, and Section 8).

The clinical efficacy of the (b) (4) 100 mg q8w and q4w dosing regimen was demonstrated in two pivotal phase 3 studies PSA3001 and PSA3002, (see Sections 8.1 and 8.2). There was no clear dose/exposure response observed as efficacy appears to reach a plateau with both the dosing regimens of guselkumab (100 mg doses given by SC injections q8w or q4w, Figure 12).

With pooled Phase 3 data, exposure-response analyses suggest that guselkumab 100 mg q8w and 100 mg q4w dose regimens achieved similar clinical efficacy in improving signs and symptoms of PsA, as measured by the proportion of subjects achieving ACR 20/50 and IGA 0/1 responses, with guselkumab 100 mg q4w showing small incremental benefit in some endpoints. Consistent with the observed ACR20, ACR50, and ACR70 data, the simulation based on longitudinal E-R modeling did not reveal discernible differences in achieving ACR20, ACR50, and ACR70 responses between the 100 mg q8w and 100 mg q4w dose regimens (Figure 14, See Appendix 15.3).

In the E-R analysis for safety, the incidence of the safety parameters of interest (ie, adverse events [AEs], serious adverse events, AEs leading to study agent discontinuation, infections, and serious infections) was not associated with observed steady-state trough serum guselkumab concentrations or model-predicted PK exposure parameters (ie, maximum plasma concentration [C_{max}], average steady-state serum concentration [$C_{ave,ss}$], and area under the concentration-time curve to Week 24 [AUC_{0-24w}]). Refer to the pharmacometrics review in Appendix 15.3 for details on the population PK and ER analysis. See Section 7 and Section 8 for additional risk/benefit assessment of the two dosing regimens.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. The significant covariates (weight and diabetes comorbidity) included in the PsA final PK model are discussed below. It should be noted that neither of these factors warrant dose adjustment in patients with PsA.

Body weight was the primary covariate contributing to the observed PK variability of guselkumab. Heavier subjects tended to have higher CL/F and V/F, and therefore, lower exposure to guselkumab.

In population PK analysis, body weight was found to be significant covariates on clearance and volume terms and diabetes comorbidity was found to be a significant covariate on CL/F in the PsA PK model. The model-predicted median trough concentration at steady state (Ctrough,ss) and area under the curve during one dose interval of guselkumab in subjects ≥100 kg were about 34.4% and 29.4% lower than in subjects <100 kg, respectively, for the 100 mg q8w dose regimen and about 30.6% and 29.4% lower for the 100 mg q4w dose regimen. Nevertheless, consistent efficacy (ACR 20) was observed for both the guselkumab 100 mg q8w and the 100 mg q4w dose regimens across different body weight strata according to either body weight quartiles or body weight cut-off of 100 kg (Table 2). Therefore, no dose adjustment is recommended with respect to the PK covariates.

Table 2 Number of Subjects Who Achieved ACR20/50/70 Response at Week 24 based on baseline body weight cutoff (100 kg)

Efficacy Endpoint (response at week 24)	Body weight ≤ 100 kg		Body weight > 100 kg	
	100 mg q8w N=298	100 mg q4w N=292	100 mg q8w N=77	100 mg q4w N=81
ACR 20[a] 95% CI of response rate[b]	59.7 % (54.0%, 65.5%)	61.6% (55.9%, 67.4%)	61% (49.5%, 72.6%)	64.2 % (53.1%, 75.3%)
ACR 50 [a] 95% CI of response rate[b]	32.6 % (27.1%, 38.0%)	32.9% (27.3%, 38.4%)	24.7% (14.4%, 35.0%)	38.3% (27.1%, 49.5%)
ACR 70 [a] 95% CI of response rate[b]	18.1% (13.6%, 22.7%)	16.1% (11.7%, 20.5%)	9.1% (2.0%, 16.2%)	13.6% (5.5%, 21.7%)

Note:
a The estimand is defined as responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed. Subjects with data missing were considered non-responders.
b The confidence intervals (CIs) for response rates and for difference in response rates between guselkumab group vs the placebo group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
(Source: Reviewer's Summary from 2.7.2 Summary of Clinical Pharmacology section 3.3.2.1, page 33 and 2.7.3 Summary of Clinical Efficacy section 3.3.1.1 page 87, & Appendix Tables Page 145, 149, 167, 171, 189, and 193.)

Diabetic comorbidity was found to have an influence on guselkumab PK after correcting for body weight effect. The model-predicted CL/F value of guselkumab was 15% higher in subjects with diabetes compared with subjects without diabetes. Nevertheless, consistent efficacy was observed for both the guselkumab 100 mg q8w and the 100 mg q4w dose regimens between subjects with and without diabetes (Table 3). Therefore, the impact of diabetic comorbidity on PK exposure does not warrant dose adjustment.

Table 3 Number of Subjects Who Achieved ACR20/50/70 Response at Week 24 based on diabetic comorbidity.

Efficacy Endpoint (response at Week 24)	Subjects with Diabetes		Subjects without Diabetes	
	100 mg q8w N=37	100 mg q4w N=32	100 mg q8w N=338	100 mg q4w N=341
ACR 20 [a] 95% CI of response rate[b]	62.2% (45.2%,79.1%)	59.4% (40.8%, 78.0%)	59.8% (54.4%, 65.1%)	62.5% (57.2%, 67.7%)
ACR 50 [a] 95% CI of response rate[b]	29.7% (13.7%, 45.8%)	25.0% (8.4%, 41.6%)	31.1% (26.0%, 36.1%)	34.9% (29.7%, 40.1%)
ACR 70 [a] 95% CI of response rate[b]	13.5% (1.1%, 25.9%)	9.4% (0.0%, 21.0%)	16.6% (12.5%, 20.7%)	16.1% (12.1%, 20.2%)

Note:
a The estimand is defined as responders who had not met any TF criteria prior to the specific visit at which the endpoint was assessed. Subjects with data missing were considered non-responders.
b The confidence intervals (CIs) for response rates and for difference in response rates between guselkumab group vs the placebo group were based on Wald statistics. If the Mantel Fleiss criterion is not satisfied the exact unconditional CI (marked with an asterisk) based on the Farrington-Manning score statistic is calculated.
(Source: Reviewer's Summary from 2.7.2 Summary of Clinical Pharmacology section 3.3.2.2, page 34 and 2.7.3 Summary of Clinical Efficacy section 3.3.1.2 page 88, & Appendix Tables,137, 141, 159, 163, 171, 181, and 185.)

What Was the Impact of Immunogenicity on guselkumab Exposure?

The overall incidence of antibodies to guselkumab through Week 24 was low (2.0%, 15 of 744 subjects) in subjects with PsA. The incidence of antibodies to guselkumab through Week 24 was similar between the 100 mg q8w (1.6%, 6 of 373 subjects) and 100 mg q4w (2.4%, 9 of 371 subjects) dose regimens.

Fifteen of 744 (2%) subjects who were positive for antibodies to guselkumab were included in the population PK analysis. In the population PK covariate analysis, the presence of antibodies to
guselkumab did not have an apparent impact on PK exposure of guselkumab. In a separate sensitivity analysis using the final model, the impact of antibodies to guselkumab as a time-varying variable did not have an apparent effect on the CL/F of guselkumab. However, due to the low incidence of antibodies to guselkumab, this result should be interpreted with caution.

Overall, the small number of subjects who were positive for antibodies to guselkumab (n=15) limits a definitive conclusion of the effect of immunogenicity on guselkumab PK.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There were no DDI studies conducted for this efficacy supplement. Population PK data analyses indicated that the clearance of guselkumab was not impacted by concomitant administration of oral corticosteroids, methotrexate (MTX), non-biologic disease-modifying antirheumatic drugs (DMARDs), or nonsteroidal anti-inflammatory drugs.

Are the Bioanalytical Methods Properly Validated to Measure PK in Plasma Samples?

Serum concentrations of guselkumab in the PsA studies were determined with a validated ECLIA method on the MSD platform. This is the same method that was used in the guselkumab PsO clinical development program. A description of the method and its revisions and addendums were included and reviewed as part of the original BLA submission for psoriasis. Please refer to the archived unireview (Reference ID: 4123785).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 4 Table of Clinical Studies

Study	Study Design/ Duration	Dosing Regimen	No. of subjects Enrolled	Endpoints	Status
PSA3001	MC, R, DB, PC, 3-arm in PsA pts with inadequate response to SOC (31% prior TNF) *60 weeks*	• GUS 100 mg SC q4w • GUS 100 mg SC at Weeks 0, 4, q8w thereafter • PBO At Week 24, PBO crossed over to GUS 100 mg SC q4w to Week 48	N= 381 • GUS q4w n=128 • GUS q8w n=127 • PBO n=126	1: ACR 20 at Week 24 2: psoriasis IGA, HAQ-DI, and SF-36 PCS	Ongoing Week 24 database lock complete
PSA3002	MC, R, DB, PC, 3-arm in PsA pts with inadequate response to SOC (biologic naïve) *100 weeks*	• GUS 100 mg SC q4w • GUS 100 mg SC at Weeks 0, 4, q8w thereafter • PBO At Week 24, PBO crossed over to GUS 100 mg SC q4w to Week 100	N=739 • GUS q4w n=245 • GUS q8w n=248 • PBO n=246	1: ACR 20 at Week 24 2: psoriasis IGA, HAQ-DI, modified vdH-S, SF-36 PCS, SF-36 MCS, dactylitis and enthesitis	Ongoing Week 24 database lock complete
PSA2001	Phase 2, MC, R, DB, PC, 2-arm in PsA pts with inadequate response to SOC (8.7% prior TNF)	GUS 100 mg SC at Weeks 0, 4, and q8w thereafter or PBO	N=149 • GUS q8w n=100 • PBO n=49	1: ACR 20 at Week 24 2: PASI 75, HAQ-DI, ACR 50, enthesitis and dactylitis	Complete

	44 weeks	At Week 24, PBO crossed over to GUS 100 mg SC at Weeks 24, 28, 36 and 44			

Abbreviations: MC=multicenter; R=randomized; DB=double-blind; PC=placebo-controlled; PsA=psoriatic arthritis; SOC=standard of care; SC=subcutaneous; GUS=guselkumab; ACR=American College of Rheumatology; PASI= Psoriasis Area and Severity Index; IGA= Investigator Global Assessment; HAQ-DI=Health assessment questionnaire disability index; Tx=received treatment ; SF-36 PCS= 36-item Short Form Health Survey Physical Component; vdH-S=van der Heijde-Sharp; SF-36 MCS=36-item Short Form Health Survey Mental Component

7.2. Review Strategy

This supplemental BLA consisted of two phase 3 studies, study CNTO1959PSA3001 (referred to as study PSA3001 in this review) and study CNTO1959PSA3002 (referred to as study PSA3002 in this review) and one phase 2 study, CNTO1959PSA2001 (referred to as study PSA2001 in this review) to provide the efficacy and safety of guselkumab in the treatment of psoriatic arthritis. Because PSA2001 was designed as an early stage, proof-of-concept study to inform subsequent trials and a limited number of subjects received guselkumab in this study, the focus of this review will be the presentation of the data from the two larger pivotal trials, PSA3001 and PSA3002.

Study PSA3001 was a multicenter, randomized, double-blind, placebo-controlled, 3-arm study of guselkumab in 381 subjects with active PsA who had an inadequate response to standard therapies (e.g., non-biologic DMARDs, apremilast or NSAIDs). In addition, 31% of the study population were previously exposed to up to two anti-TNFα agents. Subjects were randomized in a 1:1:1 ratio to either placebo, guselkumab 100 mg every four weeks (q4w), or guselkumab 100 mg at Weeks 0 and 4, then every eight weeks (q8w) thereafter. At Week 24, all subjects in the placebo group crossed over to receive guselkumab 100 mg q4w through Week 52. Subjects in the guselkumab groups remained on the dosing regimen they were randomized to through Week 52. The primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24 and the key secondary endpoints, each evaluated at Week 24, included additional assessments of signs and symptoms and physical function.

Study PSA3002 was a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in 739 subjects with active PsA who were biologic naïve and had an inadequate response to standard therapies. The subjects were randomized in a 1:1:1 ratio to the same three dosing groups as in study PSA3001. This study also had the same crossover at Week 24 and the same primary endpoint as study PSA3001. Study PSA3002 also included an assessment of radiographic change as assessed by vdH-S score. This endpoint was not evaluated in PSA3001. Dactylitis and enthesitis were also assessed as key secondary endpoints based on pooled data from PSA3001 and PSA3002.

The primary evidence of efficacy to support guselkumab dosing in psoriatic arthritis is based on the data collected through Week 24 from studies PSA3001 and PSA3002 and the assessment of the primary endpoint as well as the key secondary endpoints.

The safety assessment of guselkumab in psoriatic arthritis is based on the safety database from studies PSA3001 and PSA3002. The safety review focuses on the placebo-controlled data from these studies (24-week data) with some inclusion of the 120-day safety update to determine if there are any inconsistencies with the known safety profile of guselkumab. Additional supportive safety data are provided by Study PSA2001, a phase 2 study in 149 subjects with PsA treated with guselkumab 100 mg at weeks 0 and 4, then every eight weeks or placebo. Review

of the safety data from this study was generally consistent with the safety from PSA3001 and PSA3002 and is not further discussed in this review.

The statistical reviewer will present the Applicant's assessment of efficacy and supplement this with her own analyses. The clinical reviewer will present the Applicant's safety data with additional commentary.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study PSA3001

Study Design

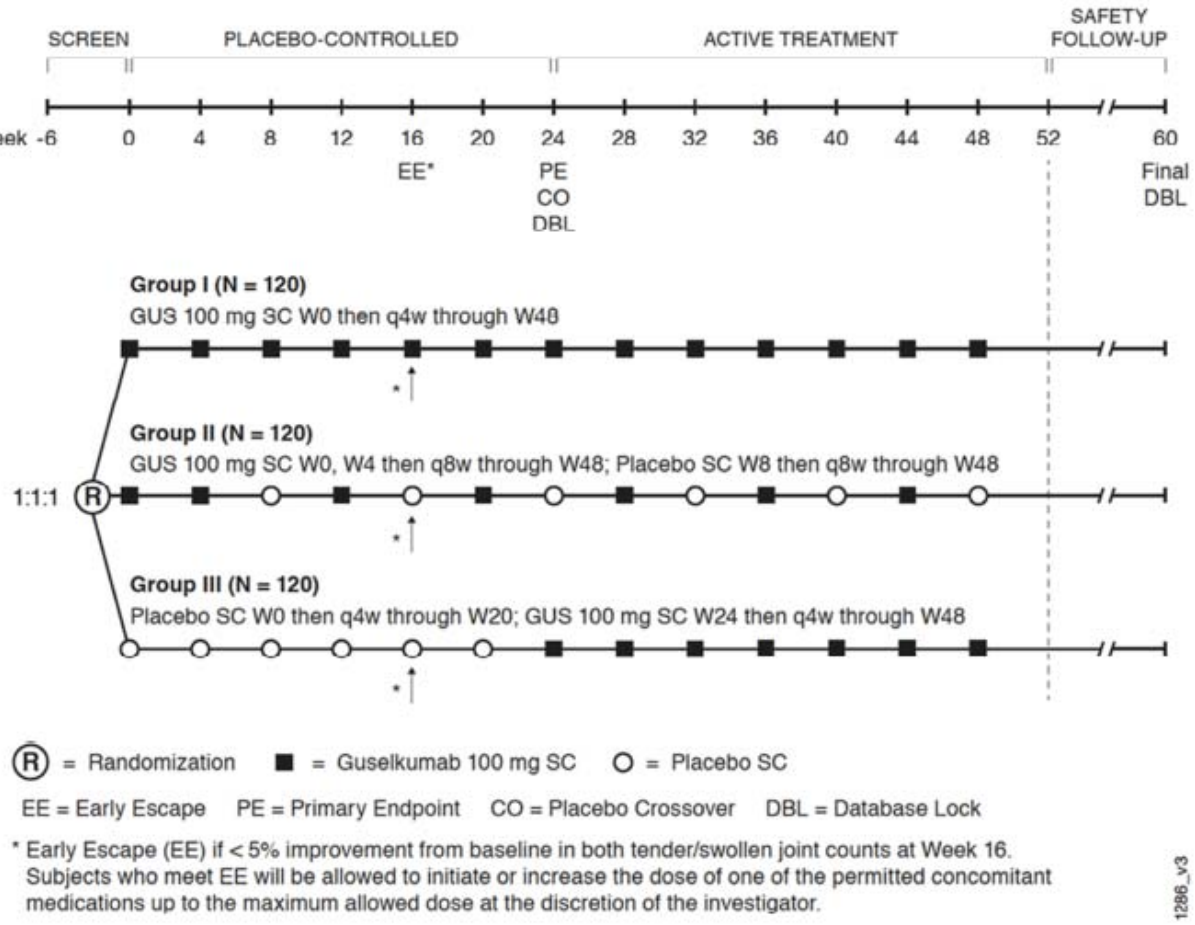
This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, 3-arm study of guselkumab in 381 subjects with active PsA who had an inadequate response to standard therapies (e.g., non-biologic DMARDs, apremilast or NSAIDs). In addition, approximately 30% of the study population may have been previously exposed to up to two anti-TNFα agents. Subjects were randomized in a 1:1:1 ratio using permuted block randomization stratified by baseline non-biologic DMARD [methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (LEF)] use (yes/no) and by prior exposure to anti-TNFα agents (yes/no) to one of three groups:

- **Group I** (n=128): SC guselkumab 100 mg every four weeks (q4w) from Week 0 through Week 48
- **Group II** (n=127): SC guselkumab 100 mg at Weeks 0 and 4, then q8w (Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48) to maintain the blind
- **Group III** (n=126): SC placebo q4w from Week 0 to Week 20, and then crossover at Week 24 to receive guselkumab 100 mg q4w through Week 48

As seen in Figure 3, at Week 24, all subjects in the placebo group (Group III) crossed over to receive guselkumab 100 mg SC q4w through Week 52. Subjects in the guselkumab groups (Groups I and II) remained on the dosing regimen they were randomized to at Week 0, through Week 52. Subjects were followed for new adverse events (AEs) and serious adverse events (SAEs) up to 12 weeks following the last study agent administration.

An independent Data Monitoring Committee (DMC) was established to monitor unblinded data on an ongoing basis through at least the Week 24 database lock (DBL) to ensure the continuing safety of the subjects enrolled in this study. Database locks were scheduled at Weeks 24 and End of Study (Week 60).

Figure 3 Study PSA3001 Schematic



Source: Study PSA3001 Protocol

Dosage and Administration

Guselkumab 100 mg and matching liquid placebo for guselkumab was provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U). Study agent was administered at the site by a health care professional (HCP) until the subject (or caregiver) was trained for self-administration. Study agent was administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, subjects could self-administer study agent at the investigative site under the supervision of an HCP. The option to begin self-administration of study agent at home began at Week 32. At Week 28, subjects (or a caregiver) who were able to self-administer were supplied study agent for self-administration away from the site (ie, at home). Subjects were instructed to contact the investigator in the event of an allergic reaction, infection, or bleeding. Doses are as described above for groups I, II, and III above.

Rescue

At Week 16, all subjects in Groups I, II, and III with < 5% improvement from baseline in both

tender and swollen joint counts were considered as meeting early escape criteria. Subjects meeting early escape criteria remained on the dosing regimen assigned at Week 0 but could initiate or increase the dose of one of the permitted concomitant medications including: NSAIDs and other analgesics, oral corticosteroids, and selected non-biologic DMARDs (limited to MTX, SSZ, HCQ, or LEF).

Concurrent Medications
Permitted concomitant medications in this study included non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, oral corticosteroids up to an equivalent to 10 mg/day of prednisone, methotrexate (MTX) up to 25mg/ week, sulfasalazine (SSZ) up to 3 grams/ day, hydroxychloroquine (HCQ) up to 400 mg/ day, and leflunomide (LEF) up to 20 mg/ day.

Study Location and Dates
This study was conducted at 86 sites in 13 countries: Australia (n=6), Malaysia (n=5), Republic of Korea (n=2), Taiwan (n=7), Czech Republic (n=5), Germany (n=5), Hungary (n=5), Poland (n=11), Russia (n=10), Spain (n=7), Ukraine (n=10), Canada (n=6), and United States (n=7).

The study was conducted from August 28, 2017 (date first subject signed informed consent) to March 14, 2019 (date of last observation for last subject recorded as part of the database for interim analysis).

Main Inclusion Criteria
- Man or woman ≥18 years old
- Diagnosis of PsA for at least six months before the first administration of study agent and meet ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening
- Had active PsA as defined by:
    - At least three swollen joints and at least three tender joints at screening and at baseline AND
    - C-reactive protein (CRP) ≥0.3 mg/dL at screening
- ≥ 1 of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.
- Active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis
- Active PsA despite previous non-biologic DMARD, apremilast, and/or NSAIDs
- May have been previously treated with up to two anti-TNFα agents (approximately 30% of the overall study population), and must document the reason for discontinuation
- If using non-biologic DMARDs (limited to MTX, SSZ, HCQ, or LEF), should have started treatment at least three months and the dose must be stable for at least four weeks before first administration of study agent and should have no serious toxic side effects attributable to the non-biologic DMARD
- If using NSAIDs or other analgesics for PsA, must be on a stable dose for at least two weeks before first administration of study agent

- If using oral corticosteroids for PsA, must be on a stable dose equivalent to ≤10 mg of prednisone/day for at least two weeks before first administration of study agent
- Contraceptive use
- TB screening criteria
- Willing to refrain from the use of complementary therapies for PsA or psoriasis within two weeks before the first study agent administration and through Week 52
- Screening laboratory test results within the following parameters:
  a. Hemoglobin ≥8.5 g/dL
  b. White blood cells ≥3.5 x 10^3/µL
  c. Neutrophils ≥1.5 x 10^3/µL
  d. Platelets ≥100 x 10^3/µL
  e. Serum creatinine ≤1.5 mg/dL
  f. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels must be ≤1.5 times the upper limit of normal range for the central laboratory conducting the test.

  A one-time repeat was allowed during the 6-week screening phase and the Investigator could consider the subject eligible if the previously abnormal laboratory test result was within acceptable range on repeat testing.

Main Exclusion Criteria

- Had other inflammatory diseases that might confound the evaluations of benefit of guselkumab therapy, including but not limited to RA, axial spondyloarthritis (this did not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, or Lyme disease
- Had ever received more than two anti-TNFα agents
- Had received infliximab (or its biosimilars) or golimumab (IV) within eight weeks before the first administration of study agent
- Had received golimumab SC, adalimumab (or its biosimilars) or certolizumab pegol within six weeks before the first administration of study agent
- Had received etanercept (or its biosimilars) within four weeks before the first administration of study agent
- Previously been treated with guselkumab
- Previously received any biologic treatment (other than anti-TNFα agents), including, but not limited to ustekinumab, abatacept, secukinumab, tildrakizumab, ixekizumab, brodalumab, risankizumab, or other investigative biologic treatment
- Previously received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other Janus kinase (JAK) inhibitor
- Previously received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within four weeks of the first administration of study agent
- Received non-biologic DMARDs (other than MTX, SSZ, HCQ, LEF) including, but not limited to chloroquine, gold preparations, and penicillamine within four weeks before the first administration of study agent

- Receiving two or more non-biologic DMARDs
- Received apremilast within four weeks prior to the first administration of study agent
- Received phototherapy or any systemic medications/treatments that could affect psoriasis evaluations (including, but not limited to, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, fumaric acid derivatives, within 4 weeks of the first administration of study agent
- Used topical medications/treatments that could affect psoriasis evaluations (including, but not limited to, topical or intralesional injection of corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within two weeks of the first administration of any study agent
- Received epidural, intra-articular, intramuscular, or IV corticosteroids, including adrenocorticotropic hormone during the four weeks before first administration of study agent
- Received lithium within four weeks of the first administration of any study agent
- Received an experimental antibody or biologic therapy or received any other experimental therapy, including an investigational medical device within 90 days or 5 half-lives (whichever is longer) prior to the first administration of study agent or is currently enrolled in another study using an investigational agent or procedure
- Had unstable suicidal ideation or suicidal behavior in the last 6 months defined by the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)
- Had a history or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (with the exception of PsA), psychiatric, genitourinary, or metabolic disturbances
- Unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation, or transient ischemic attack) in the last three months prior to screening or a cardiac hospitalization within the last three months prior to screening
- Had a malignancy or a history of malignancy within five years before screening
- History of lymphoproliferative disease
- History of chronic or recurrent infectious disease
- Had a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study agent)
- History of an infected joint prosthesis, or has ever received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced
- Serious infection, had been hospitalized or received IV antibiotics for an infection, or has had a herpes zoster infection within two months before screening
- Pregnant, nursing, or planning a pregnancy (both men and women) within 12 weeks after receiving the last administration of study agent
- Had a nonplaque form of psoriasis or current drug-induced psoriasis
- Had received, or is expected to receive, any live virus or bacterial vaccination within three months before the first administration of study agent or a BCG vaccination within

12 months of screening
- Had a chest radiograph within three months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy, significant cardiovascular or pulmonary disease or current active infection, including TB
- Had ever had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, pneumocystosis, aspergillosis
- Had HIV, hepatitis B virus, or hepatitis C virus

Safety Variables of this Study
Safety in this study was monitored by collecting information on AEs, including injection site and allergic reactions, clinical laboratory tests (hematology, serum chemistry, lipid panel), physical examinations, vital signs, eC-SSRS questionnaires, concomitant medication review, and early detection of TB, as specified in Table 41, Time and Events Schedule.

Subject Discontinuation Criteria
A subject's study treatment was discontinued if:
- The investigator believed that for safety reasons or tolerability reasons (e.g., AE) it was in the best interest of the subject to discontinue study treatment
- The subject was pregnant or planned to become pregnant
- The subject was diagnosed with a malignancy, with the exception of no more than two localized basal cell skin cancers that were treated with no evidence of recurrence or residual disease
- The subject was deemed ineligible according to the following TB screening criteria:
    - A diagnosis of active TB was made
    - A subject had symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation
    - A subject undergoing evaluation had a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB Gold test result
    - A subject receiving treatment for latent TB discontinued this treatment prematurely or was noncompliant with the therapy
- The subject initiated the following protocol-prohibited medications: apremilast, systemic immunosuppressive drugs, biologic agents, cytotoxic drugs, JAK inhibitors, or investigational agents, and systemic therapy for psoriasis
- The subject withdrew consent for administration of study agent
- The subject was unable to adhere to the study visit schedule or comply with protocol requirements
- The subject developed an allergic reaction such as bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension that occurs following a study agent administration
- The subject had a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other

recognized clinical syndromes) occurring 1 to 14 days after an injection of study agent. These may have been accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache

Discontinuation of study treatment was to be considered for subjects who reported suicidal Ideation Level 4 (Some intent to act, no plan), Ideation Level 5 (Specific plan and intent), or any suicidal behavior (Actual suicide attempts, Interrupted attempts, Aborted Attempts, or Preparatory actions) on a post-baseline (after Week 0) eC-SSRS assessment. Discussion of such subjects with the medical monitor or designee was required

Discontinuation of study agent was to be considered and discussed with the study responsible physician or designee for subjects who developed a serious or opportunistic infection

The reasons for a subject to be withdrawn from the study included: lost to follow-up, withdrawal of consent, and death.

Study Endpoints

Primary Endpoint:

The primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response [4] at Week 24.

Key Secondary Endpoints:

The secondary endpoints in this study that were included in the multiplicity control procedure were:

- Change from baseline in Health Assessment Questionnaire-Disability Index [5] (HAQ-DI) score at Week 24
- Proportion of subjects with a psoriasis response of an Investigator Global Assessment [6]

[4] ACR20 response was defined as ≥20% improvement form baseline in both tender joint count (68 joints) and swollen joint count (66 joints) and ≥20% improvement form baseline in at least 3 of the following 5 assessments: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function as measured by HAQ-DI and C-reactive protein.

[5] A 20-question instrument that assessed the degree of difficulty a person had an accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area were scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area (i.e., lower scores were indicative of better functioning). In PsA, a decrease in score of 0.35 has been determined to indicte a clinically meaning improvement.

[6] The IGA documented the investigator's assessment of the subject's psoriasis. Overall lesions were graded for induration, erythema, and scaling using 0 (no evidence), 1 (minimal), 2 (mild), 3 (moderate) and 4 (severe) scale. The IGA score of psoriasis was based on the average of induration, erythema and scaling scores. The patients' psoriasis was assessed as cleared (0), minimal (1), mild (2), moderate (3), or severe (4).

(IGA; ie, an IGA psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2-grade reduction from baseline) at Week 24 among subjects with ≥3% body surface area (BSA) psoriatic involvement and an IGA score of ≥2 (mild) at baseline

- Change from baseline in 36-item short form health survey (SF-36) Physical Component Summary [7] (PCS) at Week 24

Additional Endpoints:
The Applicant evaluated multiple other supportive endpoints outside of the multiplicity control procedure including endpoints related to reduction of signs and symptoms and physical function and endpoints related to health-related quality of life (Clinical Study Report for PSA3001, p48). These included:

- Proportion of subjects who achieved an ACR 50 response at Week 24
- Proportion of subjects who achieved an ACR 70 response at Week 24
- Proportion of subjects who achieved an ACR 20 response at Week 16
- Proportion of subjects who achieved an ACR 50 response at Week 16
- Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 24.
- Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline
- Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) at Week 24 among the subjects with enthesitis at baseline
- Change from baseline in SF-36 Mental Component Summary (MCS) at Week 24
- Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline
- Change from baseline in dactylitis scores at Week 24 among the subjects with dactylitis at baseline

Sample Size Determination
For PSA3001, a total of 360 subjects were planned to be randomized in a 1:1:1 ratio to each of treatment groups assuming a 40% ACR20 response in the guselkumab group and a 20% ACR20 response in the placebo group at Week 24 to ensure >90% statistical power at a two-sided significance level of 0.05.

Protocol Amendments
The original protocol was submitted on April 26, 2017 and there was one protocol amendment submitted on January 25, 2018. The clinical changes made to the protocol in this amendment included removing all references to the dermatology life quality index assessment because it

[7] The health status and quality of life was assessed using a multi-domiain instrument with 36 items that was self-administered bu subjects. It included 8 subscales that covered a range of functioning: physical functiongin, physical role functioning, bodily pain, general mental health, emotional role functioning, socital functioning, vitality and general health perception. Th scoring yielded a Physical Componet Summary (PCS), a Mental Componet Summary (MCS), and subscale scores. Higher scores represented better outcomes, with an increase of 5 points considered to be clinically meaningful. The SF-36 score ranges from 0 to 100.

was not being completed in this study. Since the DLQI is needed for calculating the change from baseline in modified Composite Psoriatic Disease Activity Index (mCPDAI), the section pertaining to this was also removed. In addition, for consistency within the protocol, one of the exclusion criteria was changed from has previously received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) to has previously received any systemic immunosuppressants (e.g., azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within 4 weeks of the first administration of study agent.

These changes are not expected to have impacted the study outcome.

There were four amendments to the statistical analysis plan (SAP) since May 24, 2018. The most critical amendments included:

- Treatment failure criteria were amended to include "study termination for any reason", and to remove the criterion of "Met early escape (EE) criteria at Week 16 and initiated or increased the dose of one of the permitted concomitant medications." With this amendment, the TF criteria for the study were,
  - Discontinued study agent injections due to any reason
  - Terminated study participation due to any reason
  - Initiated or increased the dose of non-biologic DMARD (MTX, SSZ, HCQ, LEF) or oral - corticosteroids over baseline for PsA
  - Initiated protocol prohibited medications/therapies for PsA.
- The analysis method of other binary endpoints was changed from a GLMM model or logistic regression to a CMH test
- For the primary endpoint of ACR20 response at Week 24, the sensitivity analyses were changed from analyses based on MAR tipping point analysis to an exhaustive scenario imputation tipping analysis to cover all possible scenarios

Compliance with Good Clinical Practices

The Applicant attests that this study was conducted in compliance with ICH Good Clinical Practice guidelines, including the archival of essential documents, and applicable regulatory requirements. Additionally, informed consent was obtained prior to a subject's participation in the clinical trial.

Financial Disclosure

For study PSA3001, there was a significant payment of other sorts of $55,073.43 made to one principal investigator, (b) (6). (b) (6) participated as a primary investigator at (b) (6). The site enrolled 8 out of 381 total subjects enrolled in the study. The steps taken to minimize the potential bias of clinical study results include the clinical trial design. The clinical studies were blinded to the study site personnel and the participating subjects through the primary endpoint collection for the studies. Each active dose of investigational drug product was identical in appearance to its matched placebo and each subject was randomly assigned to their treatment arm independent of the investigator and the study site. Additionally, the number of subjects enrolled at the investigator site was small

compared to the total number of subjects enrolled in the overall study. Therefore, the financial payment is not expected to have impacted the study results.

Data Quality and Integrity
The submitted efficacy data were generally acceptable in quality and documentation. The statistical reviewer was able to reproduce the results of important primary and secondary analyses and performed additional analyses as needed.

Subject Disposition
A total of 382 subjects were randomized, however, one subject was inadvertently counted twice. Therefore, a total of 381 subjects were randomized and received at least 1 study drug administration at 86 sites in 13 countries which included the US. Of these, there were 7 sites (8.1%) and 17 subjects (4.5%) from US. Of the 381 subjects who were randomized and received study drug, 96.1% of the subjects completed Week 24 study visit. Table 5 provides the subject disposition at Week 24 with reasons for discontinuation of treatment.

The treatment completion rate of PSA3001 through Week 24 was 95.0% with the lowest treatment completion rate in the placebo group (90.5%). Of the subjects who discontinued treatment, the most common reason was adverse event (1.6% of randomized subjects) and only subjects in the placebo group reported lack of efficacy.

Table 5 Subject Disposition at Week 24 in PSA3001

	Placebo	Guselkumab q8w	Guselkumab q4w	Total
Randomized and received study drug	N=126 (%)	N=127 (%)	N=128 (%)	N=381 (%)
Completed study participation through Week 24	117 (92.9%)	124 (97.6%)	125 (97.7%)	366 (96.1%)
Treatment through Week 24	114 (90.5%)	123 (96.9%)	125 (97.7%)	362 (95.0%)
Discontinued treatment with follow-up through Week 24	3 (2.4%)	1 (0.8%)	0 (0%)	4 (1.0%)
Discontinued study participation prior to Week 24	9 (7.1%)	3 (2.4%)	3 (2.3%)	15 (3.9%)
Discontinued treatment prior to Week 24	12 (9.5%)	4 (3.1%)	3 (2.3%)	19 (5.0%)
Adverse event	2 (1.6%)	3 (2.4%)	1 (0.8%)	6 (1.6%)
Lack of efficacy	4 (3.2%)	0 (0%)	0 (0%)	4 (1.0%)
Withdrawal of consent	3 (2.4%)	0 (0%)	1 (0.8%)	4 (1.0%)
Lost to follow-up	1 (0.8%)	0 (0%)	0 (0%)	1 (0.3%)
Initiated prohibited medication	1 (0.8%)	0 (0%)	0 (0%)	1 (0.3%)
Death	1 (0.8%)	0 (0%)	0 (0%)	1 (0.3%)
Other	0 (0%)	1 (0.8%)	1 (0.8%)	2 (0.5%)

Abbreviations: N=number of subjects randomized and received treatment; q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Protocol Violations/Deviations

Major protocol deviations (MPDs) and other deviations related to study entry criteria and study agent administration were identified through review of blinded data during site monitoring activities or internal data review activities. In PSA3001, 16 subjects (12.7%) on placebo, 17 subjects (13.4%) on guselkumab q8w and 11 subjects (8.6%) on guselkumab q4w experienced MPDs. The MPDs were categorized according to predefined criteria based on the impact on primary and major secondary efficacy analyses and the safety of the subjects on an ongoing basis. The protocol deviations were varied with limited commonality (no most common reason was identified). No subjects were required to be discontinued due to deviations related to safety. There was no protocol deviation that had a potential impact on the analyses.

Demographic Characteristics

Table 6 presents the baseline demographics of the subjects in PSA3001. In general, the distribution of demographic characteristics was balanced across treatment groups. The study population was largely white (92%) and mostly from Europe. Approximately half of the subjects were male with an average age of 48 years. Anthropometric variables were comparable across arms.

Table 6 Baseline Demographics of Subjects in PSA3001

	Placebo (N=126)	**Guselkumab q8w (N=127)**	**Guselkumab q4w (N=128)**	**Total (N=381)**
Age (years)	49.0 (11.1)	48.9 (11.5)	47.4 (11.6)	48.4 (11.4)
Sex				
Female	65 (51.6%)	59 (46.5%)	62 (48.4%)	186 (48.8%)
Male	61 (48.4%)	68 (53.5%)	66 (51.6%)	195 (51.2%)
Race				
Asian	12 (9.5%)	10 (7.9%)	7 (5.5%)	29 (7.6%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (0.8%)	0 (0%)	1 (0.3%)
White	112 (88.9%)	116 (91.3%)	121 (94.5%)	349 (91.6%)
Not reported	2 (1.6%)	0 (0%)	0 (0%)	2 (0.5%)
Ethnicity				
Hispanic or Latino	2 (1.6%)	2 (1.6%)	0 (0%)	4 (1.0%)
Not Hispanic or Latino	122 (96.8%)	124 (97.6%)	128 (100.0%)	374 (98.2%)
Not reported	2 (1.6%)	1 (0.8%)	0 (0%)	3 (0.8%)
Geographic region				
Asia Pacific	17 (13.5%)	17 (13.4%)	11 (8.6%)	45 (11.8%)
Europe	94 (74.6%)	101 (79.5%)	109 (85.2%)	304 (79.8%)
North America	15 (11.9%)	9 (7.1%)	8 (6.3%)	32 (8.4%)
Body Weight (kg)	85.2 (18.7)	86.3 (19.9)	86.7 (17.7)	86.0 (18.8)
Height (cm)	169.3 (9.5)	169.9 (9.4)	170.0 (9.2)	169.7 (9.3)
BMI (kg/m^2)	29.6 (5.7)	29.9 (6.4)	29.9 (5.4)	29.8 (5.8)

Abbreviations: N=number of subjects randomized and received treatment; BMI=Body Mass Index; Cell contents are mean (standard deviation) for continuous characteristics or frequency (percentage relative to N) for categorical characteristics; q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Table 7 presents disease characteristics for subjects in PSA3001. Baseline disease characteristics, including disease duration, age at onset, disease subtype, and enthesitis at baseline, were generally similar across treatment groups. The proportion of subjects with dactylitis at baseline was numerically greater in the placebo and guselkumab q8w groups, than the guselkumab q4w group. Mean (standard deviation) tender and swollen joint counts were generally similar across treatment groups (placebo 20 (14) and 10(7); guselkumab q8w 20(14) and 11 (9); guselkumab q4w 18(13.1) and 9 (6), respectively), while baseline median CRP level was lowest in the guselkumab q4w (0.571 mg/dL), as compared to the placebo (0.787 mg/dL) and guselkumab q8w (0.663 mg/dL) groups. The proportion of subjects who received prior anti-TNFα therapy, with baseline non-biologic DMARD use, and with baseline MTX use were also similar across treatment groups in PSA3001.

Table 7 Baseline Disease Characteristics and Therapies for PSA3001

	Placebo (N=126)	Guselkumab q8w (N=127)	Guselkumab q4w (N=128)	Total (N=381)
PsA disease duration (years)	7.2 (7.6)	6.4 (5.9)	6.6 (6.3)	6.8 (6.6)
Age at PsA diagnosis (years)	42.3 (11.6)	43.0 (12.1)	41.3 (12.5)	42.2 (12.0)
PsA subtype				
Distal interphalangeal joint involvement	9 (7.1%)	11 (8.7%)	8 (6.3%)	28 (7.3%)
Polyarticular arthritis with absence of rheumatoid nodules	56 (44.4%)	58 (45.7%)	52 (40.6%)	166 (43.6%)
Arthritis mutilans	0 (0%)	2 (1.6%)	0 (0%)	2 (0.5%)
Asymmetric peripheral arthritis	37 (29.4%)	30 (23.6%)	43 (33.6%)	110 (28.9%)
Spondylitis with peripheral arthritis	24 (19.0%)	26 (20.5%)	25 (19.5%)	75 (19.7%)
Enthesitis at Baseline	77 (61.1%)	72 (57.1%)	73 (57.0%)	222 (58.4%)
Dactylitis at Baseline	55 (43.7%)	49 (38.9%)	38 (29.7%)	142 (37.4%)
Prior Anti-TNFα Therapy	39 (31.0%)	41 (32.3%)	38 (29.7%)	118 (31.0%)
1 therapy	35 (27.8%)	34 (26.8%)	33 (25.8%)	102 (26.8%)
2 therapies	4 (3.2%)	7 (5.5%)	5 (3.9%)	16 (4.2%)
Baseline non-biologic DMARDs use	82 (65.1%)	83 (65.4%)	82 (64.1%)	247 (64.8%)
Baseline MTX use	71 (56.3%)	68 (53.5%)	72 (56.3%)	211 (55.4%)

Abbreviations: N=number of subjects randomized and received treatment; PsA=psoriatic arthritis; Cell contents are mean (standard deviation) for continuous characteristics or frequency (percentage relative to N) for categorical characteristics; TNFα=tumor necrosis factor α; DMARDs=disease modifying antirheumatic drugs; MTX=methotrexate; q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Through Week 24, mean treatment compliance was 99.9% in the overall population (placebo or guselkumab). The compliance was calculated as percentage of number of doses actually received relative to number of doses scheduled prior to Week 24 for subjects who had not terminated study treatment prior to Week 24 or through last dose for subjects who had terminated study treatment prior to Week 24. Using this definition, guselkumab injection compliance was 100% for both dose groups.

Concomitant use of NSAIDs/other analgesics, oral corticosteroids and selected non-biologic DMARDs was allowed if used at baseline and the dose/route of administration were to be stable through Week 24. The majority of subjects were using concomitant medications at baseline (94.2%) and post-baseline (97.4%).

At Week 16, 31 (8.1%) subjects met early escape criteria and were allowed to initiate or increase the dose of permitted concomitant medications up to the maximum allowed dose as selected by the investigator: 24 subjects in the placebo group, 4 subjects in the guselkumab q8w group, and 3 subjects in the guselkumab q4w group. Thirteen of the 24 eligible subjects in the placebo group and 1 of the 4 eligible subjects in the guselkumab q8w group initiated or increased permitted medications. The remaining subjects who met EE criteria, including all 3 subjects in the guselkumab q4w group, did not adjust their concomitant medications.

8.1.2. Study PSA3002

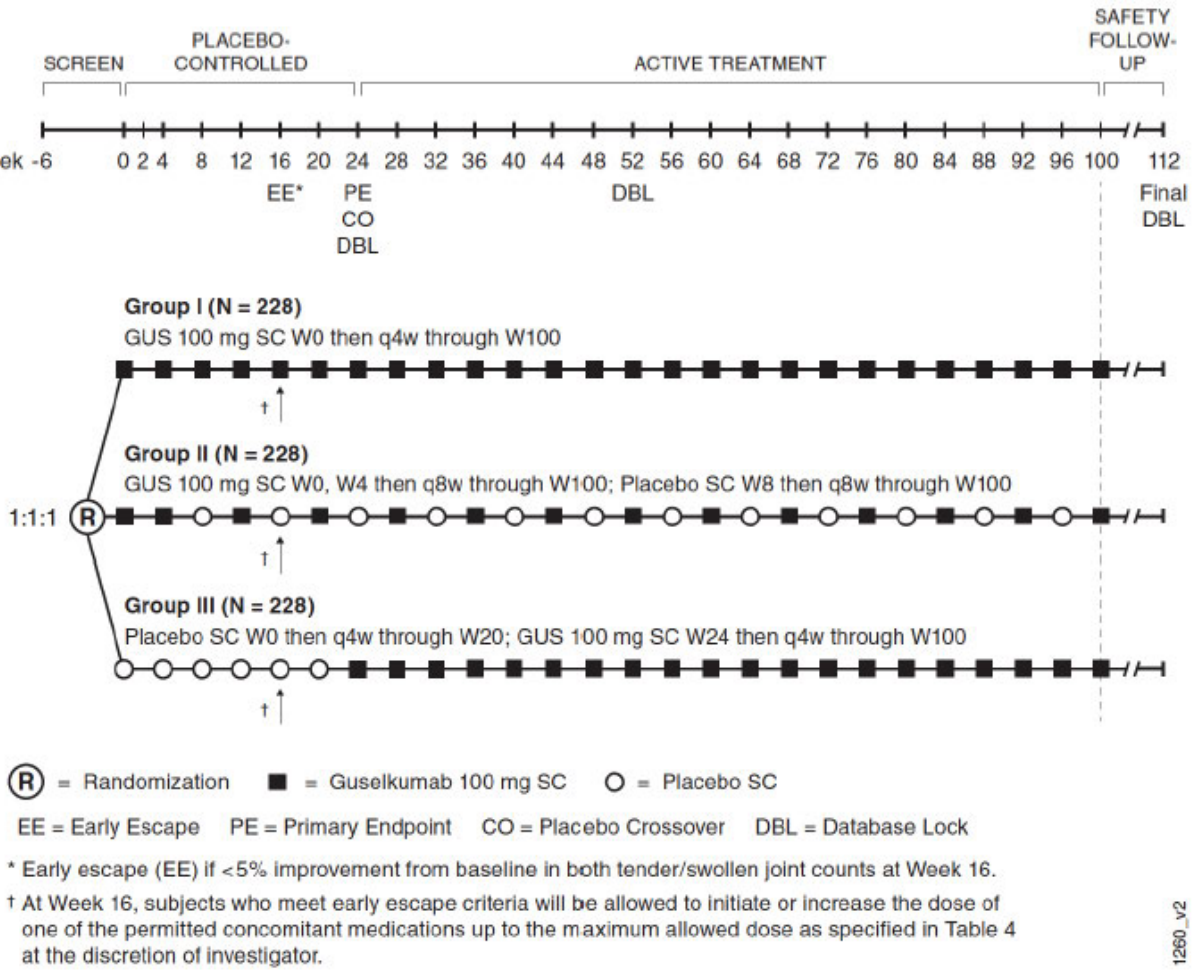
Trial Design

This was a phase 3 randomized, double-blind, placebo-controlled, multicenter, 3-arm study of guselkumab in 739 subjects with active PsA who were biologic naïve and had an inadequate response to standard therapies. The study consisted of a screening phase of up to six weeks, and a blinded treatment phase of approximately two years (ie, 100 weeks). The placebo-controlled period was from Week 0 to Week 24 followed by an active treatment phase from Week 24 to Week 100. There was a safety follow-up phase of 12 weeks after the last administration of study agent. The subjects were randomized in a 1:1:1 ratio into one of the following three treatment groups:

- **Group I** (n=245): Guselkumab 100 mg SC every 4 weeks (q4w) from Week 0 through Week 100
- **Group II** (n=248): Guselkumab 100 mg SC at Weeks 0 and 4 then q8w (Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind
- **Group III** (n=246): Placebo SC q4w from Week 0 to Week 20 and cross over at Week 24 to receive guselkumab 100 mg SC q4w from Week 24 through Week 100

As seen in Figure 4, at Week 24, all subjects in the placebo group (Group III) crossed over to receive guselkumab 100 mg SC q4w through Week 100 to collect additional safety data for the 100 mg SC q4w dose. Subjects in the guselkumab groups (Groups I and II) remained on the dosing regimen they were randomized to at Week 0, through Week 100.

Figure 4 Study PSA3002 Schematic



Source: Study PSA3002 Protocol

Dosage and Administration

Guselkumab 100 mg and matching liquid placebo for guselkumab were provided in a single-use prefilled syringe (PFS) assembled with the UltraSafe PLUS™ Passive Needle Guard (PFS-U). It was administered at the site by a health care professional until the subject (or caregiver) was trained for self-administration. Study agent was administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, subjects would self-administer study agent at the investigative site under the supervision of a health care professional. The option to begin self-administration of study agent at home began after Week 52. Doses are as described above for groups I, II, and III.

Rescue

At Week 16, all subjects in Groups I, II, and III with < 5% improvement from baseline in both tender and swollen joint counts were considered as meeting early escape criteria. Subjects meeting early escape criteria remained on the dosing regimen assigned at Week 0 but

could initiate or increase the dose of one of the permitted concomitant medications including: NSAIDs and other analgesics, oral corticosteroids, and selected non-biologic DMARDs (limited to MTX, SSZ, HCQ, or LEF). Titration to a stable dose of the medication should have been completed for subjects qualifying for early escape by the Week 24 visit.

Concurrent medications
Permitted concomitant medications in study PSA3002 included NSAIDs and other analgesics, oral corticosteroids up to an equivalent to 10 mg/day of prednisone, methotrexate up to 25mg/ week, sulfasalazine up to 3 grams/ day, hydroxychloroquine up to 400 mg/ day, and leflunomide up to 20 mg/ day.

Study Location and Dates
This study was conducted at 118 sites in 13 countries: Malaysia (n=5), Taiwan (n=1), Bulgaria (n=7), Czech Republic (n=7), Estonia (n=4), Latvia (n=3), Lithuania (n=4), Poland (n=15), Russia (n=25), Spain (n=9), Turkey (n=8), Ukraine (n=28), and United States (n=2).

The study period was from July 13, 2017 (date first subject signed informed consent) to March 6, 2019 (date of last observation for last subject recorded as part of the database for interim analysis).

Main Inclusion Criteria

- A man or a woman at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
- A diagnosis of PsA for at least six months before the first administration of study agent and meet ClASsification criteria for Psoriatic ARthritis (CASPAR) at screening
- Active PsA as defined by: at least five swollen joints and at least five tender joints at screening and at baseline and CRP ≥0.6 mg/dL at screening from the central laboratory.
- At least one of the PsA subsets: distal interphalangeal joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis
- Active plaque psoriasis, with at least one psoriatic plaque of ≥2cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis
- Active PsA despite previous non-biologic DMARD, apremilast, and/or NSAID therapy
- If using non-biologic DMARDs (limited to MTX, SSZ, HCQ, or LEF), subjects should have started treatment at least three months and the dose must be stable for at least four weeks before first administration of study agent. If not using MTX, SSZ, or HCQ, must not have received for at least four weeks before first administration of study agent. If not using LEF, must not have received for at least 12 weeks before first administration of study agent
- If using NSAIDs or other analgesics for PsA, subjects must be on a stable dose for at least two weeks before first administration of study agent. If not using NSAIDs or other analgesics for PsA, must not have received NSAIDs or other analgesics for PsA within two weeks before first administration of study agent

- If using oral corticosteroids for PsA, subjects had to be on a stable dose equivalent to ≤10 mg of prednisone/day for at least two weeks before first administration of study agent. If not using oral corticosteroids, the subject must not have received oral corticosteroids within two weeks before first administration of study agent
- Contraceptive use by men or women had to be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies
- Eligible based on tuberculosis screening criteria
- Agreed not to receive a live virus or live bacterial vaccination during the study, or within 12 weeks after the last administration of study agent
- Agreed not to receive a bacillus Calmette-Guérin (BCG) vaccination during the study, and within 12 months after the last administration of study agent
- Screening laboratory test results within the following parameters:
    - Hemoglobin ≥8.5 g/dL
    - White blood cells ≥3.5 x 10^3/µL
    - Neutrophils ≥1.5 x 10^3/µL
    - Platelets ≥100 x 10^3/µL
    - Serum creatinine ≤1.5 mg/dL
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase levels had to be ≤1.5 times the upper limit of normal range for the central laboratory conducting the test
- Agreed to avoid prolonged sun exposure and agree not to use tanning booths or other ultraviolet (UV) light sources from the first administration of study agent through 12 weeks after the final dose of study agent (for subjects with skin lesions or with documented history of psoriasis)
- Refrained from the use of complementary therapies for PsA or psoriasis including ayurvedic medicine, traditional Taiwanese, Korean, or Chinese medication(s) and acupuncture within two weeks before the first study agent administration and through Week 52

Main Exclusion Criteria

- Other inflammatory diseases that might have confound the evaluations or benefit of guselkumab therapy, including but not limited to RA, axial spondyloarthritis (this did not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, or Lyme disease
- Had previously received any biologic treatment
- Had ever received tofacitinib, baricitinib, filgotinib, peficitinib (ASP015K), decernotinib (VX-509), or any other Janus kinase (JAK) inhibitor
- Had received any systemic immunosuppressants (eg, azathioprine, cyclosporine, 6 thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus) within four weeks of the first administration of study agent
- Was receiving two or more non-biologic DMARDs
- Had received non-biologic DMARDs (other than MTX, SSZ, HCQ, LEF) including, but not

limited to chloroquine, gold preparations, and penicillamine within four weeks before the first administration of study agent

- Had received apremilast within four weeks prior to the first administration of study agent
- Had received phototherapy or any systemic medications/treatments that could affect psoriasis evaluations (including, but not limited to, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, fumaric acid derivatives, within four weeks of the first administration of study agent
- Had used topical medications/treatments that could affect psoriasis evaluations within two weeks of the first administration of any study agent
- Had received epidural, intra-articular, intramuscular, or IV corticosteroids, including adrenocorticotropic hormone during the four weeks before first administration of study agent
- Had received lithium within four weeks of the first administration of any study agent
- Had received an experimental antibody or biologic therapy within six months prior to the first administration of study agent, or received any other experimental therapy, including an investigational medical device, or new investigational agent within 90 days or 5 half-lives (whichever is longer) prior to the first administration of study agent or was enrolled in another study using an investigational agent or procedure
- Had unstable suicidal ideation or suicidal behavior in the last six months
- Had a history or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (with the exception of PsA), psychiatric, genitourinary, or metabolic disturbances
- Had unstable cardiovascular disease, defined as a recent clinical deterioration (e.g., unstable angina, rapid atrial fibrillation, or transient ischemic attack) in the last three months prior to screening or a cardiac hospitalization within the last three months prior to screening
- Had a malignancy or has a history of malignancy within five years before screening
- Had a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly
- Had a history of chronic or recurrent infectious disease or infection
- Had a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study agent)
- Was pregnant, breastfeeding, or planning a pregnancy (both men and women) within 12 weeks after receiving the last administration of study agent
- Had a nonplaque form of psoriasis or drug-induced psoriasis
- Had received, or is expected to receive, any live virus or bacterial vaccination within three months before the first administration of study agent
- Had a BCG vaccination within 12 months of screening

- Had known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments
- Had major surgery (e.g., requiring general anesthesia and hospitalization) within eight weeks before screening

Safety Variables of this Study
There was an independent Data Monitoring Committee to monitor unblinded data on an ongoing basis through at least the Week 24 database lock (scheduled at Weeks 24, 52, and 112) to ensure the continuing safety of the subjects enrolled in this study. Information on adverse events (including injection site and allergic reactions), clinical laboratory tests (including chemistry, hematology, C-reactive protein), physical examinations, vital signs, suicidal ideation or behavior (using the electronic Columbia-Suicide Severity Rating Scale questionnaires), concomitant medication review, and early detection of tuberculosis was collected as per Table 42, Time and Events Schedule.

Subject Discontinuation Criteria
Reasons for discontinuation of study treatment and for a subject to be withdrawn in study PSA3002 were the same as those in study PSA3001 as discussed above.

Study Endpoints
Primary Endpoint:
The primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24.

Key Secondary Endpoints:
The secondary endpoints in this study that were included in the multiplicity control procedure were:

- Change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI) score at Week 24
- Proportion of subjects with a psoriasis response of an Investigator's Global Assessment (IGA) (ie, an IGA psoriasis score of 0 [cleared] or 1 [minimal] AND ≥2-grade reduction from baseline) at Week 24 among the subjects with ≥3% body surface area (BSA) psoriatic involvement and an IGA score of ≥2 (mild) at baseline
- Change from baseline in modified van der Heijde-Sharp[8] (vdH-S) score at Week 24

[8] The total modified vdH-S score is an original vdH-S score, modified for the purpose of PsA radiological damage assessment, by addition of distal interphalangeal joints of the hands and assessment of pencil in cup and gross osteolysis deformities. The total modified vdH-S score includes the joint erosion scorea and the joint space narrowing score. The worst possible total modified vdH-S score for PsA is 528.

- Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline with combined data from PSA3001 and PSA3002
- Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline with combined data from PSA3001 and PSA3002
- Change from baseline in 36-item Short Form Health Survey Physical Component Summary (SF-36 PCS) at Week 24
- Change from baseline in SF-36 Mental Component Summary [9](MCS) at Week 24

Additional Endpoints:
The Applicant evaluated multiple other supportive endpoints outside of the multiplicity control procedure including endpoints related to reduction of signs and symptoms and physical function, endpoints related to health-related quality of life, and endpoints related to radiographic progression. These included:

- Proportion of subjects who achieved an ACR 50 response at Week 24
- Proportion of subjects who achieved an ACR 70 response at Week 24
- Proportion of subjects who achieved an ACR 20 response at Week 16
- Proportion of subjects who achieved an ACR 50 response at Week 16
- Change from baseline in DAS28 (C-reactive protein [CRP]) at Week 24
- Proportion of subjects with resolution of enthesitis at Week 24 among the subjects with enthesitis at baseline
- Change from baseline in enthesitis score (based on Leeds Enthesitis Index [LEI]) at Week 24 among the subjects with enthesitis at baseline
- Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline
- Change from baseline in dactylitis scores at Week 24 among the subjects with dactylitis at baseline
- Change from baseline in modified vdH-S score by visit over time through Week 100
- Change from baseline in modified vdH-S erosion score by visit over time through Week 100
- Change from baseline in modified vdH-S joint space narrowing (JSN) score by visit over time through Week 100

Sample Size Determination
For PSA3002, a total of 684 subjects were planned to be randomized in a 1:1:1 ratio to each of 3 treatment groups assuming a 45% ACR20 response in the guselkumab group and a 25% ACR20 response in the placebo group at Week 24 to provide approximately 99% statistical power at a 2-sided significance level of 0.05, and also assuming an overall mean change of 0.9 from baseline in vdH-S score in the placebo group, an overall mean change of 0.3 in the guselkumab group, and a standard deviaion of 2.5 for each treatment group to provide an approximately 90% statistical power at a two-sided significance level of 0.05.

[9] Refer to a footnote for SF-36 PCS

Protocol Amendments

There was one amendment to study PSA3002 submitted on January 23, 2018 (original protocol was submitted on March 16, 2017). The majority of changes were clarifications that were not major. In addition to these, were the following changes to the protocol:

- One change was allowing for a one time reduction in steroid dose after Week 24, as it may be medically appropriate.
- Another addition was that in addition to Sponsor-provided electronic tablets, subjects were also allowed to complete the eC-SSRS questionnaire through an Interactive Voice Response System if available. Study site personnel would train the subjects on how to use the electronic device and/or a telephone system.
- Treatment failure criteria was amended to include study termination for any reason. One of the treatment failure criteria: "Met early escape criteria at Week 16 and initiated or increased the dose of one of the permitted concomitant medications" was removed

The clinical changes are not expected to have impacted the study outcome.

There were four amendments to the statistical analysis plan (SAP) since May 24, 2018. The most critical amendments included:

- Treatment failure criteria were amended to include "study termination for any reason", and to remove the criterion of "Met early escape (EE) criteria at Week 16 and initiated or increased the dose of one of the permitted concomitant medications." With this amendment, the TF criteria for the study were,
  - Discontinued study agent injections due to any reason
  - Terminated study participation due to any reason
  - Initiated or increased the dose of non-biologic DMARD (MTX, SSZ, HCQ, LEF) or oral - corticosteroids over baseline for PsA
  - Initiated protocol prohibited medications/therapies for PsA.
- The analysis method of other binary endpoints was changed from a GLMM model or logistic regression to a CMH test
- For the primary endpoint of ACR20 response at Week 24, the sensitivity analyses were changed from analyses based on MAR tipping point analysis to an exhaustive scenario imputation tipping analysis to cover all possible scenarios
- Added/modified sensitivity analysis for change from baseline in vdH-S score at Week 24
- Revised definition for FAS1-SD. It includes all randomized subjects who received at least 1 (partial or complete) dose of study agent, regardless of whether they had a modified vdH-S score at baseline

Compliance with Good Clinical Practices

The Applicant attests that this study was conducted in compliance with ICH Good Clinical Practice guidelines, including the archival of essential documents, and applicable regulatory requirements. Additionally, informed consent was obtained prior to a subject's participation in the clinical trial.

Financial Disclosure

For study PSA3002, there was a significant payment made to one principal investigator, (b) (6) (b) (6), and two sub-investigators, (b) (6), and (b) (6) (b) (6) and therefore there was no opportunity to introduce bias. (b) (6) and (b) (6) sites (b) (6). Given that these three investigators' activity was limited to (b) (6) study, the financial payments are not expected to have impacted the study results.

Subject Disposition

Table 8 provide the subject disposition at Week 24 with reasons for discontinuation of treatment. A total of 741 subjects were randomized, however, 2 subjects were randomized in error and never treated. Therefore, a total of 739 subjects were randomized and received at least 1 study drug administration at 118 sites in 13 countries which included US. Of these, there were 2 sites (1.7%) with 6 subjects (0.8%) from the US. Of the 739 subjects who were randomized and received study drug, 98% of the subjects completed Week 24 study visit.

The treatment completion rate of PSA3002 was 96.9%, and all three groups resulted in similarly high completion rate. Of the subjects who discontinued treatment, the most common reason was adverse event (1.6% of randomized and treated subjects). Lack of efficacy was reported as a reason for discontinuation in both guselkumab dose groups, but not in the placebo group.

Table 8 Subject Disposition at Week 24 in PSA3002

	Placebo	Guselkumab q8w	Guselkumab q4w	Total
Randomized and received study drug	N=246 (%)	N=248 (%)	N=245 (%)	N=739 (%)
Completed study through Week 24	244 (99.2%)	242 (97.6%)	238 (97.1%)	724 (98.0%)
Treatment through Week 24	240 (97.6%)	240 (96.8%)	236 (96.3%)	716 (96.9%)
Discontinued treatment with follow-up through Week 24	4 (1.6%)	2 (0.8%)	2 (0.8%)	8 (1.1%)
Discontinued study participation prior to Week 24	2 (0.8%)	6 (2.4%)	7 (2.9%)	15 (2.0%)
Discontinued treatment prior to Week 24	6 (2.4%)	8 (3.2%)	9 (3.7%)	23 (3.1%)
Adverse event	4 (1.6%)	2 (0.8%)	6 (2.4%)	12 (1.6%)
Lack of efficacy	0 (0%)	3 (1.2%)	3 (1.2%)	6 (0.8%)
Withdrawal of consent	1 (0.4%)	1 (0.4%)	0 (0%)	2 (0.3%)
Lost to follow-up	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)
Other	1 (0.4%)	1 (0.4%)	0 (0%)	2 (0.3%)

Abbreviations: N=number of subjects randomized and received treatment; q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Protocol Violations/Deviations

Major protocol deviations (MPDs) and other deviations related to study entry criteria and study agent administration were identified through review of blinded data during site monitoring activities or internal data review activities. In PSA3002, 23 subjects (9.3%) in placebo, 18 subjects (7.3%) in guselkumab q8w and 17 subjects (6.9%) on guselkumab q4w had MPDs. The MPDs were categorized according to predefined criteria based on the impact on primary and major secondary efficacy analyses and the safety of the subjects on an ongoing basis. A subject may have had multiple deviations and may have been included under more than 1 deviation category. The most common reason for protocol deviation across all three treatment groups was 'entered but did not satisfy criteria'. Subjects with deviations related to concomitant medications were further evaluated to determine if they were treatment failures for the primary and major secondary analyses. Subjects with deviations related to safety and who remained under treatment when the deviation was identified were discontinued. There was no protocol deviation that had a potential impact on the analyses.

Demographic Characteristics

Table 9 presents the baseline demographics of the subjects in PSA3002. In general, the distribution of demographic characteristics was balanced across treatment groups. The study population was largely white (98%) and mostly from Europe. Approximately half of the subjects

were male with an average age of 46 years. Anthropometric variables were comparable across arms.

Table 9 Baseline Demographics of Subjects in PSA3002

	Placebo (N=246)	Guselkumab q8w (N=248)	Guselkumab q4w (N=245)	Total (N=739)
Age (years)	46.3 (11.7)	44.9 (11.9)	45.9 (11.5)	45.7 (11.7)
Sex				
Female	129 (52.4%)	119 (48.0%)	103 (42.0%)	351 (47.5%)
Male	117 (47.6%)	129 (52.0%)	142 (58.0%)	388 (52.5%)
Race				
Asian	4 (1.6%)	8 (3.2%)	3 (1.2%)	15 (2.0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)
White	242 (98.4%)	240 (96.8%)	242 (98.8%)	724 (98.0%)
Ethnicity				
Hispanic or Latino	1 (0.4%)	1 (0.4%)	0 (0%)	2 (0.3%)
Not Hispanic or Latino	245 (99.6%)	247 (99.6%)	245 (100.0%)	737 (99.7%)
Geographic region				
Asia Pacific	3 (1.2%)	7 (2.8%)	3 (1.2%)	13 (1.8%)
Europe	240 (97.6%)	240 (96.8%)	240 (98.0%)	720 (97.4%)
North America	3 (1.2%)	1 (0.4%)	2 (0.8%)	6 (0.8%)
Body Weight (kg)	84.0 (19.7)	83.0 (19.3)	85.8 (19.5)	84.3 (19.5)
Height (cm)	170.2 (9.0)	170.0 (9.7)	171.6 (9.4)	170.6 (9.3)
BMI (kg/m^2)	29.0 (6.4)	28.7 (6.3)	29.3 (5.9)	28.9 (6.2)

Abbreviations: N=number of subjects randomized and received treatment; BMI=Body Mass Index; Cell contents are mean (standard deviation) for continuous characteristics or frequency (percentage relative to N) for categorical characteristics; q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Table 10 presents disease characteristics for subjects in study PSA3002. Baseline disease characteristics, including disease duration, age at onset, disease subtype, enthesitis and dactylitis at baseline, were generally similar across treatment groups. Mean (standard deviation) tender and swollen joint counts were generally similar across treatment groups (placebo 22 (13) and 12 (7); guselkumab q8w 20 (12) and 12 (7); guselkumab q4w 22 (14) and 13 (8), respectively), as were baseline median CRP levels (placebo 1.155 mg/dL, guselkumab q8w 1.310 mg/dL, and guselkumab q4w 1.160 mg/dL). The modified vdH-S score at baseline was similar across treatment groups in PSA3002. The proportion of subjects on baseline non-biologic DMARDs and baseline MTX were also similar across treatment groups.

Table 10 Baseline Disease Characteristics and Therapies for PSA3002

	Placebo (N=246)	Guselkumab q8w (N=248)	Guselkumab q4w (N=245)	Total (N=739)
PsA disease duration (years)	5.8 (5.6)	5.1 (5.5)	5.5 (5.9)	5.5 (5.7)
Age at PsA diagnosis (years)	41.1 (11.9)	40.4 (11.8)	41.0 (11.2)	40.8 (11.6)
PsA subtype				
Distal interphalangeal joint involvement	13 (5.3%)	17 (6.9%)	17 (6.9%)	47 (6.4%)
Polyarticular arthritis with absence of rheumatoid nodules	87 (35.4%)	101 (40.7%)	93 (38.0%)	281 (38.0%)
Arthritis mutilans	2 (0.8%)	2 (0.8%)	2 (0.8%)	6 (0.8%)
Asymmetric peripheral arthritis	45 (18.3%)	55 (22.2%)	47 (19.2%)	147 (19.9%)
Spondylitis with peripheral arthritis	99 (40.2%)	73 (29.4%)	86 (35.1%)	258 (34.9%)
Enthesitis at Baseline	178 (72.7%)[1]	158 (63.7%)	170 (69.4%)	506 (68.6%)
Dactylitis at Baseline	99 (40.4%)[1]	111 (44.8%)	121 (49.4%)	331 (44.9%)
Modified vdH-S score at Baseline: total score	23.8 (37.8)	23.0 (37.7)	27.2 (42.3)	24.7 (39.3)
Baseline non-biologic DMARDs use	172 (69.9%)	170 (68.5%)	170 (69.4%)	512 (69.3%)
Baseline MTX use	156 (63.4%)	141 (56.9%)	146 (59.6%)	443 (59.9%)

Abbreviations: N=number randomized and received treatment; PsA=psoriatic arthritis; Cell contents are mean (standard deviation) for continuous characteristics or frequency (percentage relative to N) for categorical characteristics; DMARDs=disease modifying antirheumatic drugs; MTX=methotrexate; [1]Based on N=245, one in placebo had unreported enthesitis and dactylitis at baseline: q8w=once every eight weeks; q4w=once every four weeks; [Source: Reviewer]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Through Week 24 study, mean treatment compliance was 99.6% in the overall population (placebo or guselkumab). The compliance was calculated as percentage of number of doses actually received relative to number of doses scheduled prior to Week 24 for subjects who had not terminated study treatment prior to Week 24 or through last dose for subjects who had terminated study treatment prior to Week 24. Using this definition, guselkumab injection compliance was similar across treatment groups.

Concomitant use of NSAIDs/other analgesics, oral corticosteroids and selected non-biologic DMARDs was allowed if used at baseline and the dose/route of administration were to be stable through Week 24. The majority of subjects were using concomitant medications at baseline (96.1%) and post-baseline (96.8%).

At Week 16, 63 (8.5%) subjects met early escape (EE) criteria and were allowed to initiate or increase the dose of one of the permitted concomitant medications up to the maximum protocol-allowed dose as selected by the investigator: 38 subjects in the placebo group, 13 subjects in the guselkumab q8w group, and 12 subjects in the guselkumab q4w group. Fourteen of the 38 eligible subjects in the placebo group, 6 of the 13 eligible subjects in the guselkumab q8w group, and 7 of the 12 eligible subjects in the guselkumab q4w group initiated or increased their permitted medications. The remaining subjects who met EE criteria did not adjust their concomitant medications.

8.2. Statistical Methodologies for PSA3001 and PSA3002

Defining Estimands

For both studies, to address intercurrent events when defining the clinical question of interest, the Applicant specified a composite variable strategy. Under this approach, an intercurrent event is considered in itself to be informative about the subject's outcome and is therefore incorporated into the definition of the variable[10]. In this case, a subject who experienced one or more of the specified intercurrent events was treated as a treatment failure (TF) from the earliest date of that event onward through Week 24. These intercurrent events, also referred to as "TF criteria", included:

- Discontinuing study agent injections due to any reason
- Terminating study participation due to any reason
- Initiating or increasing the dose of non-biologic DMARD (MTX, SSZ, HCQ, LEF) or oral corticosteroids over baseline for PsA
- Initiating protocol prohibited medications/therapies for PsA.

For binary response variables, if a subject met any of the TF criteria, the subject was considered a non-responder. For continuous variables, the Applicant applied this composite strategy by imputing a score of no improvement (no change from baseline) from the time the subject met any TF criteria. The composite strategy was used in the main estimand analyzed for all primary and major secondary efficacy endpoints through Week 24, except for the modified vdH-S Score in PSA3002.

In addition, the Applicant specified a treatment policy strategy as a supplemental analysis for all primary and major secondary endpoints and the main analysis of the modified vdH-S Score in PSA3002. Under this approach, the occurrence of the intercurrent event was considered irrelevant in defining the treatment effect of interest: the value for the variable of interest was used regardless of whether or not the intercurrent event occurs. Thus, in this case, the

[10] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

Applicant planned to use all observed data collected for the endpoint, regardless of whether or not the subject had met any TF criterion.

Analysis Sets

The main efficacy analysis population in each study included all randomized subjects who received at least one dose (complete or partial) of study agent. Data from all subjects in this population was analyzed according to randomized treatment group regardless of the treatment actually received. This efficacy analysis set was labeled as full analysis set 1 (FAS1).

The pre-specified analysis sets for most secondary endpoints were FAS1. However, for Investigator's Global Assessment of Psoriasis (IGA) response, the analysis set included only data from FAS1 who had ≥3% Body Surface Area (BSA) psoriatic involvement and an IGA score of ≥2 at baseline. For the change from baseline in enthesitis score and the proportion of subjects with resolution of enthesitis, the analysis set included data from all subjects in FAS1 who had at least one tender enthesitis among 6 sites included in the LEI, at baseline. For the change from baseline in dactylitis score and the proportion of subjects with resolution of dactylitis, the analysis set included data from all subjects in FAS1 who had dactylitis at baseline.

Primary Efficacy Endpoint: ACR20 at Week 24

Main Analysis

The primary endpoint was the proportion of subjects who achieved an ACR20 response at Week 24. In the primary analysis, subjects who met any TF criteria prior to Week 24 were considered as non-responders at Week 24 regardless of the observed ACR20 response status. Subjects with missing data for ACR20 response status were treated as non-responders (referred to as non-responder imputation or NRI).

The treatment difference between each dose group versus the placebo group was tested using a Cochran-Mantel-Haenszel (CMH) test. The CMH test was stratified by the randomization stratification factors (baseline use of non-biologic DMARD (yes, no) and prior exposure to anti-TNFα agents (yes, no) for PSA3001; baseline use of non-biologic DMARD (yes, no) and most recent CRP value (<2.0 mg/dL, ≥2.0 mg/dL) for PSA3002) prior to randomization. The magnitude of the treatment difference was also estimated by the difference in ACR20 response rates between each dose group and placebo group with a 95% confidence interval (CI) calculated based on Wald statistics.

Sensitivity analyses and supplementary analyses

As a supplementary analysis, the Applicant evaluated ACR20 response using the treatment policy strategy. The observed ACR20 responses for all subjects were used regardless of whether TF criteria were met prior to Week 24, and the missing ACR20 response for all subjects were imputed by a multiple imputation (MI) method under the assumption of a missing at random (MAR) mechanism. Imputation was based on the Full Conditional Specification (FCS) regression

method using a multivariate imputation model, and each imputation was restricted to only impute within the possible range of values for the given variable. For ACR20 response, the imputation was performed on each component with missing data and then response status was determined based on such imputed components. Treatment comparisons for each imputation data set were based on CMH test stratified by stratifications factors for each study. The analysis results were combined according to Rubin's[11] rules and the p-value for testing the treatment difference was obtained.

To evaluate the robustness of the primary efficacy results to missing data assumptions, the Applicant performed a sensitivity analysis using a tipping point approach. This analysis, referred to by the Applicant as the "exhaustive scenario imputation tipping point analysis" was conducted by imputing all possible combinations of responder and non-responders for subjects with missing data on each treatment arm. This was a single imputation approach and did not account for underlying variability. This imputation was only for missing observations, and treatment failures were treated as non-responders as defined by the composite strategy. The CMH test with stratification factors was used to compare each dose group versus the placebo group. Note that the Applicant performed a chi-square test without stratification factors.

The Applicant also performed two-dimensional tipping point analyses based on the treatment policy estimand to assess the robustness of these results to the assumption of MAR. The predicted response rate for each missing observation was obtained individually by averaging responses across imputations from FCS MI based on the MAR assumption. Then, a shift was added onto the predicted response rate to create an adjusted response rate. This adjusted response rate was used to draw imputations from the Bernoulli distribution for each missing subject for this tipping point analysis. Since subjects each had their own response rate, different subjects reached the minimum response rate at different shift. For these analyses, only one quadrant was investigated, where guselkumab q8w (or guselkumab q4w) group has response rate lowered (a shift ranged from 0 to -100%) and the placebo group has response rate added (a shift ranged from 0 to 100%) for the missing on each group. With the new response rate, the missing response was imputed 200 times based on a Bernoulli distribution and treatment comparison was performed for each imputation. The p-value was based on the combined standardized Wilson-Hilferty transformation of the CMH test statistics from each imputation. The statistical reviewer was able to replicate these tipping point analyses.

Key Secondary Endpoints

Multiplicity Control Procedures

Each study used a gate-keeping hierarchy for controlling Type 1 error probability for testing multiple key secondary endpoints across multiple doses against placebo. The hierarchies for

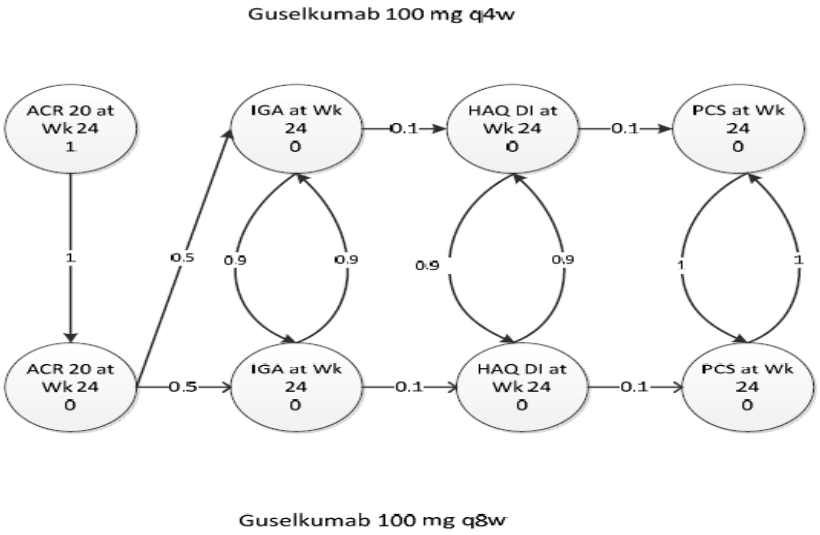
[11] Rubin, DB. Multiple Imputations for Nonresponse in Survey, New York: John Wiley & Sons. 1987.

evaluating each dose were designed to control the overall probability of Type 1 error at 0.025 (two-sided 5% significance level) in both studies (Figure 5 and Figure 6).

In PSA3001, the initial testing order of the secondary endpoints, tested at each dose versus placebo were:

- Proportion of subjects who achieved an Investigator's Global Assessment of Psoriasis (IGA) response at Week 24 among the subjects with ≥3% Body Surface Area (BSA) psoriatic involvement and an IGA score of ≥2 at baseline
- Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 24
- Change from baseline in 36-Item Short-form Health Survey Physical Component Score (SF-36 PCS) at Week 24

Figure 5 Multiple Comparison Procedure for PSA3001

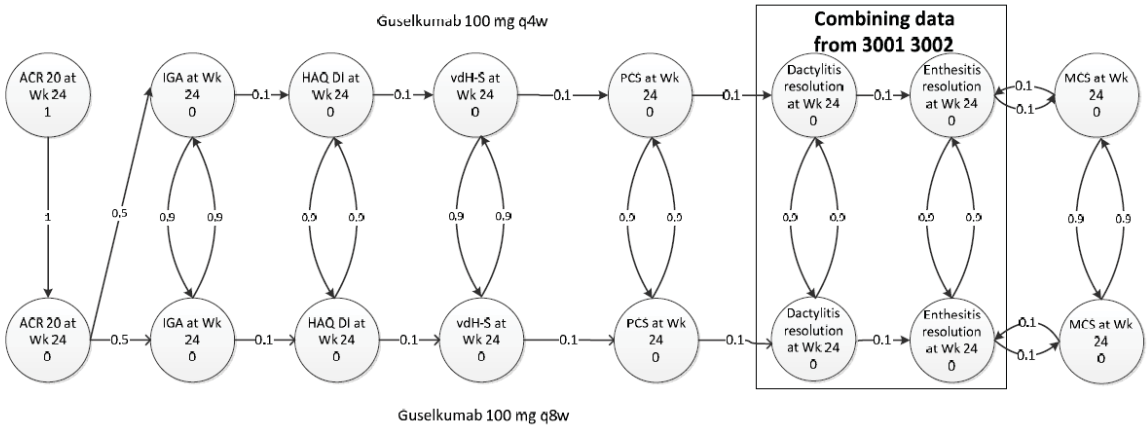


Abbreviation: ACR20=American College of Rheumatology 20 Index; IGA= Investigator's Global Assessment of Psoriasis; HAQ-DI=Health Assessment Questionnaire-Disability Index; PCS=36-Item Short-Form Health Survey Physical Component Score; q8w=once every eight weeks; q4w=once every four weeks; [Source: Clinical Study Report for PSA3001, p58]

In PSA3002, the initial testing order of the secondary endpoints, tested for each dose versus placebo were:

- Proportion of subjects who achieved a psoriasis IGA response at Week 24 among the subjects with ≥3% BSA psoriatic involvement and an IGA score of ≥2 at baseline
- Change from baseline in HAQ-DI score at Week 24
- Change from baseline in modified van der Heijde-Sharp (vdH-S) score at Week 24
- Change from baseline in SF-36 PCS at Week 24
- Proportion of subjects with resolution of dactylitis at Week 24 among the subjects with dactylitis at baseline with combined data from PSA3001 and PSA3002
- Proportion of subjects with resolution of enthesitis (based on LEI) at Week 24 among the subjects with enthesitis at baseline with combined data from PSA3001 and PSA3002.
- Change from baseline in SF-36 MCS at Week 24

Figure 6 Multiple Comparison Procedure for PSA3002



Abbreviation: ACR20=American College of Rheumatology 20 Index; IGA= Investigator's Global Assessment of Psoriasis; HAQ-DI=Health Assessment Questionnaire-Disability Index; vdH-S=van der Heijde-Sharp; PCS=36-Item Short-Form Health Survey Physical Component Score; MCS=36-Item Short-Form Health Survey Mental Component Score; q8w=once every eight weeks; q4=once every four weeks; [Source: Clinical Study Report for PSA3002, p63]

Main Analyses of Secondary Endpoints

For the analyses of response endpoints, subjects meeting any TF criteria prior to a visit were considered as non-responders. A Cochran-Mantel-Haenszel (CMH) test was performed for treatment comparison. The CMH test was stratified by randomization stratification factors. As in the main analysis of ACR20, NRI was applied for subjects with missing data for these endpoints. For resolution of enthesitis and resolution of dactylitis endpoints that were based on data combined from PSA3001 and PSA3002, the analysis was stratified by the study and randomization stratification factors.

For the primary analyses of continuous endpoints except for change from baseline in vdH-S score, subjects meeting any TF criteria were considered as having no change from (no improvement) from baseline at and after meeting TF criteria. For subjects with missing data, the multiple imputation method was applied to impute the missing values under the assumption of MAR. Imputation was based on the FCS regression method, and each imputation was restricted to only impute within the possible range of values for the given variable. An Analysis of Covariance (ANCOVA) for each MI dataset was performed. The least square (LS) mean and 95% CI for each treatment and for differences between groups were obtained. The treatment difference between each guselkumab group versus the placebo group was tested for each imputation dataset and the analysis results across all MI datasets were combined. The treatment difference in the change from baseline was estimated by the average of the treatment differences over the MI datasets. The estimate of the variance of the treatment difference in the change from baseline was the weighted sum of the average within-

imputation variance and the between-imputation variance, under the assumption of homogeneity of variance between treatment groups for performing ANCOVA within each imputation dataset. The confidence interval was based on the critical values from the t-distribution. The ANCOVA model included treatment group, baseline score, and randomization stratification factors as explanatory factors.

For change from baseline in vdH-S score, the main analysis used all observed data regardless of meeting treatment failure criteria (treatment policy estimand). Missing data was assumed to be MAR and was imputed using MI with the FCS regression method. Treatment comparisons for each imputation data were based on an ANCOVA model adjusted for baseline score and baseline stratification factors. The analysis results from imputed datasets were combined according to Rubin's rule and the p-value for testing the treatment difference was obtained.

Sensitivity analyses and supplementary analyses of secondary endpoints

As a supplementary analysis, the treatment policy estimand was evaluated for each secondary endpoint for which the main analysis was based on the composite estimand. For binary response endpoints, subjects with missing data were imputed using MI with the FCS regression method and the sensitivity analysis method described above for ACR20 response was applied to the treatment comparisons. The tipping point analysis based on MI with the FCS regression method described above for ACR20 response was applied to evaluate the impact when the missing data deviated from the MAR assumption. For continuous endpoints, subjects with missing data were imputed using MI with the FCS regression method and an ANCOVA model was used for treatment comparison for each imputed dataset. P-values are obtained by combining treatment difference from all MI imputed datasets. For a tipping point analysis, missing data were imputed using MI under MAR, and a shift was added to the imputed values. The ANCOVA model used for the main analysis of the endpoint was used for each imputation set, and the analysis results from all imputation datasets were combined for each shift, according to Rubin's rule, and the p-values for testing treatment difference were presented. The ANCOVA model included treatment group, baseline score and stratification factors as explanatory factors. Various types of sensitivity analyses were conducted for change from baseline in vdH-S score. The sensitivity analysis included; 1) using MI and an ANOVA model on van der Waerden Normal Scores[12], 2) using a 2-step MI and an ANCOVA, 3) using MI and a mixed effect linear growth curve model, 4) using Last Observation Carried Forward (LOCF) and an ANOVA model on van der Waerden Normal Scores, 5) using linear extrapolation and an ANOVA model on van der Waerden Normal Scores, 6) assuming missing data is Missing Completely at Random (MCAR) excluding subjects with missing vdH-S score and using an ANCOVA model. For tipping point analysis, missing data were imputed using MI under MAR, and a shift was added to the imputed values. The ANCOVA model used for the main analysis of the endpoint was used for each imputation set, and the analysis results from all imputation

[12] Computed normal score from the rank for that observation using van der Waerden's method (Conover WJ, Practical Nonparametric Statistics (3rd ed), Wiley 1999)

datasets were combined for each shift and the results were presented. The ANCOVA model included treatment group, baseline score and stratification factors as explanatory factors.

Analyses of other continuous secondary endpoints

For other continuous secondary endpoints not included in the multiplicity control, including the components of ACR, a mixed-model repeated measures (MMRM) model was used for treatment comparison. The MMRM model included treatment group, baseline score, stratification factors, interaction terms as appropriate. The model used an unstructured covariance matric for repeated measured within a subject and Kenward-Roger's approximation for degree of freedom. Under the assumption of MAR, the missing data were accounted through correlation of repeated measures in the model.

Subgroup analyses

Subgroup analyses were performed using a logistic regression model to evaluate treatment consistency in proportion of subjects who achieved an ACR20 response at Week 24 over baseline demographics, baseline disease characteristics, and prior and baseline medication use. Additional analyses were performed using a logistic regression model to evaluate the interaction of the treatment and the subgroups when a subgroup had two or more categories.

Additional Reviewer Analyses

To evaluate the robustness of the primary efficacy results to missing data assumptions, the Applicant performed a sensitivity analysis, referred to by "exhaustive scenario imputation tipping point analysis." Instead of using a prespecified CMH test with stratification factors, the Applicant performed a chi-square test without stratification factors. The statistical reviewer performed the CMH test with stratification factors and the results are included in Table 12.

The statistical reviewer performed a simple comparison between two dose levels for the primary endpoint, ACR20 response at Week 24. Because this comparison was not pre-planned and the study was not designed to show differences between doses, this analysis only provided supplemental information. The results are presented in Section 8.5 of this review.

The statistical reviewer performed a model based analysis for 7 ACR components for both studies. Using MMRM model, the analyses of change from baseline in each component were performed. The model included treatment, visit, baseline score, stratification factors, and treatment by visit interaction terms. The results are presented in Table 15 and Table 16.

The statistical reviewer performed some of the Applicant's tipping point analyses with different seeds and reduced number of imputations to reduce computing time and obtained consistent results.

8.3. Efficacy Results for PSA3001 and PSA3002

Data Quality and Integrity for PSA3001 and PSA3002

The submitted efficacy data were generally acceptable in quality and documentation. The statistical reviewer was able to reproduce the results of important primary and secondary analyses and performed additional analyses as needed.

On February 28, 2020, the Applicant reported errata in the submission due to coding errors and submitted updated datasets and analysis results. The errors resulted in incorrectly adjusted joint counts for one subject in PSA3002. As a result, a number of tables and graphs were updated. Overall, the report indicated resulting changes were minimal, and the conclusions remained the same after the correction of these errata.

Efficacy Results for PSA3001 and PSA3002– Primary Endpoint

Primary analyses

In both studies, there was a significantly greater proportion of subjects in both guselkumab dose groups achieving an ACR20 response compared with subjects in the placebo group (Table 11). In PSA3001, 59.4% in the guselkumab q4w arm and 52.0% in the guselkumab q8w arm achieved an ACR20 response compared with subjects in the placebo arm (22.2%). In PSA3002, 63.7% in guselkumab q4w arm and 64.1% in the guselkumab q8w arm achieved an ACR20 response compared with subjects in the placebo arm (32.9%). In both studies, ACR20 responses rates were similar in the guselkumab q8w and q4w arms.

Table 11 Primary Analysis: ACR20 Response at Week 24 Based on the Composite Estimand

	N	Responders	Non-Responders			Comparison to placebo (95% CI): p-value
			Due to TF	Observed	Missing	
PSA3001						
Placebo	126	28 (22.2%)	21 (16.8%)	77 (61.1%)	0	
Guselkumab q8w	127	66 (52.0%)	7 (5.5%)	54 (42.5%)	0	29.8% (18.6, 41.1}: <0.001
Guselkumab q4w	128	76 (59.4%)	3 (2.3%)	49 (38.3%)	0	37.1% (26.1, 48.2): <0.001
PSA3002						
Placebo	246	81 (32.9%)	17 (6.9%)	147 (59.8%)	1 (0.4%)	
Guselkumab q8w	248	159 (64.1%)	12 (4.8%)	75 (30.2%)	2 (0.8%)	31.2% (22.9, 39.5): <0.001
Guselkumab q4w	245	156 (63.7%)	13 (5.3%)	76 (31.0%)	0 (0%)	30.8% (22.4, 39.1): <0.001

Abbreviations: N= number of subjects randomized and received treatment; q8w=once every eight weeks; q4w=once every four weeks; TF=treatment failure; CI=confidence interval based on Wald statistics; Subjects with missing data are assumed to be non-responders. The p-values are based on the CMH test stratified by baseline stratification factors (DMARD use and prior exposure to anti-TNFα for PSA3001 and DMARD use and CRP value for PSA3002); [Source: Reviewer]

Sensitivity analyses

Although planned, sensitivity analyses using the primary estimand composite strategy were performed for PSA3001 because there were no missing data under this approach. In PSA3002, there were 3 missing observations (1 from placebo and 2 from guselkumab q8w) and sensitivity analyses via the exhaustive scenario were performed for these missing observations. For this analysis for each possible scenario, the Applicant used a chi-square test without adjusting for baseline stratification factors. The statistical reviewer replicated these sensitivity analyses based on exhaustive scenarios using all six possible combinations of missing observations (Table 12), used the CMH test stratified by stratification factors and calculated the corresponding 95% confidence interval (CI) based on Wald statistics.

Table 12 shows the results from all possible 6 combinations. The difference between guselkumab q4w and the placebo was ranged from 30.3% to 30.8% and the difference between guselkumab q8w and the placebo was 30.8% to 32.0%. These results were consistent with the primary results.

Table 12 Reviewer's exhaustive scenario sensitivity analysis of ACR20 response at Week 24

Placebo (N=246)	Guselkumab q8w (N=248)	Guselkumab q4w (N=245)	Placebo vs q8w (95% CI): p-value	Placebo vs q4w (95% CI): p-value
Responders (%)	Responders (%)	Responders (%)		
81 (32.9%)	159 (64.1%)	156 (63.7%)	31.2% (22.9, 39.5): <0.001	30.8% (22.4, 39.1): <0.001
81 (32.9%)	160* (64.5%)	156 (63.7%)	31.6% (23.3, 39.9): <0.001	30.8% (22.4, 39.1): <0.001
81 (32.9%)	161 (64.9%)	156 (63.7%)	32.0% (23.7, 40.3): <0.001	30.8% (22.4, 39.1): <0.001
82 (33.3%)	159 (64.1%)	156 (63.7%)	30.8% (22.4, 39.1): <0.001	30.3% (22.0, 38.7): <0.001
82 (33.3%)	160* (64.5%)	156 (63.7%)	31.2% (22.8, 39.5): <0.001	30.3% (22.0, 38.7): <0.001
82 (33.3%)	161 (64.9%)	156 (63.7%)	31.6% (23.3, 39.9): <0.001	30.3% (22.0, 38.7): <0.001

*Either one of the two missing observations was considered "yes"; Abbreviations: N=number of subjects randomized and received treatment; q8w= once every eight weeks; q4w= once every four weeks; CI=confidence interval based on Wald statistics; The p-values are based on the CMH test stratified by baseline DMARD use and CRP value; [Source: Reviewer]

It should be noted that this approach imputes outcomes, rather than drawing from an underlying distribution with varying response probabilities which may be preferred for appropriately accounting for the variability across response outcomes. However, given the small number of missing data, it is the reviewer's opinion that this approach to the exhaustive scenario tipping point analysis is acceptable and provides additional support to the primary analyses.

Supplemental analyses

PSA3001

Table 13 shows the results from supplementary analyses based on the treatment policy estimand where all observed data collected for the endpoint were used and no TF rules were applied. There were 8, 4 and 1 subject with missing data in the placebo, guselkumab q8w and

guselkumab q4w groups, respectively, in PSA3001. Missing data were imputed by MI with a MAR mechanism. The results were consistent with the primary analysis, with each guselkumab dose showing significant efficacy over placebo.

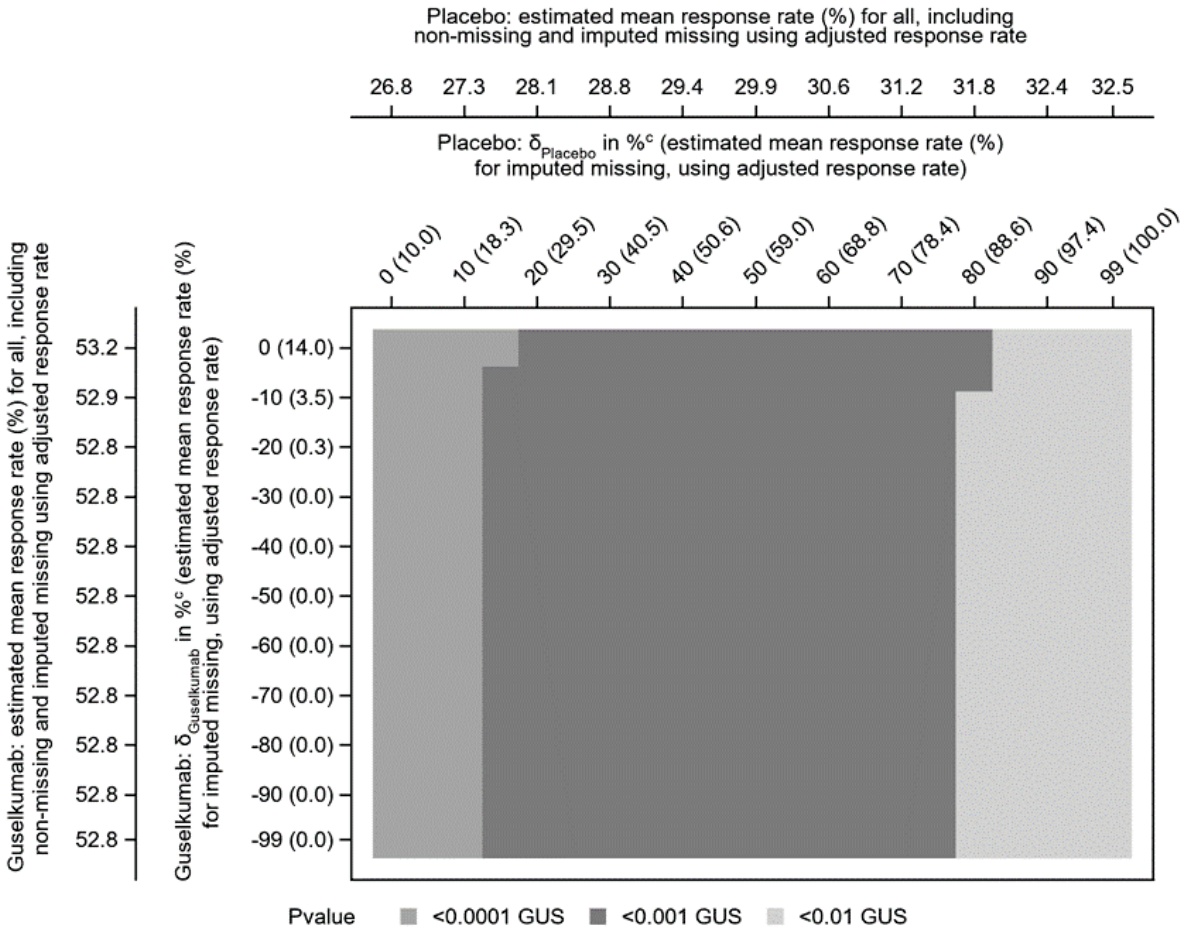
Table 13 ACR20 Response at Week 24 based on the Treatment Policy Estimand (PSA3001)

	Number of subjects with observed data	Mean response rate[1] (observed and imputed)	Comparison to placebo (95% CI): p-value
Placebo (N=126)	118	26.8%	
Guselkumab q8w (N=127)	123	53.2%	26.4% (14.7, 38.1): <0.0001
Guselkumab q4w (N=128)	127	60.6%	33.7% (22.3, 45.2): <0.0001

Abbreviations: N=number of subjects randomized and received treatment; CI=confidence interval based on the combined Wald statistics; q8w=once every eight weeks; q4w=once every four weeks; [1]The average response rate over the MI datasets with both observed and imputed; The analysis results from imputations were combined according to Rubin's rule and the p-value for testing the treatment difference was obtained. The p-value was based on the combined standardized Wilson-Hilferty transformation of the CMH test (stratified by baseline stratification factors) statistic [Source: Reviewer]

The results from the tipping point analysis based on the treatment policy estimand are shown in Figure 7**.** for the placebo group vs guselkumab q8w group. In this figure, the vertical axis shows the estimated response rate (%) in the missing subjects, the shift (%) in the response rate of the missing subjects, and the resulting estimated response rate (%) in all subjects on guselkumab q8w group including the missing. The horizontal axis corresponds to the same values for the placebo group. For these analyses, only one quadrant was investigated, where the q8w (or the q4w) group has response rate lowered (a shift ranged from 0 to -100%) and the placebo group has response rate added (a shift ranged from 0 to 100%) for the missing on each group, with increments of 10%. For all shifts considered, the treatment effect of guselkumab q8w was statistically significant compared to the placebo group. Similarly, for the tipping point analysis comparing guselkumab q4w to placebo, the p-value was <0.0001 for all possible shifts. Therefore, the tipping points analysis supported the results of primary analysis of efficacy.

Figure 7 Tipping point analysis for achieving ACR20 response at Week 24 based on the treatment policy estimand in PSA3001: guselkumab q8w vs placebo



GUS=guselkumab, p-value for each shaded area; delta shown here ranged from 0 to 99% with increments of 10% for the placebo on x-axis and 0 to -99% with decrements of 10% for guselkumab dose on y-axis; [Source: Reviewer]

PSA3002

Table 14 shows the results from supplementary analyses based on the treatment policy estimand where all observed data collected for the endpoint were used and no TF rules were applied. There were 3, 5, and 5 subjects with missing data in the placebo, guselkumab q8w and guselkumab q4w groups, respectively, in PSA3002. Missing data were imputed by MI with a MAR mechanism. The results were consistent with the primary analysis, with each guselkumab dose showing significant efficacy over placebo.

Table 14 ACR20 Response at Week 24 based on Treatment Policy Estimand with MI (PSA3002)

	Number of subjects with observed data	Mean response rate[1] (observed and imputed)	Comparison to placebo (95% CI): p-value
Placebo (N=246)	243	34.8%	
Guselkumab q8w (N=248)	243	66.1%	31.2% (22.8, 39.6): <0.0001
Guselkumab q4w (N=245)	240	66.1%	31.2% (22.8, 39.6): <0.0001

Abbreviations: N=number of subjects randomized and received treatment; CI=confidence interval based on the combined Wald statistics; q8w=once every eight weeks; q4w=once every four weeks; [1]The average response rate over the MI datasets with both observed and imputed; The analysis results from imputations were combined according to Rubin's rule and the p-value for testing the treatment difference was obtained. The p-value was based on the combined standardized Wilson-Hilferty transformation of the CMH test (stratified by baseline stratification factors) statistic; [Source: Reviewer]

Tipping point analysis was performed based on the treatment policy estimand. The analysis procedures were similar to PSA3001. For all shifts considered, the treatment effect of guselkumab q8w was statistically significant compared to the placebo group. Similarly, for the tipping point analysis comparing guselkumab q4w to placebo, the p-value remained <0.0001 for all possible shifts. Therefore, the tipping points analysis supported the results of primary analysis of efficacy.

Change from Baseline in ACR Components at Week 24

Table 15 and Table 16 show that the results of the analyses of the mean change from baseline in each component of ACR in both studies using MMRM. The model included treatment, visit, baseline score, stratification factors, and treatment by visit interaction terms. These results show that all 7 ACR components were in favor of both doses compared to placebo.

Table 15 Change from Baseline in ACR Components at Week 24 for PSA3001

	Treatment Group (N)	n	Adjusted mean (SE)[1]	Comparison to Placebo	
				Mean diff (SE)	95% CI
SJC	Placebo (126)	118	-4.8 (0.5)		
	Guselkumab q8w (127)	123	-6.3 (0.5)	-1.6 (0.7)	-2.9, -0.3
	Guselkumab q4w (128)	127	-6.3 (0.5)	-1.5 (0.7)	-2.8, -0.2
TJC	Placebo (126)	118	-6.4 (0.9)		
	Guselkumab q8w (127)	123	-10.0 (0.9)	-3.6 (1.2)	-5.9, -1.2
	Guselkumab q4w (128)	127	-9.9 (0.9)	-3.5 (1.2)	-5.8, -1.1
PGA	Placebo (126)	118	-1.0 (0.2)		
	Guselkumab q8w (127)	123	-2.4 (0.2)	-1.4 (0.3)	-2.0, -0.8
	Guselkumab q4w (128)	127	-2.7 (0.2)	-1.7 (0.3)	-2.3, -1.2
PhGA	Placebo (126)	117	-2.1 (0.2)		
	Guselkumab q8w (127)	122	-3.4 (0.2)	-1.3 (0.3)	-1.8, -0.8
	Guselkumab q4w (128)	127	-3.8 (0.2)	-1.7 (0.3)	-2.2, -1.2
HAQ-DI	Placebo (126)	118	-0.1 (0.05)		
	Guselkumab q8w (127)	123	-0.3 (0.04)	-0.2 (0.1)	-0.4, -0.1
	Guselkumab q4w (128)	127	-0.4 (0.04)	-0.3 (0.1)	-0.4, -0.2
CRP	Placebo (127)	119	0.0 (0.2)		
	Guselkumab q8w (127)	123	-0.5 (0.2)	-0.5 (0.2)	-1.0, -0.02
	Guselkumab q4w (128)	127	-0.6 (0.2)	-0.6 (0.2)	-1.1, -0.1
Pain	Placebo (126)	118	-0.7 (0.2)		
	Guselkumab q8w (127)	123	-2.2 (0.2)	-1.4 (0.3)	-2.0, -0.8
	Guselkumab q4w (128)	127	-2.4 (0.2)	-1.6 (0.3)	-2.2, -1.1

Abbreviations: N= number of subjects randomized and received treatment; n= number of subjects evaluated at Week 24; q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; diff=difference; CI=confidence interval; SJC= number of swollen joints; TJC= number of tender joints; PGA= patient's global assessment of disease activity; PhGA= physician's global assessment of disease activity; HAQ-DI= disability index of the health assessment questionnaire; CRP= C-reactive protein; Pain= patient's assessment of pain; [1]Adjusted mean and comparison to placebo based on MMRM model with treatment, visit (week 16 and week 24), baseline score, stratification factors, and treatment by visit in the model; [Source: reviewer]

Table 16 Change from Baseline in ACR Components at Week 24 for PSA3002

	Treatment Group (N)	n	Adjusted mean (SE)[1]	Comparison to Placebo	
				Mean diff (SE)	95% CI
SJC	Placebo (246)	243	-6.4 (0.3)		
	Guselkumab q8w (248)	243	-8.3 (0.3)	-2.0 (0.5)	-2.8, -1.1
	Guselkumab q4w (245)	240	-8.4 (0.3)	-2.0 (0.5)	-2.9, -1.1
TJC	Placebo (246)	243	-7.0 (0.6)		
	Guselkumab q8w (248)	243	-10.8 (0.8)	-3.8 (0.8)	-5.4, -2.3
	Guselkumab q4w (245)	240	-11.3 (0.6)	-4.3 (0.8)	-5.9, -2.8
PGA	Placebo (246)	243	-1.2 (0.1)		
	Guselkumab q8w (248)	243	-2.5 (0.1)	-1.3 (0.2)	-1.7, -0.9
	Guselkumab q4w (245)	240	-2.5 (0.1)	-1.3 (0.2)	-1.7, -0.9
PhGA	Placebo (246)	243	-2.4 (0.1)		
	Guselkumab q8w (248)	242	-3.8 (0.1)	-1.4 (0.2)	-1.8, -1.0
	Guselkumab q4w (245)	238	-3.9 (0.1)	-1.5 (0.2)	-1.9, -1.1
HAQ-DI	Placebo (246)	242	-0.1 (0.03)		
	Guselkumab q8w (248)	243	-0.4 (0.03)	-0.2 (0.04)	-0.3, -0.2
	Guselkumab q4w *(245)	240	-0.4 (0.03)	-0.3 (0.04)	-0.4, -0.2
CRP	Placebo (246)	240	-0.4 (0.1)		
	Guselkumab q8w (248)	243	-1.0 (0.1)	-0.6 (0.1)	-0.9, -0.4
	Guselkumab q4w (245)	239	-1.1 (0.1)	-0.7 (0.1)	-1.0, -0.5
Pain	Placebo (246)	243	-1.0 (0.1)		
	Guselkumab q8w (248)	243	-2.5 (0.1)	-1.4 (0.2)	-1.8, -1.0
	Guselkumab q4w (245)	240	-2.5 (0.1)	-1.4 (0.2)	-1.8, -1.0

Abbreviations: N= number of subjects randomized and received treatment; n= number of subjects evaluated at Week 24; q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; diff=difference; Cl=confidence interval; SJC= number of swollen joints; TJC= number of tender joints; PGA= patient's global assessment of disease activity; PhGA= physician's global assessment of disease activity; HAQ-DI= disability index of the health assessment questionnaire; CRP= C-reactive protein; Pain= patient's assessment of pain; [1]Adjusted mean and comparison to placebo based on MMRM model with treatment, visit (week 16 and week 24), baseline score, stratification factors, and treatment by visit in the model [Source: reviewer]

Efficacy Results for PSA3001 and PSA3002 – Secondary and other relevant endpoints

Key Secondary Endpoints

Key secondary endpoints were tested using multiplicity-controlled testing procedures. There were 3 key secondary endpoints in PSA3001 and 7 key secondary endpoints in PSA3002. For the dactylitis and enthesitis endpoints, the data from PSA3001 and PSA3002 were pooled.
For response endpoints, the Applicant used a composite strategy for the primary analysis. Under this strategy, a subject who met TF criteria prior to Week 24 or with missing data was considered non-responder. Additional analyses based on a treatment policy strategy was conducted as supplementary analyses.

For continuous endpoints, the Applicant used a composite strategy for the primary analysis. Under this strategy, a subject was defined as having no improvement from baseline (change from baseline=0) if a subject met TF criteria prior to Week 24. This baseline observation carried forward (BOCF) handling of these intercurrent events is a type of single imputation, and the variability in the resulting estimate is often underestimated as a result. Furthermore, it is not clear that setting a value of 0 improvement for subjects who met TF criteria targets the most clinically meaningful estimand. Approaches to handle missing data and intercurrent events should target most clinically meaningful estimand with plausible assumptions[13]. This composite strategy approach may not handle subjects who meet TF and have subsequent outcome values worse than the baseline values in a meaningful way. Therefore, the analyses using a treatment policy strategy provide important additional information to the main analysis. This was done as supplementary analyses for all continuous secondary endpoints except vdH-S score in PSA3002. The main analysis for vdH-S score used treatment policy estimand based on observed data with no TF rules applied.

Detailed descriptions for the analysis procedures are included in Major Secondary Endpoints of Section 8.2 Statistical Methodologies for PSA3001 and PSA3002.

HAQ-DI at Week 24

The analysis set for HAQ-DI included subjects who were randomized and received treatment. For the main analysis based on the composite strategy, a significantly greater reduction from baseline in HAQ-DI score was observed in both dose groups compared with placebo (Table 17). In PSA3001, the adjusted mean change from baseline at Week 24 was -0.07, -0.32, -0.40 in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. In PSA3002, the adjusted mean change from baseline at Week 24 was -0.13, -0.37, -0.40 in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. The observed change from baseline in HAQ-DI score compared to placebo was similar between the two dose levels.

[13] https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

Table 17 Change from baseline in HAQ-DI at Week 24: Main Analysis

Treatment Group (N)	n	Adjusted Mean[1] (SE)	Comparison to Placebo (95% CI): p-value[2]
PSA3001			
Placebo (126)	126	-0.07 (0.04)	
Guselkumab q8w (127)	127	-0.32 (0.04)	-0.25 (-0.36, -0.13): <0.001
Guselkumab q4w (128)	128	-0.40 (0.04)	-0.32 (-0.44, -0.21): <0.001
PSA3002			
Placebo (246)	244	-0.13 (0.03)	
Guselkumab q8w (248)	246	-0.37 (0.03)	-0.24 (-0.32, -0.15): <0.001
Guselkumab q4w (245)	245	-0.40 (0.03)	-0.27 (-0.35, -0.19): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; n=number of subjects with an observed change from baseline at this visit or met TF criteria prior to this visit; [1]Model based estimates using an ANCOVA, the model included treatment, baseline score and stratification factors; [2]unadjusted p-value for the comparison of the guselkumab vs the placebo; [Source: Reviewer]

The Applicant conducted supplementary analysis based on the treatment policy strategy and the results are shown in Table 18. The adjusted mean values from main analysis and supplementary analysis were comparable, and the results from supplementary analysis were consistent with the main analysis.

Table 18 Change from Baseline in HAQ-DI at Week 24: Supplementary Analysis

Treatment Group (N)	No. Observed[1]	Adjusted Mean[1] (95% CI)	Comparison to Placebo (95% CI): p-value[2]
PSA3001			
Placebo (126)	118	-0.09 (-0.18, 0.0)	
Guselkumab q8w (127)	123	-0.32 (-0.41, -0.23)	-0.23 (-0.35, -0.11): <0.001
Guselkumab q4w (128)	127	-0.40 (-0.48, -0.31)	-0.30 (-0.42, -0.18): <0.001
PSA3002			
Placebo (246)	242	-0.14 (-0.20, -0.08)	
Guselkumab q8w (248)	243	-0.38 (-0.44, -0.32)	-0.24 (-0.32, -0.15): <0.001
Guselkumab q4w (245	240	-0.43 (-0.49, -0.36	-0.28 (-0.37, -0.20): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; [1] Number of subjects with observed data; [1]Model based estimates using an ANCOVA, the model included treatment, baseline score and stratification factors; [2]unadjusted p-value for the comparison of the guselkumab vs the placebo; [Source: Clinical Study Report for PSA3001, p295-p296 and Clinical Study Report for PSA3002, p355-p356]

The Applicant performed tipping point analysis and for this analysis, a shift ranged from 0 to 3 was added to guselkumab penalizing guselkumab and a shift ranged from 0 to -3 was added to placebo favoring placebo for the missing on each group with increments of 0.3. In PSA3001, tipping point analysis showed that the loss of significance occurred at only the most extreme shifts added to imputed data in each group (for example, -3 to the placebo and 3 to both guselkumab groups) [Source: Clinical Study Report for PSA3001, p295-p296]. However, this shift appears to be relatively implausible because mean values for each group at Week 24 were -0.09, -0.32, and -0.37 for the placebo, guselkumab q8w and guselkumab q4w, based on subjects either had an observed value or met TF criteria. Therefore, a shift value of 3 or -3 seems unrealistic. Tipping point analyses were also performed for PSA3002. For all shifts considered, the treatment effect of guselkumab q8w or q4w was statistically significant compared to the placebo group, with a p-value <0.05, supporting the main analysis. The reviewer verified the Applicant's results by replicating the analyses.

IGA response at Week 24

The analysis set for IGA included only subjects who had ≥3% BSA of psoriasis involvement and an IGA score ≥2 at baseline. For the main analysis based on the composite strategy, a significantly greater proportion of subjects in both dose groups achieved an IGA response compared with placebo for both studies (Table 19). In PSA3001, there were 15.4%, 57.3%, and 75.3% response rates in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively, showing the numerically highest efficacy in the higher dose. In PSA3002, there

were 19.1%, 70.5%, and 68.5% response rates in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively, and guselkumab 8w showed the highest efficacy though the numerical difference between two dose levels was small (2%). The results from supplementary analysis using treatment policy estimand were consistent with the main analysis. The Applicant performed tipping point analysis and showed that the results were robust supporting the main analysis.

Table 19 IGA Response at Week 24: Main Analysis

Treatment Group (N)	n	Responder	Non-Responder	Compared to Placebo (95% CI): p-value[1]
PSA3001				
Placebo (78)	78	12 (15.4%)	66 (84.6%)	
Guselkumab q8w (82)	81	47 (57.3%)	35 (42.7%)	42.0% (28.9, 55.1): <0.001
Guselkumab q4w (89)	89	67 (75.3%)	22 (24.7%)	60.0% (48.3, 71.9): <0.001
PSA3002				
Placebo (183)	182	35 (19.1%)	148 (80.9%)	
Guselkumab q8w (176)	175	124 (70.5%)	52 (29.6%)	50.9% (42.2, 59.7): <0.001
Guselkumab q4w (184)	183	126 (68.5%)	58 (31.5%)	49.8% (41.2, 58.4): <0.001

Abbreviations: q8w= once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval based on the Wald statistic; N=number of subjects who had ≥3% BSA of psoriasis involvement and an IGA score ≥2 at baseline; n=number of subjects with observed change from baseline; Subjects who met treatment failure or with missing data were considered non-responders; [1]The p-values are based on the CMH test stratified by baseline stratification factors (DMARD use and prior exposure to anti-TNFα for PSA3001 and DMARD use and CRP value for PSA3002) and unadjusted; [Source: Reviewer]

SF-36 PCS at Week 24

The analysis set for SF-36 PCS included subjects who were randomized and received treatment. For the main analysis based on the composite strategy, a significantly greater improvement from baseline in SF-36 PCS score was observed in both dose groups compared with placebo (Table 20). In PSA3001, there was one subject with missing data in the q8w arm. In PSA3002, there were 2 subjects with missing data in the placebo, and 2 subjects with missing data in the q8w group. In PSA3001, the adjusted mean change from baseline at Week 24 was 1.96, 6.10, and 6.87 in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. In PSA3002, the adjusted mean change from baseline at Week 24 was 3.42, 7.39, and 7.04 in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. Adjusted mean values for all three groups are slightly larger numerically in PSA3002 compared to PSA3001. Improvement in SF-36 PCS was numerically greater for guselkumab q4w in PSA3001, however, improvement was greater for guselkumab q8w as compared to guselkumab q4w in PSA3002.

Table 20 Change from Baseline in SF-36 PCS at Week 24: Main Analysis

Treatment Group (N)	n	Adjusted Mean[1] (SE)	Comparison to Placebo (95% CI): p-value[2]
PSA3001			
Placebo (126)	126	1.96 (0.65)	
Guselkumab q8w (127)	127	6.10 (0.65)	4.14 (2.42, 5.85): <0.001
Guselkumab q4w (128)	127	6.87 (0.65)	4.91 (3.19, 6.63): <0.001
PSA3002			
Placebo (246)	244	3.42 (0.46)	
Guselkumab q8w (248)	246	7.39 (0.46)	3.97 (2.75, 5.20): <0.001
Guselkumab q4w (245)	245	7.04 (0.46)	3.62 (2.39, 4.85): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; n=number of subjects who had an observed change from baseline at this visit or met TF criteria prior to this visit; [1]Model based estimates using an ANCOVA, the model included treatment, baseline score and stratification factors; [2]unadjusted p-value for the comparison of the guselkumab vs the placebo; [Source: Reviewer]

The results from supplementary analysis using treatment policy estimand were consistent with the main analysis. The Applicant performed tipping point analysis and for this analysis, a shift ranged from 0 to 100 was added to guselkumab and a shift ranged from 0 to -100 was added to placebo for the missing on each group with increments of 10. In PSA3001, loss of significance occurred at some shifts added to imputed data in each group (for example, 30 to the placebo and -30 to both guselkumab groups). However, this shift appears implausible because mean values for each group at Week 24 were 2.1, 6.2, and 6.4 for the placebo, guselkumab q8w and guselkumab q4w, based on subjects either had an observed value or met TF criteria. Therefore, a shift value of 30 or -30 seems unrealistic. Similarly, loss of significance occurred at some shifts in PSA3002 (for example, 70 to the placebo and -70 to guselkumab). However, this shift appears implausible because mean values for each group at Week 24 were 3.64, 7.53, 6.94 for the placebo, guselkumab q8w and guselkumab q4w, based on subjects either had an observed value or met TF criteria. Therefore, a shift value of 70 or -30 seems unrealistic. The results appeared robust supporting the main analysis [Source: Clinical Study Report for PSA3001, p93 and Clinical Study Report for PSA3002, p104].

SF-36 MCS at Week 24

Though it was not a key secondary endpoint in PSA3001, the change from baseline in SF-36 MCS scores at Week 24 were analyzed and each dose level was compared to the placebo group. In comparison to the placebo group, the nominal p-values for differences were not significant in both dose levels. The p-values from the differences between each dose level to placebo were 0.398 for q8w vs. placebo and 0.214 for q4w vs placebo, respectively (Table 21) .

In PSA3002, SF-36 MCS endpoint was a key secondary endpoint and controlled for multiplicity. The analysis set included subjects who were randomized and received treatment. Though the mean changes were shown to have nominal (unadjusted p-value in the table) statistical significance compared to placebo, the mean change was not statistically significant in both dose

groups compared with the placebo group under multiplicity testing procedures. Adjusted p-values were calculated using the pre-specified multiple comparison procedure and the adjusted p-value for both guselkumab groups vs. the placebo was 0.072 in both comparisons. Both dose levels showed similar numerical efficacy over the placebo.

Table 21 Change from Baseline in SF-36 MCS at Week 24

Treatment Group (N)	n	Adjusted Mean[1] (95% CI)	Comparison to Placebo (95% CI): p-value[2]
PSA3001			
Placebo (126)	126	2.37 (0.93, 3.81)	
Guselkumab q8w (127)	127	3.20 (1.78, 4.63)	0.83 (-1.10, 2.77): 0.398
Guselkumab q4w (128)	127	3.60 (2.17, 5.02)	1.23 (-0.71, 3.16): 0.214
PSA3002			
Placebo (246)	244	2.14 (0.55)	
Guselkumab q8w (248)	246	4.17 (0.54)	2.02 (0.56, 3.49): 0.007
Guselkumab q4w (245)	245	4.22 (0.55)	2.07 (0.60, 3.54): 0.006

Abbreviations: q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; n=number of subjects either had an observed change from baseline at this visit or met TF criteria prior to the visit; [1]Model based estimates using an ANCOVA, the model included treatment, baseline score and stratification factors; [2]unadjusted p-value for the comparison of the guselkumab vs the placebo; [Source: Clinical Study Report for PSA3001, p676; Reviewer and Clinical Study Report for PSA3002, p730]

The changes from baseline in the eight SF-36 subscale scores (physical functioning, physical role functioning, bodily pain, general health perception, vitality, social functioning, emotional role functioning, and general mental health) are summarized in Table 22. With few exceptions, in general, SF-36 subscale scores were numerically greater in both guselkumab groups compared with the placebo group in both studies.

Table 22 Change from baseline in norm based scores of SF-36 scales at Week 24

	Treatment	PSA3001			PSA3002		
		N	n	Mean (SD)	N	n	Mean (SD)
Physical function	Placebo	126	126	1.47 (8.33)	246	244	3.52 (7.43)
	Guselkumab q8w	127	127	5.73 (7.94)	248	246	6.79 (8.46)
	Guselkumab q4w	128	127	6.50 (8.43)	245	245	6.54 (7.60)
Physical role	Placebo	126	126	2.42 (7.21)	246	244	3.55 (7.37)
	Guselkumab q8w	127	127	5.02 (8.14)	248	246	6.61 (7.72)
	Guselkumab q4w	128	127	5.09 (7.48)	245	245	6.09 (7.14)
Bodily pain	Placebo	126	126	2.78 (6.80)	246	244	3.65 (7.92)
	Guselkumab q8w	127	127	6.84 (8.76)	248	246	7.93 (8.43)
	Guselkumab q4w	128	127	7.04 (9.07)	245	245	7.48 (7.37)
General health	Placebo	126	126	1.56 (6.38)	246	244	2.24 (6.85)
	Guselkumab q8w	127	127	4.40 (7.16)	248	246	5.68 (7.84)
	Guselkumab q4w	128	127	4.95 (7.09)	245	245	4.89 (7.28)
Vitality	Placebo	126	126	2.31 (8.22)	246	244	3.99 (8.75)
	Guselkumab q8w	127	127	5.54 (9.47)	248	246	7.45 (9.44)
	Guselkumab q4w	128	127	6.01 (7.85)	245	245	6.56 (9.40)
Social function	Placebo	126	126	2.39 (7.86)	246	244	2.98 (10.01)
	Guselkumab q8w	127	127	5.72 (8.88)	248	246	6.11 (9.59)
	Guselkumab q4w	128	127	4.82 (9.50)	245	245	5.50 (8.42)
Emotional role	Placebo	126	126	1.47 (8.53)	246	244	1.87 (9.41)
	Guselkumab q8w	127	127	2.47 (10.00)	248	246	4.36 (10.00)
	Guselkumab q4w	128	127	3.62 (9.26)	245	245	3.87 (8.72)
Mental health	Placebo	126	126	1.54 (7.62)	246	244	2.51 (8.78)
	Guselkumab q8w	127	127	4.04 (9.85)	248	246	4.28 (9.60)
	Guselkumab q4w	128	127	4.76 (8.57)	245	245	4.43 (8.80)

Abbreviations: N=number of subjects randomized and received treatment; n=subjects either had an observed change from baseline or met TF criteria; SD=standard deviation; q8w=once every eight weeks; q4w=once every four weeks; [Source: Clinical Study Report for PSA3001, p762 and Clinical Study Report for PSA3002, p764]

Modified vdH-S Score

The comparison for change from baseline in modified vdH-S score at Week 24 between guselkumab groups and the placebo group based on the treatment policy estimand (the main analysis in this case) is shown in Table 23. For this analysis using the treatment policy strategy, all data was included, regardless of TF criteria. There were 1, 1, and 5 subjects with missing data in the placebo, q8w, and q4w groups, respectively. Missing data were assumed to be MAR and were imputed using MI.

The mean change was statistically significant in the guselkumab q4w group compared with the placebo group, but was not significant in the guselkumab q8w compared with the placebo

group based on nominal (unadjusted) p-values nor adjusted p-values obtained under the multiplicity testing procedure. The adjusted p-value was 0.011 for the guselkumab q4w vs. the placebo and 0.072 for the guselkumab q8w vs the placebo.

Table 23 Change from Baseline in Modified vdH-S score at Week 24: Main Analysis (PSA3002)

Treatment Group (N)	n	Adjusted Mean[1] (SE)	Comparison to Placebo (95% CI): p-value[2]
Placebo (246)	245	0.95 (0.17)	
Guselkumab q8w (248)	247	0.52 (0.17)	-0.43 (-0.90, 0.03): 0.068
Guselkumab q4w (245)	240	0.29 (0.17)	-0.66 (-1.13, -0.19): 0.006

Abbreviations: q8w=once very eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; n=number of subjects with observed change from baseline; [1]Model based estimates using an ANCOVA, the model included treatment, baseline score and stratification factors; [2]unadjusted p-value for the comparison of the guselkumab vs the placebo; [Source: Reviewer]

As described in Major Secondary Endpoints of Section 8.2 Statistical Methodologies for PSA3001 and PSA3002, the sensitivity analyses were conducted by handling missing data in six different ways and these analyses included LOCF and linear extrapolation as well as MI. While there are deficiencies with some of these approaches, e.g., LOCF and linear extrapolation are less preferred because they do not properly account for variability and rely on strong, unverifiable assumptions, for all analyses the nominal p-values were consistent with the main analysis [Source: Clinical Study Report for 3002, p102].

For tipping point analyses, we focused on guselkumab q4w, as the guselkumab q8w did not show a significant difference compared to placebo in the main analysis. The Applicant performed tipping point analyses and for this analysis, a shift ranged from 0 to 20 was added to guselkumab q4w and a shift ranged from 0 to -20 was added to the placebo with increments of 2. Loss of significance occurred at some shifts added to imputed data in each group (for example, -10 to the placebo and 10 to guselkumab). However, this shift appears extreme because mean values for each group at Week 24 were 0.9 and 0.3 for the placebo and guselkumab q4w, based on subjects who have an observed change from baseline. Therefore, the results appeared robust, supporting the main analysis for guselkumab q4w [Source: Clinical Study Report for 3002, p103].

Dactylitis (pooled)

Subjects with dactylitis at baseline were pooled from PSA3001 and PSA3002 for this analysis. A total of 142 subjects were from PSA3001 and a total of 331 subjects were from PSA3002. The proportion of subjects with dactylitis resolution was significantly greater in both dose groups compared with the placebo group (Table 24). There were 42.2%, 59.4%, and 63.5% response rates in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. The response

rates were similar between the guselkumab q8w and guselkumab q4w groups based on the pooled analysis.

Table 24 Resolution of Dactylitis at Week 24 (Pooled): Main Analysis

Treatment Group (N)	n	Responder	Non-Responder	Compared to Placebo (95% CI): p-value[1]
Placebo (154)	154	65 (42.2%)	89 (57.8%)	
Guselkumab q8w (160)	160	95 (59.4%)	65 (40.6%)	18.0% (7.4, 28.6): <0.001
Guselkumab q4w (159)	159	101 (63.5%)	58 (36.5%)	21.3% (10.5, 32.0): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every 4 weeks; CI= confidence interval; N=number of subjects with dactylitis at baseline; n=number of subjects evaluable (who had observed response status or met TF criteria prior to Week 24); [1]The -p-values are based on the CMH test stratified by study and baseline stratification factors and unadjusted; [Source: Reviewer]

The results from supplementary analysis based on the treatment policy estimand were consistent with the main analysis. The Applicant performed tipping point analyses and for these analyses, the q8w (or the q4w) group has response rate lowered (a shift ranged from 0 to -100%) and the placebo group has response rate added (a shift ranged from 0 to 100%) for the missing on each group, with increments of 10%. For all shifts considered, the treatment effect of guselkumab q8w was statistically significant compared to the placebo group. Similarly, for the tipping point analysis comparing guselkumab q4w to placebo, the p-value remained <0.01 for all possible shifts. Therefore, the tipping points analysis supported the results of main analysis of efficacy [Source: Clinical Study Report for PSA3002, p109].

Though the pre-specified analysis was based on pooled data, the reviewer also assessed the efficacy from each study separately to ensure consistent trends in improvement were observed across studies, given approximately 70% of subjects in pooled data were from PSA3002. Table 25 shows the resolution of dactylitis at Week 24 from each study. While both dose levels did not show nominal statistical significance in PSA3001, there was a higher proportion of subjects with dactylitis resolution on both doses compared to placebo. Both doses showed nominal statistical significance, with a higher proportion of subjects with dactylitis resolution on both doses compared to placebo in PSA3002.

Table 25 Resolution of Dactylitis at Week 24

Treatment Group (N)	n	Responder	Compared to Placebo (95% CI): p-value[1]
PSA3001			
Placebo (55)	55	27 (49.1%)	
Guselkumab q8w (49)	49	32 (65.3%)	16.6% (-1.5, 34.8): 0.088
Guselkumab q4w (38)	38	24 (63.2%)	13.4% (-6.9, 33.7): 0.212
PSA3002			
Placebo (99)	99	38 (38.4%)	
Guselkumab q8w (111)	111	63 (56.8%)	18.7% (5.7, 31.7): 0.007
Guselkumab q4w (121)	121	77 (63.6%)	24.5% (11.8, 37.1): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every 4 weeks; CI= confidence interval; N=number of subjects with dactylitis at baseline; n=number of subjects evaluable (who had observed response status or met TF criteria prior to Week 24); [1]The -p-values are based on the CMH test stratified by baseline stratification factors and unadjusted; [Source: Clinical Study Report for PSA3002, p110]

Enthesitis (pooled)

Subjects with enthesitis at baseline were pooled from PSA3001 and PSA3002 for this analysis. A total of 222 subjects were from PSA3001 and a total of 506 subjects were from PSA3002. The proportion of subjects with enthesitis resolution was significantly greater in both dose groups compared with the placebo group (Table 26). There were 29.4%, 49.6%, and 44.9% response rates in the placebo, guselkumab q8w, and guselkumab q4w groups, respectively. The response rates were similar for the guselkumab q8w as compared to the guselkumab q4w group based on the pooled analysis.

Table 26 Resolution of Enthesitis at Week 24 (Pooled): Main Analysis

Treatment Group (N)	n	Responder	Non-Responder	Compared to Placebo (95% CI): p-value[1]
Placebo (255)	255	75 (29.4%)	180 (70.6%)	
Guselkumab q8w (230)	230	114 (49.6%)	116 (50.4%)	20.1% (11.8, 28.5): <0.001
Guselkumab q4w (243)	243	109 (44.9%)	134 (55.1%)	14.6% (6.4, 22.7): <0.001

Abbreviations: q8w=once every eight weeks; q4w=once every 4 weeks; CI= confidence interval; N=number of subjects with enthesitis at baseline; n=number of subjects evaluable (who had observed response status or met TF criteria prior to Week 24); [1]The -p-values are based on the CMH test stratified by study and baseline stratification factors and unadjusted; [Source: Reviewer]

The results from supplementary analysis based on the treatment policy estimand were consistent with the main analysis. The Applicant performed tipping point analyses and for these analyses, the q8w (or the q4w) group has response rate lowered (a shift ranged from 0 to -100%) and the placebo group has response rate added (a shift ranged from 0 to 100%) for the missing on each group, with increments of 10%. For all shifts considered, the treatment effect of guselkumab q8w was statistically significant compared to the placebo group. Similarly, for the tipping point analysis comparing guselkumab q4w to placebo, the p-value remained <0.05 for all possible shifts. Therefore, the tipping points analysis supported the results of main analysis of efficacy [Source: Clinical Study Report for 3002, p107].

Though the pre-specified analysis was based on pooled data, the reviewer also assessed the efficacy from each study separately to ensure consistent trends in improvement were observed across studies, given approximately 70% of subjects in pooled data were from PSA3002. Table 27 shows the resolution of enthesitis at Week 24 from each study. While both dose levels did not show nominal statistical significance in PSA3001 (only guselkumab q4w), there was a higher proportion of subjects with dactylitis resolution on both doses compared to placebo. Both doses showed nominal statistical significance, with a higher proportion of subjects with dactylitis resolution on both doses compared to placebo, in PSA3002.

Table 27 Resolution of Enthesitis at Week 24

Treatment Group (N)	n	Responder	Compared to Placebo (95% CI): p-value[1]
PSA3001			
Placebo (77)	77	21 (27.3%)	
Guselkumab q8w (72)	72	29(40.3%)	13.0% (-1.6, 27.5): 0.094
Guselkumab q4w (73)	73	35 (47.9%)	19.8% (4.9, 34.6): 0.013
PSA3002			
Placebo (178)	178	54 (30.3%)	
Guselkumab q8w (158)	158	85 (53.8%)	23.3% (13.1, 33.5): <0.001
Guselkumab q4w (170)	170	74 (43.5%)	12.3% (2.6, 22.1): 0.017

Abbreviations: q8w=once every eight weeks; q4w=once every 4 weeks; CI= confidence interval; N=number of subjects with enthesitis at baseline; n=number of subjects evaluable (who had observed response status or met TF criteria prior to Week 24); [1]The -p-values are based on the CMH test stratified by baseline stratification factors and unadjusted; [Source: Clinical Study Report for PSA3002, p108]

Efficacy Results – Exploratory COA (PRO) endpoints

The Applicant also evaluated Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) to assess a subject's level of fatigue and tiredness over the last 7 days. The FACIT-Fatigue score was calculated based on the FACIT-Fatigue questionnaire that is comprised of 13 questions, with each question graded on a 5-point scale (0-4; higher score indicates less fatigue).

In both studies, a numerical improvement from baseline was observed in both dose levels compared to the placebo at Week 24 based on the composite estimand using MMRM model. If a subject met TF criteria, the change from baseline was considered 0 (no improvement). This endpoint was not multiplicity controlled but nominal p-values less than 0.001 were observed for both dose levels in both studies (Table 28) . The results using the treatment policy estimand were supportive of the main analysis.

Table 28 Change from Baseline in FACIT-Fatigue score at Week 24

Treatment Group (N)	n	Adjusted Mean[1] (95% CI)	Compared to Placebo (95% CI)
PSA3001			
Placebo (126)	126	2.21 (0.77, 3.64)	
Guselkumab q8w (127)	127	5.61 (4.18, 7.04)	3.40 (1.44, 5.36)
Guselkumab q4w (128)	128	5.84 (4.42, 7.27)	3.64 (1.68, 5.59)
PSA3002			
Placebo (246)	244	3.56 (2.50, 4.62)	
Guselkumab q8w (248)	246	7.55 (6.50, 8.60)	3.99 (2.53, 5.45)
Guselkumab q4w (245)	245	7.11 (6.05, 8.17)	3.55 (2.08, 5.02)

Abbreviations: q8w=once every eight weeks; q4w=once every four weeks; SE= standard error; CI= confidence interval; N=number of subjects randomized and received treatment; n=number of subjects with observed change from baseline at this visit or met TF criteria prior to this visit; [1]Model based estimates using MMRM, the model included treatment, visit (Week 8, 16 and 24) , baseline score, stratification factors and treatment by visit interaction term; [Source: Clinical Study Report for PSA3001, p129 and Clinical Study Report PSA3002, p152]

A Clinical Outcome Assessment (COA) consult was requested to review the evidence to support the validity and reliability of this patient-reported outcome instrument for the treatment of adult patients with active psoriatic arthritis, and the interpretation of clinically meaningful within-patient change. The COA team determined that based on the evidence provided, they agree that fatigue appears to be an important and common symptom in patients with PsA. However, based on the Applicant's submission, the content validity of the FACIT-Fatigue has not been fully established in this patient population and there are limitations of the instrument including:

- The threshold for clinically meaningful within-patient change to assess fatigue severity in the clinical trials could not be estimated using anchor-based methods, because the clinical trials did not include appropriate anchor scales,
- The observed treatment effect on the FACIT-Fatigue instrument (in both clinical trials) was modest. Given the lack of clear documentation of content validity and the limitations of the FACIT-Fatigue described above, it is not possible to know whether the modest effect was due to the impact of the drug on fatigue or to the limitations of the FACIT-Fatigue.

Therefore, while fatigue appears to be a relevant concept for patients with PsA, the threshold for clinically meaningful within-patient change to assess fatigue severity in the clinical trials could not be estimated using anchor-based methods, because the clinical trials did not include anchor scales and the proposed threshold of ≥4 has not been adequately justified. (b) (4) (b) (4). Refer to COA review by Dr. Yasmin Choudhry, dated July 5, 2020, for additional details. While the review team does not agree that the Applicant-proposed 4-point threshold is justified as meaningful, the separation between guselkumab groups and the placebo group was also evident at higher levels of response and the changes were seen in both studies. Based on these considerations, providing a qualitative description of the findings in the product labeling is reasonable.

Dose/Dose Response

Compared to placebo, both guselkumab groups demonstrated statistically significant improvements in efficacy in terms of ACR20 response at Week 24. Comparison between two dose levels did not show statistical significance, however, this comparison was not pre-planned and the study was not designed to test differences between doses. Therefore, this analysis only provides supplemental information. A larger numerical improvement in guselkumab q4w compared to guselkumab q8w was observed in most secondary endpoints, though there were also secondary endpoints (IGA response, 36-SF PCS and enthesitis (from pooled data)) in PSA3002, with less numerical improvement in guselkumab q4w compared to guselkumab q8w. Thus, there is considerable uncertainty around the comparison between the doses (b) (4) (b) (4)

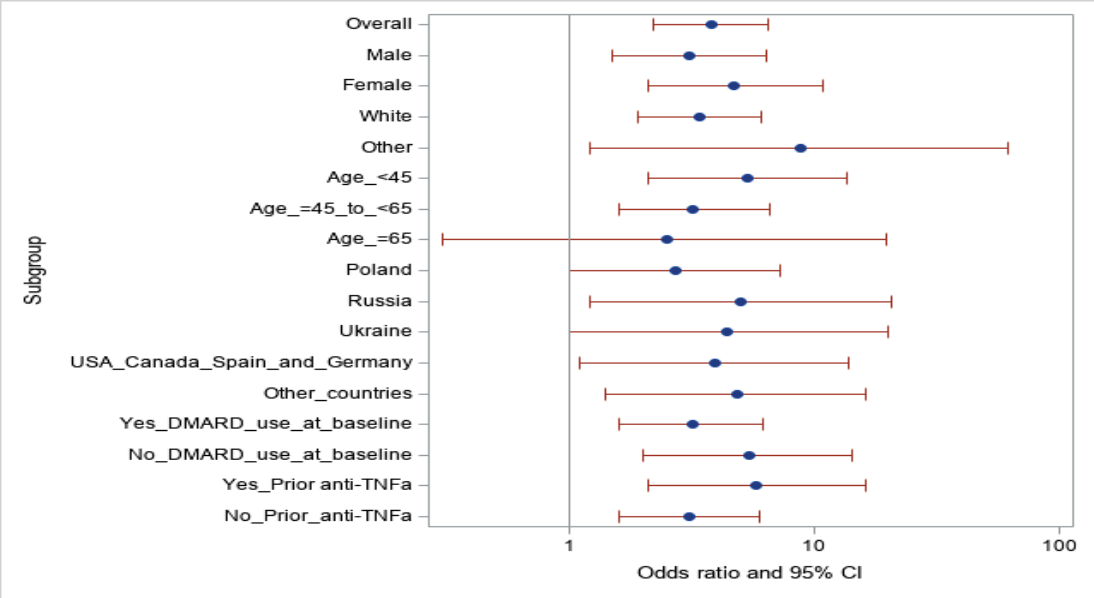
Additional Analyses Conducted on the Individual Trial

The subgroup analyses using a logistic regression model compared ACR20 response at Week 24 across treatment groups within subgroups defined by sex, race, age, geographic region, and prior and baseline medication use. The number of subjects from US was combined with Canada, Spain and Germany in PSA3001, and with Spain in PSA3002 because the number was too small (17 subjects in PSA3001 and 6 subjects in PSA3002). The resulting odds ratio and the corresponding 95% confidence intervals are shown in Figure 8 to Figure 11. All of the subgroups reported odds ratios greater than 1.0, in favor of guselkumab, except for subjects age ≥ 65 in PSA3002. This group reported an odds ratio of 1.0 with a 95% confidence interval of (0.2, 5.4) in guselkumab q4w vs. placebo. Additionally, in some subset of subgroups, the lower limit of the 95% confidence interval did not exceed 1.0. However, we note that in several subgroups, the number of subjects within the category was too small to calculate reliable odds ratios, e.g., in the "other" race for both studies and age 65 or over in both studies. Regardless of baseline DMARD use, the odds ratios were greater than 1.0 in both studies, in favor of guselkumab. In PSA3001, guselkumab q8w showed odds ratios over placebo of 3.2 (95% CI: 1.6, 6.2) for baseline DMARD use and 5.4 (95% CI: 2.0, 14.2) for no baseline DMARD use. In the same study, guselkumab q4w showed odds ratios over placebo of 4.6 (95% CI: 2.4, 9.0) for baseline DMARD use and 6.4 (95% CI: 2.4, 16.8) for no baseline DMARD use. In PSA3002, guselkumab q8w showed odds ratios over placebo of 3.0 (95% CI: 1.9, 4.7) for baseline DMARD use and 5.8 (95%

CI: 2.9, 11.7) for no baseline DMARD use. In the same study, guselkumab q4w showed odds ratios over placebo of 2.7 (95% CI: 1.8, 4.2) for baseline DMARD use and 7.0 (95% CI: 3.4, 14.3) for no baseline DMARD use. Similar results were obtained regardless of prior exposure to anti-TNFα in PSA3001. The findings from the subgroup analyses were generally comparable to the overall population results.

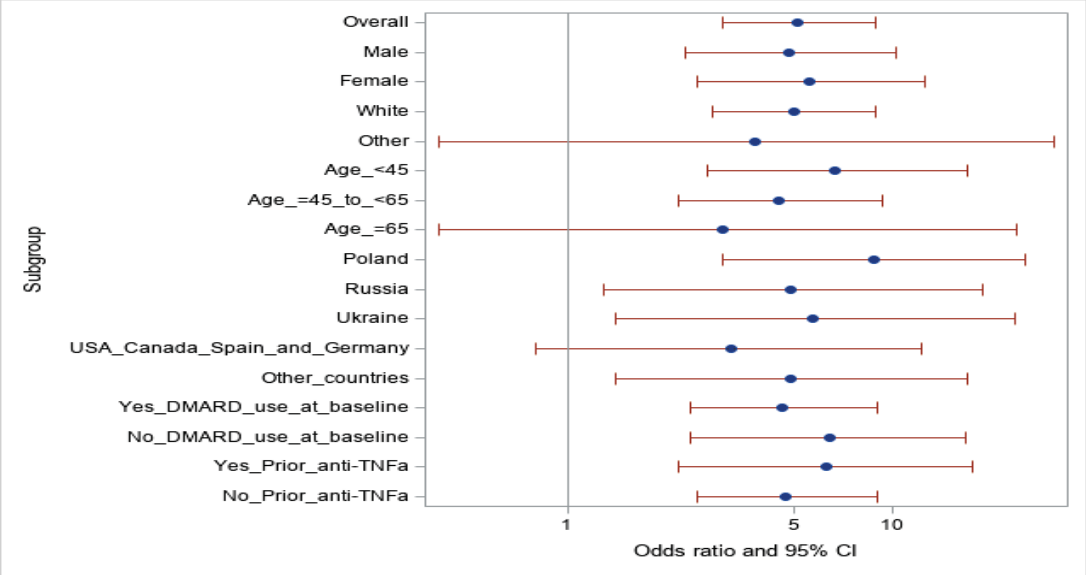
Table 39 and Table 40 in Appendix 19.4 also summarize the results with odds ratios from these logistic regression models for PSA3001 and PSA3002, respectively.

Figure 8 Subgroup Analysis from PSA3001: Placebo vs Guselkumab q8w on ACR20 Response



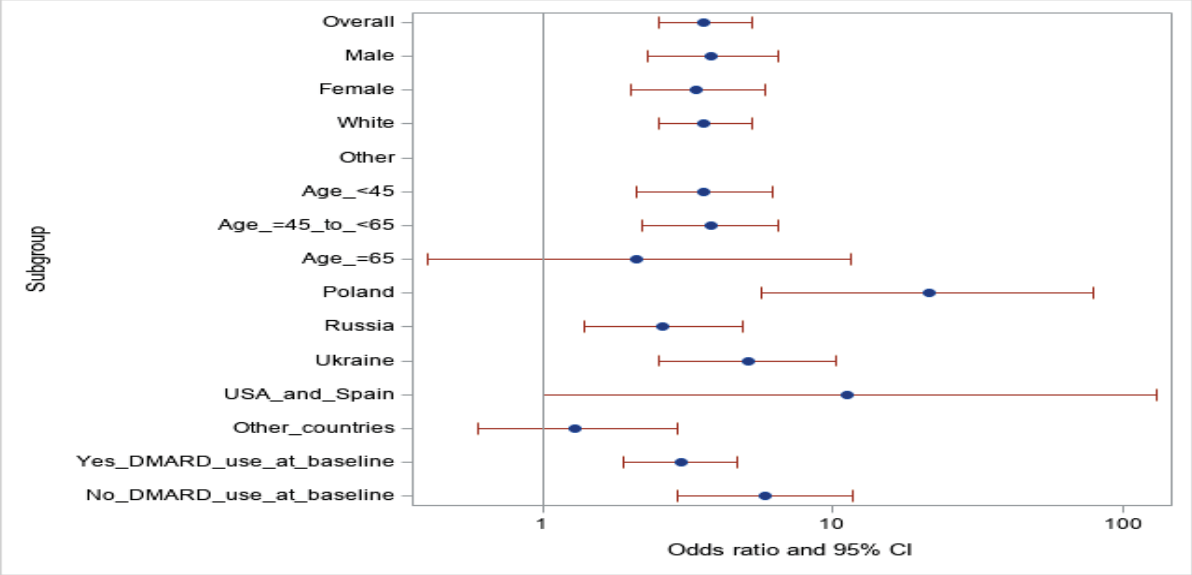
Odds ratio from logistic regression model with the corresponding 95% confidence interval. Horizontal axis is shown in log scale with base 10. Vertical line indicates odds ratio=1; [Source: Reviewer]

Figure 9 Subgroup Analysis from PSA3001: Placebo vs Guselkumab q4w on ACR20 Response



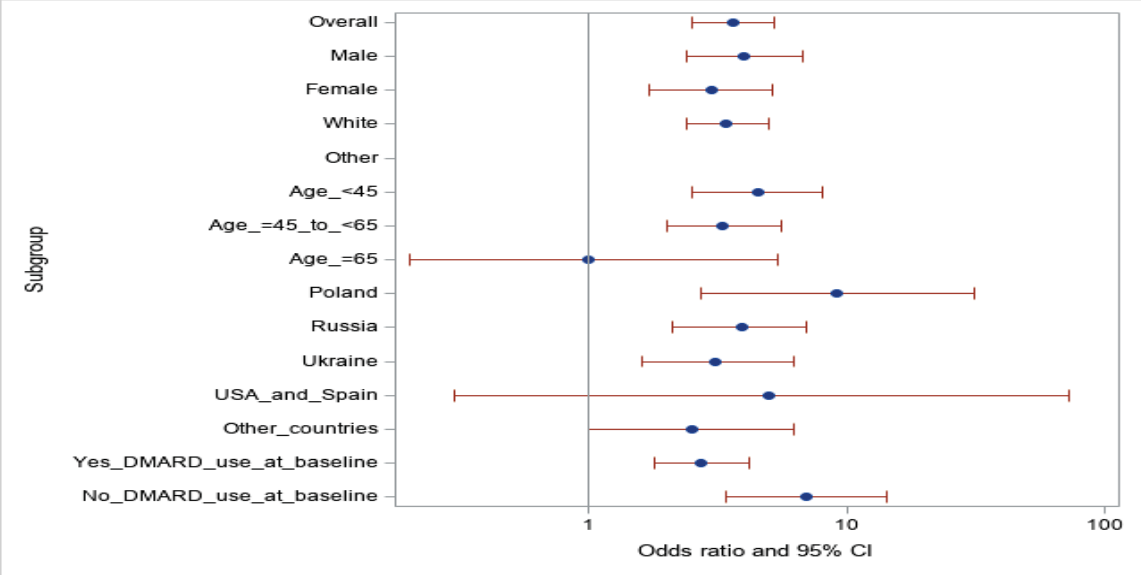
Odds ratio from logistic regression model with the corresponding 95% confidence interval. Horizontal axis is shown in log scale with base 10. Vertical line indicates odds ratio=1; [Source: Reviewer]

Figure 10 Subgroup Analysis from PSA3002: Placebo vs Guselkumab q8w on ACR20 Response



Odds ratio from logistic regression model with the corresponding 95% confidence interval. Horizontal axis is shown in log scale with base 10. Vertical line indicates odds ratio=1; [Source: Reviewer]

Figure 11 Analysis from PSA3002: Placebo vs Guselkumab q4w on ACR20 Response



Odds ratio from logistic regression model with the corresponding 95% confidence interval. Horizontal axis is shown in log scale with base 10. Vertical line indicates odds ratio=1; [Source: Reviewer]

In addition to the logistic regression subgroup analyses discussed above, the p-values for interaction of the treatment group and the subgroup were obtained when a subgroup had at least two categories. The model included treatment, subgroup, and treatment by subgroup interaction term. There were no significant interaction effects in PSA3001. In PSA3002, there was some evidence of interaction between treatment and region (p=0.003) in guselkumab q8w

vs. placebo and between treatment in DMARD use at baseline (p=0.03) in guselkumab q4w vs. placebo. Other countries showed the smallest effect of guselkumab q8w in terms of odds ratio relative to other complementary subgroups, and its lower limit of the 95% confidence intervals did not exceed 1.0. Though both subgroups were in favor of guselkumab q4w, DMARD use at baseline (Yes) showed smaller effect of guselkumab q4w relative to DMARD use at baseline (No).

8.3.1. Integrated Assessment of Effectiveness

The effectiveness of guselkumab was evaluated in the two studies, PSA3001 and PSA3002. The primary objective was to evaluate the efficacy of guselkumab in subjects with active PsA by assessing the reduction in signs and symptoms of PsA. PSA3001 evaluated subjects who had an inadequate response to standard therapies (e.g., non-biologic DMARDs, apremilast or NSAIDs) and 31% of the study population was previously exposed to up to two anti-TNFα agents. PSA3002 evaluated subjects who had an inadequate response to standard therapies and who were biologic naïve. In both studies, two dosing regimens of guselkumab (q8w and q4w) were compared to placebo.

In both studies, both guselkumab dosing regimens provided statistically significant differences compared to the placebo in ACR20 response at Week 24, supporting the effectiveness of guselkumab in PsA. Key secondary endpoints, assessed at Week 24, such as IGA response, change from baseline in HAQ-DI, change from baseline in SF-36 PCS also provided statistical significance supporting the efficacy of both guselkumab doses. Resolution of dactylitis and resolution of enthesitis endpoints were assessed using the pooled data from PSA3001 and PSA3002, and the results supported the efficacy of both guselkumab doses. Change from baseline in modified vdH-S score was only assessed in PSA3002. The statistical significance was demonstrated in guselkumab q4w over the placebo, but not in guselkumab q8w.

8.4. Review of Safety

8.4.1. Safety Review Approach

The safety assessment of guselkumab in psoriatic arthritis is primarily based on the safety data from the two phase 3 studies, studies PSA3001 and PSA3002. A summary of the key design features for these studies is presented in Table 4. Studies PSA3001 and PSA3002 enrolled subjects with PsA who had comparable baseline demographics and disease characteristics to those of the targeted patient population in the US. Each of the studies provided controlled comparisons between guselkumab 100 mg SC at Week 0, 4, and every 4 weeks thereafter (q4w), guselkumab 100 mg SC at Week 0, 4, and every 8 weeks thereafter (q8w), and placebo. After Week 24, all placebo-treated subjects received treatment with guselkumab 100 mg q4w. The safety population included all randomized subjects who received at least one dose of the study drug.

The safety of each study is analyzed separately for the 24 week placebo-controlled period. In addition, safety data from the 120-day safety update was generally consistent with the safety in the controlled period and is described for less common AEs and AESI.

8.4.2. Review of the Safety Database

Overall Exposure

As seen in Table 29, through August 15, 2019, a total of 1,100 subjects with active PsA were exposed to guselkumab in studies PSA3001 and PSA3002. This included 1,065 (97%) subjects treated for at least six months, including 364 subjects who received guselkumab q8w and 701 subjects who received guselkumab q4w or placebo followed by guselkumab q4w. In addition, 763 (69%) subjects were treated for at least one year, including 326 subjects who received guselkumab q8w and 437 subjects who received guselkumab q4w or placebo followed by guselkumab q4w.

Table 29 Extent of Exposure in Safety Database through August 15, 2019 for Studies PSA3001 and PSA3002 Combined

	Guselkumab q8w N=375 n (%)	Guselkumab q4w N=373 n (%)	Placebo -> Guselkumab q4w N=352 n (%)	Guselkumab q4w combined N=725 n (%)
Studies PSA3001 and PSA3002				
≥ 6 months	364 (97)	362 (97)	339 (96)	701 (97)
≥ 12 months	326 (87)	331 (89)	106 (30)	437 (60)

Source: Adapted from Table 2 in the 120-day safety update

Adequacy of the Safety Database:

The PsA database is comprised of 1100 subjects exposed to guselkumab in the phase 3 studies. In the 24-week placebo-controlled period, 375 subjects were randomized to guselkumab q8w, 373 subjects were randomized to guselkumab q4w, and 372 subjects were randomized to placebo. Additional supportive safety data for the guselkumab q8w regimen are provided by the study PSA2001 and the available safety data from guselkumab in psoriasis. The types of safety assessments conducted were also consistent with reasonable monitoring for the known AEs of guselkumab and for this patient population. Overall, the studies provide adequate data in regards to drug exposure in the targeted patient population to support the safety assessment of guselkumab q4w and guselkumab q8w in subjects with PsA, in the context of the established safety profile in the approved indication of plaque psoriasis.

8.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality
No specific concerns arose regarding data integrity and submission quality as they relate to the safety assessment.

Categorization of Adverse Events

In both study PSA3001 and PSA3002, adverse events and serious adverse events were defined using standard definitions. An assessment of severity grade was made using mild, moderate, and severe categories. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 in both studies.

In both studies, the predefined AEs of special interest were malignancy, potential opportunistic infections, active tuberculosis, other infections of interest including those related to IL-23 pathways, anaphylaxis, serum sickness or serum sickness-like reactions, and pregnancies with negative outcome.

Routine Clinical Tests
Clinical laboratory evaluations for both studies included:
Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and bands
Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin (with fractionation of hyperbilirubinemia), total protein, and uric acid
Lipids (collected only at Week 0): total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides
Inflammatory markers: High sensitivity C-reactive protein

8.4.4. Safety Results

An overview of the adverse events reported in the phase 3 studies, PSA 3001 and PSA 3002 is presented in Table 30**.**

Table 30 Overview of Adverse Events in Studies PSA3001 and PSA3002 through Week 24

	PSA3001			PSA3002		
	Placebo N=126 n (%)	**Guselkumab q8w N=127 n (%)**	**Guselkumab q4w N=128 n (%)**	**Placebo N=246 n (%)**	**Guselkumab q8w N=248 n (%)**	**Guselkumab q4w N=245 n (%)**
Subjects with ≥1 TEAE	75 (59.5)	68 (53.5)	71 (55.5)	100 (40.7)	114 (46.0)	113 (46.1)
Deaths	1 (0.8)	0	0	0	0	0
Serious Adverse Events	5 (4.0)	4 (3.1)	0	7 (2.8)	3 (1.2)	8 (3.3)
AEs leading to drug d/c	3 (2.4)	3 (2.4)	1 (0.8)	4 (1.6)	2 (0.8)	6 (2.4)
AEs of Interest						
Infections	32 (25.4)	33 (26.0)	31 (24.2)	45 (18.3)	40 (16.1)	49 (20.0)
Serious Infections	2 (1.6)	0	0	1 (0.4)	1 (0.4)	3 (1.2)
Injection-Site Reactions	0	2 (1.6)	1 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)
Suicidal Ideation	1 (0.8)	1 (0.8)	0	1 (0.4)	0	1 (0.4)
Malignancy	0	1 (0.8)	0	1 (0.4)	1 (0.4)	0

Abbreviations: TEAE=treatment emergent adverse event; d/c=discontinuation; AE=adverse event

Deaths

There were a total of two deaths reported in the guselkumab PsA clinical development program. In study PSA3001 one death (0.8%) occurred due to cardiac failure in the placebo group, while there were no deaths in the guselkumab groups through Week 24. The placebo-treated subject who experienced cardiac failure was a 50 year old male with family history of hypertension and stroke, who was found deceased at his home on Study Day 166. It was reported that he died due to heart failure secondary to essential hypertension. The subject never received guselkumab treatment. Additionally, through the data cut (May 1, 2019), pneumonia leading to a death on study Day 183 was reported in one additional subject in the placebo group. This subject did not receive any treatment with guselkumab prior to death.

In study PSA3002, no deaths occurred in any of the treatment groups.

No additional deaths were reported in either study through August 15, 2019 in the 120-day safety update.

Serious Adverse Events

In study PSA3001, during the 24 week placebo-controlled period, SAEs were reported by similar proportions of subjects in the guselkumab q8w and placebo groups; no SAEs were reported by subjects in the guselkumab q4w group. SAEs were reported by 4 subjects (3.1%) in the guselkumab q8w group and included supraventricular arrhythmia, ileus, plasma cell myeloma (discussed under AEs leading to discontinuation), and cervical dysplasia. In the placebo group, five subjects (4.0%) reported SAEs of cardiac failure, pain, limb abscess, upper respiratory tract infection, and chronic obstructive pulmonary disease. Reported SAEs were singular by preferred term. Except for the SAE of cervical dysplasia, all SAEs in the guselkumab q8w group were considered not/doubtfully related to study drug. No serious infections occurred in the guselkumab group, as compared to two subjects (1.6%) with serious infections in the placebo group. The SAE of cardiac failure in the placebo group was the only adjudicated major adverse cardiovascular event (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, in study PSA3001 in any dose group through Week 24.

In the 120-day safety update, three additional guselkumab-treated subjects reported SAEs. One subject in the guselkumab q8w group reported lumbar spinal stenosis, one in the guselkumab q4w group reported meniscus injury, and one in the placebo group who crossed over to guselkumab q4w at Week 24 reported urosepsis.

In study PSA3002, SAEs were reported by similar proportions of subjects in the guselkumab q4w and placebo groups (3.3% and 2.8%, respectively), and a numerically lower proportion in the guselkumab q8w group (1.2%). SAEs by preferred term are shown in Table 31. All events occurred in one (0.4%) subject each. SAEs were most frequently reported in the Infections and infestations System Organ Class (SOC). Serious infections included acute hepatitis B, oophoritis, and pneumonia influenza; all were reported by single subjects in the guselkumab q4w group. Four subjects balanced by treatment group reported SAEs in the Injury, poisoning, and procedural complications SOC; these included events of ankle fracture, femur fracture, lower limb fracture, metal poisoning, and post procedural fistula. An SAE of nonfatal ischemic stroke in the guselkumab q4w group was the only MACE event in study PSA3002 in any dose group through Week 24. One subject receiving guselkumab q8w reported an SAE of coronary artery disease. Based on review of the narrative, the subject was a 59 year old smoker, with hypertension and diabetes who was hospitalized for chest pain and, on evaluation, was found to have a positive stress test, and underwent coronary artery angiography with stent placement.

Table 31 Study PSA3002 Serious Adverse Events through Week 24

	Placebo N=246 n (%)	Guselkumab q8w N= 248 n (%)	Guselkumab q4w N= 245 n (%)
Infections and infestations	**0**	**0**	**3 (1.2)**
Acute hepatitis B	0	0	1 (0.4)
Oophoritis	0	0	1 (0.4)
Pneumonia influenzal	0	0	1 (0.4)
Injury, poisoning and procedural complications	**1 (0.4)**	**1 (0.4)**	**2 (0.8)**
Ankle Fracture	0	1 (0.4)	0
Femur Fracture	0	0	1 (0.4)
Lower limb fracture	0	0	1 (0.4)
Metal poisoning	0	0	1 (0.4)
Post procedural fistula	1 (0.4)	0	0
Cardiac disorders	**1 (0.4)**	**1 (0.4)**	**0**
Coronary artery disease	0	1 (0.4)	0
Unstable Angina	1 (0.4)	0	0
General disorders and administration site conditions	**0**	**1 (0.4)**	**0**
Pyrexia	0	1 (0.4)	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.4)**
Osteoarthritis	0	0	1 (0.4)
Nervous system disorders	**0**	**0**	**1 (0.4)**
Ischemic stroke	0	0	1 (0.4)
Vascular disorders	**0**	**0**	**1 (0.4)**
Blue toe syndrome	0	0	1 (0.4)
Gastrointestinal disorders	**1 (0.4)**	**0**	**0**
Inflammatory bowel disease	1 (0.4)	0	0
Hepatobiliary disorders	**1 (0.4)**	**0**	**0**
Drug-induced liver injury	1 (0.4)	0	0
Metabolism and nutrition disorders	**1 (0.4)**	**0**	**0**
Obesity	1 (0.4)	0	0
Neoplasms benign, malignant and unspecified	**1 (0.4)**	**0**	**0**
Clear cell renal cell carcinoma	1 (0.4)	0	0
Renal and urinary disorders	**1 (0.4)**	**0**	**0**
Tubulointerstitial nephritis	1 (0.4)	0	0

Source: Adapted from study PSA3002 CSR table 30

In the 120-day safety update, 11 additional guselkumab-treated subjects reported SAEs. In the guselkumab q8w group, one of each of the following SAEs was reported: urinary tract infection, lower limb fracture, transient ischemic attack, and hypertension. In the guselkumab q4w group one SAE each of: diabetes mellitus inadequate control, ischemic stroke, gastric ulcer, and sinus perforation occurred. In the placebo group who crossed over to guselkumab q4w at Week 24, the SAE of osteoarthritis was reported in two subjects, and meningitis listeria was reported in one subject. The SAE of ischemic stroke occurred in a 52-year-old man had a medical history of prior stroke and hypertension. This was considered a serious MACE. The SAE of listeria meningitis was reported on Study Day 376 in a 51-year old woman who was receiving concomitant methotrexate. The subject was originally randomized to placebo and subsequently received guselkumab treatment. Guselkumab was discontinued and the subject was recovering from the event per the 120-day safety update.

Overall, SAEs were generally similar between the guselkumab treatment groups and placebo groups, and consistent with the known safety profile of guselkumab.

Dropouts and/or Discontinuations Due to Adverse Effects

The number of discontinuations due to AEs was low in studies PSA3001 and PSA3002 and generally similar across treatment arms. In study PSA3001, three subjects (2.4%) each in the placebo and guselkumab q8w dosing groups had adverse events (AE) leading to drug discontinuations through Week 24. One (0.8%) subject in the guselkumab q4w group had AE leading to drug discontinuation. AEs leading to discontinuation in the guselkumab q4w group included dyspepsia, gastritis, hiatal hernia, reported by a single subject. AEs leading to discontinuation in the guselkumab q8 w group included bronchitis, psoriatic arthropathy, and plasma cell myeloma. AEs leading to discontinuation in the placebo group included cardiac failure and psoriasis. Two subjects in the placebo group discontinued treatment for AE of psoriasis, all other AEs leading to discontinuation occurred in 1 subject each. The placebo-treated subject who reported AE leading to discontinuation of cardiac failure is discussed under deaths above. The AE leading to discontinuation of plasma cell myeloma occurred in a 73 yo female with baseline elevation in total protein, beta-2microglobulin level, M protein, excess free kappa light chain production, and a marked abnormal kappa/lambda ratio. She developed worsening hearing in her right ear, MRI showed multiple bone metastases, and a SAE of plasma cell myeloma was reported on Study Day 15. Guselkumab was discontinued.

Clinical laboratory analysis of a serum sample collected prior to the first administration of guselkumab indicated an elevated level of gamma globulin and

In the 120-day safety update, an AE leading to discontinuation of study agent was reported in two guselkumab-treated subjects in study PSA3001: asthenia in one subject in the guselkumab q8w group and squamous cell carcinoma left upper arm/malignant melanoma in situ right lateral brow in one subject in the group that crossed over from placebo to guselkumab q4w at Week 24.

In study PSA3002, four subjects (2%) in the placebo group, two subjects (0.8%) in the

guselkumab q8w dose group, and six subjects (2%) in the guselkumab q4w group had adverse events leading to drug discontinuations through Week 24. AEs leading to discontinuation were generally singular by PT and SOC, except for infections and infestations in which there were 2 AEs leading to discontinuation (acute hepatitis B and rhinovirus infection), both reported in the guselkumab q4w group. AEs leading to discontinuation in the guselkumab q4w group included acute hepatitis B, rhinovirus infection, dermatitis allergic, injection site erythema, injection site swelling, injection site warmth, and ischemic stroke. AEs leading to discontinuation in the guselkumab q8w group included rash and malignant melanoma in situ. AEs leading to discontinuation in the placebo group included drug-induced liver injury, clear cell renal cell carcinoma, inflammatory bowel disease, and tubulointerstitial nephritis. The guselkumab-treated subject with malignant melanoma in situ was a 60 year old male who had a pre-existing skin lesion and underwent biopsy that revealed malignant melanoma in situ on Study Day 41. Study treatment was subsequently discontinued. The placebo-treated subject with drug-induced liver injury had hepatotoxicity thought to be due to isoniazid therapy.

In the 120-day safety update, an AE leading to discontinuation of study agent was reported in three guselkumab-treated subjects in study PSA3002: one nonserious urinary tract infection in the guselkumab q8w group, nonalcoholic fatty liver disease in one subject in the placebo group who crossed over to guselkumab q4w group, and meningitis listeria in one subject in the placebo who crossed over to guselkumab q4w group as mentioned above in the SAE section.

Overall, AEs leading to discontinuation were similar between the guselkumab treatment groups and placebo groups, and consistent with the known safety profile of guselkumab.

Significant Adverse Events
In study PSA3001 and study PSA3002, the predefined AEs of special interest were: potential opportunistic infections, active TB, other infections of interest including those related to IL-23 pathways, pregnancies with negative outcome, anaphylaxis, serum sickness or serum sickness-like reactions, and malignancy.

Infections:
Infections were reported in a similar number of subjects across treatment arms in studies PSA3001 and PSA3002.

In study PSA3001, 32 subjects (25.4%) had infections in the placebo group, 34 subjects (26.8%) in the guselkumab q8w dose group, and 29 subjects (22.7%) in the guselkumab q4w group through Week 24. Serious infections were reported by 2 subjects (1.6%) in the placebo group (abscess limb and upper respiratory tract infection) and no subjects in the guselkumab groups. Nasopharyngitis and upper respiratory tract infection were the most common infection in all groups by preferred term. Nasopharyngitis was reported most frequently in the guselkumab q8w group (12.6%), and of similar frequency in the guselkumab q4w (5.5%) and placebo groups (6.3%). Upper respiratory tract infections were generally balanced across the guselkumab q4w group (8.6%), guselkumab q8w (5.5%), and placebo groups (7.1%).

In study PSA3002, 45 subjects (18.3%) had infections in the placebo group, 40 subjects (16.1%) in the guselkumab q8w group, and 49 subjects (20.0%) in the guselkumab q4w dose group through Week 24. Serious infections were reported in three subjects (1.2%) in the guselkumab q4w group, and 1 subject each (0.4%) in the guselkumab q8w and placebo groups. Serious infections included acute hepatitis B, oophoritis, and pneumonia influenza (guselkumab q4w), as well as pyrexia (guselkumab q8w), and post procedural fistula (placebo). The most common infections in the guselkumab groups were nasopharyngitis, upper respiratory infection, and bronchitis by preferred term. Nasopharyngitis was reported by similar proportions of subjects in the guselkumab q4 w (4.9%), guselkumab q8w (4.0%), and placebo groups (3.7%). Upper respiratory tract infections were reported most frequently by subjects in the guselkumab q4w group (4.9%), as compared to the guselkumab q8w group (2.4%), and placebo groups (3.3%). Bronchitis was reported most frequently by subjects in the guselkumab q4w group (4.1%), as compared to the guselkumab q8w group (0.4%) and placebo groups (1.2%).

No subjects experienced active TB or other opportunistic infections through Week 24 in either study. In the 120 day Safety Update, there was 1 report of an opportunistic infection, meningitis listeria, as discussed under SAEs above, and no reports of active TB. Other reported serious infections include urosepsis (placebo to guselkumab q4w) in PSA3001, and events of sinus perforation (guselkumab q4w), severe urinary tract infection (guselkumab q8w), and severe meningitis listeria (placebo to guselkumab q4w, discussed above).

Pregnancy:
No pregnancies were reported in study PSA3001 through Week 24. In study PSA3002, through Week 24, there was one report of a pregnancy involving the partner of a subject in the placebo group. No additional pregnancies were reported in the 120 day Safety Update.

Anaphylaxis:
No anaphylactic reactions or events of serum sickness/serum sickness-like reactions were reported through Week 24 in any dose group in either study. There were no reports of serious hypersensitivity reactions in the 120-day safety update.

Injection Site Reactions:
An injection site reaction (ISR) was defined as any unfavorable or unintended sign that occurred at the injection site, including pain, erythema, and/or induration.

In study PSA3001, two subjects (1.6%) reported injection site reactions in the guselkumab q8w dose group and one subject (0.8%)reported in the guselkumab q4w group. No subjects in the placebo group reported ISR. All ISRs were mild in intensity.

In study PSA3002, one subject (0.1%) in the placebo group reported an ISR, while three subjects (1.2%) reported ISR in each of the guselkumab q8w group and in the guselkumab q4w groups. All ISR were mild in intensity, except for one moderate ISR in the guselkumab q4w group.

Malignancy:
In study PSA3001, one case of malignancy (plasma cell myeloma) occurred in the guselkumab q8w dose group and none in the other groups. This case of plasma cell myeloma was reported in a 73-year old subject 15 days after the first study agent administration and is discussed under AEs leading to discontinuation. Following the data cut, an additional 65 year old subject (placebo to guselkumab q4w) with history of actinic keratoses and in situ squamous cell cancer, and maternal history of malignant melanoma, was reported to have squamous cell carcinoma in situ and malignant melanoma in situ on Study Day 260. Treatment with guselkumab was discontinued.

In study PSA3002, one case of malignancy occurred in the placebo group and one in the guselkumab q8w group; both AEs led to discontinuation of study treatment. The placebo-treated subject was diagnosed with clear cell renal cell carcinoma that was considered moderate in severity, and resolved with sequelae by Week 24. The one subject in the guselkumab q8w group was diagnosed with malignant melanoma in situ that was considered severe, not related to study agent, and was resolved by Week 24.

No new malignancies were reported in either study in the 120-day safety update. Based on comparisons conducted by the Applicant, the rates of malignancies other than cervical cancer in situ and non-melanoma skin cancer in the pooled analysis set were compared to expected rates for the general population in the United States, using SIR based on the SEER database (2000 to 2016. When the SIR is greater than 1, the observed number of subjects with malignancies is higher than the expected number of cases. Through the data cut, the SIR for malignancies other than cervical cancer in situ and NMSC was 1.02 (95% CI: 0.12, 3.69) in the guselkumab q8w group, 0 (95% CI: 0, 1.49) in the guselkumab q4w group, and 0.33 (95% CI: 0.01, 1.82) in the guselkumab q4w combined group. Interpretation was limited by the small number of subjects with events, but does not suggest an overall increased risk of malignancy in subjects with PsA treated with guselkumab over the period studied.

Suicidal Ideation:
In study PSA3001, there were 2 suicidal ideation events reported by one subject (0.8%) each in the placebo group and guselkumab q8w group. There were no subjects with suicidal ideation in the guselkumab q4w group. Both subjects had histories of suicidal ideation, and the guselkumab-treated subject also had a history of depression and was receiving an anti-depressant at baseline. No interruption or discontinuation of guselkumab occurred due to this AE. No suicidal behavior or non-suicidal self-injurious behavior was reported through Week 24.

In study PSA3002, there were two suicidal ideation events reported by one subject (0.8%) each in the placebo group and guselkumab q4w group. There were no subjects with suicidal ideation in the guselkumab q8w group. The placebo-treated subject had suicidal ideation at the screening visit based on the lifetime assessment. The guselkumab-treated subject did not have any suicidal ideation at baseline, had level 1 ideation (wish to be dead) at the Week 2 visit; the subject underwent psychiatric assessment and was judged not to be at risk to continue treatment. No suicidal behavior or non-suicidal self-injurious behavior was reported through

Week 24.

Treatment Emergent Adverse Events
Study PSA3001
In study PSA3001, treatment emergent adverse events (TEAEs) were generally balanced by treatment group. Through Week 24, 75 subjects (59.5%) had at least one TEAE in the placebo group, 68 (53.5%) in the guselkumab q8w dose group, and 71 (55.5%) in the guselkumab q4w group. In study PSA3001, four severe AEs occurred in three subjects (2.4%) in the placebo group (one cardiac failure, one limb abscess, one tooth abscess, and one vaginal hemorrhage), two (1.6%) in the guselkumab q8w group (one ileus and one plasma cell myeloma), and none in the guselkumab q4w dose group. All severe AEs were singular by preferred term.

The most frequently reported AEs were reported in the following Infections and Infestations SOC (25% in the placebo group, 27% in the guselkumab q8w dose group ,and 23% in the guselkumab q4w group) and the Musculoskeletal and Connective Tissue Disorders SOC (19% in the placebo group, 14% in the guselkumab q8w dose group and 17% in the guselkumab q4w). The most frequently reported AEs by PT within the Infections and Infestations SOC were nasopharyngitis and upper respiratory tract infection, as discussed under Infections above. The most frequently AEs by PT within the Musculoskeletal and Connective Tissue Disorders SOC were enthesopathy, back pain, osteoarthritis, spinal osteoarthritis, arthralgia, dactylitis, and psoriatic arthritis. Dactylitis, psoriatic arthritis, and arthralgia were more frequently reported by subjects in the placebo group, while the other TEAEs were generally similar across treatment groups.

The most common PTs with a frequency ≥5% in any treatment group through Week 24 are presented in Table 32.

Table 32 Study PSA3001 AEs with a frequency ≥5% in any treatment group through Week 24

Preferred Term	Placebo N=126 n %	Guselkumab q8w N=127 n %	Guselkumab q4w N=128 n %
Nasopharyngitis	8 (6.3)	16 (12.6)	7 (5.5)
Upper respiratory tract infection	8 (6.3)	7 (5.5)	11 (8.6)
Alanine aminotransferase increased	3 (2.4)	8 (6.3)	5 (3.9)
Aspartate aminotransferase increased	3 (2.4)	9 (7.1)	3 (2.3)

Adapted from study PSA3001 CSR table 26

The other most common (≥2%) adverse events observed included: bronchitis (3.9% in the guselkumab q8w group and 0.8% in the placebo and guselkumab q4w groups); enthesopathy (4.8% in the placebo group, and 4.7% in each of the guselkumab groups); diarrhea (3.1% in the guselkumab q8w group and 1.6% in the placebo and guselkumab q4w groups); and headache (0.8% in the placebo group, 1.6% in the guselkumab q8w group, and 3.1% in the guselkumab q4w group). These are presented in Table 43.The overall numbers of these events were low, and generally balanced between the treatment groups.

Subjects were separated into the following subgroups based on use of DMARDs at baseline: none (n=134), MTX (n=211), any non-MTX DMARDs (n=36), SSZ (n=21), HCQ (n=0), LEF (n=15), and any DMARDs (n=247). In the group of subjects with baseline use of any DMARDs, the number of subjects with one or more adverse events was 55% in the placebo group, 48% in the guselkumab q8w dose group and 60% in the guselkumab q4w group through Week 24. As in the general study population, Infections and Infestations was the most frequently reported SOC, with upper respiratory tract infection and nasopharyngitis being the most common preferred term, and were overall balanced between the treatment groups.

In the group of subjects with prior anti-TNFα use, the number of subjects with one or more adverse events was 64% in the placebo group, 50% in the guselkumab q8w dose group, and 66% in the guselkumab q4w group through Week 24. Similarly, Infections and Infestations were the most frequently reported adverse events in the guselkumab dose groups; AEs were numerically greater in the guselkumab q4w group (32%) as compared to the placebo group (23%) and in the guselkumab q8w group (24%). Upper respiratory tract infection was the most common AE by PT for the placebo group (5%) and the guselkumab q4w group (16%), while nasopharyngitis was the most common AE by PT for the guselkumab q8w group (12%). Musculoskeletal and connective tissue disorders (31%) were the most frequently reported adverse events in the placebo group.

Study PSA3002

In study PSA3002, TEAEs were generally balanced by treatment group. Through Week 24, 100 subjects (40.7%) had at least one TEAE in the placebo group, 114 subjects (46.0%) in the guselkumab q8w group, and 113 subjects (46.1%) in the guselkumab q4w group. Severe AEs occurred in two subjects (0.8%) in the placebo group (one drug-induced liver injury and one tubulointerstitial nephritis), one (0.4%) in the guselkumab q8w dose group of malignant melanoma in situ, and two (0.8%) in the guselkumab q4w group (one osteoarthritis and one blue toe syndrome). All severe AEs were singular by preferred term.

The most frequently reported TEAEs were reported in the Infections and Infestations SOC (17.1% in the placebo group, 15.7% in the guselkumab q8w dose group, and 17.6% in the guselkumab q4w group) through Week 24. The most frequently reported AEs of infections by PT were nasopharyngitis, upper respiratory tract infection, and bronchitis, as discussed under Infections above. The second most frequent SOC was Investigations among which AEs occurred more frequently in the guselkumab treatment groups than in the placebo group (7.7% in the placebo group, 14.5% in the guselkumab q8w dose group, and 14.3% in the guselkumab q4w

group). The most frequently reported TEAEs within Investigations were alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. TEAEs of ALT elevations occurred more frequently in the guselkumab q4w group (10.2%), as compared to the placebo (4.5%) and guselkumab q8w (6.0%) groups. AST elevations occurred more commonly in the guselkumab q8w (5.6%) and q4w (4.5%) groups as compared to the placebo group (2.4%).

As presented in Table 43, the other most common (≥2%) adverse reactions included: bronchitis (1.2% in the placebo group, 0.4% in the guselkumab q8w group, and 4.1% in the guselkumab q4w group); enthesopathy (2.8% in the placebo group, 2.0% in the guselkumab q8w group, and 2.9% in the guselkumab q4w group); dactylitis (2.8% in the placebo group, 2.4% in the guselkumab q8w group, and 2.0% in the guselkumab q4w group); neutropenia (1.2% in the placebo group, 2.4% in the guselkumab q8w group, and 0.4% in the guselkumab q4w group); leukopenia (2.4% in the guselkumab q8w group, and 0.4% in the placebo and guselkumab q4w groups); anemia (2.4% in the placebo group, 2.0% in the guselkumab q8w group, and 0.4% in the guselkumab q4w group); and headache (0.8% in the placebo group, 2.4% in the guselkumab q8w group, and 1.2% in the guselkumab q4w group). The overall numbers were low and generally balanced between the treatment groups.

Subjects were separated into the following subgroups based on use of DMARDs at baseline: none (n=227), MTX (n=443), any non-MTX DMARDs (n=69), SSZ (n=31), HCQ (n=3), LEF (n=35), and any DMARDs (n=512). In the group of subjects with baseline use of any DMARDs, the number of subjects with one or more adverse events was 45% in the placebo group, 51% in the guselkumab q8w dose group, and 46% in the guselkumab q4w group through Week 24. The proportions of subjects in the any DMARD at baseline group was higher than those in the MTX at baseline group (46%, 53%, and 47% for placebo, guselkumab q8w, and guselkumab q4w, respectively) and the no baseline DMARD use subgroup (30%, 35%, and 47% for the placebo, guselkumab q8w, and guselkumab q4w groups, respectively). In the baseline use of any DMARDs subgroup, Infections and Infestations was the most frequently reported SOC with upper respiratory tract infection (3% and 4%) and nasopharyngitis (4% and 5%) being the most common preferred terms in the placebo and guselkumab q8w groups (respectively) and nasopharyngitis (4%) and bronchitis (4%) in the guselkumab q4w group.

Study PSA3001 and PSA3002

No consistent differences were observed in the overall safety profile of guselkumab in PsA by baseline use of non-biologic DMARDs or prior exposure to anti-TNFα agents. The common TEAEs are generally consistent with the known safety profile of guselkumab in psoriasis.

Laboratory Findings

Hematology

- Anemia

Study PSA3001: Grade 1 anemia was the most frequently observed post-baseline hematology laboratory abnormality in all groups (15% in placebo and guselkumab q8w group, and 9% in the guselkumab q4w group). Grade 2 anemia was observed in 3% of placebo, and 0.8% in each of the guselkumab groups. No grades 3 or 4 anemia were observed in any group.

Study PSA3002: Grade 1 anemia was the most frequently observed post-baseline hematology laboratory abnormality in all groups (25% in placebo, 20% in guselkumab q8w group, and 16% in the guselkumab q4w group). Grade 2 anemia was observed in 5% of placebo, 2% of the guselkumab q8w group, and 1% of the guselkumab q4w group. Grade 3 anemia was observed in 0.4% of the guselkumab q8w group, and not observed in the other groups. No grade 4 anemia was observed in any group.

In PSA3001 and PSA3002, laboratory findings of anemia were generally balanced by treatment group and did not demonstrate dose-dependent changes.

- Lymphocyte decrease

Study PSA3001: Grade 1 lymphocyte decrease was more frequent in the guselkumab q4w group (4%), versus 0.8% in the other groups. However, in the guselkumab q8w group, a Grade 3 decrease in lymphocyte was observed in 2% of subjects, and no Grade 3 anemia was observed in the other groups. No grade 4 lymphocyte decreases were observed in any group. Lymphocyte decreases were generally not associated with infections, except for one subject with a Grade 2 lymphocyte decrease that occurred with a Grade 2 decrease in WBC and concurrent AEs of pulpitis dental and tooth abscess, which subsequently resolved.

Study PSA3002: Grade 1 lymphocyte decrease was observed in all three groups (3% in placebo, 2% in the guselkumab q8w group, and 0.4% in the guselkumab q4w group). Grade 2 lymphocyte count decrease was also observed in all three groups (6% in placebo, 3% in the guselkumab q8w group, and 4% in the guselkumab q4w group). In the placebo group, a 0.4% Grade 3 lymphocyte count decrease was observed, and no Grade 3 decreases in lymphocyte count was observed in the guselkumab groups. No grade 4 lymphocyte decreases were observed in any group.

In PSA3001 and PSA3002, laboratory findings of lymphocyte decreased were generally balanced by treatment group and did not demonstrate dose-dependent changes.

- Neutrophil count decrease

Study PSA3001: Grade 1 neutrophil count decrease was observed in all three groups (3% in placebo, 4% in the guselkumab q8w group, and 8% in the guselkumab q4w group). Grade 2 decrease in neutrophil count was observed in 2% of the guselkumab q4w group, compared with 0.8% in the guselkumab q8w group and none in the placebo group. No grade 3 or 4 decreases in neutrophil count were observed in any group. Neutrophil count decreases were not associated with infections and did not result in discontinuation in guselkumab-treated subjects.

Study PSA3002: Grade 1 neutrophil count decrease was observed in all three groups (3% in placebo, 7% in the guselkumab q8w group, and 5% in the guselkumab q4w group). Grade 2 neutrophil count decrease was also observed in all three groups (1% in placebo, and 2% in the

guselkumab groups). A Grade 3 decrease in neutrophil count was observed in 0.4% of the placebo group, and no Grade 3 decreases in neutrophil counts were observed in the guselkumab groups. Grade 4 decrease in neutrophil count was observed in 0.4% of the guselkumab q4w group and no Grade 4 decreases in neutrophil count were observed in the other groups. Grade ≥ 2 neutrophil count decreases were not associated with infections and did not lead to study drug interruption or discontinuation in guselkumab-treated subjects.

- Platelet decrease

Study PSA3001: Grade 1 platelet count decrease occurred in 6% of subjects in the guselkumab q8w group, 2% in the guselkumab q4w group, and no Grade 1 platelet count decrease were observed in the placebo group. No Grades 2-4 platelet count decreases were observed in any subgroup.

Study PSA3002: Grade 1 platelet decrease was observed in all three groups (2% in placebo, 0.4% in the guselkumab q8w group, and 2% in the guselkumab q4w group). Grade 2 platelet decrease was observed in 0.8% of the guselkumab q8w group and there was no Grade 2 platelet decrease observed in the other groups. No Grade 3 or 4 decreases in platelets were observed in any group.

- White blood cell decrease

Study PSA3001: Grade 1 decreases in white blood cells were observed in all three groups (2% in placebo, 4% in the guselkumab q8w group, and 7% in the guselkumab q4w group). In addition, Grade 2 decreases in white blood cells were observed in 2% of the guselkumab q4w group, versus 0.8% in the other two groups. No Grade 3 or 4 decreases in white blood cells were observed in any group. Among the subjects with Grade 2 WBC decreases, the events did not result in discontinuation. One case with WBC decrease and lymphocyte decrease had associated AEs of pupitis dental and tooth abscess (described above); no other Grade 2 decreases in WBC were associated with infection.

Study PSA3002: Grade 1 decreases in white blood cells were observed in all three groups (3% in placebo, 9% in the guselkumab q8w group, and 4% in the guselkumab q4w group). In addition, Grade 2 decreases in white blood cells were observed in 0.8% of the placebo group, 1% in the guselkumab q8w group, and 2% in the guselkumab q4w group. No Grades 3 or 4 decreases in white blood cells were observed in any group.

In summary, there were generally low grade hematology changes observed in the PsA program. Decreases in neutrophil and WBC counts were slightly higher in the guselkumab groups compared to the placebo group, and were generally similar between the guselkumab q8w and guselkumab q4w groups, based on the pooled analysis.

Chemistry

- Alanine aminotransferase (ALT) increase

Study PSA3001: The percentage of subjects with Grade 1 increase in ALT was 33% in placebo, 31% in the guselkumab q8w group, and 41% in the guselkumab q4w group. In the placebo

group, 0.8% of subjects had a Grade 2 ALT increase versus 2% in the guselkumab dose groups. In the placebo group, 0.8% had Grade 3 ALT increase, and no subjects in the guselkumab dose groups had Grade 3 ALT increases. No grade 4 ALT increases were observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 increase in ALT was 28% in placebo, 27% in the guselkumab q8w group, and 32% in the guselkumab q4w group. In the placebo group, 2% of subjects had Grade 2 ALT increase, versus 0.4% in the guselkumab q8w group, and 3% in the guselkumab q4w group. Grade 3 increases in ALT occurred in 0.4% of placebo, 1% of guselkumab q8w group, and 2% of guselkumab q4w group. Grade 4 increase in ALT occurred in 0.4% of the placebo group, and no Grade 4 increases in ALT occurred in the guselkumab groups.

Based on the pooled analysis, there was a dose-dependent increase in Grade 1 and 2 ALT increase in the guselkumab-treated subjects.

- Aspartate Aminotransferase (AST) increase

Study PSA3001: The percentage of subjects with Grade 1 increase in AST was 19% in placebo, 25% in the guselkumab q8w group, and 27% in the guselkumab q4w group. Both Grade 2 and Grade 3 increases in AST were observed in 2% of the placebo group, versus 0.8% in the guselkumab groups. No Grade 4 AST increases were observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 increase in AST was 20% in placebo, 15% in the guselkumab q8w group, and 19% in the guselkumab q4w group. Grade 2 increases in AST were observed in 2% of each of the guselkumab groups and no Grade 2 increases in AST were observed in placebo. Grade 3 increases in AST were observed in 0.8% of the placebo group, 0.4% of the guselkumab q8w group, and 2% of the guselkumab q4w group. No Grade 4 AST increases were observed in any group.

Based on the pooled analysis, there were Grade 1 AST increase occurred with similar frequency across the treatment groups, however Grade 2 AST increases were more frequent in the guselkumab-treated subjects. Grade 3 AST increases occurred most frequently in the guselkumab q4w (1.6%), as compared to the placebo (1.1%) and guselkumab q8w (0.5%) through Week 24.

- Alkaline Phosphatase increase

Study PSA3001: The percentage of subjects with Grade 1 increase in alkaline phosphatase was 11% in placebo, 8% in the guselkumab 1 q8w group, and 9% in the guselkumab q4w group. No Grades 2-4 increases in alkaline phosphatase were observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 increase in alkaline phosphatase was 11% in placebo, 6% in the guselkumab q8w group, and 7% in the guselkumab q4w group. Grade 2 increases in alkaline phosphatase were observed in 0.4% of the placebo and guselkumab q4w groups, and no Grade 2 increases in alkaline phosphatase were observed in the guselkumab q8w group. Grade 3 increase in alkaline phosphatase was observed in 0.4% of the placebo group, and no Grade 3 increases in alkaline phosphatase were observed in the guselkumab groups. No Grade 4 increases in alkaline phosphatase were reported in any group.

- Hyperkalemia

Study PSA3001: The percentage of subjects with Grade 1 hyperkalemia was 6% in placebo, 7% in the guselkumab q8w group, and 9% in the guselkumab q4w group. The percentage of subjects with Grade 2 hyperkalemia was 2% in placebo, 3% in the guselkumab q8w group, and 4% in the guselkumab q4w group. Grade 3 hyperkalemia was observed in 0.8% of the placebo and the guselkumab q8w groups, and no Grade 3 hyperkalemia was observed in the guselkumab q4w group. No Grade 4 hyperkalemia was observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 hyperkalemia was 7% in placebo, 5% in the guselkumab q8w group, and 11% in the guselkumab q4w group. The percentage of subjects with Grade 2 hyperkalemia was 7% in placebo, 6% in the guselkumab q8w group, and 3% in the guselkumab q4w group. Grade 3 hyperkalemia was observed in 0.4% of the guselkumab q8w group, and no Grade 3 hyperkalemia was observed in the other groups. No Grade 4 hyperkalemia was observed in any group.

Overall, hyperkalemia was generally similar across the treatment groups.

- Hypernatremia

Study PSA3001: The percentage of subjects with Grade 1 hypernatremia was 6% in placebo, 12% in the guselkumab q8w group, and 7% in the guselkumab q4w group. The percentage of subjects with Grade 2 hypernatremia was 0.8% in all dose groups. No Grades 3 or 4 hypernatremia was observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 hypernatremia was 7% in placebo, 8% in the guselkumab q8w group, and 3% in the guselkumab q4w group. The percentage of subjects with Grade 2 hypernatremia was 0.8% in placebo and the guselkumab q8w group, and 2% in the guselkumab q4w group. No Grades 3 or 4 hypernatremia were observed in any group.

The incidence of Grade 2 or higher hypernatremia was low and similar across treatment groups.

- Creatinine increase

Study PSA3001: The percentage of subjects with Grade 1 increase in creatinine was 0% in placebo, 5% in the guselkumab q8w group, and 2% in the guselkumab q4w group. The percentage of subjects with Grade 2 increase in creatinine was 2% in placebo, and none in the guselkumab groups. Grade 3 increase in creatinine was observed in 0.8% of the guselkumab q4w group, and no Grade 3 increases in creatinine was observed in the other groups. No Grade 4 increases in creatinine were reported in any group.

Study PSA3002: The percentage of subjects with Grade 1 increase in creatinine was 2% in all groups. The percentage of subjects with Grade 2 increase in creatinine was 2% in placebo, 1% in the guselkumab q8w group, and none in the guselkumab q4w group. No Grade 3 increases in creatinine were observed in any group. Grade 4 increase in creatinine was observed in 0.4% of the placebo group and no Grade 4 increases in creatinine were observed in the guselkumab groups.

The incidence of Grade 2 or higher creatinine increase was low and similar across treatment groups.

- Blood Bilirubin increase

Study PSA3001: The percentage of subjects with Grade 1 increase in bilirubin was 0.8% in placebo, 2% in the guselkumab q8w group, and 7% in the guselkumab q4w group. The percentage of subjects with Grade 2 increase in bilirubin was 2% in placebo and the guselkumab q8w group, and no Grade 2 increases in bilirubin were observed in the guselkumab q4w group. No Grade 3 or 4 increase in bilirubin were observed in any group.

Study PSA3002: The percentage of subjects with Grade 1 increase in bilirubin was 1% in placebo, 6% in the guselkumab q8w group, and 5% in the guselkumab q4w group. The percentage of subjects with Grade 2 increase in bilirubin was 0.8% in placebo and the guselkumab q4w group, and 0.4% in the guselkumab q8w group. No Grade 3 or 4 increase in bilirubin were observed in any group.

Grade 1 blood bilirubin increase occurred more frequently in the guselkumab treatment groups, however Grade 2 and higher increases were low and balanced across the treatment groups. AST and ALT increases occurred in both studies; the majority of increases in AST and ALT were Grade 1. There was a dose dependent increase in Grade 1 and 2 ALT increase in the guselkumab-treated subjects. Grade 2 and 3 AST increases occurred most frequently in the guselkumab q4w group. Grade 1 AST and ALT increases were mostly less than 2 times the upper limit of normal, did not result in study drug interruption or discontinuation, and were not associated with clinically significant increases in bilirubin. Grade 2 or higher increases in AST or ALT resulted in study drug discontinuation in three subjects in the guselkumab q4w group in study PSA3002. In one subject who had a history of alcohol use and MTX use at baseline, study agent was interrupted due to the AEs of AST and ALT increased, cholecystitis chronic, chronic pancreatitis, and fatty liver, and the subject was discontinued after the Week 24 visit. In the two other subjects, the study agent was discontinued due to an AE of drug-induced liver injury (drug [isoniazid]- induced hepatitis) in one subject and an SAE of acute hepatitis B in one subject. No cases met Hy's Law criteria. The other chemistry abnormalities reported were few in number and generally not clinically meaningful.

Vital Signs
In both study PSA3001 and PSA3002, evaluation of vital signs and changes from baseline in these values through Week 24 did not reveal any clinically meaningful changes in any of the treatment groups. In addition, no significant changes in weight occurred across the treatment groups.

Electrocardiograms (ECGs)
In both studies, electrocardiograms were performed at screening only.

Immunogenicity
The overall incidence of antibodies to guselkumab through Week 24 was low (2.0%, 15 of 744

subjects) in subjects with PsA. The incidence of antibodies to guselkumab through Week 24 was similar between the q8w (1.6%, 6 of 373 subjects) and q4w (2.4%, 9 of 371 subjects) dose regimens.
In study PSA3001, of the five subjects with ADA, one (20%) subject in the guselkumab q4w group had neutralizing antibodies (NAbs) to guselkumab. In study PSA3002, none of the ten subjects with positive antibodies to guselkumab status were positive for NAbs to guselkumab. ACR20 response rates were similar between subjects who were ADA positive and ADA negative (57% vs. 62%, respectively), while ACR50 response rates were lower (14% vs. 33%). The proportion of subjects with ADA who had 1 or more AEs through Week 24 (60%) was generally similar to subjects without ADA (49%). None of the 15 subjects with ADA had an injection site reaction (ISR) through Week 24, while 7 (1%) of the ADA negative subjects had at least one ISR. There were no events of hypersensitivity through Week 24. Overall, the number of subjects with ADA were too small to draw conclusions on the impact of ADA on efficacy or safety.

8.4.5. Analysis of Submission-Specific Safety Issues

As described in section 8.4.4, in both studies, the potential risks, and thus, AESIs were identified based on the known biologic activity related to IL-23 pathways as well as the safety profile of other biologic DMARDs and the known safety profile of guselkumab from the psoriasis program. The predefined AEs of special interest were malignancy, potential opportunistic infections, active tuberculosis, other infections, anaphylaxis, serum sickness or serum sickness-like reactions, and pregnancies with negative outcome. These AESIs are discussed in section 8.4.4.

8.4.6. Safety Analyses by Demographic Subgroups

The Applicant conducted safety analyses over the placebo-controlled period through Week 24 and over the reporting period through the data cut (01 May 2019) using the pooled phase 3 PsA data for each of the following subgroups: sex, age, weight, and body mass index (BMI). The TEAE profile, including AEs, SAEs, AEs leading to discontinuation, infections, and serious infections, was not influenced by any of these subgroups. In addition, the subgroup of race was evaluated; however, approximately 96% of the subjects in the pooled phase 3 PsA studies safety analysis set were white. While the subjects who were a race other than white more frequently reported AEs and infections, the interpretation of data regarding the impact of race upon safety is limited due to the small number of subjects who were a race other than white.

8.4.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
No data on human carcinogenicity or tumor development are included, nor required, for this supplement.

Human Reproduction and Pregnancy
As of 12 July 2019, 51 reports of pregnancy were identified in ongoing and completed studies of guselkumab in PsA, plaque psoriasis, (b) (4) or palmar plantar pustulosis,

including 24 pregnancies in female subjects exposed to guselkumab participating in these studies. Of the 24 pregnancies, there were seven live births, two spontaneous abortions, two elective abortions, one unspecified abortion, and 12 not reported or continuing outcomes. There were 27 pregnancies in female partners of male subjects exposed to guselkumab participating in these studies; there were 11 live births, three spontaneous abortions, one elective abortion, one induced abortion, and 11 not reported or continuing. There were 27 pregnancies in female partners of male subjects exposed to guselkumab participating in these studies; there were 11 live births, three spontaneous abortions, one elective abortion, one induced abortion, and 11 not reported or continuing.

Pediatrics and Assessment of Effects on Growth
At this time, guselkumab is not indicated for any pediatric populations. See Section 10 for details regarding the plan for pediatric assessment **i**n juvenile PsA**.**

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Single intravenous doses of guselkumab up to 10 mg/kg (maximum dose of 987 mg) in healthy volunteers and single SC doses of guselkumab up to 300 mg in subjects with plaque psoriasis have been administered in clinical studies without dose-limiting toxicity. There were no known occurrences of overdose during any of the guselkumab PsA clinical studies. There is no evidence that guselkumab is associated with the potential for addiction or abuse. None of the PsA studies examined withdrawal or rebound of PsA since no definition for rebound exists. The occurrence of psoriasis rebound following withdrawal of guselkumab was evaluated volunteers and single SC doses of guselkumab up to 300 mg in subjects with plaque psoriasis have been administered in clinical studies without dose-limiting toxicity. There were no known occurrences of overdose during any of the guselkumab PsA clinical studies. There is no evidence that guselkumab is associated with the potential for addiction or abuse. None of the PsA studies examined withdrawal or rebound of PsA since no definition for rebound exists. The occurrence of psoriasis rebound following withdrawal of guselkumab was evaluated in study PSO3002 and discussed in the initial marketing application for psoriasis.

8.4.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Jannsen's last Periodic Benefit Risk Evaluation Report (PBRER) analyzed the global postmarket experience with guselkumab through the database lock date of January 12, 2020. An estimated 6, 282 subjects have been exposed to guselkumab in completed and ongoing clinical studies. Exposure to guselkumab is estimated to be 22,867 person-years during the reporting interval (July 1, 2019 through December 31, 2019) and (b) (4) patient-years cumulatively from marketing experience. During the reporting period, 2 new adverse drug reactions of anaphylaxis and injection site reactions were identified from post-marketing cases.

On June 1, 2020, a labeling supplement 009 to BLA 761061 was approved for guselkumab. In this submission, the WARNINGS AND PRECAUTIONS Sections of the TREMFYA USPI was updated

to include newly identified adverse drug reactions (ADRs) of anaphylaxis. The Applicant identified the safety signal based on 2 spontaneous cases which were received during the Periodic Benefit Risk Evaluation Report reporting period of January 13, 2019 to July 12, 2019. Hypersensitivity Reactions was relocated to Section 5.1 in the WARNINGS AND PRECAUTIONS section of labeling and revised as follows: "Serious hypersensitivity reactions, including anaphylaxis, may occur" in the highlights section and in section 5.1: "Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of TREMFYA. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue TREMFYA and initiate appropriate therapy."

No cases of anaphylaxis or serum sickness reaction were reported through the data cut in studies PSA3001 and PSA3002.

Expectations on Safety in the Postmarket Setting

Based on the safety analyses in the PsA population, there are no new safety issues that cause concern when considering how the drug may be used in the postmarket setting. As discussed in Section 12, no new safety issues have been identified to warrant a need for additional risk management activities.

8.4.9. Integrated Assessment of Safety

In the pooled analysis of PSA3001 and PSA3002 through Week 24, there were no deaths in the guselkumab treatment group. SAEs were lower in numbers in the guselkumab treatment groups (2.1% and 1.9% for the guselkumab q4w and q8w groups, respectively) than the placebo group (3.2%). The most frequently reported SAEs were in the Infections and Infestations SOC. All SAEs were singular by PT. AEs leading to drug discontinuation was low and generally balanced by treatment group (1.9%, 1.3%, and 2.1% for placebo, guselkumab q8w, and guselkumab q4w, respectively). Four guselkumab-treated subjects (1 subject on q8w, 3 subjects on q4w) discontinued study treatment due to AEs of infections. No AE led to discontinuation in more than 1 subject. There was one adjudicated major adverse cardiovascular event (MACE) of cardiac failure in the placebo group in study PSA3001 and one nonfatal ischemic stroke in the guselkumab q4w group in study PSA3002.

The predefined AEs of special interest in the PsA program were active tuberculosis, potential opportunistic infections, malignancy, anaphylaxis, serum sickness or serum sickness-like reactions, and pregnancies with negative outcome.

In studies PSA3001 and PSA3002, no subjects experienced active TB or other opportunistic infections through Week 24. One subject (placebo to guselkumab q4w) had an event of listeria meningitis after the 24-week controlled period. Few subjects reported malignancies through the data cut and these were generally balanced by treatment group; there were two subjects in the guselkumab q8w group (malignant melanoma in situ and plasma cell myeloma), one in the placebo to guselkumab q4w group with two malignancies (squamous cell carcinoma in situ and malignant melanoma in situ) and one subject in the placebo group (clear cell renal cell

carcinoma) who reported malignancies. While the small numbers of subjects with events limit conclusions, based on comparisons conducted by the Applicant, the rates of malignancies other than cervical cancer in situ and non-melanoma skin cancer to not suggest an increased risk over the general population.

There were no anaphylactic reactions or events of serum sickness/serum sickness-like reactions reported through Week 24. There were no reported pregnancies in either study in the guselkumab dose groups.

Elevations in AST and ALT were reported in subjects in both studies; however, there were only three subjects in the guselkumab q4w group in study PSA3002 who had study drug interruption or discontinuation due to this increase. These cases were confounded by use of other drugs (MTX, isoniazid), history of alcohol use, and viral hepatitis. There were no cases that met Hy's Law criteria.

The labeled warnings and precautions for guselkumab from the psoriasis program include: hypersensitivity reactions, infections, and tuberculosis. The most common (≥1%) adverse reactions associated with TREMFYA in the United States prescribing information include upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. In the PsA program, there were fewer AEs of gastroenteritis, tinea infections, and herpes simplex infections; however, there were slightly higher numbers of bronchitis in the guselkumab groups as well as increased AEs of conjunctivitis, pharyngitis, and anemia. Overall, the number of events were low and generally balanced between the treatment groups.

It is also of note that guselkumab is under investigation in other indications, including Crohn's disease (CD), Ulcerative Colitis, Hidradenitis Suppurativa (HS), and Familial adenomatous polyposis. A phase 2b study in Crohn's disease, and the phase 2 HS studies evaluated induction dose regimens up to a maximum dose of guselkumab 1200 mg IV q4W for a total of 3 doses, and maintenance doses from 100 mg SC q8W to 200 mg SC q4W. A serious adverse event of 'toxic hepatitis' was reported in the phase 2/3 Crohn's study in a participant who received guselkumab 1200 mg IV at weeks 0, 4, and 8, and 200 mg SC at week 12. Based on the hepatocellular pattern of injury, temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event was thought to represent drug-induced liver injury possibly related to guselkumab. Subsequent studies in Crohn's Disease have evaluated lower doses of guselkumab 200 mg IV q4w for 3 doses followed by maintenance with 100 mg q8w or 200 mg q4w. While the guselkumab doses administered in the Crohn's Disease study were significantly higher than the doses proposed for psoriatic arthritis, (b) (4)

In conclusion, the safety data from guselkumab in the PsA studies are consistent with the known safety profile of guselkumab in psoriasis. AEs were generally similar across both guselkumab dosing regimens, with numerical increase in AEs leading to discontinuation, and

TEAEs of ALT increased, upper respiratory tract infection, and bronchitis in the guselkumab q4w group, however, differences between treatment groups are due to small numbers of subjects. While no major safety signals were observed within the psoriatic arthritis phase 3 program, PSA3001 and PSA3002 were limited to 24 weeks of controlled data. (b) (4)

8.5. Statistical Issues

For the review of this application, the statistical reviewer identified several statistical issues:

- Potential effect of missing data and intercurrent events on reliability of efficacy results and interpretable estimands
- Radiographic progression (b) (4)
- Efficacy of each dose level (b) (4)
- Pooling of data across studies to support the enthesitis and dactylitis endpoints

The first issue concerns the potential effect of missing data and the intercurrent events on the reliability and interpretability of the efficacy results and to assess the robustness of the primary analysis results. The analysis set for the primary analyses included all randomized subjects who received at least one dose (complete or partial) of study agent. The primary estimand for the primary endpoint of ACR20 response was a composite estimand such that subjects who met treatment failure criteria prior to Week 24 or at Week 24 are considered non-responders. In addition, missing observations were imputed as non-responders. To evaluate the robustness of the primary efficacy results to missing data assumptions, a sensitivity analysis using an exhaustive scenario tipping point approach was performed and the results supported the primary analysis results. Though this composite estimand is useful in evaluating a treatment effect that incorporates adherence and tolerability, it is also useful to assess treatment effect with an alternative handling of intercurrent events for the primary endpoint. Therefore, analyses based on the treatment policy estimand, including all observed data, were conducted as supplementary analyses. The results from these analyses supported the primary analyses.

(b) (4) Furthermore, the statistical significance was demonstrated in guselkumab q4w over the placebo, but not in guselkumab q8w. While the sponsor submitted additional analyses of the guselkumab q4w data in PSA3002 to evaluate the robustness of the results of this radiographic endpoint, we continue to have concerns with the lack of additional support to establish substantial evidence for this finding. This support would ideally come from an additional independent study replicating this finding. We note that there is also a lack of support from other potential sources such as supportive prior information of an effect from a related indication (such as rheumatoid arthritis), or prior effects on this radiographic endpoint within the drug class of IL-23 inhibitors. (b) (4)

(b) (4)
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(b) (4)
. The current labeling for guselkumab for psoriasis recommends 100 mg at once every 8 weeks after the first two injections. (b) (4)
(b) (4). In both studies, two dose levels of guselkumab were evaluated for the efficacy claim, and both dose levels demonstrated efficacy over the placebo. However, there is considerable uncertainty around the comparison between the doses (b) (4)
(b) (4)
The reviewer performed a comparison between two dose levels to provide additional information. We note that, because this comparison was not pre-planned and the study was not designed to show differences between doses, this analysis only provides supplemental information. There were no statistical differences between the two dose levels for ACR20 response at Week 24 for both studies (p=0.22 in PSA3001 and p=0.92 on PSA3002). Furthermore, for some secondary endpoints (IGA response, 36-SF PCS and enthesitis (from pooled data)) in PSA3002, less numerical improvement was obtained in guselkumab q4w compared to guselkumab q8w.

This lack of confirmed advantage in terms of efficacy is compounded by the uncertainty surrounding the safety of the higher dosing regimen. While no major safety signals were observed within the psoriatic arthritis phase 3 program, PSA3001 and PSA3002 were limited to 24 weeks of controlled data. (b) (4)
(b) (4)

Additional statistical consideration was also needed for the results based on the combined data from the two studies. For the dactylitis (the proportion of subjects with dactylitis resolution) and enthesitis (the proportion of subjects with enthesitis resolution) endpoints, the pre-specified approach by the Applicant was to pool the data from PSA3001 and PSA3002 and test these as key secondary endpoints under the multiplicity control defined for PSA3002. Both endpoints were statistically significant with pooled data. However, it should be noted that the pooled efficacy results appeared to be largely influenced by PSA3002 (70% of subjects in the analysis set were from PSA3002) due to the larger sample size. It is the statistical reviewer's opinion that independent substantiation of efficacy is preferable by assessing each study separately to support efficacy endpoints and therefore the reviewer evaluated each endpoint within each study. The studies were not appropriately powered to show statistical significance within a study, and significant differences were not consistently observed, however, each guselkumab dose showed numerical improvement in these endpoints over placebo in the

individual studies. Thus, this supplemental analysis provides some additional support for the evaluation of enthesitis and dactylitis.

8.6. Conclusions and Recommendations

The primary data to support this application are derived from two phase 3 studies: study CNTO1959PSA3001 (referred to as PSA3001 in the document) and study CNTO1959PSA3002 (referred to as PSA3002 in this document). Both studies were multicenter, randomized, double-blind, placebo-controlled, 3-arm studies of guselkumab in subjects with active PsA who had an inadequate response to standard therapies. Study PSA3001 assessed 381 subjects with an inadequate response to prior TNFα-inhibitors, as well as other non-biologic therapies, while study PSA3002 enrolled 739 subjects naïve to biologic DMARD therapy. Subjects in both studies were randomized to treatment with guselkumab at Weeks 0, 4, and then every 4 weeks thereafter (q4w) or every 8 weeks thereafter (q8w), or placebo. In both studies, the primary endpoint was the proportion of subjects who achieved an ACR 20 response at Week 24. A greater proportion of subjects on guselkumab q4w (59% and 64%) and q8w (52% and 64%) compared to placebo (22% and 33%) achieved an ACR20 response at Week 24 in studies PSA3001 and 3002, respectively. The primary endpoint was significant when comparing both guselkumab doses to placebo. The efficacy of guselkumab over placebo was further supported by secondary endpoints at Week 24 including HAQ-DI, IGA response, and DAS28(CRP).

However, there was not strong evidence to indicate that more frequent dosing of guselkumab (guselkumab q4w) would result in additional efficacy compared to less frequent dosing (guselkumab q8w) for the primary efficacy endpoint, ACR20 response at Week 24, in both studies. Furthermore, for some secondary endpoints (IGA response, 36-SF PCS and enthesitis (from pooled data)) in PSA3002, less numerical improvement was obtained in guselkumab q4w compared to guselkumab q8w. While the guselkumab q4w showed a significant difference in the radiographic endpoint compared to placebo, no significant difference was observed in guselkumab q8w. We note that this assessment was evaluated in only one study, PSA3002. We further note that vdH-S score is a biomarker that needs to be interpreted in the context of a lack of dose dependent findings on clinical outcomes. Additionally, there is also a lack of support from other potential sources such as supportive prior information of an effect from a related indication (such as rheumatoid arthritis), and prior effects on this radiographic endpoint within the drug class of IL-23 inhibitors. (b) (4)

This lack of confirmed advantage in terms of efficacy is compounded by the uncertainty surrounding the safety of the higher dosing regimen. While no major safety signals were observed within the psoriatic arthritis phase 3 program, PSA3001 and PSA3002 were limited to 24 weeks of controlled data. (b) (4)
(b) (4)

In conclusion, studies PSA3001 and PSA3002 provide substantial evidence on the efficacy of guselkumab q8w dosing regimen for the treatment of adults with active psoriatic arthritis. (b) (4) Therefore, we recommend approval of the guselkumab q8w dosing regimen, that is guselkumab 100 mg SC at Weeks 0, 4, and every 8 weeks thereafter, for the treatment of adults with active PsA.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not held for this supplemental BLA. No issues were identified warranting advisory committee input.

10 Pediatrics

A proposed initial pediatric study plan (iPSP), outlining a proposal for a request of full waiver from the requirements of pediatric studies in PsA, was agreed upon on January 12, 2017.

Following the pediatric juvenile idiopathic arthritis workshop in October 2019 and internal discussion, the Agency notified the Applicant of the Division's reconsideration of the approach to PREA for psoriatic arthritis. Based on the evolving understanding of the high degree of similarity of the disease between adults and pediatric subjects with PsA and the considerations of a pharmacokinetic (PK)-matching and extrapolation of efficacy from adults to pediatric subjects, the Division considers that pediatric studies are possible. The Division recommended that the Applicant could address the PREA requirements with a PK study in juvenile psoriatic arthritis (jPsA) subjects to support extrapolation of efficacy from adult PsA indication. Assessment of safety from the PK study could be supplemented by safety information from the ongoing pediatric plaque psoriasis study.

The Applicant's proposed pediatric assessment was submitted on March 31, 2020. Janssen requested a waiver for pediatric age groups jPsA for birth to 1 year and 1 to less than 5 years due to studies being impossible or highly impractical. In addition, the sponsor requested a deferral for submission of the pediatric assessment for children ≥ 5 years to < 18 years as the drug or biological product is ready for approval for use in adults before pediatric studies are complete. The Applicant proposed a single-arm, open-label, multicenter study to evaluate PK, safety, and efficacy in 30 subjects with jPsA ages 5 to less than 18 years.

As the approved dosing regimen for adults with plaque psoriasis (PsO) is the same as guselkumab dose with a favorable benefit-risk in PsA, and pediatric PK and safety information will be collected under the PREA PMR for PsO, the Agency advised the Applicant that the pediatric assessment for juvenile PsA could be supported based on the following information:

1) Information to support the similarity between adult and juvenile PsA,
2) Adequate justification that the PK would be expected to be similar in pediatric PsO and juvenile PsA,
3) A rationale for PK bridging (comparable exposure) between adult PsA and juvenile PsA,
4) Appropriate justification and relevant information to support the extrapolation of efficacy in juvenile PsA patients from adult PsA,
5) Justification of the relevance of the PK and safety data from pediatric PsO for juvenile PsA.

The proposed pediatric plan was discussed at the Pediatric Review Committee (PeRC) meeting on June 16, 2020. The request for a waiver in children <5 years of age was found to be reasonable. The PeRC also agreed with a deferral for PK and safety information to support (b) (4) (b) (4) of guselkumab for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Table 33 presents a high-level summary of the labeling proposal and subsequent interactions between the Applicant and the Agency.

Table 33 Summary of Significant Labeling Changes (High Level Edits)

Section	Labeling Discussions
Highlights, 1.2 Indications and Usage	The Agency agreed with the proposed new indication: *Treatment of adult patients with active psoriatic arthritis*
Highlights, 2.2 Dosage and Administration	• (b) (4) • A statement that Tremfya (b) (4) as revised to "*conventional disease-modifying anti-rheumatic drug*" for consistency with labeling practice
5 Warnings and Precautions	The Agency agreed with the Applicant's proposed revisions: • Section 5.1 was revised to state that a similar risk of infection was seen in placebo-controlled trials in PsA • Section 5.2 was revised to include the number of patients in clinical studies in PsA with latent TB
6.1 Clinical Trials Experience	• (b) (4) • The Agency did not agree with the statement (b) (4) • The Agency agreed with addition of the following statement:

	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. Data describing the observed AEs of bronchitis and neutrophil count decreased were included
6.2 Immunogenicity	Updated to include description of immunogenicity observed in PsA
8.1 Pregnancy	Pregnancy exposure registry information was added
8.4 Geriatrics	Updated to include geriatric subjects with PsA in total geriatric subjects exposed
12.2 Pharmacodynamics	The Agency advised (b) (4)
12.3 Pharmacokinetics	Description of PK in PsA added
14 Clinical Studies	Updated to reference NCT numbers (b) (4) (b) (4)
14.2 Psoriatic Arthritis (b) (4)	• The Agency advised (b) (4) • The Agency recommended removal of the Applicant's statement related to (b) (4) and the Agency agreed with inclusion of the following statement: *Similar responses were seen regardless of prior anti-TNFα exposure in PsA1, and in both trials similar responses were seen regardless of concomitant cDMARD use, previous treatment with cDMARDs, gender and body weight* • Revisions to the statements about dactylitis and enthesitis, as well as psoriasis skin manifestations were made for clarity and brevity
14.2 (b) (4)	The Agency advised to (b) (4)

	(b) (4)
14.2 Physical Function and Other Health-Related Outcomes	(b) (4)
Medication Guide	Revisions to patient labeling were made to align with the revised prescribing information, including the addition of the PsA indication

Labeling consultants, including the OBP labeling team, DMEPA, OPDP, and DMPP, have reviewed the submitted labeling and their recommendations which pertain primarily to internal consistency, improving readability and clarity of the labeling, the patient package insert, and carton and container labels, have been considered and conveyed to the Applicant. All labeling changes were agreed upon with the Applicant.

12 Risk Evaluation and Mitigation Strategies (REMS)

No new risk management plans are submitted as part of this supplement. As no new safety signals have been identified, a Risk Evaluation and Management Strategy (REMS) is not recommended for this product.

13 Postmarketing Requirements and Commitment

In accordance with the Pediatric Research Equity Act (PREA), the Applicant will provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age.

The Applicant has confirmed agreement with the following timelines:

Study/Trial Completion: 10/2023
Final Report Submission: 04/2024

14 Division Director (DRTM) Comments

The Applicant, Janssen Research & Development, LLC (Janssen), submitted a supplemental BLA on September 13, 2019 for a new indication, treatment of adults patients with active psoriatic arthritis. The data supporting the application are derived from two confirmatory studies, PSA3001 and PSA3002, and supportive evidence from an earlier proof-of-concept study PSA2001. Details of the studies are summarized in the clinical review. Study PSA2001 explored only one dosing regimen, 100 mg SC 0, 4, and every 8 weeks (100 mg q8w). This is the dosing regimen recommended for the approved indication of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. However, in the confirmatory studies, PSA3001 and PSA3002, the Applicant also employed a higher dosing regimen of 100 mg SC 0, 4, and every 4 weeks (100 mg q4w). (b) (4) (b) (4). Of note, the q4w dosing resulted in approximately 3- to 5-fold higher median steady-state trough serum guselkumab concentrations compared with those in the guselkumab 100 mg q8w group, as detailed in the Clinical Pharmacology section of this review. (b) (4)

Benefit

Clinical Response:
In both confirmatory studies, PSA3001 and PSA3002, both doses tested showed significantly greater proportions of subjects in both guselkumab dose groups achieving an ACR20 response (the primary endpoint) compared with subjects in the placebo group, providing substantial evidence of efficacy in the Clinical Response domain. However, in both studies, ACR20 responses rates were similar in the guselkumab q8w and q4w arms, as detailed in Section Efficacy Results of this review. Thus, there is considerable uncertainty around the comparison between the doses (b) (4) (b) (4)

Physical Function:
A significantly greater reduction from baseline in HAQ-DI score was observed in both dose groups compared with placebo providing substantial evidence of efficacy in the Physical Function domain. Similar to the ACR responses, the change from baseline in HAQ-DI scores were similar between the two dose levels.

Additional clinical outcomes:
Other clinical outcomes tested included, SF-36 (MCS, PCS, and domains), and FACIT-F, enthesitis and dactylitis.

Improvement in SF-36 PCS was numerically greater for guselkumab q4w in PSA3001, however, improvement was greater for guselkumab q8w as compared to guselkumab q4w

in PSA3002. For SF-36 MCS, both dose levels showed similar numerical efficacy over the placebo.

In both studies, a numerical improvement from baseline in FACIT-F was observed in both dose levels compared to the placebo. The results were numerically in favor of the q8w dosing.

The response rates for dactylitis and enthesitis were similar for the guselkumab q8w as compared to the guselkumab q4w group based on the pooled analysis.

Radiographic Response:
Radiographic endpoints were assessed in a single study, PSA3002. In that study, compared with the placebo group, the mean change from baseline in modified vdH-S score at Week 24 was statistically significant in the guselkumab q4w group, but was not significant in the guselkumab q8w.

(b) (4)

Based on the descriptive statistics, the majority of the patients did not have radiographic progression (defined as vdH-S > 0.0 at Week 24) and the proportions of subjects who progressed were very similar across all three treatment arms.

Importantly, there did not appear to be large dose-dependent effects on clinical endpoints that directly measure how patients feel or function. While the Agency has recognized that radiographic endpoints are important to both clinicians and patients, I also note that the radiographic outcome is a biomarker that is challenging to interpret without the context of clinical endpoints such as clinical response and physical function. In the case of study PSA3002, there is a discordance between the lack of dose-dependent effects on clinical endpoints and the apparent dose dependent radiographic results. This discordance raises additional concerns regarding the validity of this single significant finding.

[14] Stelara FDA-approved labeling

(b) (4)

In summary, in both studies, the primary endpoint was significant when comparing both guselkumab doses to placebo. The efficacy of guselkumab over placebo was further supported by secondary endpoints at Week 24 including HAQ-DI, IGA response, and DAS28(CRP). However, there was no consistent evidence that more frequent dosing (guselkumab q4w) would result in additional efficacy compared to less frequent dosing (guselkumab q8w) for the primary efficacy endpoint, ACR20 response at Week 24, in both studies. Furthermore, for some secondary endpoints (IGA response, 36-SF PCS and enthesitis (from pooled data)) in PSA3002, less numerical improvement was obtained in guselkumab q4w compared to guselkumab q8w. While the guselkumab q4w showed a significant difference in the radiographic endpoint compared to placebo, no significant difference was observed in guselkumab q8w. However, this assessment was evaluated in only one study, PSA3002, without other corroborating data. This is further compounded by the lack of clear benefit of the more frequent dosing regimen for clinical outcomes that measure how a patient feels and functions.

Risk

At the time of the initial submission, a total of 1,229 subjects with active PsA were exposed to guselkumab across the phase 2 (PSA2001) and phase 3 PsA (PSA3001 and PSA3002) studies, including 588 treated for at least 1 year.

(b) (4), guselkumab q8w, is the approved dosing for the treatment of patients with plaque psoriasis. The safety of this dosing regimen has been well-characterized in the approved plaque psoriasis indication and appears to be consistent with the safety seen in patients with PsA treated with guselkumab q8w, supporting the favorable benefit risk of this dosing regimen in PsA (b) (4) The PsA clinical program was designed to provide controlled safety assessments between the two dosing regimens and placebo for only the first 24 weeks, after which time all patients from the placebo group were crossed over to guselkumab q4w dosing by design. This resulted in limited six-month controlled data with approximately 373 subjects in the guselkumab 100 mg q4w group. While the team acknowledged that no major safety signals were observed within the PsA phase 3 program, the controlled safety database for the guselkumab 100 mg q4w group is limited to adequately inform the potential risks associated with the higher exposures with this dosing regimen. The team also acknowledged that the submission provided additional safety from 614 and 265 patients exposed for 6 and 12 months, respectively, to the 100 mg q4w dosing regimen. However, these data are uncontrolled which makes the reliable interpretation of safety challenging to adequately assess the risk associated with the higher exposures, particularly of rare and latent adverse events of interest. These concerns were expressed by the Agency in the advice provided to the Applicant at the pre-phase 3 Type C written responses,

dated July 14, 2016, in which the Division stated that "Given that all patients on placebo in your proposed phase 3 studies will cross over to guselkumab at Week 24, evaluations beyond Week 24 will be uncontrolled and limited conclusions about long-term safety and efficacy will be possible. Therefore, consider including an active comparator arm in at least one of your phase 3 trials to provide long-term (e.g., at least one year) randomized, controlled, double-blind comparisons against standard-of-care." The team also noted that in the guselkumab clinical development program for other indications where higher doses are being studied, a case of Hy's law was reported raising concerns about the limited safety information with the safety of the 100 mg q4w dosing regimen in PsA. (b) (4) .

Benefit-risk Assessment

The clinical efficacy and safety data submitted to support the (b) (4), guselkumab 100 mg SC q8w (b) (4), are derived from two adequate and well-controlled investigations, in two distinct patient populations, those with inadequate response to prior TNFα-inhibitors, as well as other non-biologic therapies (Study PSA3001), and those naïve to biologic DMARD therapy (Study PSA3002). The team concluded, and I agree, that both studies provide substantial evidence on the efficacy of guselkumab q8w dosing regimen for the treatment of adults with active psoriatic arthritis. (b) (4) the team has determined that the benefit-risk of the guselkumab q8w dosing regimen, for the treatment of adults with active PsA is favorable and this dosing regimen should be approved. I agree with these assessments and recommendations.

Pediatric Assessment

To address the requirements under Pediatric Research Equity Act (PREA), the Applicant will provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age. I note that the Applicant had an agreed iPSP outlining a plan to request a full waiver of such requirements. However, since the agreed iPSP was issued, the policy on the PREA requirements for PsA has evolved and the Agency has considered a PK-based extrapolation of efficacy approach for jPsA in children 5 to 17 years of age, as detailed in Section 10, Pediatrics, above. Respectively, the Applicant will provide this assessment under a PMR.

No other PMRs, PMCs, or REMS are warranted based on this submission.

Regulatory Action

Based on the above considerations, the supplement BLA was administratively split following Agency policy:

Supplement 007: Regulatory Action is Approval

> This Prior Approval supplemental biologics application provides for the new indication: Treatment of adult patients with active psoriatic arthritis in adult patients at doses of 100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter

Supplement (b) (4): This supplement (b) (4)

> The review team's considerations on Supplement (b) (4):
>
> (b) (4)
>
> The team's recommendation regarding information needed to address the above considerations:
>
> - (b) (4)

15 Appendices

15.1. References

Gladman DD, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 suppl 2:ii14-17.

Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-2673.

Jasvinder A. Singh, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis & Rheumatology Vol. 71, No. 1, January 2019, pp 5–32.

ICH E9(R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, EMA/CHMP/ICH/436221/2017.

Rubin, DB. Multiple Imputations for Nonresponse in Survey, New York: John Wiley & Sons. 1987.

Addendum on Estimands and Sensitivity Analysis in Clinical Trials: To the Guideline on Statistical Principles for Clinical Trials E9(R1), Adoped on 20 November 2019.

15.2. Financial Disclosure

Details regarding the financial disclosures provided by the Applicant for the pivotal studies CNTO1959PSA3001 (study PSA3001) and CNTO1959PSA3002 (study PSA3002) are included below. See Section 8.1.1 and Section 8.1.2 for details regarding the adequacy of the financial disclosures.

Covered Clinical Study (Name and/or Number): CNTO1959PSA3001 (study PSA3001) and CNTO1959PSA3002 (study PSA3002)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **study PSA3001: 320 and study PSA3002: 377: TOTAL: 697**		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): **none**		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **Financial disclosure forms were collected from all primary and sub-investigators**		
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: **none** Significant payments of other sorts: **study PSA3001: 1 and study PSA3002: 3** Proprietary interest in the product tested held by investigator: **none** Significant equity interest held by investigator in study: **none** Sponsor of covered study: **none**		
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) **none**		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Pharmacometrics Review

Population PK

Data: The serum guselkumab concentration data collected from PSA3001 and PSA3002 through Week 24 were utilized to perform a population PK analysis using a nonlinear mixed-effect modeling approach. The first-order conditional estimation with interaction method was used. The pooled data set comprised 254 subjects from PSA3001 and 492 subjects from PSA3002. A total of 5,626 quantifiable serum guselkumab concentration-time records were included in the population PK analysis. Nine samples (0.16%) were below the limit of quantitation and were excluded from the population PK analysis.

Model: The guselkumab concentration-time profiles in PsA subjects were adequately described by a 1-compartment linear population PK model with first-order absorption and first-order elimination. The final PK model consisted of the effects of body weight on CL/F and V/F, and the effects of diabetic comorbidity on CL/F. The parameter estimates of the final are shown in Table 34. The model was assessed via goodness-of-fit and visual predictive check.

Table 34 Parameter Estimates of the final population PK model

Parameters[a]	Estimate[b]	95% Confidence Interval	Magnitude of Change[c]
CL/F (L/day)[d]	0.596 (1.66)	0.577-0.615	--
Baseline body weight (BWT) on CL/F	0.926 (7.17)	0.796-1.06	-14.4% – 14.5%
Diabetes (DIAB) on CL/F	1.15 (3.54)	1.07-1.23	15%
V/F (L)[e]	15.5 (1.65)	15.0-16.0	--
Baseline body weight on V/F	0.861 (7.65)	0.732-0.990	-13.5% – 13.5%
Ka (1/day)	0.572 (8.69)	0.475-0.669	--
IIV of CL/F (%)	38.9 (6.09) [3.51]	36.5-41.2	--
IIV of V/F (%)	33.3 (10.6) [14.3]	29.6-36.6	--
IIV of Ka (%)	93.4 (16.8) [61.7]	76.5-107.7	--
Correlation between IIV of CL/F and V/F	0.101 (8.40)	--	--
Proportional residual error (CV%)	19.1% (2.89)	18.0%-20.2%	--
Additive residual error (µg/mL)	0.00289 (--)	--	--

[a] CL/F= apparent clearance; V/F= apparent volume of distribution; Ka= first-order absorption rate constant; IIV= inter-individual variability; calculated as (variance)$^{1/2}$×100%.
[b] Mean (RSE%) [Shrinkage %] estimates by NONMEM from the final PK dataset.
[c] 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 25th percentile to 75th percentile of the population.
[d] $\frac{CL}{F} = 0.596 \times \left(\frac{BWT}{84}\right)^{0.926} \times 1.15^{DIAB}$
[e] $\frac{V}{F} = 15.5 \times \left(\frac{BWT}{84}\right)^{0.861}$

Source: Table 7 in the Pop PK report

Covariate Effects on Exposure Metrics: The final population PK model was used to simulate 5,000 concentration-time profiles following the two guselkumab SC dose regimens, 100 mg q8w and 100 mg q4w, to assess body weight and diabetic comorbidity on exposure metrics. The results are summarized in Table 35.

Table 35 Summary of Covariate Effects on Exposure Metrics

PK Parameter	Group	Number of Subject	Mean	Median	5th-95th Percentiles
100 mg q8w					
$AUC_{0\text{-}w8,ss}$ (µg/mL×d)	weight<90kg	3021	209	191	96.9-389
	weight≥90kg	1979	147	136	71.3-265
	non-diabetes	4561	188	169	83-359
	diabetes	439	151	137	70.3-274
$C_{trough,ss}$ (µg/mL)	weight<90kg	3021	1.27	1.08	0.318-2.87
	weight≥90kg	1979	0.864	0.719	0.215-2.01
	non-diabetes	4561	1.14	0.94	0.277-2.68
	diabetes	439	0.773	0.655	0.182-1.71
100 mg q4w					
$AUC_{0\text{-}w4,ss}$ (µg/mL×d)	weight<90kg	3021	209	191	96.9 - 389
	weight≥90kg	1979	147	136	71.3 - 265
	non-diabetes	4561	188	169	83-359
	diabetes	439	151	137	70.3-274
$C_{trough,ss}$ (µg/mL)	weight<90kg	3021	4.7	4.18	1.79-9.39
	weight≥90kg	1979	3.25	2.91	1.22-6.48
	non-diabetes	4561	4.22	3.68	1.52-8.64
	diabetes	439	3.17	2.85	1.18-6.28

Simulations were based on final reduced population PK model (n=5000).
Key: $AUC_{0\text{-}w4,ss}$=Area under the curve from 0 to 4 weeks at steady state; $AUC_{0\text{-}w8,ss}$=Area under the curve from 0 to 8 weeks at steady state; $C_{trough,ss}$=Trough concentration at steady state; q4w= every 4 weeks; q8w= every 8 weeks

Source: Table 8 in Pop PK report

Comedication: In the population PK analysis dataset, 425 (57.0%) subjects had baseline MTX use, 78 (10.5%) subjects had baseline non-biologic DMARD use other than MTX, 475 (63.7%) subjects had baseline NSAIDs use and 130 (17.4%) subjects had baseline corticosteroids use. Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and conventional synthetic DMARDs such as methotrexate, did not affect the clearance of guselkumab.

Immunogenicity (Antibodies to Guselkumab)

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, and none developed injection site reactions through Week 24. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics and efficacy, and safety of guselkumab. This is consistent with the proposed labeling statement.

Exposure Response Analyses: Efficacy

The E-R analysis for efficacy was first evaluated based on observed trough serum guselkumab concentration quartiles in each individual phase 3 study. Further efficacy E-R analyses were performed with PK/PD modeling approaches (landmark and longitudinal modeling analyses)

using pooled phase 3 data. Clinical efficacy data including American College of Rheumatology (ACR) 20 and ACR 50 at Weeks 20 and 24, change from baseline in Disease Activity Score in 28 joints (DAS28) (CRP) at Weeks 20 and 24 and Investigator Global Assessment (IGA) response at Weeks 20 and 24 were used in the E-R analyses. The exposure metrics include model-predicted area under the concentration-time curve to Week 24 (AUC0-24w), model-predicted average steady-state serum concentration (Cave,ss), and Ctrough at Week 20 (Ctrough,wk20).
The landmark analysis approach used ordinal logistic regression to correlate ACR or IGA responses at Week 20 or Week 24 with guselkumab PK exposure metrics. A maximum drug effect (Emax) relationship between PK exposure metrics and efficacy response rates was assumed. Parameter estimates from the final landmark E-R models for ACR20/50/70 responses at Weeks 24 and 20 using AUC0-24w, Cave,ss, and Ctrough,wk20 as the exposure metrics are summarized in Table 36. The parameter estimates by the final landmark E-R models for IGA0/1 and IGA0 responses at Week 24 using AUC0-24w or Cave,ss as the exposure metrics are summarized in Table 37. These models were assessed via goodness-of-fit (Figure 12, Figure 13).

Baseline body weight and diabetic comorbidity status were identified to be significant covariates in the final population PK model, they were included in the covariate selection. These two covariates were not selected as significant covariates in either the ACR or the IGA E-R model. Overall, consistent efficacy was observed for both the guselkumab 100 mg q8w and the 100 mg q4w dose regimens in different weight groups, and between subjects with and without diabetes (see section 6). Thus, no dose adjustment is warranted.

Table 36 Parameter Estimates From the Final Landmark Exposure-response Models for ACR20/50/70 at Weeks 24 and 20

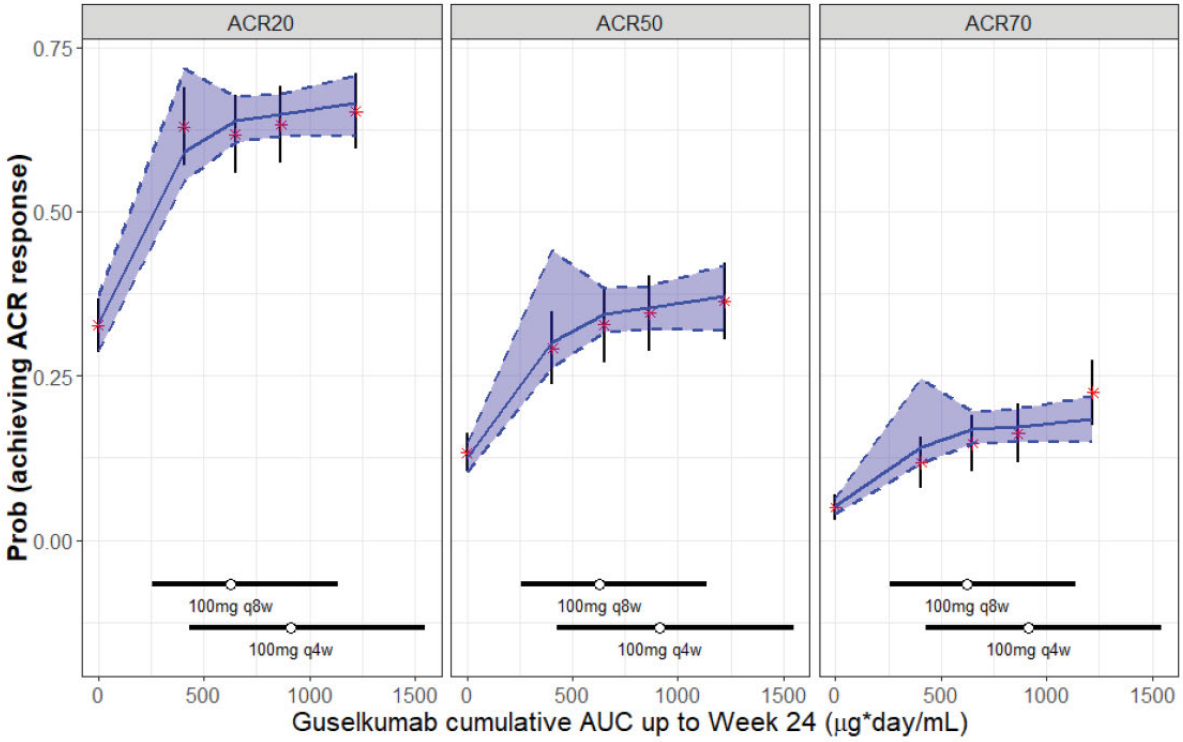
Parameters	Week 24 using $AUC_{0\text{-}24w}$[a]	Week 24 using $C_{ave,ss}$[a]	Week 20 using $C_{trough,wk20}$[a]
Run#	102	202	302
β_1	-1.94 (6.62)	-1.92 (6.74)	-1.86 (6.94)
d_2	1.23 (5.35)	1.23 (5.45)	1.15 (6.02)
d_0	0.979 (7.64)	1.00 (7.66)	1.09 (7.77)
E_{max}	1.44 (19.7)	1.53 (18.2)	1.26 (12.9)
BDAS on E_{max}	-0.847 (27.1)	-0.827 (27.5)	-0.981 (21.5)
BPAS on E_{max}	-	0.142 (35.9)	0.169 (30.2)
EC_{50}	134 (127)	1.06 (100)	0.150 (83.3)

[a] Parameter estimate (%RSE).

Abbreviations: ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; $AUC_{0\text{-}24w}$=cumulative area under the concentration-time curve from Week 0 to Week 24 (unit: day*µg/mL); $\beta_0/\beta_1/\beta_2$=baseline response rate in logit scale where $\beta_0=\beta_1-d_0$ and $\beta_2=\beta_1+d_2$; BDAS=baseline Disease Activity Score in 28 joints; BPAS=baseline Psoriasis Area and Severity Index score; $C_{ave,ss}$=average concentration at steady state (unit: µg/mL); $C_{trough,wk20}$=trough serum concentration at Week 20 (unit: µg/mL); EC_{50}= guselkumab exposure at half maximum drug effect (unit: same as respective PK metrics in the E-R analysis); E_{max}=maximum drug effect in logit scale; RSE=relative standard error.

Source: Table 8 in Exposure-Response-Report Landmark Analysis

Figure 12 Exposure-response of ACR20/50/70 at Week 24 Using AUC0-24w as Exposure Metric



The observed ACR20/50/70 response rates (red asterisks) and corresponding 90% confidence intervals were determined according to the bins for the model-predicted guselkumab exposure metrics and were plotted as the median exposure for each bin. The solid blue lines are the simulated median responses. The dotted blue lines and shaded areas both represent the simulated 90% prediction intervals from 1000 simulations incorporating model parameter uncertainties. The solid black lines at the bottom of the chart show the 5th to the 95th percentile for the exposure metrics, and the open circles are plotted at the median values for the 100 mg q8w and 100 mg q4w treatment groups, respectively.

Abbreviations: ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; AUC=cumulative area under the concentration-time curve; $AUC_{0\text{-}24w}$=AUC from Week 0 to Week 24; prob=probability; q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Source: Figure 1 in Exposure-Response-Report

Table 37 Parameter Estimates for the Final Landmark Exposure-response Models for IGA at Week 24

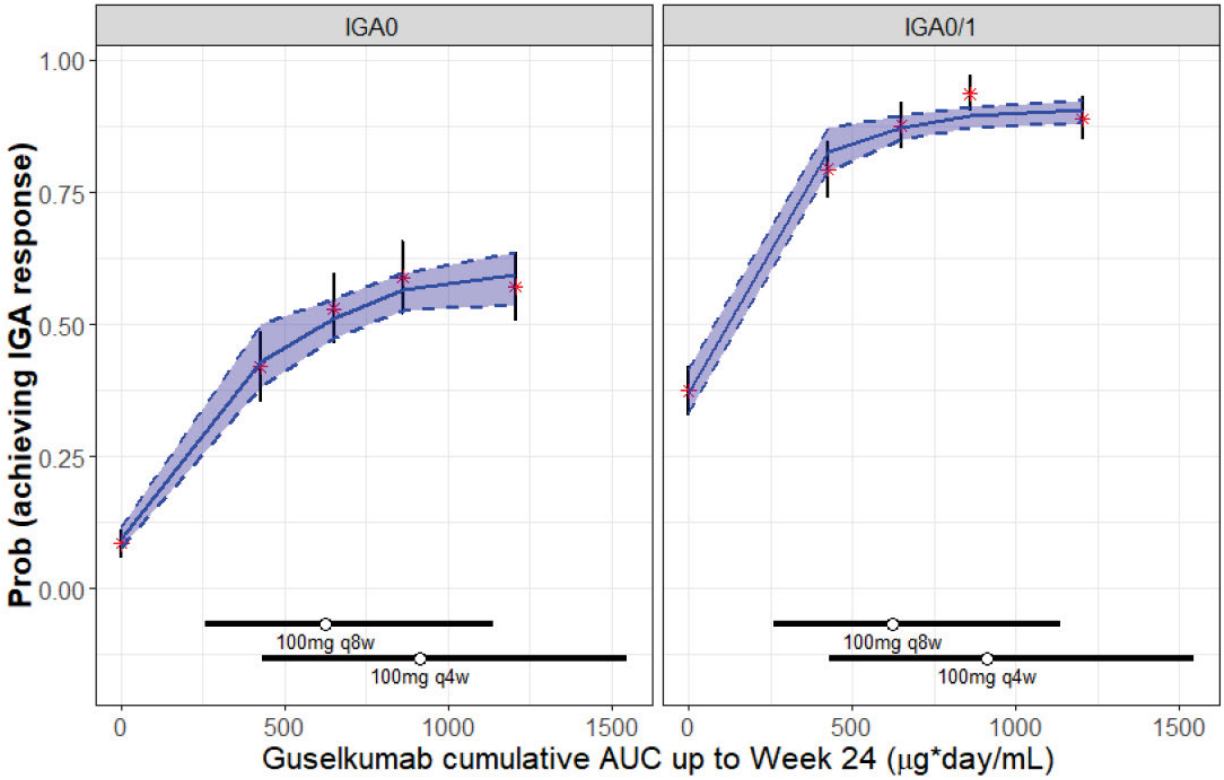
Parameters	Week 24 using $AUC_{0\text{-}24w}$[a]	Week 24 using $C_{ave,ss}$[a]
IGA Categorical Modeling		
Run#	402	502
β_1	-0.450 (27.6)	-0.447 (27.8)
BPAS on β_1	-0.779 (16.6)	-0.785 (16.4)
d_0	1.91 (5.45)	1.93 (5.51)
E_{max}	3.05 (10.9)	3.09 (9.27)
BPAS on E_{max}	0.217 (27.9)	0.214 (27.8)
EC_{50}	166 (48.3)	0.922 (39.5)

[a] Parameter estimate (%RSE).

Abbreviations: $AUC_{0\text{-}24w}$=cumulative area under the concentration-time curve from Week 0 to Week 24 (unit: day*µg/mL); β_0/β_1=baseline response rate in logit scale where $\beta_0=\beta_1-d_0$; BPAS=baseline Psoriasis Area and Severity Index score; $C_{ave,ss}$=average concentration at steady state (unit: µg/mL); EC_{50}=guselkumab exposure metrics to reach 50% maximum drug effect (unit: same as respective PK metrics in the E-R analysis); E_{max}=maximum drug effect in logit scale; IGA=Investigator's Global Assessment score; IGA0=IGA score of cleared (0); IGA0/1=IGA score of cleared (0) or minimal (1); RSE=relative standard error.

Source: Table 9 in Exposure-Response-Report Landmark Analysis

Figure 13 Exposure response for IGA response (IGA0/1 and IGA0) at Week 24 Using AUC0-24w as the Exposure Metric



The observed IGA0/1 and IGA0 response rates (red asterisks) and corresponding 90% confidence intervals were determined according to the bins of the model-predicted guselkumab exposure metrics, and were plotted as median exposure for each bin. The solid blue lines are the simulated median responses. The dotted blue lines and shaded areas both represent the simulated 90% prediction intervals from 1000 simulations incorporating model parameter uncertainties. The solid black lines at the bottom of the chart show the 5th to the 95th percentile for the exposure metrics, and the open circles are plotted at the median values for the 100 mg q8w and 100 mg q4w treatment groups, respectively.

Abbreviations: AUC=cumulative area under the concentration-time curve; $AUC_{0\text{-}24w}$=AUC from Week 0 to Week 24; IGA=Investigator's Global Assessment; IGA0=IGA score of cleared (0); IGA0/1=IGA score of cleared (0) or minimal (1); prob=probability; q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Source: Figure 4 in Exposure-Response-Report

For the longitudinal E-R analyses, a sequential longitudinal E-R modeling approach was used to characterize the ACR response-time profiles; for ACR responses, a proportional-odds logistic regression model was used, with an additive placebo effect over time and a semi-mechanistic indirect response model. The parameter estimates of the final model is shown in Table 38. The model was assessed via visual predictive check(data not shown).

The model predicted that guselkumab 100 mg q8w and 100 mg q4w resulted in similar ACR20/50/70 responses over 24 weeks in the overall population. The predicted differences in ACR20, ACR50, and ACR70 responses at Week 24 were <2% between the 2 dose regimens (Figure 14). A similar magnitude of differences (<3%) in ACR20, ACR50, and ACR70 responses between the 2 dose regimens was predicted for each of the subgroups that were stratified by the median BPAS (≤5.8 and >5.8), by the median BDAS (≤5.1 and >5.1) or by the median BCRP (≤0.94 and >0.94 mg/dL) (data not shown). Therefore, no dose adjustment is warranted.

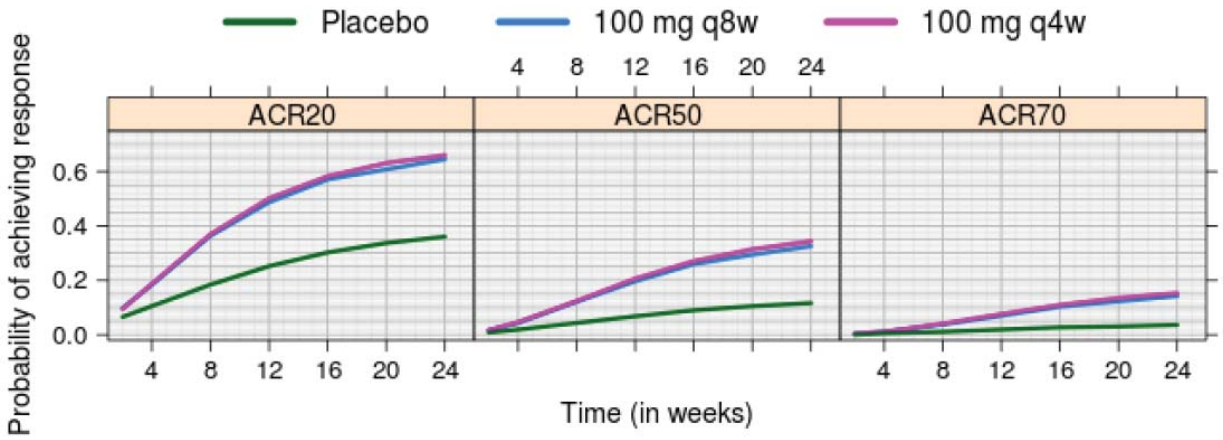
Table 38 Parameter Estimates by the Final Longitudinal Exposure-response Model: ACR

Parameter	Estimates	%RSE
α_1	-8.31	3.99
BDAS-5.1 on α_1	-0.368	26.3
α_1 - α_0	1.95	4.14
α_2 - α_1	2.60	2.74
PB_{MX}	4.94	7.54
k (1/day)	0.0160	13.8
k_{out} (1/day)	0.0218	24.9
EC_{50} (µg/mL)	0.173	257
BPAS-5.8 on EC_{50}	-0.535	91.4
BCRP-0.94 (ug/mL) on EC_{50}	-2.19	88.8
DE_{MX}	2.75	11.5
ω^2 (inter-subject variability of intercept)	6.69	6.94

Abbreviations: α_0=intercept for ACR70; α_1=intercept for ACR50; α_2=intercept for ACR20; ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; BCRP=baseline C-reactive protein (ug/mL); BDAS=baseline DAS28 score; BPAS=baseline Psoriasis Area and Severity Index score; DE_{MX}=maximum drug effect; EC_{50}=potency; k=rate of placebo effect onset; k_{out}=disease amelioration rate; PB_{MX}=maximal placebo effect; RSE=relative standard error; ω^2=variance of between-subject variability of intercept.

Source: Table 7 in Exposure-Response-Report Longitudinal Analysis

Figure 14 Model-predicted Median Overall ACR Response Profiles



Placebo, solid green line; 100 mg q4w, solid blue line; 100 mg q4w, solid magenta line.
Abbreviations: ACR=American College of Rheumatology; ACR20/50/70=20%, 50%, or 70% improvement in arthritis activity relative to baseline; q4w=every 4 weeks; q8w=every 8 weeks (100 mg at Weeks 0 and 4, then every 8 weeks).

Source: Figure 2 in Exposure-Response-Report Longitudinal Analysis.

In summary, using pooled Phase 3 data, exposure-response analyses suggest that SC guselkumab 100 mg at Weeks 0 and 4, then q8w and 100 mg q4w had similar effects in improving the signs and symptoms of PsA, as measured by ACR20/50/70 and IGA0/1 responses in subjects with PsA. Consistent with the observed ACR20, ACR50, and ACR70 data, the simulation based on longitudinal E-R modeling did not reveal discernible differences in achieving ACR20, ACR50, and ACR70 responses between the guselkumab 100 mg q8w and 100 mg q4w dose regimens.

Exposure Response Analyses: Safety

The E-R analysis for safety was evaluated based on observed trough serum guselkumab concentration quartiles and model-predicted exposure parameters using the pooled data from PSA3001 and PSA3002. Descriptive analyses to evaluate the relationship between systemic guselkumab exposure (e.g., observed steady-state trough serum guselkumab concentration) and the occurrence of selected safety events (i.e., adverse events [AEs], serious adverse events [SAEs], AEs leading to discontinuation of study agent, infections, and serious infections) were performed. Analyses of the relationships between model-predicted exposure parameters (Cmax, Cave,ss, and AUC0-24w) and the rates of occurrence of selected safety events were also performed. Overall, the incidence of these safety parameters of interest were not associated with steady-state trough serum guselkumab concentrations.

15.4. Additional Tables

Table 39 Subgroup analyses on ACR20 response at Week 24 in PSA3001

	Placebo	Guselkumab q8w		Guselkumab q4w	
	n/N (%)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)
Overall	28/126 (22.2%)	66/127 (52.0%)	3.8 (2.2, 6.5)	76/128 (59.4%)	5.1 (3.0, 8.9)
Sex					
Male	17/61 (27.9%)	37/68 (54.4%)	3.1 (1.5, 6.4)	43/66 (65.2%)	4.8 (2.3, 10.3)
Female	11/65 (16.9%)	29/59 (49.2%)	4.7 (2.1, 10.8)	33/62 (53.2%)	5.6 (2.5, 12.7)
Race					
White	26/112 (23.2%)	59/116 (50.9%)	3.4 (1.9, 6.1)	73/121 (60.3%)	5.0 (2.8, 8.9)
Other	2/12 (16.7%)	7/11 (63.6%)	8.7 (1.2, 61.7)	3/7 (42.9%)	3.8 (0.4, 31.6)
Age					
<45	9/45 (20.0%)	25/44 (56.8%)	5.3 (2.1, 13.5)	32/51 (62.7%)	6.7 (2.7, 17.0)
≥45 to <65	17/69 (24.6%)	38/74 (51.4%)	3.2 (1.6, 6.6)	41/69 (59.4%)	4.5 (2.2, 9.3)
≥65	2/12 (16.7%)	3/9 (33.3%)	2.5 (0.3, 19.5)	3/8 (37.5%)	3.0 (0.4, 24.2)
Region					
Poland	10/37 (27.0%)	18/36 (50.0%)	2.7 (1.0, 7.2)	26/34 (76.5%)	8.8 (3.0, 25.7)
Russia	4/22 (18.2%)	10/19 (52.6%)	5.0 (1.2, 20.5)	12/23 (52.2%)	4.9 (1.3, 19.1)
Ukraine	3/19 (15.8%)	10/22 (45.5%)	4.4 (1.0, 19.8)	15/29 (51.7%)	5.7 (1.4, 23.9)
USA, Canada, Spain and Germany	5/23 (21.7%)	13/25 (52.0%)	3.9 (1.1, 13.8)	9/19 (47.4%)	3.2 (0.8, 12.4)
Other countries	6/25 (24.0%)	15/25 (60.0%)	4.8 (1.4, 16.1)	14/23 (60.9%)	4.9 (1.4, 17.1)
DMARD use at baseline					
Yes	20/82 (24.4%)	42/83 (50.6%)	3.2 (1.6, 6.2)	49/82 (59.8%)	4.6 (2.4, 9.0)
No	8/44 (18.2%)	24/44 (54.5%)	5.4 (2.0, 14.2)	27/46 (58.7%)	6.4 (2.4, 16.8)
Prior anti-TNFα					
Yes	7/39 (17.9%)	23/41 (56.1%)	5.8 (2.1, 16.3)	22/38 (57.9%)	6.3 (2.2, 17.8)
No	21/87 (24.1%)	43/86 (50.0%)	3.1 (1.6, 6.0)	54/90 (60.0%)	4.7 (2.5, 9.0)

Abbreviations: OR=odds ratio, from a logistic regression model; q8w=once every eight weeks; q4w=once every four weeks; Cl=confidence interval; N=number of subjects in the subgroup; n=number of responders in the subgroup; [Source: Reviewer]

Table 40 Subgroup analyses on ACR20 response at Week 24 in PSA3002

	Placebo	Guselkumab q8w		Guselkumab q4w	
	n/N (%)	n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)
Overall	81/246 (32.9%)	159/248 (64.1%)	3.6 (2.5, 5.3)	156/245 (63.7%)	3.6 (2.5, 5.2)
Sex					
Male	42/117 (35.9%)	88/129 (68.2%)	3.8 (2.3, 6.5)	98/142 (69.0%)	4.0 (2.4, 6.7)
Female	39/129 (30.2%)	71/119 (59.7%)	3.4 (2.0, 5.8)	58/103 (56.3%)	3.0 (1.7, 5.1)
Race					
White	81/242 (33.5%)	155/240 (64.6%)	3.6 (2.5, 5.3)	153/242 (63.2%)	3.4 (2.4, 5.0)
Other	0/4 (0%)	4/8 (50.0%)	-	3/3 (100%)	-
Age					
<45	36/104 (34.6%)	84/128 (65.6%)	3.6 (2.1, 6.2)	76/108 (70.4%)	4.5 (2.5, 8.0)
≥45 to <65	40/131 (30.5%)	68/109 (62.4%)	3.8 (2.2, 6.5)	75/126 (59.5%)	3.3 (2.0, 5.6)
≥65	5/11 (45.5%)	7/11 (63.6%)	2.1 (0.4, 11.6)	5/11 (45.5%)	1.0 (0.2, 5.4)
Region					
Poland	6/35 (17.1%)	22/27 (81.5%)	21.3 (5.7, 78.8)	15/23 (65.2%)	9.1 (2.7, 31.0)
Russia	27/92 (29.3%)	40/77 (51.9%)	2.6 (1.4, 4.9)	64/104 (61.5%)	3.9 (2.1, 7.0)
Ukraine	23/65 (35.4%)	61/83 (73.5%)	5.1 (2.5, 10.2)	46/73 (63.0%)	3.1 (1.6, 6.2)
USA and Spain	1/6 (16.7%)	9/13 (69.2%)	11.2 (1.0, 130.2)	3/6 (50.0%)	5.0 (0.3, 72.8)
Other countries	24/48 (50.0%)	27/48 (56.3%)	1.3 (0.6, 2.9)	28/39 (71.8%)	2.5 (1.0, 6.2)
DMARD use at baseline					
Yes	62/172 (36.0%)	107/170 (62.9%)	3.0 (1.9, 4.7)	103/170 (60.6%)	2.7 (1.8, 4.2)
No	19/74 (25.7%)	52/78 (66.7%)	5.8 (2.9, 11.7)	53/75 (70.7%)	7.0 (3.4, 14.3)

Abbreviations: OR=odds ratio, from a logistic regression model; q8w=once every eight weeks; q4w=once every four weeks; Cl=confidence interval; N=number of subjects in the subgroup; n=number of responders in the subgroup; [Source: Reviewer]

Table 41 Study PsA 3001 Time and Events Schedule through Week 60

Phase	Screening[a]	Placebo-controlled Treatment[b]							Active Treatment[b]							Safety Follow-up
Week		0[c]	4	8	12	16	20	24	28	32	36	40	44	48	Final Efficacy Visit[d]/ Week 52	Final Safety Visit[b]/ Week 60
Study Procedures[d]																
Screening/Administrative																
Informed consent (ICF/eICF[e])	X															
Pharmacogenomics (DNA) (optional)[f] ICF/eICF[e]	X															
Review of Inclusion/ Exclusion Criteria	X	X														
Demography/Medical History	X															
Pre-planned Surgery/Procedure(s)	X															
Pre-study Therapy Review for Eligibility	X	X														
Study Agent Administration[g]																
Randomization		X														
Study agent administration		X	X	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]		
Early Escape																
Early Escape						X[i]										
Safety Assessments																
Physical examination (including skin)	X							X								X
eC-SSRS[j]	X	X	X	X	X	X	X	X	X		X		X		X	X
Vital signs[k]	X	X	X	X	X	X	X	X	X		X		X		X	X
Height		X														
Weight		X						X							X	
Local 12-lead ECG		X[l]														
Tuberculosis evaluation[m]	X	X	X	X	X	X	X	X	X		X		X		X	X
Chest radiograph[n]	X															
Pregnancy test[o]	X	X	X	X	X	X	X	X	X	X[p]	X	X[p]	X	X[p]	X	X
Injection site reaction evaluation		X	X	X	X	X	X	X	X	X[p]	X	X[p]	X	X[p]		
Efficacy Assessments																
PsA Evaluations for Arthritis[q]	X	X	X	X	X	X	X	X	X		X		X		X	
HAQ-DI[r]		X	X	X	X	X	X	X	X		X		X		X	
Patient's Global Assessment of Disease Activity (arthritis and psoriasis)[s]		X		X		X		X							X	
Patient's Assessment of Skin Disease Activity (Skin VAS)[t]		X		X		X		X							X	
Dactylitis assessments		X	X	X		X		X			X		X		X	

Study Procedures[d]															
Enthesitis assessments (LEI, SPARCC)		X	X	X		X		X			X		X		X	
BASDAI[f,s]		X		X		X		X							X	
SF-36[f]		X		X		X		X			X				X	
FACIT-fatigue[f]		X		X		X		X			X				X	
PROMIS 29[f]		X		X		X		X			X				X	
BSA % Involvement of Psoriasis		X														
IGA – Psoriasis		X				X		X							X	
PASI		X				X		X							X	
Clinical Laboratory Assessments																
QuantiFERON®-TB test[t]	X															
Hepatitis B and C Serologies[u]	X															
HIV Antibody Test[u]	X															
Hematology[u]	X	X	X	X	X	X	X	X	X		X		X		X	X
Chemistry[u]	X	X	X	X	X	X	X	X	X		X		X		X	X
Lipid Panel[u]		X														
C-reactive Protein[u]	X	X	X	X	X	X	X	X	X		X		X		X	X
Rheumatoid factor[u,v]	X															
Follicle Stimulating Hormone[u,w]	X															

Study Procedures[d]															
Pharmacokinetics/ Immunogenicity[x]															
Serum guselkumab concentration		X	X	X	X	X	X	X	X		X		X		X	X
Population PK				X[y]												
Antibodies to study agent		X	X		X			X	X						X	X
Pharmacogenomics (DNA)															
DNA Collection (Whole Blood in EDTA)[f]		X	X					X							X	
Other Biomarkers															
Serum Biomarkers		X	X					X							X	
Whole Blood (RNA)		X	X					X							X	
Ongoing Subject Review															
Concomitant therapy	X----------X															
Adverse events	X----------X															

a: The screening visit is to occur within 6 weeks before administration of study agent at Week 0. The screening visit may be completed in a single visit or may be divided into more than 1 visit. It is recommended that after obtaining informed consent, the investigator complete all laboratory tests at the first visit. The subject may then return for the remainder of the screening procedures only if the subject is eligible for the study as determined by the central laboratory test results.

b: Through Week 24, study visits will have a visit window of ± 4 days; after Week 24, study visits at the site will have a visit window of ± 7 days; Week 60 or the final safety visit (12 weeks after the last dose in subjects who discontinued study treatment) will have a visit window of ±14 days.

c: Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for lipid panel (Week 0). All other visits can be non-fasting.

d: If a subject permanently discontinues study agent administration at or after the Week 24 and before the Week 52 visit, the final efficacy visit should occur at the time of discontinuation or as soon as possible and all assessments under the Week 52/final efficacy visit should be performed. Fasting is not required for the final efficacy visit. The subject should also return for a final safety visit approximately 12 weeks after the last study agent administration.

e: An eICF will be used at a limited number of sites to obtain informed consent to participate in the study, and to obtain informed consent to participate in the optional DNA research component of the study, as applicable.

f: To participate in the optional DNA research component of this study, subjects must sign the DNA research ICF (or eICF) indicating willingness to participate. Blood samples for pharmacogenomic and epigenetic research will be collected only from subjects who give informed consent for DNA research.

g: Study agent will be administered SC at the site by a health care professional during visits to the site until the subject (or caregiver) is trained for self-administration. Study agent will be administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, and after appropriate and documented training, subjects will self-administer study agent at the investigative site under the supervision of a health care professional. Safety and efficacy assessments, including blood samples for clinical laboratory and pharmacokinetics/immunogenicity, should be performed before study agent administration.

h: The option to begin self-administration of study agent at home will begin at Week 32; subjects will record study agent administration on a diary card. Subjects who self-administer are not required to visit the study site at Weeks 32, 40 and 48. Subjects unable to have injection(s) administered away from the study site will be required to return to the site at these study weeks for administration of study agent injection(s). An injection site evaluation and AE review will be done at the site at the time of injection.

i: At Week 16, all subjects who qualify for early escape will continue on the dosing regimen to which they were randomized and will be allowed to initiate or increase the dose of one of the permitted concomitant medication interventions up to the maximum dose as specified in Table 3, at the discretion of the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.

j: The eC-SSRs should be performed after the joint assessment at the screening visit (after signing informed consent) At Week 0/baseline and at all post-baseline visits, the eC-SSRS should be the first assessment/questionnaire that the subject completes prior to study agent administration. See Section 9.4.2 for more details.

k: Vital signs include blood pressure and heart rate.
l: 12-lead ECG must be done prior to administration of study agent.
m: Subjects (as outlined in Inclusion Criterion 15) must undergo testing for TB (Attachment 2 or Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB.
n: The chest radiograph may be taken within 3 months prior to the first administration of study agent.
o: Females of childbearing potential who are dosed at the clinic must have a negative urine pregnancy test at all dosing visits prior to administration of study agent. For subjects not dosed at the clinic a urine pregnancy test is not required prior to administration of study agent.
p: Only performed for subjects who are dosed at the site.
q: PsA evaluations for arthritis include joint assessments (swollen and tender joint counts), patient's assessment of pain, patient's global assessment of disease activity (arthritis), and physician's global assessment of disease activity on VAS. These procedures should be performed prior to study agent administration at each visit, as applicable.
r: All patient questionnaires should be completed before any other tests, procedures, or evaluations on the day of the visit for baseline and post-baseline visits.
s: The BASDAI will be completed only in subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA (confirmation of sacroiliitis should be performed at the screening visit by the investigator, with documentation of spondylitis from a prior pelvic or SI joint x-ray or pelvic MRI when available).
t: A tuberculin skin test is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in the country in which this study is being conducted, with the exception noted in Inclusion Criterion 15.
u: Laboratory tests are listed in Section 9.4.1.
v: This test is optional. It can be done only if needed to confirm whether CASPAR criteria are met.
w: Prior to randomization, FSH is required for selected female subjects with amenorrhea for less than 12 months. Two FSH measurements are needed to confirm amenorrhea in these subjects. This test should not be done for any female subject of childbearing potential or female subjects with amenorrhea for at least 12 months. Refer to Inclusion Criterion 11 for details.
x: All blood samples must be collected before study agent administration at visits when a study agent administration is scheduled. Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab, and a back-up sample. Details will be provided in the Laboratory Manual.

y: An additional study visit, at which a venous blood sample (approximately 4 mL) for population PK analysis will be collected from all subjects, must occur on a random day between Week 4 to Week 12, but not on the same days of the scheduled Weeks 4, 8 or 12 visits. Additionally, this blood sample cannot be collected within 24 hours (either prior to or after) of the actual time of study agent administration at Weeks 4, 8 or 12. The serum sample for population PK will be split into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as a back-up sample).

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA = body surface area; CASPAR = classification criteria for psoriatic arthritis; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EDTA = ethylenediaminetetraacetic acid; eICF = electronic informed consent form; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle-stimulating hormone; HAQ-DI = Disability Index of the Health Assessment Questionnaire; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator's Global Assessment; LEI = Leeds Enthesitis Index; MRI = Magnetic Resonance Imaging; PASI = Psoriatic Area and Severity Index; PROMIS = Patient-Reported Outcomes Measurement Information System; PsA = psoriatic arthritis; RNA = ribonucleic acid; SF-36 = 36-item short form health survey; SPARCC = Spondyloarthritis Research Consortium of Canada; TB = tuberculosis; VAS = visual analog scale

Source: Applicant's Protocol PsA 3001 Time and events schedule

Table 42 Study PsA 3002 Time and Events Schedule through Week 24

Phase	Screening[a]	Placebo-controlled Treatment[b]							
Week		0[c]	2	4	8	12	16	20	24
Study Procedures[d]									
Screening/Administrative									
Informed Consent (ICF/eICF[e])	X								
Pharmacogenomics (DNA) (optional)[f] ICF/eICF[e]	X								
Review of Inclusion/Exclusion Criteria	X	X							
Demography/Medical History	X								
Pre-planned Surgery/Procedure(s)	X								
Pre-study Therapy Review for Eligibility	X	X							
Study Agent Administration[g]									
Randomization		X							
Study Agent Administration		X		X	X	X	X	X	X
Early Escape									
Early Escape							X[h]		
Safety Assessments									
Physical Examination (including skin)	X								X
eC-SSRS[i]	X	X	X	X	X	X	X	X	X
Vital Signs[j]	X	X	X	X	X	X	X	X	X
Height		X							
Weight		X							X
Local 12-lead ECG		X[k]							
Tuberculosis Evaluation[l]	X	X	X	X	X	X	X	X	X
Chest Radiograph[m]	X								
Pregnancy Test[n]	X	X		X	X	X	X	X	X
Injection Site Reaction Evaluation		X		X	X	X	X	X	X

Efficacy Assessments									
PsA Evaluations for Arthritis[o]	X	X	X	X	X	X	X	X	X
HAQ-DI[p]		X	X	X	X	X	X	X	X
Patient's Global Assessment of Disease Activity (Arthritis and Psoriasis)[p]		X			X		X		X
Patient's Assessment of Skin Disease Activity (Skin VAS)[p]		X			X		X		X
Dactylitis assessments		X	X	X	X		X		X
Enthesitis assessments (LEI)		X	X	X	X		X		X
Radiographs of Hands and Feet[q,r]	X								X
BASDAI[p,s]		X			X		X		X
Pelvic x-ray[t]	X								
SF-36[p]		X			X		X		X
DLQI[p]		X			X		X		X
FACIT-fatigue[p]		X			X		X		X
WPAI:PsA[p]		X					X		X
EQ-5D[p]		X					X		X
BSA % Involvement of Psoriasis		X							
IGA-Psoriasis		X					X		X
PASI		X					X		X

Clinical Laboratory Assessments									
QuantiFERON-TB test[u]	X								
Hepatitis B and C Serologies[v]	X								
HIV Antibody Test[v]	X								
Hematology[v]	X	X		X	X	X	X	X	X
Chemistry[v]	X	X		X	X	X	X	X	X
Lipid Panel[v]		X							
C-reactive Protein[v]	X	X	X	X	X	X	X	X	X
Rheumatoid Factor[v,w]	X								
Follicle Stimulating Hormone[v,x]	X								
Pharmacokinetics/Immunogenicity[y]									
Serum Guselkumab Concentration		X	X	X	X	X	X	X	X
Population PK					X[z]				
Antibodies to Study Agent		X		X		X			X
Pharmacogenomics (DNA)									
DNA Collection (Whole Blood in EDTA)[f]		X		X					X
Other Biomarkers									
Serum Biomarkers		X		X					X
Whole Blood (RNA)		X		X					X
Ongoing Subject Review									
Concomitant Therapy	X----------X								
Adverse Events	X----------X								

a: The screening visit is to occur within 6 weeks before administration of study agent at Week 0. The screening visit may be completed in a single visit or may be divided into more than 1 visit. It is recommended that after obtaining informed consent, the investigator complete all laboratory tests at the first visit. The subject may then return for the remainder of the screening procedures only if the subject is eligible for the study as determined by the central laboratory test results.
b: Through Week 24, study visits will have a visit window of ±4 days.
c: Subjects must fast (ie, no food or beverages [except water]) for at least 8 hours before blood is drawn for the lipid panel (Week 0). All other visits can be nonfasting.
d: If a subject permanently discontinues study agent administration at Week 24, the final efficacy visit should occur at the time of discontinuation or as soon as possible and all assessments under the Week 100/final efficacy should be performed, including radiographs of hands and feet (see footnote "r" below), with the exception of study agent administration. Fasting is not required for the final efficacy visit. The subject should also return for a final safety visit approximately 12 weeks after the last study agent administration.
e: An eICF will be used at a limited number of sites to obtain informed consent to participate in the study, and to obtain informed consent to participate in the optional DNA research component of the study, as applicable.
f: To participate in the optional DNA research component of this study, subjects must sign the DNA research ICF (or eICF) indicating willingness to participate. Blood samples for pharmacogenomic and epigenetic research will be collected only from subjects who give informed consent for DNA research.
g: Study agent will be administered SC at the site by a health care professional during visits to the site until the subject (or caregiver) is trained for self-administration. Study agent will be administered by site personnel at Weeks 0 and 4. Beginning at Week 8, at the discretion of the investigator and subject, and after appropriate and documented training, subjects may self-administer study agent at the investigative site under the supervision of a health care professional. A caregiver may also be trained to administer study agent. Safety and efficacy assessments, including blood samples for clinical laboratory and pharmacokinetics/immunogenicity, should be performed before study agent administration.
h: At Week 16, all subjects who qualify for early escape will continue on the dosing regimen they were randomized to and will be allowed to initiate or increase the dose of one of the permitted concomitant medication interventions up to the maximum dose as specified in Table 4, at the discretion of the investigator. Titration to a stable dose of the medication should be completed for subjects qualifying for early escape by the Week 24 visit.
i: The eC-SSRS should be performed after the joint assessment at the screening visit (after signing informed consent). At Week 0/baseline and at all post-baseline visits, the eC-SSRS should be the first assessment/questionnaire that the subject completes prior to study agent administration (see Section 9.7.2 for details).
j: Vital signs include blood pressure and heart rate.
k: 12-lead ECG must be done prior to administration of study agent.
l: Subjects (as outlined in Inclusion Criterion 14) must undergo testing for TB (Attachment 2 or Attachment 3) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB.
m: The chest radiograph may be taken within 3 months prior to the first administration of study agent.
n: Females of childbearing potential must have a negative serum pregnancy test prior to randomization and a negative urine pregnancy test at all dosing visits prior to administration of study agent.

o: PsA evaluations for arthritis include joint assessments (swollen and tender joint counts), patient's assessment of pain, patient's global assessment of disease activity (arthritis), and physician's global assessment of disease activity on VAS. These procedures should be performed prior to study agent administration at each visit, as applicable.
p: All patient questionnaires should be completed before any other tests, procedures, or evaluations on the day of the visit for baseline and post-baseline visits.
q: To minimize unnecessary x-rays, it is recommended that subjects have the baseline radiographs of hands and feet taken after the inclusion and exclusion criteria have been checked and the subject appears eligible to enter the study. All eligible subjects should have radiographs taken approximately 2 weeks but not greater than 4 weeks prior to randomization.
r: Week 24 radiographs should be taken within ±2 weeks of the Week 24 visit. For subjects who discontinue study agent prior to Week 24, radiographs of the hands and feet should be performed at the time of study agent discontinuation. If discontinuation occurs prior to or at Week 16, the subject should also have radiographs performed at the Week 24 visit. If discontinuation occurs after Week 16, the radiographs do not need to be repeated at Week 24. For subjects who also discontinue study participation at any time during the study, radiographs should be performed at the time of study discontinuation unless another set of radiographs has been obtained within the past 6 weeks.
s: The BASDAI will be completed only in subjects with spondylitis with peripheral arthritis as their primary arthritic presentation of PsA.
t: For patients with spondylitis, confirmation of sacroiliitis should be performed at the screening visit by a locally performed pelvic x-ray (single anterior-posterior view) unless a pelvic or SI joint x-ray or pelvic MRI has been previously performed. Results must be documented.
u: A tuberculin skin test is additionally required if the QuantiFERON®-TB Gold test is not approved/registered in the country in which this study is being conducted, with the exception noted in Inclusion Criterion 14.
v: Laboratory tests are listed in Section 9.7.1.
w: This test is optional. It can be done if needed to confirm whether CASPAR criteria are met.
x: Prior to randomization, FSH is only required for female subjects with amenorrhea for less than 12 months. Two FSH measurements are needed to confirm amenorrhea in these subjects. This test should NOT be done for any female subject of childbearing potential or female subjects with amenorrhea for at least 12 months. Refer to Inclusion Criterion 10 for details.
y: All blood samples must be collected before study agent administration at visits when a study agent administration is scheduled. Blood collected from one venipuncture will be divided into multiple aliquots of serum for the measurement of guselkumab concentration, antibodies to guselkumab, and a back-up sample. Details will be provided in the Laboratory Manual.

z: An additional study visit, at which a venous blood sample (approximately 4 mL) for population PK analysis will be collected from all subjects, must occur on a random day between Week 4 to Week 12, but not on the same days of the scheduled Weeks 4, 8 or 12 visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study agent administration at Weeks 4, 8, or 12 (ie, it cannot be collected within 24 hours before or after study agent administration). The serum sample for population PK will be split into 2 aliquots (1 aliquot for serum guselkumab concentration and 1 aliquot as a back-up sample).

Abbreviations: BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BSA = body surface area; CASPAR = ClASsification criteria for Psoriatic Arthritis; DLQI = Dermatology Life Quality Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; EDTA = ethylenediaminetetraacetic acid; eICF = electronic informed consent form; EQ-5D = EuroQol five dimensions questionnaire; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HAQ-DI = Disability Index of the Health Assessment Questionnaire; HIV = human immunodeficiency virus; ICF = informed consent form; IGA = Investigator's Global Assessment; LEI = Leeds Enthesitis Index; MRI = magnetic resonance imaging; PASI = Psoriatic Area and Severity Index; PsA = psoriatic arthritis; RNA = ribonucleic acid; SF-36 = 36-item Short Form Health Survey; SI =TB = tuberculosis; VAS = visual analog scale; WPAI = Work Productivity and Activity Impairment Questionnaire.

Source: Applicant's Protocol PsA 3002 Time and events schedule

Table 43 Studies PSA3001 and PSA3002 AEs by preferred term with a frequency ≥2% in any treatment group through Week 24

	PSA3001			PSA 3002		
	Placebo N=126 n (%)	Guselkumab q8w N=127 n (%)	Guselkumab q4w N=128 n (%)	Placebo N=246 n (%)	Guselkumab q8w N=248 n (%)	Guselkumab q4w N=245 n (%)
Nasopharyngitis	8 (6.3)	16 (12.6)	7 (5.5)	9 (3.7)	10 (4.0)	12 (4.9)
Upper RTI	9 (7.1)	7 (5.5)	11 (8.6)	8 (3.3)	6 (2.4)	12 (4.9)
Viral Upper RTI	2 (1.6)	1 (0.8)	4 (3.1)	2 (0.8)	2 (0.8)	0
Bronchitis	1 (0.8)	5 (3.9)	1 (0.8)	3 (1.2)	1 (0.4)	10 (4.1)
Enthesopathy	6 (4.8)	6 (4.7)	6 (4.7)	7 (2.8)	5 (2.0)	7 (2.9)
Arthralgia	6 (4.8)	1 (0.8)	2 (1.6)	0	2 (0.8)	1 (0.4)
Dactylitis	5 (4.0)	1 (0.8)	2 (1.6)	7 (2.8)	6 (2.4)	5 (2.0)
Psoriatic Arthropathy	5 (4.0)	2 (1.6)	0	6 (2.4)	2 (0.8)	0
Headache	1 (0.8)	2 (1.6)	4 (3.1)	2 (0.8)	6 (2.4)	3 (1.2)
Diarrhea	2 (1.6)	4 (3.1)	2 (1.6)	1 (0.4)	2 (0.8)	2 (0.8)
ALT increase	3 (2.4)	8 (6.3)	5 (3.9)	11 (4.5)	15 (6.0)	25 (10.2)
AST increase	3 (2.4)	9 (7.1)	3 (2.3)	6 (2.4)	14 (5.6)	11 (4.5)
Neutropenia	0	0	0	3 (1.2)	6 (2.4)	1 (0.4)
Leukopenia	1 (0.8)	0	0	1 (0.4)	6 (2.4)	1 (0.4)
Anemia	2 (1.6)	2 (1.6)	2 (1.6)	6 (2.4)	5 (2.0)	1 (0.4)
Hyperkalemia	3 (2.4)	0	1 (0.8)	0	0	2 (0.8)
Diabetes Mellitus	3 (2.4)	1 (0.8)	1 (0.8)	0	1 (0.4)	2 (0.8)
Hypertension	2 (1.6)	3 (2.4)	3 (2.3)	4 (1.6)	3 (1.2)	1 (0.4)
Psoriasis	5 (4.0)	0	0	7 (2.8)	1 (0.4)	0

Source: Adapted from Study PSA3001 CSR Table TSFAE02 and Study PSA3002 CSR Table TSFAE02
Abbreviations: RTI=respiratory tract infection; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase

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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/

RACHEL GLASER
07/13/2020 02:58:33 PM

NIKOLAY P NIKOLOV
07/13/2020 03:01:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761061Orig1s007

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD, 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: BLA 761061/007 – Tremfya (Guselkumab) subcutaneous injection

FROM: Yasmin Choudhry, M.D.
Clinical Outcome Assessment (COA) Reviewer
Division of Clinical Outcome Assessment (DCOA)

Onyeka Illoh, OD, MPH
COA Team Leader
DCOA

SUBJECT: Division of Rheumatology and Transplant Medicine consult to DCOA requesting review of the evidence to support the validity and reliability of the patient-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy-Fatigue, for the treatment of adult patients with active psoriatic arthritis.

DRUG SPONSOR: Janssen Biotech, Inc.

COA TRACKING NUMBER: C2020210

Please check all that apply

☐ Rare Disease/Orphan Designation
☐ Pediatric

EXECUTIVE SUMMARY

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by Division of Rheumatology and Transplant Medicine (DRTM) on May 18, 2020 for BLA 761061/S-007 regarding guselkumab for the treatment of active psoriatic arthritis (PsA). This COA consult is related to review of the evidence to support validity and reliability of the patient-reported outcome instrument, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), in this context of use, as well as the interpretation of clinically meaningful within-patient change.

Conclusion:

1. Based on the evidence provided, we agree that fatigue appears to be an important and common symptom in patients with PsA. However, based on the Applicant's submission, the content validity of the FACIT-Fatigue has not been fully established in this patient population and there are limitations of the instrument (See Review Findings below).
2. The threshold for clinically meaningful within-patient change to assess fatigue severity in the clinical trials could not be estimated using anchor-based methods, because the clinical trials did not include anchor scales.
3. The observed treatment effect on the FACIT-Fatigue instrument (in both clinical trials) was modest. Given the lack of clear documentation of content validity and the limitations of the FACIT-Fatigue described above, it is not possible to know whether the modest effect was due to the impact of the drug on fatigue or to the limitations of the FACIT-Fatigue.
4. In summary, there was limited information to support the content validity and measurement properties in PsA population, and treatment effect appeared modest and without support for a meaningful within-patient change threshold. However, based on evaluation of the cumulative distribution function curves, there was clear separation across the range of improvement (including higher levels of improvement) in the low dose group in both trials. Therefore, clinical judgment should be used to decide whether and how to describe the modest improvement in FACIT-Fatigue endpoint in the product label. If the Division proceeds with labeling claims, it would be important to consider describing which of the FACIT-Fatigue items are driving the total score.
5. For future clinical trials in patients with PsA, we recommend that sponsors conduct patient interviews to determine the relevance and importance of the different aspects of fatigue in the clinical trial target population. It is important to evaluate patients' understanding of the content of the instrument. We recommend that sponsors review the *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm193282.pdf.

   We strongly recommend that sponsors utilize appropriate anchor measures in their clinical trials to enable the anchor-based methods to determine the clinically meaningful within-patient change in scores to identify responder(s). Early engagement with FDA during drug development on clinical outcome assessments is highly encouraged.

BACKGROUND

FACIT-Fatigue includes 13 items that are rated on a 5-point scale with a score range of 0-52 (based on reversed scoring, lower scores indicate greater fatigue). See Attachments 1 and 2 of this review for the conceptual framework and a copy of the instrument, respectively.

The Applicant completed two randomized, double-blind placebo-controlled phase 3 clinical trials (Study CNTO1959PSA3001 and study CNTO1959PSA3001; from here on referred to as Studies 3001 and 3002) in adults with active PsA who had inadequate response to standard therapies. The primary endpoint of both studies was the proportion of subjects who achieve an American College of Rheumatology (ACR) 20 response at Week 24.

In both studies, FACIT-Fatigue was utilized as exploratory endpoints (not adjusted for multiplicity) to assess: 1) Change from baseline at Week 24, and 2) the proportion of subjects who achieve ≥ 4-point improvement from baseline at Week 24. FACIT-Fatigue was assessed at baseline and Weeks 8, 16, and 24.

This NDA submission included a copy of the White paper[1] as supportive evidence for use of the FACIT-Fatigue in PsA patients. The Division seeks DCOA's input on the adequacy of the submitted evidence in support of FACIT-Fatigue for the possibility of a labeling claim. The Applicant's proposed FACIT-Fatigue-related labeling claim (in Section 14.2 of the annotated draft label) is as follows:

"*Other Health-Related Outcomes*

(b) (4)

In order to evaluate content validity of an instrument, it is important to define the concept of interest. Fatigue has been defined as "an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities, including the ability to work effectively and to function at one's usual level in family or social roles" (Christodoulou et al, 2008)[2]. Of note, according to this definition, fatigue is a sustained experience and impacts daily functioning.

REVIEW FINDINGS

Content validity:

1. For content validity and reliability of the FACIT-Fatigue in patients with PsA, the Applicant is solely relying on the available data from the literature, which are largely

[1] Janssen Research & Development. Evidence for the use of FACIT-Fatigue in Psoriatic Arthritis: A Literature Review of Psychometric Properties and Clinical Relevance. Approved, 09 December 2016.

[2] Christodoulou et al. Cognitive Interviewing in the Evaluation of Fatigue Items: Results from the Patient-Reported Outcomes Measurement Information System (PROMIS). Qual Life Res. 2008 December; 17(10): 1239–1246. doi:10.1007/s11136-008-9402x.

in patients with rheumatoid arthritis (RA) and other inflammatory conditions. To evaluate whether the items of the FACIT-Fatigue adequately capture the concept of "fatigue" from the perspective of PsA and RA patients, the Applicant conducted a literature review of qualitative studies involving PsA or RA patients to map descriptors of fatigue elicited by PsA and RA patients during focus group interviews to the items of the FACIT-Fatigue as a means of examining content validity. The Applicant's results are shown in the Table 1:

Table 1. Applicant's results of mapping between patients' descriptors and FACIT-Fatigue items (taken from the White paper)

	FACIT-Fatigue item	Descriptor	Frequency of mapping
1	I feel fatigued	Exhausted / tired / fatigued / weary Heaviness Overwhelming physical tiredness (Most) burdensome Unbelievable/overwhelming	10
2	I feel weak all over	Weakness Lack of strength Totally depleted Head to toe fatigue Generally unwell	6
3	I feel listless ("washed out")	Wiped out Drained Worn out Lethargic Battery gone	12
4	I feel tired	Always tired/tiredness	6
5	I have trouble starting things because I am tired	Hard to take initiative to get started Might delay a day in […]/don't want to do things	3
6	I have trouble finishing things because I am tired	Cut activities short Activities tiring by end of day	2
7	I have energy	I've lost all the energy I used to have/constant lack of energy/no energy left / energy (have/lack) Energy zapped of you	5
8	I am able to do my usual activities	To limit their normal activities Impacted ability to do household chores Holds me back from doing anything Struggle to do even the minimal amount of things	6
9	I need to sleep during the day	Nodding off with company/friends Nodding off while at work/needing to take a nap Need to sleep during the day despite sleeping at night Can't keep eyelids open	5
10	I am too tired to eat	Loss of appetite and weight	1
11	I need help doing my usual activities	Lean on other people Being driven to work Get somebody to do work tasks	5
12	I am frustrated by being too tired to do the things I want to do	Frustrating Frustrating to be exhausted all the time Irritability due to fatigue Frustration of living with a body that moves too slowly	11
13	I have to limit my social activity because I am tired	Not being able to participate in valued social activities/ social activities became limited Less social activities on weekend Inability to travel or participate in leisure	6

Of note, (per the White paper) mapping between patients' descriptors and FACIT-Fatigue items was based on the limited verbatim patient input reported in the manuscript and/or authors' description of patient input.

Note that in the table above, Items 5, 6, 7, 10, and 11 were mapped less frequently than the rest of the items. Also, note that the information in the table above comes from literature from both the RA and PsA population.

2. Therefore, this reviewer reviewed the following literature[3] [4] which appeared to be supportive of fatigue as an important concept in PsA patients as shown by the following patient quotes:

> '. . . And [I] keep myself going but it's really difficult because the tiredness just takes you over, takes over . . . it is hard. It's hard because you can't keep your eyelids open, you're fighting it'.
>
> 'It's the fatigue . . . and it's just absolutely, it's like having flu but not having flu, it's absolute bone weariness'
>
> '. . . this kind of feeling of just being generally unwell and not being able to motivate myself . . .'

However, this publication specifically examined patient experience during PsA flare from qualitative interviews in a sample of 18 patients with PsA, and it is unclear whether this represented the patient population in the clinical trials.

FACIT-Fatigue content:

1. Evidence of PsA patients' understanding of this instrument's content and format (i.e., cognitive testing) was also not included in the submission nor in the referenced literature.

2. Some of the FACIT-Fatigue items are suboptimal. As exemplified below.
    a. "I am too tired to eat" may be interpreted differently by different patients (e.g., some patients may interpret it is as including preparing meals and others may not). Additionally, this item was not found to be relevant based on the literature review reported in the Table 1.
    b. We do not know how patients understand the following items, "I am able to do my usual activities" and "I need help doing my usual activities", as these are expected to be influenced by factors other than fatigue (e.g., PsA flare causing painful, swollen joints). Additionally, these items are reverse-framed in comparison to the other FACIT-Fatigue items, which may confuse patients.
    c. The first 4 items (fatigued, weak all over, feel listless, tired) appear to be measuring a very similar concept and it is unclear whether and how they are distinguishable from the perspective of patients. This is important because if there is redundancy, this could mean that these items may be over weighted in the overall score.
3. Evidence of relevancy/importance of all concepts included in this instrument was not included in the submission nor in the referenced literature. Qualitative protocols, interview guides, study reports and patient transcripts were not included in the submission nor in the referenced literature.

[3] Moverley et al. It's not just the joints, it's the whole thing: qualitative analysis of patients' experience of flare in psoriatic arthritis. Rheumatology (Oxford, England). 2015;54(8):1448–1453.
[4] Seina Lee et al. The Burden of Psoriatic Arthritis, A Literature Review from a Global Health Systems Perspective. December 2010 P&T Vol. 35 No. 12: 680-689.

Study Results (Studies 3001 and 3002): FACIT-Fatigue

1. As stated above, the two FACIT-Fatigue endpoints were not adjusted for multiplicity. However, both endpoints achieved nominal statistical significance at the 5% level for both guselkumab groups (100 mg q8 and 100 mg q4 weeks) compared with placebo. The result are as follows. For context, the baseline FACIT-Fatigue scores demonstrated a wide range (i.e., 3-52).

    a. The A modest effect on FACIT-Fatigue scores was observed in both dose groups at Week 24 in both Study 3001 and Study 3002 (see tables below).

    Table 2. Study 3001

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Change from baseline in FACIT-Fatigue score[a,h]			
Week 24			
Subjects evaluable[b]			
N	126	127	128
Mean (SD)	2.151 (7.8374)	5.756 (10.1776)	5.445 (7.7213)
Median	0.000	5.000	5.000
Range	(-22.00; 28.00)	(-20.00; 40.00)	(-20.00; 24.00)
IQ range	(-1.000; 5.000)	(-1.000; 12.000)	(0.000; 11.000)
Model Based Estimates of the Mean Change[a,c]			
LSMean (95% CI)[d]	2.206 (0.773, 3.638)	5.609 (4.181, 7.036)	5.841 (4.416, 7.267)
LSMean difference (95% CI)		3.403 (1.442, 5.364)	3.636 (1.677, 5.594)
p-value[d]		< 0.001	< 0.001

    Table 3. Study 3002

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Change from baseline in FACIT-Fatigue score[a,h]			
Week 24			
Subjects evaluable[b]			
N	244	246	245
Mean (SD)	3.734 (8.6950)	7.691 (9.8682)	6.702 (8.6340)
Median	2.000	6.000	5.000
Range	(-16.00; 37.00)	(-19.00; 41.00)	(-26.00; 35.00)
IQ range	(-1.000; 9.000)	(1.000; 14.000)	(1.000; 11.000)
Model Based Estimates of the Mean Change[a,c]			
LSMean (95% CI)[d]	3.559 (2.500, 4.619)	7.550 (6.496, 8.603)	7.111 (6.051, 8.171)
LSMean difference (95% CI)		3.990 (2.526, 5.454)	3.551 (2.082, 5.021)
p-value[d]		< 0.001	< 0.001

    b. The FACIT-Fatigue item-level analysis shows (See attachment 3 of this review):

    In Study 3001:

    - The only items with a median change from Baseline of 1 category were Items 1 (Feel fatigued), 2 (Feel weak all over) and Item 4 (Feel

tired). The latter (feel tired) showed a median change in only one dose group (guselkumab 100mg q 8weeks).

- The median change from Baseline at week 24 was 0 for 10 of the 13 items i.e., Item 3 (Listless), Item 5 (Trouble starting things), Item 6 (Trouble finishing things), Item 7 (Energy), Item 8 (Do usual activities), Item 9 (Sleep during day), Item 10 (Too tired to eat), Item 11 (Help with usual activities), Item 12 (Frustrated with tiredness) and Item 13 (Limit social activity).

Therefore, in Study 3001, the overall score appeared to be driven by only a few items. Additionally, impact of fatigue on patients' "usual activities" did not demonstrate a median change, and the concept of impact of fatigue on "usual activities" is important to the definition of fatigue.

In Study 3002:

- The following 8 items showed a median change from baseline of 1 category: Item 1 (Feel fatigued), Item 2 (Feel weak all over), Item 3 (Feel listless), Item 4 (Feel tired), Item 5 (Trouble starting things), Item 6 (Trouble finishing things), Item 12 (Frustrated with tiredness) and Item 13 (Limit social activity).
- The remaining 5 items showed a median change from Baseline at week 24 of 0: (i.e., Item 7 (Energy), Item 8 (do usual activities), Item 9 (Sleep during the day), Item 10 (Too tired to eat) and Item 11 (Help with usual activities).

The results in Study 3002, showed change in a larger number of items compared with 3001; however, similar to 3001, there was no observed median change in impact on "usual activities".

Interpretation of clinically meaningful within-patient change:

1. The proposed minimal clinically important difference (MCID) responder (i.e., ≥ 4-point; derived from RA patients)[5], is based on a distribution-based method. The Applicant did provide distribution-based analyses for the current studies in PsA patients. Additionally, the Applicant has not provided justification for extrapolating the clinically meaningful change threshold from RA patients to PsA patients.

   From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., improvement threshold) from the patient perspective derived from anchor-based methods. Therefore, we do not agree that the 4-point threshold derived from the distribution-based methods is clinically meaningful.

2. The usual primary methods for estimating meaning change thresholds are anchor-based

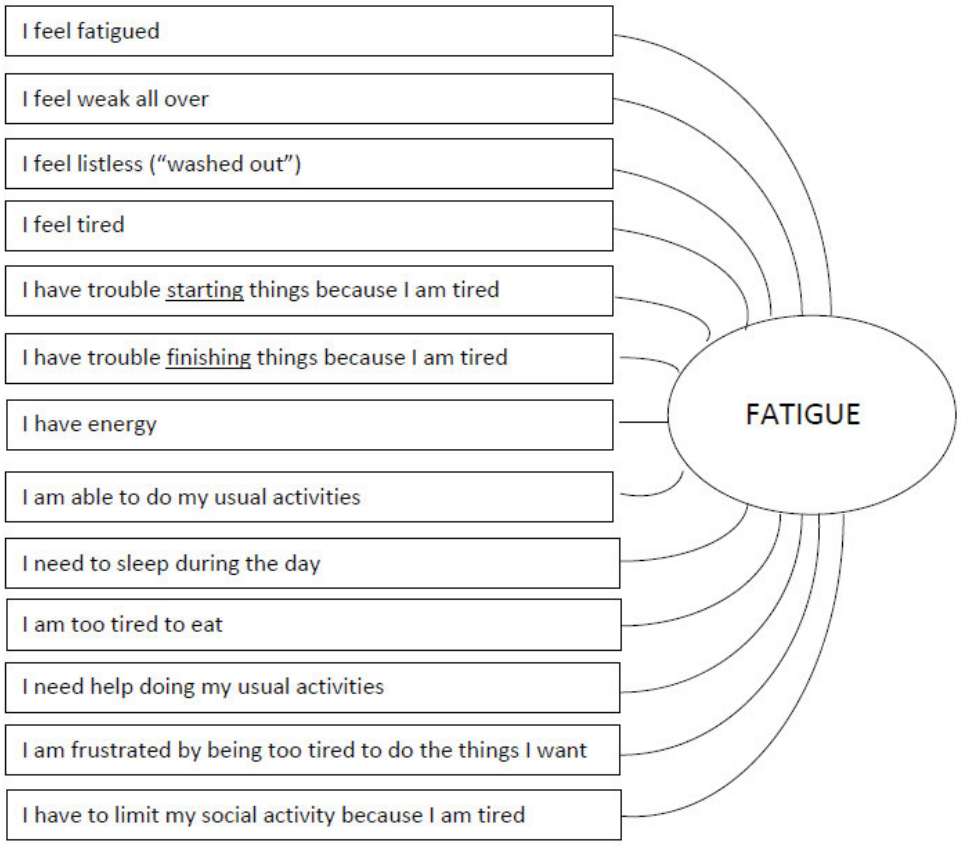
[5] The White paper (Section 4.4.2) states the following: "Of note, although none of the studies where the MID of the FACIT-Fatigue was evaluated used data from patients with PsA, the review of the literature indicated that the 4-point MID value derived in RA samples is widely used in PsA randomized controlled trials to evaluate the percentage of patients who report clinically meaningful change in fatigue."

methods. The two clinical trials did not include patient-reported anchor scales to allow us to determine a clinically meaningful within-patient change threshold. However, we reviewed the empirical cumulative distribution function (eCDF) curves showing the distribution of response by treatment group that was provided by the Applicant. Separation between the placebo and treatment groups was observed for small improvements from Baseline to Week 24 in both studies (See Attachment 4 of this review for the eCDF curves for Study 3001 and 3002). It is unclear whether the range over which most of the separation is observed represents a clinically meaningful response.

3. There is a different shape of the eCDF curves between treatment groups in both trials. Looking at the higher level of improvement, Guselkumab 100mg q 8 week appears to show a larger separation from placebo compared with Guselkumab 100 q 4 weeks, which did not appear to show a convincing between-group separation at the higher range of improvement.

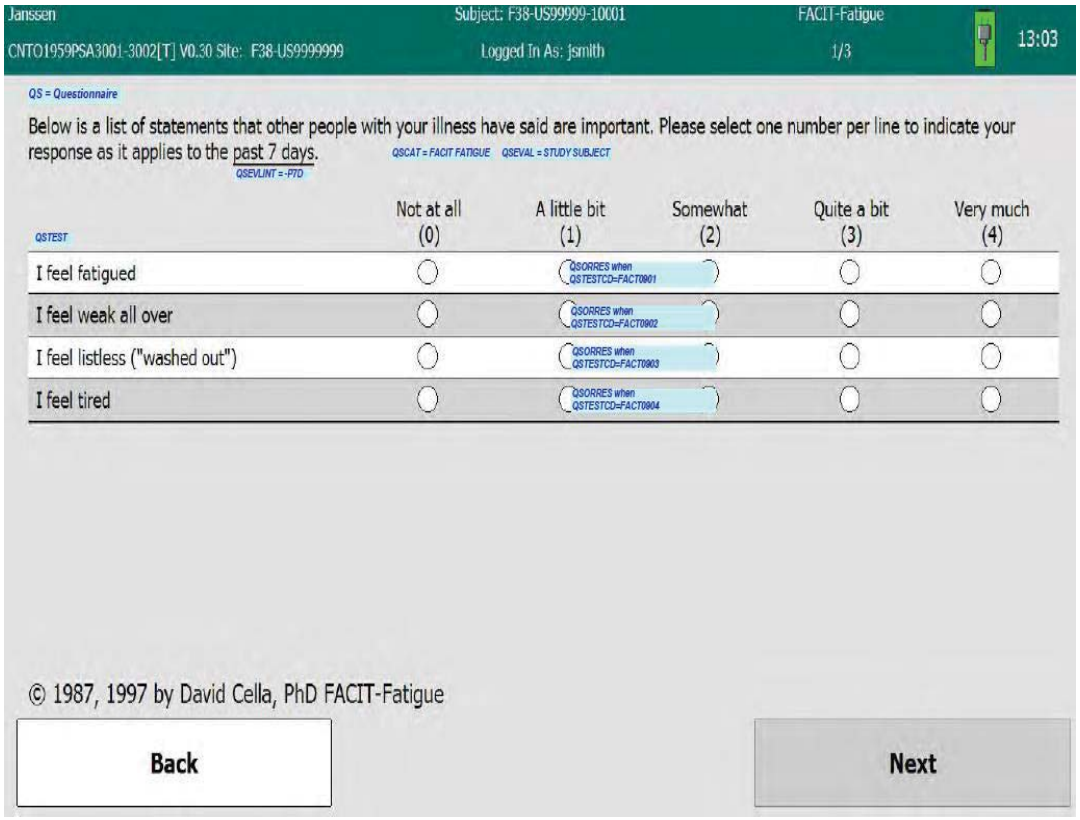
Attachments:
Attachment 1: Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Conceptual Framework
Attachment 2: Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
Attachment 3: Item-level analyses (Study 3001 and Study 3002)
Attachment 4: Empirical Cumulative Distribution Function curves (Study 3001 and Study 3002)

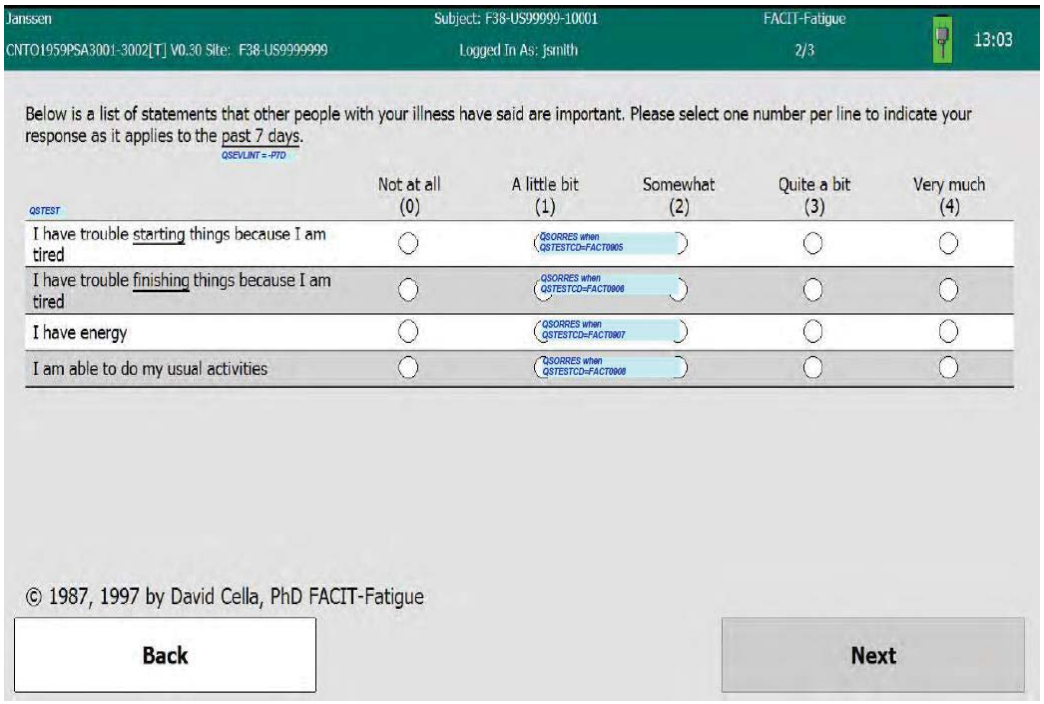
Attachment 1
Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
Conceptual Framework

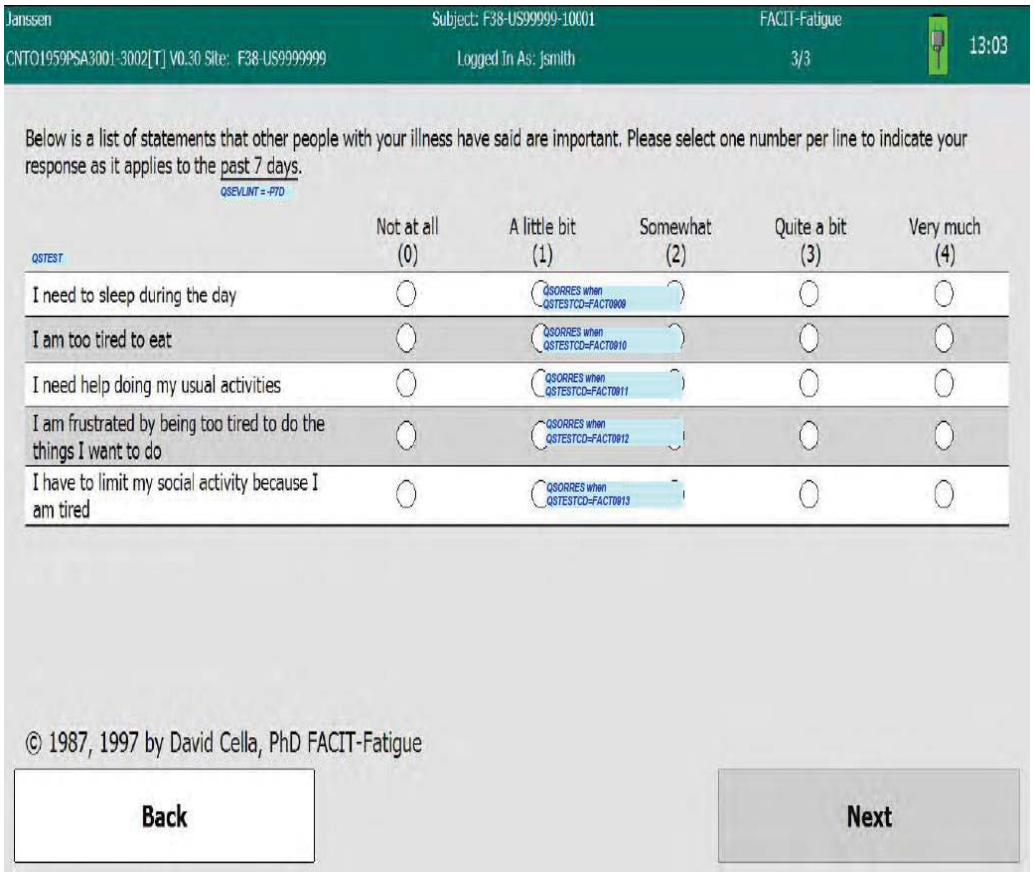


Attachment 2

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue






Janssen
Subject: F38-US99999-10001
FACIT-Fatigue
13:03
CNTO1959PSA3001-3002[T] V0.30 Site: F38-US9999999
Logged In As: jsmith
3/3
Below is a list of statements that other people with your illness have said are important. Please select one number per line to indicate your response as it applies to the past 7 days.
QSEVLINT = -P7D
QSTEST
Not at all (0)
A little bit (1)
Somewhat (2)
Quite a bit (3)
Very much (4)
I need to sleep during the day
QSORRES when QSTESTCD=FACT0909
I am too tired to eat
QSORRES when QSTESTCD=FACT0910
I need help doing my usual activities
QSORRES when QSTESTCD=FACT0911
I am frustrated by being too tired to do the things I want to do
QSORRES when QSTESTCD=FACT0912
I have to limit my social activity because I am tired
QSORRES when QSTESTCD=FACT0913
© 1987, 1997 by David Cella, PhD FACIT-Fatigue
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Attachment 3

Item-level analyses (Study 3001 and Study 3002)

AH_TEFFACIT01: Summary of the Improvement from Baseline in FACIT-Fatigue Questions at Week 24, Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Q1 - I feel fatigued[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.40 (1.063)	0.62 (1.284)	0.55 (0.833)
Median	0.00	1.00	1.00
Range	(-2.0; 3.0)	(-3.0; 4.0)	(-1.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q2 - I feel weak all over[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.36 (1.129)	0.69 (1.202)	0.60 (1.018)
Median	0.00	1.00	1.00
Range	(-2.0; 4.0)	(-2.0; 4.0)	(-2.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q3 - I feel listless[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.29 (1.148)	0.56 (1.229)	0.46 (1.060)
Median	0.00	0.00	0.00
Range	(-3.0; 4.0)	(-3.0; 4.0)	(-3.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q4 - I feel tired[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.28 (1.061)	0.63 (1.168)	0.48 (1.045)
Median	0.00	1.00	0.00
Range	(-2.0; 3.0)	(-2.0; 4.0)	(-2.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q5 - Trouble starting things, tired[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.20 (1.051)	0.33 (1.296)	0.56 (1.036)
Median	0.00	0.00	0.00
Range	(-3.0; 3.0)	(-3.0; 4.0)	(-2.0; 4.0)
IQ range	(-1.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q6 - Trouble finishing things, tired[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.20 (1.017)	0.41 (1.273)	0.46 (1.014)
Median	0.00	0.00	0.00
Range	(-2.0; 3.0)	(-3.0; 4.0)	(-2.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q7 - I have energy[a,b]			
Week 24			
N	118	123	127
Mean (SD)	0.09 (0.934)	0.24 (1.097)	0.50 (1.214)

AH_TEFFACIT01: Summary of the Improvement from Baseline in FACIT-Fatigue Questions at Week 24, Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Median	0.00	0.00	0.00
Range	(-3.0; 2.0)	(-4.0; 3.0)	(-3.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q8 - Able to do my usual activities[a,b]			
Week 24			
N	118	123	127
Mean (SD)	0.06 (1.040)	0.33 (1.178)	0.30 (1.115)
Median	0.00	0.00	0.00
Range	(-3.0; 4.0)	(-4.0; 3.0)	(-4.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q9 - I need to sleep during the day[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	-0.08 (1.047)	0.22 (1.060)	0.18 (0.955)
Median	0.00	0.00	0.00
Range	(-4.0; 2.0)	(-2.0; 3.0)	(-3.0; 2.0)
IQ range	(-1.00; 0.00)	(0.00; 1.00)	(0.00; 1.00)
Q10 - I am too tired to eat[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.06 (0.936)	0.15 (1.006)	0.13 (0.797)
Median	0.00	0.00	0.00
Range	(-3.0; 3.0)	(-2.0; 3.0)	(-3.0; 4.0)
IQ range	(0.00; 0.00)	(0.00; 0.00)	(0.00; 0.00)
Q11 - Need help doing usual activities[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.10 (0.999)	0.37 (0.926)	0.40 (0.809)
Median	0.00	0.00	0.00
Range	(-3.0; 3.0)	(-2.0; 3.0)	(-1.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q12 - Frustrated by being too tired[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.11 (1.259)	0.72 (1.156)	0.50 (1.097)
Median	0.00	0.00	0.00
Range	(-3.0; 4.0)	(-2.0; 4.0)	(-2.0; 4.0)
IQ range	(-1.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q13 - Limit social activity, tired[a,b,c]			
Week 24			
N	118	123	127
Mean (SD)	0.24 (1.084)	0.60 (1.129)	0.42 (0.859)
Median	0.00	0.00	0.00
Range	(-2.0; 4.0)	(-2.0; 4.0)	(-1.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)

AH_TEFFACIT01: Summary of the Improvement from Baseline in FACIT-Fatigue Questions at Week 24, Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)

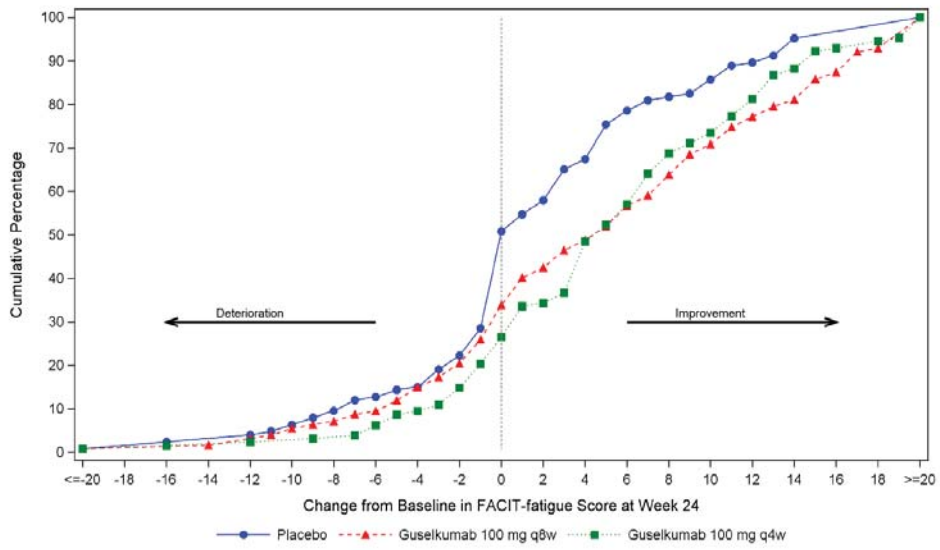
	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Analysis set: Full Analysis Set 1	246	248	245
Q1 - I feel fatigued[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.48 (1.039)	0.84 (1.118)	0.73 (1.001)
Median	0.00	1.00	1.00
Range	(-2.0; 4.0)	(-2.0; 4.0)	(-3.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.00)
Q2 - I feel weak all over[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.43 (1.065)	0.86 (1.145)	0.67 (1.013)
Median	0.00	1.00	1.00
Range	(-3.0; 4.0)	(-2.0; 4.0)	(-3.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.00)
Q3 - I feel listless[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.36 (1.148)	0.74 (1.241)	0.63 (0.990)
Median	0.00	1.00	1.00
Range	(-3.0; 4.0)	(-3.0; 4.0)	(-3.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.00)
Q4 - I feel tired[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.46 (1.039)	0.90 (1.183)	0.71 (0.993)
Median	0.00	1.00	1.00
Range	(-2.0; 4.0)	(-2.0; 4.0)	(-3.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.00)
Q5 - Trouble starting things, tired[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.45 (1.046)	0.71 (1.189)	0.65 (1.083)
Median	0.00	1.00	1.00
Range	(-2.0; 4.0)	(-3.0; 4.0)	(-2.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q6 - Trouble finishing things, tired[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.40 (1.131)	0.70 (1.144)	0.66 (1.067)
Median	0.00	0.00	1.00
Range	(-3.0; 4.0)	(-2.0; 4.0)	(-2.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q7 - I have energy[a,b]			
Week 24			
N	242	243	240
Mean (SD)	0.09 (1.097)	0.37 (1.176)	0.22 (1.249)

AH_TEFFACIT01: Summary of the Improvement from Baseline in FACIT-Fatigue Questions at Week 24, Based on the Treatment Policy Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)

	Placebo	Guselkumab 100 mg q8w	Guselkumab 100 mg q4w
Median	0.00	0.00	0.00
Range	(-4.0; 4.0)	(-4.0; 4.0)	(-4.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q8 - Able to do my usual activities[a,b]			
Week 24			
N	242	243	240
Mean (SD)	0.14 (1.104)	0.37 (1.183)	0.19 (1.265)
Median	0.00	0.00	0.00
Range	(-4.0; 4.0)	(-4.0; 4.0)	(-4.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q9 - I need to sleep during the day[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.13 (1.097)	0.34 (1.125)	0.29 (0.950)
Median	0.00	0.00	0.00
Range	(-4.0; 3.0)	(-3.0; 3.0)	(-3.0; 3.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q10 - I am too tired to eat[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.08 (0.916)	0.22 (0.949)	0.29 (0.790)
Median	0.00	0.00	0.00
Range	(-3.0; 2.0)	(-4.0; 3.0)	(-2.0; 3.0)
IQ range	(0.00; 0.00)	(0.00; 0.00)	(0.00; 1.00)
Q11 - Need help doing usual activities[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.17 (0.991)	0.42 (0.994)	0.45 (0.962)
Median	0.00	0.00	0.00
Range	(-3.0; 3.0)	(-3.0; 4.0)	(-4.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)
Q12 - Frustrated by being too tired[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.31 (1.137)	0.75 (1.256)	0.76 (1.202)
Median	0.00	0.00	1.00
Range	(-3.0; 3.0)	(-2.0; 4.0)	(-3.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 2.00)	(0.00; 1.50)
Q13 - Limit social activity, tired[a,b,c]			
Week 24			
N	242	243	240
Mean (SD)	0.25 (0.958)	0.77 (1.127)	0.71 (1.030)
Median	0.00	1.00	1.00
Range	(-2.0; 3.0)	(-2.0; 4.0)	(-2.0; 4.0)
IQ range	(0.00; 1.00)	(0.00; 1.00)	(0.00; 1.00)

Attachment 4
Empirical Cumulative Distribution Function curves
(Study 3001 and Study 3002)

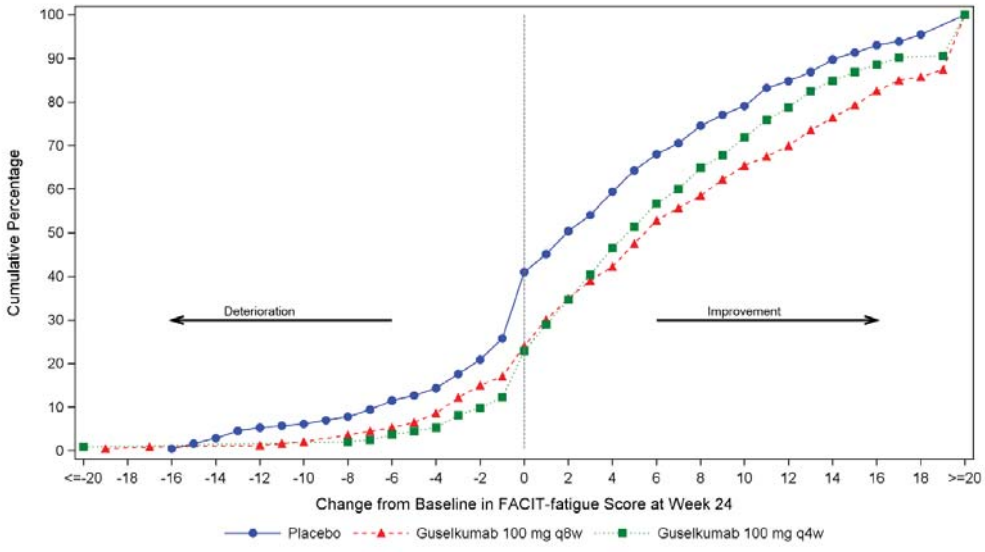
AH_GEFFACIT01: Cumulative Percent of Patients by Change from Baseline in FACIT-Fatigue Score at Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3001)



The FACIT-Fatigue scores can range from 0 to 52; a decrease in score indicates worsening in fatigue.

[AH_GEFFACIT01.RTF] [CNTO1959\PSA3001\DBR_WEEK_24\RE_WEEK_24\PROD\AH_GEFFACIT01.SAS] 13JUN2019, 14:01

AH_GEFFACIT01: Cumulative Percent of Patients by Change from Baseline in FACIT-Fatigue Score at Week 24 Based on the Composite Estimand; Full Analysis Set 1 (Study CNTO1959PSA3002)



The FACIT-Fatigue scores can range from 0 to 52; a decrease in score indicates worsening in fatigue.

[AH_GEFFACIT01.RTF] [CNTO1959\PSA3002\DBR_WEEK_24\RE_WEEK_24\PROD\AH_GEFFACIT01.SAS] 13JUN2019, 14:01

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 20, 2020

To: Sadaf Nabavian, Pharm.D., Senior Regulatory Project Manager
Division of Rheumatology and Transplant Medicine (DRTM)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for TREMFYA (guselkumab) injection, for subcutaneous use

BLA: 761061 / Supplement 007

In response to DRTM consult request dated November 27, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for TREMFYA (guselkumab) injection, for subcutaneous use. This supplement (S007) provides for the addition of active psoriatic arthritis indication to the labeling.

PI and Medication Guide: OPDP's review of the proposed labeling is based on the draft PI and Medication Guide received by electronic mail from DRTM (Sadaf Nabavian) on May 7, 2020, and are provided below. We do not have any comments on the proposed PI and Medication Guide.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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

PATIENT LABELING REVIEW

Date:	May 11, 2020
To:	Sadaf Nabavian, PharmD Senior Regulatory Project Manager **Division of Rheumatology and Transplant Medicine (DRTM)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted: Medication Guide (MG)
Drug Name (established name):	TREMFYA (guselkumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	sBLA 761061 S007
Applicant:	Janssen Biotech, Inc.

1 INTRODUCTION

On September 13, 2019, Janssen Biotech, Inc. submitted for the Agency's review a supplemental Biological License Application for TREMFYA (guselkumab) injection, for subcutaneous use. The purpose of the submission is to support the approval of TREMFYA for the treatment of adults with active psoriatic arthritis (PSA).

On November 27, 2020, the Division of Rheumatology and Transplant Medicine (DRTM) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed MG for TREMFYA (guselkumab) injection, for subcutaneous use.

This memorandum documents the DMPP review and concurrence with the Applicant's proposed MG for TREMFYA (guselkumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft TREMFYA (guselkumab) MG received on September 13, 2019, revised by the review division throughout the review cycle and received by DMPP on May 7, 2020.
- Draft TREMFYA (guselkumab) Prescribing Information (PI) received on September 13, 2019, revised by the Review Division throughout the review cycle and received by DMPP on May 7, 2020.

3 CONCLUSIONS

We find the Applicant's proposed MG is acceptable as submitted to DMPP.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	April 14, 2020
Requesting Office or Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Application Type and Number:	BLA 761061/S-007
Product Name, Dosage Form, and Strength:	Tremfya (guselkumab) injection, 100 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Janssen Biotech, Inc
FDA Received Date:	September 13, 2019
OSE RCM #:	2019-2438
DMEPA Safety Evaluator:	Sarah K. Vee, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Janssen Biotech submitted a Prior Approval Supplement (PAS) to BLA 761061/S-007 on September 13, 2019 for Agency review. The supplement is an efficacy supplement for a new indication for the treatment of adult patients with active psoriatic arthritis (PsA). We evaluated the proposed prescribing information for areas of vulnerability that could lead to medication errors.

2 REGULATORY HISTORY

Tremfya was approved on July 13, 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. A prefilled syringe (PFS) presentation was approved at the time of initial approval. In OSE Review #2016-2621 and 2016-2649[a] we reviewed human factors (HF) validation study results for the PFS. The study included 30 injection-naïve participants (n=15 Psoriasis or Crohn's patients and n=15 Caregivers) and 30 injection-experienced participants (n=15 Rheumatoid Arthritis (RA) patients and 15 healthcare providers (HCP)). We found the HF validation study results acceptable.

Consequently, the single-dose 100 mg/mL One-Press patient-controlled injector was approved on January 28, 2019 (S-001). In OSE Review #2018-703 and 2018-705[b] we reviewed HF validation study results for the One-Press patient-controlled injector. The Applicant submitted results from two HF validation studies. The first study was conducted with trained participants with RA, PsA, Ulcerative Colitis, Psoriasis or Crohn's disease, caregivers and/or HCPs. No use errors were reported.

Because the first HF validation study was conducted with all trained participants, we recommended that the Applicant conduct a supplemental HF study with untrained participants. The Applicant conducted a supplemental HF study with 33 untrained participants (17 patients with RA, PsA, Ulcerative Colitis, Psoriasis or Crohn's disease, 16 caregivers and/or HCPs). All study participants performed one unaided injection without receiving prior training. One incomplete injection use error was reported. We concluded that the design mitigations (tactile, visual, and audible cues and the Instructions for Use) to communicate to the user when the full dose has been administered are adequate and no further mitigations are required.

In the April 24, 2019 Type B Meeting Pre-sBLA[c] meeting preliminary comments, we stated that

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[a] Mena-Grillasca, C. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. OSE Review #2016-2621 and 2016-2649.

[b] Mena-Grillasca, C. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 31. OSE Review #2018-703 and 2018-705.

[c] Do, N-L. Meeting Preliminary Comments for guselkumab (IND 124177). Silver Spring (MD): FDA, CDER, OND, DPARP (US); 2019 APR 17.

"Given that the proposed products are the same as the products approved under BLA 761061 and the previously evaluated human factors validation studies included participants that are representative of the intended users for the proposed indications, we find your proposal to leverage human factors validation data reasonable.

It would also be reasonable to rely on the verification and validation data included in BLA 761061. We recommend that you provide an updated risk analysis to include any differences in risk given the new indication. A justification/discussion should also be included for why these specifications/acceptance criteria are appropriate for this intended user and patient populations."

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Regulatory Information for Prefilled Syringe And Selfdose One-Press Patient-Controlled Injector Devices	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant is proposing to use the currently marketed Tremfya PFS and One-Press patient-controlled injector devices for the proposed indication of adults with active PsA. The proposed recommended dose for PsA is 100 mg at Week 0, Week 4, and every 8 weeks (b) (4) (b) (4). The currently marketed products are available in a 100 mg strength.

The Applicant states, in the Regulatory Information (Appendix F) submitted to support the use of the PFS and One-Press patient-controlled injector, that they had (b) (4) (b) (4) The HF validation study results included representation of

the intended users for the proposed indication and we maintain that it is reasonable to leverage HF data previously submitted. Therefore, we find the Applicant's proposal to use the currently marketed products for the proposed PsA indication acceptable.

We note that there are no other changes to the proposed PI other than the addition of the proposed indication and related information.

5 CONCLUSION & RECOMMENDATIONS

We find the labeling acceptable from a medication error perspective and we do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tremfya received on September 13, 2019 from Janssen Biotech, Inc.

Table 2. Relevant Product Information for Tremfya	
Initial Approval Date	July 13, 2017
Proper Name	guselkumab
Indication	For the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Proposed: for the treatment of adult patients with active psoriatic arthritis
Route of Administration	Subcutaneous injection
Dosage Form	injection
Strength	100 mg/mL
Dose and Frequency	Plaque Psoriasis: The recommended dose is 100 mg at Week 0, Week 4, and every 8 weeks thereafter. Psoriatic Arthritis: The recommended dose is 100 mg at Week 0, Week 4, and every 8 weeks (b) (4). TREMFYA may be administered alone or in combination with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) (e.g., methotrexate).
How Supplied	• Single-dose 100 mg/mL prefilled syringe • Single-dose 100 mg/mL One-Press patient-controlled injector
Storage	• Store in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF). • 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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 27, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Tremfya. Our search identified six previous reviews and we confirmed that our previous recommendations were implemented.

Mena-Grillasca, C. Label, and Labeling Review for Tremfya (BLA 761061/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jan 15. RCM Nos.: 2018-703-1
Mena-Grillasca, C. Human Factors, Label, and Labeling Review for Tremfya (BLA 761061/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 31. RCM Nos.: 2018-703 and 2018-705
Patel, M, Label, and Labeling Review for Tremfya (BLA 761061/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 20. RCM No.: 2018-2042
Hoste, S. Human Factors Study Report Review for Tremfya (IND 105004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 May 30. RCM No.: 2018-418
Mena-Grillasca, C. Human Factors, Label, and Labeling Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 May 12. RCM Nos.: 2016-2621 and 2016-2649
Mena-Grillasca, C. Human Factors Protocol Review for Guselkumab (IND 105004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Apr 10. RCM Nos.: 2013-2859 and 2014-400

APPENDIX F. REGULATORY INFORMATION FOR PREFILLED SYRINGE AND SELFDOSE ONE-PRESS PATIENT-CONTROLLED INJECTOR DEVICES

Information available from **\\CDSESUB1\evsprod\BLA761061\0096**

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Tremfya labeling submitted by Janssen Biotech, Inc.

- Prescribing Information (Image not shown) received on September 13, 2019, available from **\\CDSESUB1\evsprod\BLA761061\0096**

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SARAH K VEE
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Clinical Inspection Summary

Date	March 23, 2020
From	Tina Chang, M.D., Reviewer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sadaf Nabavian, PharmD, RPM, DPARP Nadia Habal, M.D., Clinical Reviewer Rachel Glaser, M.D., Clinical Team Leader Division of Pulmonary, Allergy, and Rheumatology Products
NDA/BLA #	761061/S-007
Applicant	Janssen Biotech, Inc.
Drug	TREMFYA (guselkumab)
NME (Yes/No)	No
Therapeutic Classification	Recombinant human immunoglobulin G1 lambda monoclonal antibody that bind to interleukin-23
Proposed Indication(s)	Treatment of adult patients with active psoriatic arthritis (PSA).
Consultation Request Date	October 24, 2019
Summary Goal Date	June 12, 2020
Action Goal Date	July 13, 2020
PDUFA Date	July 13, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Akgun, Korgulec, and Wiland) were selected for inspection for two Phase 3 studies (Studies CNTO1959PSA3001 and CNTO1959PSA3002).

Based on the results of these inspections, the data generated by these clinical investigators sites submitted by the Sponsor appear acceptable and in support of this BLA.

II. BACKGROUND

Janssen Biotech, Inc. submitted an efficacy supplement to BLA 761061 to propose a new indication for the use of guselkumab alone, or in combination with a conventional synthetic disease-modifying antirheumatic drug (e.g., methotrexate) to expand the indication to treatment of adults with active psoriatic arthritis (PsA) with a proposed dosing regimen

previously approved for plaque psoriasis, 100 mg subcutaneous (SC) at Week 0, Week 4, and every 8 weeks thereafter. (b) (4) [redacted]

Guselkumab is a fully human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 protein subunit of human interleukin-23 (IL-23) and blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 mediated intracellular signaling.

Two Phase 3 studies, CNTO1959PSA3001 and CNTO1959PSA3002, will be evaluated to support the new proposed indication.

Study CNTO1959PSA3001

Study Title: "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis Including Those Previously Treated with Biologic Anti-TNFα Agent(s)

This was a Phase 3 multi-center, randomized, double-blind, placebo-controlled, 3-arm study in adults with active Psoriatic Arthritis (PsA) to evaluate the efficacy of guselkumab treatment in subjects with PsA by assessing the reduction in signs and symptoms of PsA. Subjects were randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:

- Group I: guselkumab SC 100 mg every 4 weeks (q4w) from Week 0 through Week 48.
- Group II: guselkumab SC 100 mg at Weeks 0 and 4, then every 8 weeks (q8w; Weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, and 48) to maintain the blind.
- Group III: placebo SC q4w from Week 0 to Week 20 and crossed over at Week 24 to receive guselkumab 100 mg q4w through Week 48.

The primary efficacy endpoint was the proportion of subjects who achieve an ACR 20 response at Week 24. ACR 20 response is defined as:

1. ≥20% improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),
   AND
2. ≥20% improvement from baseline in 3 of the following 5 assessments:
   - Patient's assessment of pain Visual Analogue Scale (VAS)
   - Patient's Global Assessment of Disease Activity (arthritis, VAS)
   - Physician's Global Assessment of Disease Activity (VAS)
   - Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
   - C-reactive protein (CRP)

A greater proportion of subjects in both the guselkumab 100 mg q4w and guselkumab 100 mg q8w groups (59.4% and 52.0%, respectively) achieved an ACR 20 response at Week 24 compared with subjects in the placebo group (22.2%).

The first patient was enrolled on 28 August 2017 and the last patient completed the study on 14 March 2019. A total of 382 patients were enrolled in 86 clinical sites in 13 countries: Australia (n=6), Malaysia (n=5), Republic of Korea (n=2), Taiwan (n=7), Czech Republic (n=5), Germany (n=5), Hungary (n=5), Poland (n=11), Russia (n=10), Spain (n=7), Ukraine (n=10), Canada (n=6), and United States (n=7).

Study CNTO1959PSA3002

Study Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis

This was a Phase 3 multi-center, randomized, double-blind, placebo-controlled, 3-arm study in adults with active Psoriatic Arthritis Subjects were randomly assigned to 1 of the following 3 treatment groups in a 1:1:1 ratio:

- Group I: Guselkumab 100 mg SC every 4 weeks (q4w) from Week 0 through Week 100.
- Group II: Guselkumab 100 mg SC at Weeks 0 and 4 then every 8 weeks (q8w; Weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (Weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind.
- Group III: Placebo SC q4w from Week 0 to Week 20 and cross over at Week 24 to receive guselkumab 100 mg SC q4w from Week 24 through Week 100.

The primary efficacy endpoint was the proportion of subjects who achieve an ACR 20 response at Week 24. ACR 20 response is defined as:

1. ≥20% improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),
   AND
2. ≥20% improvement from baseline in 3 of the following 5 assessments:
   - Patient's assessment of pain Visual Analogue Scale (VAS)
   - Patient's Global Assessment of Disease Activity (arthritis, VAS)
   - Physician's Global Assessment of Disease Activity (VAS)
   - Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI)
   - C-reactive protein (CRP)

A greater proportion of subjects in both the guselkumab 100 mg q4w and guselkumab 100 mg q8w groups (63.7% and 64.1%, respectively) achieved an ACR 20 response at Week 24

compared with subjects in the placebo group (32.9%).

The first patient was enrolled on 13 July 2017 and the date of the last observation for last subject recorded as part of the database for interim analysis was 6 March 2019. A total of 739 subjects were enrolled in 118 clinical sites in 13 countries: Malaysia (n=5), Taiwan (n=1), Bulgaria (n=7), Czech Republic (n=7), Estonia (n=4), Latvia (n=3), Lithuania (n=4), Poland (n=15), Russia (n=25), Spain (n=9), Turkey (n=8), Ukraine (n=28), and United States (n=2).

Rationale for Site Selection

Three clinical investigator sites were selected for clinical inspections: Dr. Ince Akgun (Site #US10005) for being an investigator in both phase 3 studies; Dr. Marek Krogulec (Site# PL 10013) for Study CNTO1959PSA3002 due to high enrollment and high response rate; and Dr. Wiland Piotr (Site# PL10010 for Study CNTO1959PSA3001 and Site# PL10016 for Study CNTO1959PSA3002) for being a clinical investigator in both phase 3 studies and high enrollment.

III. RESULTS (by site):

1. **Dr. Ince Akgun, Site # US10005 (522 N New Ballas Rd Ste 240, Saint Louis, MO, 63141-6819); Inspection dates: 12/9/2019 – 12/11/2019.**

   For Protocol CNTO1959PSA3001, one subject was screened, enrolled and completed the 24 Weeks Placebo-Controlled Treatment Phase of the Study.

   For Protocol CNTO1959PSA3002, this site screened 7 subjects and enrolled 5 subjects. All 5 subjects completed the 24 Weeks Placebo-Controlled Treatment Phase of the Study. These 5 subject records were comprehensively reviewed.

   The inspection evaluated the following documents: both protocols, IRB approvals, informed consent forms, subject medical records, financial disclosure reports, case report forms, subject questionnaires, drug accountability records, site signature and responsibility logs, and site training documentation.

   All subjects' records were reviewed for eligibility, protocol adherence, adverse event reporting and test article accountability. All subject records were reviewed to verify informed consent was obtained according to regulations.

   Source documents for the raw data used to assess the primary endpoint was verifiable at the study site. No under-reporting of adverse events was noted.

   This clinical site appeared to be in compliance with Good Clinical Practices. No Form FDA 483 was issued and there were no issues discussed with Dr. Ince at the conclusion of

the inspection. Data submitted by this clinical site appear acceptable in support of the proposed indication.

2. **Dr. Marek Krogulec, Site #PL10013 (Nzoz Lecnica Mak-Med S.C., U1., Wisiniowa 22, Nadarzyn, Mazowieckie, Poland); Inspection dates: 1/20/2020 - 1/23/2020.**

   For Protocol CNTO1959PSA3002, this site screened 14 subjects and enrolled 11 subjects. All 11 subjects completed the study. All 11 subject records were comprehensively reviewed during this inspection.

   The inspection evaluated the following: Ethics committee oversight, informed consent, eligibility, protocol adherence, concomitant medications, adverse events and test article accountability.

   Source documents for the raw data used to assess the primary endpoint was verifiable at the study site. No under-reporting of adverse events was noted.

   At the conclusion of the inspection, the following item was discussed with the clinical investigator at the close-out meeting:

   - The protocol states that a woman of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at Week 0. Although Subject (b) (6) had the required pregnancy test at Screening, this subject did not have the required pregnancy test at Week 0 prior to the first treatment dose. According to the source notes, the pregnancy test was not performed by error, and the subject did not have a urine pregnancy test until Week 4. The site held a meeting for the research team discussing this event. The clinical team believed that since the subject had been experiencing amenorrhea for several months prior to enrollment that she may have been pre-menopausal. It was emphasized to the clinical team, the necessity for performing pregnancy test for all patients with childbearing potential. Dr. Krogulec stated that he will be certain to complete all required pregnancy tests for subjects in future trials or have documentation that the subject is menopausal/post-menopausal.

   Reviewer's comment: This is an isolated incident with acceptable corrective active taken and appeared not to have an impact on safety or efficacy data.

   In general, this clinical site appeared to be in compliance with Good Clinical Practices except the single item described above that was discussed with the investigator at the close-out meeting. No Form FDA-483 was issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

3. **Dr. Piotr Wiland, Site# PL10010 for study PSA3001 and Site# PL10016 for study PSA3002 (Biogene, P1. Bzowy 1, Wroclaw, Dolnoslaskie, Poland); Inspection dates: 1/27 - 1/31/2020.**

For Protocol CNTO1959PSA3001, this site screened 18 subjects and enrolled 13 subjects. All 13 subjects completed the 24 Weeks Placebo-Controlled Treatment Phase of the Study. These 13 subject records were comprehensively reviewed.

For Protocol CNTO1959PSA3002, this site screened 17 subjects and enrolled 14 subjects. All 14 completed the study through week 24. These 14 subject records were comprehensively reviewed.

The inspection evaluated the following: Ethics committee oversight, informed consent, eligibility, protocol adherence, concomitant medications, adverse events and test article accountability.

There was no under-reporting of adverse events in the study. The raw data for the primary efficacy endpoint was verifiable.

At the end of the inspection, a Form FDA-483 was issued to Dr. Wiland for the following two items pertaining to Protocol CNTO1959PSA3002:

1. Failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation.

   Specifically,

   - Source documentation for several visits for the Physicians Global Assessment of Diseases (GAD) Activity is missing for five study subjects. There was no record of the assessments as direct-entry into the ePro Tablet electronic device or paper format in the Subject Binder for Week 2 for Subjects (b) (6), (b) (6), (b) (6), Week 12 for Subject (b) (6), and Week 20 for Subject (b) (6). Dr. Wiland responded in writing that per the protocol for source documentation that the Physician GAD assessments should be recorded directly into the electronic device and will be considered source data. The data collected would then be wirelessly transferred to the vendor's Study Works Portal.

   Reviewer's comment: The omission of data for the Physicians GAD Activity for Week 2 for Subjects (b) (6), (b) (6), (b) (6), Week 12 for Subject (b) (6), and Week 20 for Subject (b) (6) was due to human error. The investigator failed to record the data in the ePRO Tablet, and the data did not get transmitted to the vendor. The majority of these errors occurred relatively early in the study (e.g., Week 2). Dr. Wiland promised to improve the documentation process into the required electronic tablet. As a corrective action, Dr. Wiland stated that he will continue to re-train all delegated site staff to ensure appropriate direct-entry into the ePRO Tablet and how to check completion status of each assessment to confirm all are completed. If the assessment cannot be completed, the issue will be reported to the vendor Helpdesk and the Janssen representative will be notified about the situation and described in the subject's medical records. Appropriate corrective action was taken. The investigator's planned corrective actions in his written response on February 18, 2020 to this observation are considered appropriate and acceptable.

2. Investigational drug disposition records are not adequate with respect to dates and use by subjects.

   Specifically,

   - The Clinical Investigator signed Packing Lists and Drug Shipment Receipts that demonstrate the study site received 410 Kits of the investigational product (guselkumab 100 mg/placebo) from the sponsor between September 2017 and July 2019. The signed Investigational Product Destruction Forms show the return of only 361 kits for destruction. As of 27 January 2020, the Clinical Investigator only had seven unused kits in his research drug storage refrigerator that were available for dispensing. No documentation was available for the final disposition of the 42 unused kits of investigational products. The clinical research team identified an error with the Interactive Web Response System (IWRS). When/if a Study Nurse entered a dispensed drug as "damaged", the IWRS will automatically issue a new investigational product in the system as a replacement.

   Reviewer's comment: Dr. Wiland responded in writing on February 18, 2020 and stated that the 42 kits were in "damaged" status in IWRS but did not appear on the Investigational Product Destruction Form generated by IWRS. He states the problem with documenting the status of 42 kits appears to be an error with not effectively following the process for IP reconciliation. According to Dr. Wiland, the damaged kits were sent to Geminus in June 2019 for destruction. As a corrective action, the site staff will be retrained by Dr. Wiland in effectively following the process of investigational product reconciliation. In this reviewer's opinion, the Clinical Investigator's written response is acceptable.

In general, this clinical site appeared to be in compliance with Good Clinical Practices except for the observations described above. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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/

SUYOUNG T CHANG
03/23/2020 10:19:22 AM

MIN LU
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