**BLA Multi-Disciplinary Review and Evaluation**

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| **Application Type** | Supplement |
| **Application Number(s)** | BLA 7610161/S-028 |
| **Priority or Standard** | Priority |
| **Submit Date(s)** | November 27, 2024 |
| **Received Date(s)** | November 27, 2024 |
| **PDUFA Goal Date** | September 27, 2025 |
| **Division/Office** | DDD/OII |
| **Review Completion Date** | September |
| **Established/Proper Name** | Tremfya |
| **(Proposed) Trade Name** | guselkumab |
| **Pharmacologic Class** | Interleukin-23 antagonist |
| **Code name** | CNTO 1959 |
| **Applicant** | Janssen |
| **Dosage form** | Solution for injection |
| **Applicant proposed Dosing Regimen** | Plaque Psoriasis: 100 mg SC at Weeks 0, 4, and q8wks thereafter |
| **Applicant Proposed Indication(s)/Population(s)** | for the treatment of patients 6 years of age and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | 200965009 (plaque psoriasis) |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | for the treatment of adult and pediatric patients 6 years of age and older who also weigh ≥ 40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | 200965009 (plaque psoriasis) |
| **Recommended Dosing Regimen** | Same as approved dosing regimens |

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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
DRISK=Division of Risk Management
DMPP =Division of Medical Policy Programs

## Signatures

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Clinical Pharmacology Reviewer | Rakesh Gollen, Ph.D. | ODP/DIIP | Section: 6 and 19.4.1 | **Select one:**<br>__X_ Authored<br>___ Approved |
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| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
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## Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDS | Clinical Data Science |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DHOT | Division of Hematology Oncology Toxicology |
| DMC | data monitoring committee |
| DRTM | Division of Rheumatology and Transplant Medicine |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Conference on Harmonisation |
| IGA | Investigator's Global Assessment |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

The Applicant, Janssen Biotech, Inc., submitted a supplemental Biologics License Application for BLA 76061 (sBLA-028) to support the following change to the proposed indication for guselkumab:

> TREMFYA is an interleukin-23 antagonist indicated for the treatment of patients 6 years of age and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

TREMFYA (guselkumab) injection, for subcutaneous use is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of human 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.

On July 13, 2017, the FDA approved guselkumab for the treatment adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The approved dosing regimen for adults with plaque psoriasis is 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. At the time of initial approval, the following postmarketing requirement was issued under the Pediatric Research Equity Act (PREA):

> 3225-1 Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 years to less than 18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

The Applicant conducted Trial CNTO1959PSO3011 (PROTOSTAR, also referred to as Trial 3011) to address the required pediatric assessment under PREA. The data in pediatric subjects with moderate to severe plaque psoriasis (PsO) was intended to support an expansion of the indication to include pediatric patients ages 6 to 17 years old. However, the review team identified deficiencies (b) (4)

In response to Agency concerns, the Applicant (b) (4) amended the sBLA to propose administration of guselkumab to pediatric patients 6 years of age and older who also weigh at least 40 kg by a

healthcare provider or by a caregiver using pre-filled syringe (PFS), One-Press injector or the prefilled pen.

Currently, TREMFYA is also approved for the treatment of adult patients with active psoriatic arthritis (approved July 13, 2020), the treatment of adult patients with moderately to severely active ulcerative colitis (approved September 11, 2024) and the treatment of adult patients with moderately to severely active Crohn's disease (approved March 20, 2025). Supplement -029 which is under review by Division of Rheumatology and Transplant Medicine [DRTM]) provides for the expansion of the patient population to include pediatric patients ages 6 years and older with active psoriatic arthritis. To address this pediatric assessment under PREA, DRTM agreed to full extrapolation. The safety of guselkumab in pediatric patients with psoriatic arthritis is supported by safety data in the relevant population of pediatric subjects with psoriasis from Trial CNTO1959PSO3011; the efficacy is extrapolated from the adult population with psoriatic arthritis based on a pharmacokinetic (PK) exposure matching approach.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from one adequate and well-controlled clinical Trial CNTO1959PSO3011 which provided substantial evidence of the effectiveness of guselkumab for the treatment of moderate to severe PsO in pediatric patients 6 years of age and older who also weigh ≥ 40 kg. Part 1 of Trial 3011 evaluated the efficacy, safety, and pharmacokinetics (PK) of guselkumab in pediatric subjects during a 16-week randomized, placebo- and active-controlled (etanercept) period followed by an uncontrolled period of continued treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. No formal comparison between etanercept and guselkumab was performed as specified in the statistical analysis plan.

<u>The Co-Primary Efficacy Endpoints were:</u>

- Proportion of subjects achieving an Investigator's Global Assessment (IGA) score of 0 (cleared) or 1 (minimal) at Week 16.
- Proportion of subjects with a Psoriasis Area and Severity Index (PASI 90) response (defined as subjects who achieved at least 90% reduction in the PASI composite score from baseline) at Week 16.

In this trial, guselkumab was statistically superior to placebo on both co-primary efficacy endpoints (p-values ≤ 0.003). A total of 65.9% of subjects in the guselkumab group achieved an IGA score of 0 (cleared) or 1 (minimal) compared to 16.0% in the placebo group at Week 16. While 56.1% of subjects in the guselkumab group achieved a PASI 90 response compared to 16.0% in the placebo group at Week 16. The Applicant has demonstrated that guselkumab is effective for its intended use in the target population and has met the evidentiary standard to support approval.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL23) and inhibits its interaction with the IL23 receptor. IL23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines. Guselkumab was approved for marketing under the trade name TREMFYA® on July 13, 2017. The approved dosage of TREMFYA® (guselkumab) injection for the treatment of moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in adults is 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter.

The Applicant submitted a supplemental Biologics License Application (sBLA 761061 S-028) to support the use of guselkumab in a new patient population. The proposed indication is for the treatment of adult and pediatric patients 6 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy. Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution (Feldman 2015). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The presentation of psoriasis in the pediatric population can be different than adults. Face and scalp involvement are common in children. Scalp psoriasis may be the initial presentation of chronic plaque psoriasis in this age group (Blauvelt and Ehst 2015).

FDA approved treatment options for pediatric patients with moderate to severe disease or when psoriasis is refractory to topical therapy, progressive or associated with arthritis, include: TNF-alpha inhibitors (etanercept approved 2016 for ≥4 years); IL-12 and IL-23 inhibitors (ustekinumab approved 2022 for ≥6 years); IL-17A inhibitors (ixekizumab approved 2020 for ≥6 years and secukinumab approved 2021 for ≥6 years); and PDE4 inhibitors (apremilast approved 2024 for ≥6 years.)

The Applicant submitted data from one adequate and well-controlled trial (CNTO1959PSO3011) that was conducted in 120 subjects ≥6 to <18 years of age. Enrolled subjects had a diagnosis of chronic plaque-type psoriasis for at least 6 months (with or without psoriatic arthritis), prior to first administration of study intervention, defined as IGA score ≥3 (moderate), PASI score ≥12, ≥10% body surface area (BSA) involvement and at least one of the following [very thick lesions, clinically relevant facial, genital, or hand/ foot involvement, PASI ≥20, >20% BSA involvement or IGA=4 (severe)]).

Part 1 of the trial was divided into Part 1a (≥12 to <18 years of age [i.e., adolescents]) and Part 1b (≥6 to <12 years of age). Part 1a was designed to enrolled and randomize at least 60 subjects in a 2:1:1 ratio to receive either guselkumab (n=30), placebo (n=15), or etanercept (n=15). Part 1b was designed to enrolled and randomize at least 30 subjects in a 1:1:1 ratio to receive either guselkumab (n=10), placebo (n=10), or etanercept (n=10). The protocol specified stratifying the randomization by age group (6 to <12 years and 12 to <18 years) and pooled region (North America [NA], Europe [EU]).

The protocol specified co-primary efficacy endpoints were:

- Proportion of subjects achieving an IGA score of 0 (cleared) or 1 (minimal) at Week 16.
- Proportion of subjects with a PASI 90 response (defined as subjects who achieved at least 90% reduction in the PASI composite score from baseline) at Week 16.

The protocol specified secondary efficacy endpoints (controlled for multiplicity) were:

- Proportion of subjects achieving a PASI 75 response at Week 16.
- Proportion of subjects achieving an IGA score of 0 (cleared) at Week 16.
- Proportion of subjects achieving a PASI 100 response at Week 16.
- Change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16

Guselkumab was statistically superior to placebo on both co-primary efficacy endpoints (p-values ≤ 0.003) and all key secondary efficacy endpoints (p-values ≤ 0.002) in Trial CNTO1959PSO3011.

Analysis of the data in this submission identified no new safety signals in the pediatric population who received guselkumab. There were no deaths in Trial CNTO1959PSO3011. Three subjects who received guselkumab developed SAEs. In Part 1, two SAEs were reported among subjects who received guselkumab (2.9%) and none in subjects who received placebo (0%) or etanercept (0%). One SAE occurred during the controlled, double-blind period (fracture); one SAE occurred during the maintenance period in a subject originally randomized to placebo (tonsillitis.) One SAE occurred in the open-label Part 2 (1.4%, fall with fracture/injuries). The review team assessed all SAEs as not related to guselkumab except the adverse event of tonsillitis. Based on the mechanism of action as an immunosuppressive agent, a role for guselkumab in the exacerbation of chronic tonsillitis could not be excluded. There were no SAEs or adverse reactions related to suicidal ideation and behavior, hypersensitivity, malignancy or serious infection including tuberculosis. There were 2 adverse events (AEs) leading to discontinuation (1 subject from Part 1 due to pregnancy, 1 subject from Part 2 due to suicidal ideation deemed to be mild and doubtful in relationship to guselkumab)

The most common adverse reactions were upper respiratory infections (26.8%), headache (7.3%), injection site reactions (2.4%). These AR are

already included in Section 6 (Adverse Reactions) of guselkumab labeling. Despite the limited safety database in the pediatric population, the distribution of adverse event terms was similar to those observed in adults and included in current labeling.

The available safety and efficacy data support the approval of TREMFYA® (guselkumab) injection for use in adults and pediatric patients 6 years of age and older who also weigh ≥40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy. There are limited FDA approved treatment options for this indication in children and none provides a cure or universal response. Because treatment may be complicated by inadequate response, loss of response, and adverse reactions, there is a need for additional therapeutic options. (b) (4) the Applicant will be required to propose and/or develop a new device for the administration of guselkumab to pediatric patients who weigh 40 kg or less to fulfill PMR 3225-1.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the U.S. is approximately 4.6 %, of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Psoriasis affects approximately 0.5% to 2% of the pediatric population (Firek, 2025). Comorbidities that have been reported to be potentially associated with psoriasis include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome. | Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and potential for associated comorbidities. |
| Current Treatment Options | • FDA approved drugs for the treatment of moderate to severe psoriasis in children include TNF-alpha inhibitors (etanercept approved 2016 for ≥4 years); IL-12 and IL-23 inhibitors (ustekinumab approved 2022 for ≥6 years); IL-17A inhibitors (ixekizumab approved 2020 for ≥6 years and secukinumab approved 2021 for ≥6 years); and PDE4 inhibitors (apremilast approved 2024 for ≥6 years.)<br>• Other treatment options include phototherapy with either PUVA (UVA | Therapeutic options are expanding for pediatric patients with psoriasis. There are FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults and children. However, none of these treatments provides a permanent cure or universal response, and all these |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | light combined with methoxsalen) or UVB light (narrow or broadband).<br>• All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. Systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product. | products are associated with one or more serious risks.<br>Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options for adults and children. |
| Benefit | • Data from Trial CNTO1959PSO3011 provided substantial evidence of the effectiveness of guselkumab for the treatment of moderate to severe plaque psoriasis in pediatric subjects who are candidates for systemic therapy or phototherapy. Enrolled subjects had an IGA score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a PASI≥12, and a minimum affected BSA of ≥10%, and at least one of the following: 1) very thick lesions, 2) clinically relevant facial, genital, or hand/foot involvement, 3) PASI ≥20, 4) BSA >20% or 5) IGA=4 ("severe"). Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.<br>• A total of 92 subjects were randomized to receive subcutaneous injection of either TREMFYA (N=41) or placebo (N=25) at Weeks 0, 4, and 12 or an active biological comparator (N=26). An additional 28 subjects enrolled in a TREMFYA open-label arm. In the TREMFYA group, subjects with a body weight less than 70 kg received 1.3 mg/kg TREMFYA and subjects with a body weight of 70 kg or more | The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive.<br><br>Efficacy was demonstrated on clinically meaningful endpoints. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | received 100 mg TREMFYA.<br>• Efficacy was assessed at Week 16 on two coprimary efficacy endpoints:<br>○ the proportion of subjects who achieved an IGA score of 0 ("cleared") or 1 ("minimal").<br>○ the proportion of subjects who achieved a PASI 90 response.<br>• Most subjects were White (85%), male (55%) with a mean body weight of 57.3 kg, a mean age of 12.9 years and a third of the subjects were less than 12 years old.<br>• At baseline, subjects had a median affected BSA of 20%, a median PASI score of 17, and 3% had a history of psoriatic arthritis. Approximately 22% of subjects had an IGA score of 4 ("severe"). Prior phototherapy or prior conventional systemic therapy was received by 32% of subjects and prior biologic systemic therapy was received by 10% of subjects.<br>• 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 (66% and 56%, respectively) than in the placebo group (16% 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 (39% vs. 4%). The proportion of subjects who achieved a PASI 100 response at Week 16 was higher in the guselkumab group compared to the placebo group (34% vs. 0%). | |
| Risk and Risk Management | • Trial CNTO1959PSO3011 enrolled a total of 120 pediatric subjects with moderate to severe psoriasis. The overall exposure to guselkumab in the phase 3 development program included 114 pediatric subjects. | The overall safety database was sufficient to characterize the safety of guselkumab for the treatment of moderate to severe plaque psoriasis in pediatric subjects ages 6 to < 18 |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • There were no deaths. A total of 3 subjects developed serious adverse events (2 SAEs of fracture in two subjects in the guselkumab group and 1 SAE of tonsillitis in one subject in the placebo to guselkumab group). There were 2 discontinuations due to adverse events in 2 subjects (pregnancy and suicidal ideation).<br>• The most common TEAEs in the guselkumab group by pooled term during the double-blind period through Week 16 and with greater frequency than placebo were headache (7.3% vs 0%) and injection site reaction (4.8% vs 4.0%).<br>• The Applicant reported 1 pregnancy in the development program for moderate to severe psoriasis in the pediatric population. The pregnancy resulted in a live birth of a heathy infant, with no congenital anomalies or major maternal complications.<br>• The review identified no new safety signals. | years old who are candidates for systemic therapy or phototherapy. The data are sufficient to characterize the safety profile of guselkumab in the target pediatric population.<br><br>Prescription labeling, Medication Guide, Instructions for Use, and routine pharmacovigilance activities are adequate to manage the risks of the product.<br><br>To fulfill PMR 3225-1, the FDA granted a deferral extension request to develop/propose a device for administration of guselkumab to pediatric patients 6 years of age and older who also weigh less than 40 kg. |

## 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 |
| | □ | Clinical outcome assessment (COA) data, such as | | |
| | | X | Patient reported outcome (PRO) | See section 8.1.2.7 |
| | | □ | Observer reported outcome (ObsRO) | |
| | | X | Clinician reported outcome (ClinRO) | See section 8.1 |
| | | □ | 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): | | |
| X | **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 | | |
| | X | Patient-focused drug development or other stakeholder meeting summary reports | | See section 2.1 |
| | □ | 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**

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution (Feldman 2015). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines that trigger and perpetuate the inflammatory cascade (Blauvelt and Ehst 2015).

In the United States and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively (Blauvelt and Ehst 2015). It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80% of those affected by psoriasis have mild-to-moderate disease, and 20% have moderate-to-severe psoriasis affecting more than 5% of the body surface area (BSA). The most common form of psoriasis is plaque psoriasis, affecting about 80% to 90% of patients with psoriasis (Menter et al. 2008).

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20 to 30 years of age and a second peak at 50 to 60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35% to 50%, it is before the age of 20 years. The age of onset is earlier in women than in men (Blauvelt and Ehst 2015). Psoriasis affects approximately 0.5% to 2% of the pediatric population (Firek, 2025).

The natural history of psoriasis is chronic with intermittent remissions. Plaque psoriasis is the most common presentation; other forms include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history taking and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions (Blauvelt and Ehst 2015).

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often involves the diaper area with symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than are adults (Blauvelt and Ehst 2015).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes,

hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders (Korman 2017).

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social, and emotional effects, including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient-Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as children and pregnant women.

## 2.2. Analysis of Current Treatment Options

FDA approved treatment for psoriasis in children includes both topical and systemic therapies. Therapeutic options are expanding for pediatric patients with psoriasis. Early diagnosis and personalized treatment strategies are critical for mitigating the impacts on children. For mild-to-moderate disease, initial treatment includes the use of topical therapies such as corticosteroids, calcineurin inhibitors, phosphodiesterase inhibitors and vitamin D analogues or phototherapy (Firek, 2025).

For pediatric patients with moderate to severe disease or when psoriasis is refractory to topical therapy, progressive or associated with arthritis, systemic therapy is indicated (2020 guidelines-Joint American Academy of Dermatology-National Psoriasis Foundation.) Such agents include: TNF-alpha inhibitors (etanercept approved 2016 for ≥4 years); IL-12 and IL-23 inhibitors (ustekinumab approved 2022 for ≥6 years); IL-17A inhibitors (ixekizumab approved 2020 for ≥6 years and secukinumab approved 2021 for ≥6 years); and PDE4 inhibitors (apremilast approved 2024 for ≥6 years.) Other biologic products and small molecules (e.g., tyrosine kinase 2 inhibitors) are under development for use in the pediatric population.

Some key systemic therapies that are FDA approved for the treatment of moderate to severe plaque psoriasis are described in the table below. (This tabulation is not exhaustive).

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| Antimetabolite/ Immuno-suppressant | Methotrexate 1972 | Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; but only when diagnosis established by biopsy and/or dermatologic consultation. Must rule out undiagnosed concomitant disease affecting immune responses | Starting dose schedules:<br>1. Weekly single oral, IM or IV dose: 10 to 25 mg per week until adequate response is achieved<br>2. Divided oral dose: 2.5 mg at 12 hr intervals for three doses<br>30 mg/week should not ordinarily be exceeded | No efficacy information for psoriasis in labeling | BW: potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis" | Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphopro-liferative disorders<br>Recommend periodic liver biopsy if tx long-term<br>Pregnancy: X |
| Tumor Necrosis Factor Inhibitor | Infliximab (Remicade) 2006 | Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate | 5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks | From labeling: 3 R, DB, PC trials PASI 75 at week 10<br>1. Inflix (5 mg/kg)-80% vs. 3% placebo<br>2. Inflix (5 mg/kg)-75% vs. 2% placebo<br>3. Inflix (5 mg/kg)-88% vs. Inflix (3 mg/kg) 72% vs. 6% placebo | BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including hepatosplenic T-cell lymphomas (adolescents and young adults)<br>Warnings: Hepatitis B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy | Pregnancy: B |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| Tumor Necrosis Factor Inhibitor | Adalimumab (Humira) 2008 | Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy | 80 mg via SC initial dose, followed by 40 mg SC every other week starting 1 week after initial dose | From labeling: 2 R, DB, PC trials PASI 75 at Week 16<br>1. Ada-71% vs. 7% placebo<br>2. Ada-78% vs. 19% placebo | BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma<br>Warnings: hypersensitivity reactions, hepatitis B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome | Pregnancy: B |
| Tumor Necrosis Factor Inhibitor | Etanercept (Enbrel) 2004; 2016 | Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy; 11/2016–approved for patients 4 years of age and older | 50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly. | From labeling: 2 R, DB, PC trials PASI 75 at 3 months<br>1. Etan-47% vs. 4% placebo<br>2. Etan-46% vs. 3% placebo | BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies<br>Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, hepatitis B reactivation | Pregnancy: B |
| IL-12 and IL-23 Blocker | Ustekinumab (Stelara) 2009 | Moderate to severe psoriasis, candidates for phototherapy or systemic therapy | Patients weighing <100 kg: 45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks; patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks | From labeling: 2 R, DB, PC trials PASI 75 at Week 12<br>1. Uste (90 mg)-66% vs. uste (45 mg)-67% vs. 3% placebo<br>2. Uste (90 mg)-76% vs. uste (45 mg)-67% vs. 4% placebo | W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB | Pregnancy: B |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| IL-17A Blocker | Secukinumab (Cosentyx) 2015 | Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy | 300 mg SC at weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable | From labeling: 4 R, DB, PC trials PASI 75 at Week 12<br>1. Sec (300 mg)-82% vs. sec (150 mg)-71% vs. 4% placebo<br>2. Sec (300 mg)-76% vs. sec (150 mg)-67% vs. 5% placebo<br>3. Sec (300 mg)-75% vs. sec (150 mg)-69% vs. 0% placebo<br>4. Sec (300 mg)-87% vs. sec (150 mg)-70% vs. 3% placebo | W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB | Pregnancy: B |
| IL-17A Blocker | Ixekizumab (Taltz) 2016 | Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy | 160 mg (two 80 mg injections) SC at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks | From labeling: 3 R, DB, PC trials PASI75 at Week 12<br>1. Ixe (80 mg q2wk) 89% vs. 4% placebo<br>2. Ixe (80 mg q2wk) 90% vs. 2% placebo<br>3. Ixe (160 mg × 1, then 80 mg q2wk) 87% vs. 7% placebo | W&Ps: infections (upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; inflammatory bowel disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB | |
| IL-17 Receptor A Antagonist | Brodalumab (Siliq) 2017 | Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and who have failed to respond or have lost response to other systemic therapies | 210 mg by SC injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks | From labeling: 3 R, DB, PC trials PASI 75 and sPGA of 0 (clear) or 1 (almost clear) at Week 12<br>1. Bro (210 mg q2wk) PASI 75 83% vs. 3% placebo; sPGA 0 or 1 bro 76% vs. 1% placebo<br>2. Bro (210 mg q2wk) PASI 75 86% vs. 8% placebo; sPGA 0 or 1 bro 79% vs. 4% placebo; PASI 100 bro 44% vs. uste 22%<br>3. Bro (210 mg q2wk) PASI 75 85% vs. 6% placebo; sPGA 0 or 1 bro 80% vs. 4% placebo; PASI 100 bro 37% vs. uste 19% | BW for suicidal ideation and behavior<br><br>W&Ps: Suicidal ideation and behavior; infections (serious infections and fungal infections); Crohn's disease; pretreatment eval for TB; avoid live vaccines | REMS requires prescribers and pharmacies to be certified; patients must sign a patient-prescriber agreement form |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| IL-23 Blocker | Guselkumab (Tremfya) 2017 | Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy | 100 mg by SC injection at week 0, week 4, and every 8 weeks thereafter | From labeling: 3 R, DB, PC, AC trials; 1 & 2: PASI 90 and sPGA of 0 ("cleared") or 1 ("minimal") at Week 16<br>1. Gus (100 mg weeks 0 & 4 then q8wk) PASI 90 73% vs. 3% placebo; IGA 0 or 1 85% vs. 7% placebo<br>2. Gus (100 mg Weeks 0 & 4 then q8wk) PASI 90 70% vs. 2% placebo; IGA 0 or 1 84% vs. 8% placebo<br>3. Subjects began tx with uste; at wk16 subjects with IGA ≥2 R to gus or continued uste; endpoint at Week 28 IGA 0 or 1 with ≥2 grade improvement; gus 31% vs. 14% uste | W&Ps: infections (upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections); pretreatment eval for TB; avoid live vaccines | |
| IL-23 Blocker | Risankizumab (Skyrizi) 2019 | Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy | 150 mg by SC injection at week 0, week 4, and every 12 weeks thereafter | From Labeling: 4 R, DB, PC trials; PASI 90 and sPGA of 0 ("clear") or 1 ("almost clear") at Week 16.<br>1. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 75% vs. 5% placebo; IGA 0 or 1 88% vs. 8% placebo<br>2. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 75% vs. 2% placebo; IGA 0 or 1 84% vs. 5% placebo<br>3. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 73% vs. 2% placebo; IGA 0 or 1 84% vs. 7% placebo | W&Ps: infections (upper respiratory tract infections, tinea infections); pretreatment eval for TB; avoid live vaccines | |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| T-Cell Inhibitor/ Immuno-suppressant | Cyclosporine 1997 | Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy | Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day | From labeling: PASI 75 - 51% at 8 weeks, 79% at 16 weeks | BW: Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUV-A, UV-B, coal tar or radiation Rx-↑ risk of skin malignancies Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy, malignancies, serious infection, neurotoxicity | Pregnancy category: C |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| Retinoid | Acitretin (Soriatane) 1996 | Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments | Starting dose: 25 to 50 mg orally (PO) per day, maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx | From labeling: 2 DB, PC trials-Mean change in PGA at 8 weeks<br>A. Acitretin (50 mg)-2 vs. -0.29 on placebo<br>B. Acitretin (50 mg)-1.57 vs. Acitretin (25 mg)-1.06 vs. -0.06 on placebo (no multiplicity adjustment for trial B) | BW: pregnancy must be prevented during Rx and for 3 years following because of teratogenicity, no ethanol ingestion by FOCBP because of metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @FDA for details. Patients cannot donate blood for 3 years post-Rx; see label for data on pregnancies in partners of male patients on acitretin | W&P: hepatotoxicity, skeletal abnormalities, lipids ↑, cardiovascular risk ↑, ophthalmologic effects, pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression<br>Pregnancy category: X |
| Phosphodiesterase 4 (PDE4) Inhibitor | Apremilast (Otezla) 2014 | Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy | To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg per oral twice daily | From labeling: 2 R, DB, PC trials<br>PASI 75 at 16 weeks<br>1. Aprem 33% vs. 5% in placebo<br>2. Aprem 28.8% vs. 5.8% in placebo | W&Ps: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine phenytoin) | Diarrhea, nausea, URI, headache<br>Pregnancy category: C |

| FDA-Approved Treatment | Product(s) Name/Year Approved | Relevant Indication | Dosage and Administration | Efficacy Information | Important Safety and Tolerability Issues | Other Comments |
|---|---|---|---|---|---|---|
| Phototherapy | PUVA-8-MOP (methoxsalen) + UV-A therapy | Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy | 20-70 mg per oral (based on weight) taken 2-4 hr before exposure to UV-A light | No efficacy information for psoriasis in the labeling | BW: should only be used by MDs who have special competence in psoriasis management.<br>Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma) | Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) of eyes and skin for 24 hr after ingestion<br>Pregnancy category: C |

Source: Reviewer's table from the Unireview of BLA 761067
Abbreviations: AC, active comparator; ada, adalimumab; aprem, apremilast; bro, brodalumab; BW, boxed warning; DB, double-blind; etan, etanercept; gus, guselkumab; inflix, infliximab; Ixe, ixekizumab; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area Severity Index; PC, placebo-controlled; R, randomized; sec, secukinumab; uste, ustekinumab; RKZ, risankizumab; W&Ps, warnings and precautions; FDA, U.S. Food and Drug Administration; sPGA, static Physician's Global Assessment; REMS, risk evaluation and mitigation strategy; IM, intramuscular; IV, intravenous; MD, Doctor of Medicine; AE, adverse event; UV, ultraviolet; CHF, congestive heart failure; SC, subcutaneous injection; FOCBP, females of childbearing potential; IGA, Investigator's Global Assessment; IL, interleukin; TB, tuberculosis; URI, upper respiratory infection; tx, treatment; q8wk, every 8 weeks

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

TREMFYA (guselkumab) is a human IgG1/lambda monoclonal antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. The FDA approved guselkumab under BLA 761061 for –

- treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (approved July 13, 2017 by Division of Dermatology and Dentistry [DDD])

- treatment of adult patients with active psoriatic arthritis (approved July 13, 2020 by Division of Rheumatology and Transplant Medicine [DRTM])
    - The recommended dosing of guselkumab for plaque psoriasis and psoriatic arthritis is 100 mg subcutaneously (SC) at Week 0, Week 4, and every 8 weeks thereafter.

- treatment of adult patients with moderately to severely active ulcerative colitis (approved September 11, 2024 by Division of Gastroenterology [DG])
    - The recommended dosing of guselkumab for ulcerative colitis is – induction at 200 mg iv over at least one hour Week 0, Week 4, and Week 8; and maintenance at 100 mg sc Week 16, and every 8 weeks thereafter, or 200 mg sc Week 12, and every 4 weeks thereafter, with use of the lowest effective recommended dosage to maintain therapeutic response.

- treatment of adult patients with moderately to severely active Crohn's disease (approved March 20, 2025 by DG)
    - The recommended dosing of guselkumab for Crohn's disease is the same as that for ulcerative colitis, with an additional option for induction with 400 mg SC at Weeks 0, 4, and 8.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed guselkumab injection under IND 105004. The FDA agreed with the Initial Pediatric Study Plan (Letter dated November 21, 2014) which included a waiver of the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable and a deferral of assessments in the pediatric population ages 6 years to 17 years until the FDA reviewed the data in the adult population.

On July 13, 2017, the FDA approved guselkumab (under BLA 761061) for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Among the postmarketing requirements (PMRs) issued with the approval of TREMFYA was the following deferred study under the Pediatric Research Equity Act (PREA):

> 3225-1 Conduct a Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 years to less than18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

The timeline included the following milestones:

| | |
|---|---|
| Initial Protocol Submission: | 10/2017 |
| Final Protocol Submission: | 04/2018 |
| Trial Completion: | 10/2023 |
| Final Report Submission: | 04/2024 |

On October 11, 2017, the FDA held a teleconference with the Applicant to discuss the development program for guselkumab for the treatment of pediatric subjects with moderate to severe plaque psoriasis (Meeting Minutes dated October 23, 2017). To address PMR 3225-1, the Applicant proposed to conduct Trial CNTO1959PSO3011, a multicenter, randomized, placebo- and active comparator-controlled trial to evaluate the efficacy, safety, and pharmacokinetics (PK) of guselkumab for the treatment of chronic plaque psoriasis in the pediatric population ≥6 years to <18 years of age who are candidates for phototherapy or systemic treatment of plaque psoriasis or cannot be adequately controlled with phototherapy and/or topical agents.

The FDA provided guidance regarding the study population (Psoriasis Area and Severity Index (PASI) ≥12, Body Surface Area [BSA] ≥10% and Investigator Global Assessment [IGA] score of at least 3 [moderate]), the proposed study design, need for rationale for proposed weight based dosing of 1.3 mg/kg for pediatric subjects with body weight <70 kg , the primary and secondary endpoints including patient reported outcome measures, safety monitoring, sample size, performance testing for (b) (4) UltraSafe Plus devices, (b) (4) [redacted].

The Applicant submitted clarifying questions on October 19, 2017 (SD 263) and proposed revised inclusion criteria and sample size. The FDA agreed with the revised inclusion criteria but not the sample size (Sponsor continued to propose to evaluate (b) (4) subjects in the guselkumab arm for Part 1A). The FDA stated that 30 subjects may be reasonable if there are a sufficient

number with low body weight (e.g. less than 30 kg) enrolled in the trial. (Advice Letter dated December 8, 2017.)

On December 27, 2017, the Applicant submitted Protocol CNTO1959PSO3011 (SD 277) which incorporated FDA recommendations. Key comments included in the Advice Letter (AL) (dated 3/16/2018) addressed the study design, study population and the (b) (4) use of the (b) (4) device ((b) (4).) The FDA recommended "using the same co-primary efficacy endpoints used for the pivotal Phase 3 trials in adults (i.e., IGA score of 0 or 1 and PASI 90 at Week 16). PASI 75 at Week 16 can be a secondary efficacy endpoint. You should modify the definition of responder for treatment withdrawal at Week 16 to be based on the IGA (i.e., an IGA score of 0 or 1). In addition, the criterion for retreatment should be modified to be based on the IGA instead of PASI." The FDA also provided comments regarding the (b) (4) including the (b) (4) Injection Checklist and (b) (4) Injection Assessment Questionnaire and the dosing limitations using the device (e.g., (b) (4) .)

The FDA provided additional comments regarding the (b) (4) device (AL dated July 6, 2018 and meeting minutes dated May 20, 2019, advised revision of (b) (4) ), and endpoints (AL dated October 22, 2018).

On June 29, 2023, the Applicant submitted a deferral extension request (DER) to the Division for the submission of the final study report for the pediatric assessment under PREA from April 2024 to December 2024. PeRC discussed the request (meeting held on August 8, 2023) and agreed to the DER.

The FDA held a Pre-sBLA with the Applicant on May 7, 2024 (meeting minutes dated June 13, 2024). The Applicant proposed to provide pooled data from the pivotal phase 3 trials (3001 and 3002) to provide context for the pediatric data using appropriate statistical methods, provide shift tables for laboratory results and proposed "to assess if it may be appropriate to recommend a 100 mg fixed dose body weight cutoff <70 kg (e.g., 40 kg) in pediatric patients." In addition, the Applicant clarified that "(b) (4)

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

## 4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission is adequate. The Division did not request that the Office of Scientific Investigations (OSI) conduct clinical inspections of domestic and international sites.

## 4.2. Product Quality

This efficacy supplement proposes to add a new indication for the treatment of moderate-to-severe plaque psoriasis (PsO) in pediatric patients 6 years or older and weighing at least 40 kg to address Clinical PMC 3225-1 at a recommended dose of 100 mg. No new CMC information was submitted for the currently approved Tremfya 100 mg presentations (1 mL PFS-U, PFS-S, (b) (4) ). No changes were made to the CMC sections of the USPI that required additional OPQA III assessment. Validation of the immunogenicity assays used to assess anti-drug antibodies (ADA) and neutralizing antibodies (NAb) have been reviewed under the original BLA, Suppl-21, and Suppl-24. The immunogenicity assays were re-evaluated specifically for the pediatric PsO population and deemed adequate to support clinical immunogenicity assessment.

In addition, the Applicant requests categorical exclusion from the requirements of preparing an environmental assessment under 21 CFR 25.31 (c). This is acceptable from an OPQA-III perspective.

The drug product lots used in the clinical studies to support the new indication were lots manufactured and controlled as described in the license (e.g., commercial lots).

The review team recommend that PAS 761061/S-28 be approved from a product quality perspective. (Memorandum of Assessment dated August 12, 2025)

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Devices and Companion Diagnostic Issues

**Office of Product Quality (OPQ)**
Initial submission of this supplement (b) (4)

(b) (4)

. In Trial CNTO1959PSO3011, subjects who weighed ≥ 70 kg used the PFS while subjects who weighed < 70 kg used the (b) (4). Although Office of Product Quality (OPQ) sought additional information regarding product quality review issues (b) (4) (IR dated June 2, 2025 with the responses submitted in sequence 1070), no approvability issues were identified by the OPQ review team (OPQAIII, OPMA and CDRH) from product quality, microbiology, and device perspectives. (Memorandum of Assessment dated August 12, 2025)

(b) (4)

DMEPA 1 noted that Janssen submitted HF validation study results for the Tremfya 100 mg PFS that included pediatric participants (submitted November 16, 2016). DMEPA 1 reviewed the HF validation study results report at that time and found it acceptable.[1] As such, DMEPA 1 determined that Janssen does not need to submit additional HF data for Tremfya 100 mg PFS for pediatric PsO and jPsA use. Based on the Janssen's aforementioned information, for these current efficacy supplements (BLA 761061/S-028 and BLA 761061/S-029), DMEPA 1 has no additional HF comments and recommendations. Refer to the DMEPA 1 review dated August 13, 2025, in DARRTS for additional details.

**Center for Devices and Radiological Health (CDRH)**

(b) (4)

[1] Mena-Grillasca, CM. Human Factors, Label, Labeling, and Packaging Review for Tremfya (BLA 761061). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 12. OSE RCM No.: 2016-2621 and 2016-2649.


**Clinical: data analysis**

Subgroup analyses of the efficacy and safety data from clinical Trial CNTO1959PSO3011 demonstrated comparable findings for both devices. Efficacy results for the primary efficacy endpoint showed no substantial difference between the group administering guselkumab using the (b) (4) and the group administering guselkumab using the PFS. These results are presented in the table below.

**Table 1: Results of Co-Primary Efficacy Endpoint by Device**

| | Trial CNTO1959PSO3011 | | |
|---|---|---|---|
| | Placebo (N=25) | Guselkumab (N=41) | Difference (95% CI) |
| **Proportion of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16** | | | |
| Weighing < 70 kg (b) (4) | 3/20 (15%) | 19/29 (66%) | 51% (23%, 73%) |
| Weighing ≥ 70 kg (Approved PFS) | 1/5 (20%) | 8/12 (67%) | 47% (-9%, 85%) |
| **Proportion of participants with a PASI 90 response[4] at Week 16** | | | |
| Weighing < 70 kg (b) (4) | 3/20 (15%) | 17/29 (59%) | 44% (15%, 66%) |
| Weighing ≥ 70 kg (Approved PFS) | 1/5 (20%) | 6/12 (50%) | 30% (-25%, 72%) |

[1] Full Analysis Set (FAS): all randomized participants in Part 1a and Part 1b. Participants with missing data after application of ICEs were considered as non-responders.
[2] CIs are based on exact method
[3] P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled).
[4] PASI 90 response: subjects who achieved at least 90% reduction in the PASI composite score from baseline.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adigai.xpt and adpasii.xpt

A comparison of treatment emergent adverse events (TEAEs) in subjects receiving guselkumab via (b) (4) (< 70 kg) versus pre-filled syringe (≥ 70 kg) showed minor imbalances in abdominal pain, and headache (See the table below). Due to the small sample size, the review team could not draw a conclusion regarding the clinical meaningfulness of these imbalances.

**Table 2: Subjects with TEAEs By Device Used to Administer Guselkumab: Week 0-16**

| Preferred Term | Guselkumab (< 70kg) N = 29 n (%) | Guselkumab (>= 70kg) N = 12 n (%) |
|---|---|---|
| Any AE | 13 (44.8) | 4 (33.3) |
| Abdominal pain | 2 (6.9) | 0 (0.0) |
| Acarodermatitis | 1 (3.4) | 0 (0.0) |
| Acne | 1 (3.4) | 0 (0.0) |
| Asthma | 0 (0.0) | 1 (8.3) |
| Blood alkaline phosphatase increased | 1 (3.4) | 0 (0.0) |
| Blood glucose increased | 1 (3.4) | 0 (0.0) |
| Bone pain | 1 (3.4) | 0 (0.0) |
| Covid-19 | 1 (3.4) | 0 (0.0) |
| Enteritis | 1 (3.4) | 0 (0.0) |
| Enterobiasis | 1 (3.4) | 0 (0.0) |
| Headache | 3 (10.3) | 0 (0.0) |
| Injection site erythema | 1 (3.4) | 0 (0.0) |
| Injection site swelling | 1 (3.4) | 0 (0.0) |
| Lethargy | 1 (3.4) | 0 (0.0) |
| Ligament sprain | 1 (3.4) | 0 (0.0) |
| Muscle strain | 0 (0.0) | 1 (8.3) |
| Myopia | 0 (0.0) | 1 (8.3) |
| Nasopharyngitis | 3 (10.3) | 2 (16.7) |
| Pharyngitis | 1 (3.4) | 0 (0.0) |
| Radius fracture | 1 (3.4) | 0 (0.0) |
| Rhinitis | 0 (0.0) | 1 (8.3) |
| Upper respiratory tract infection | 3 (10.3) | 1 (8.3) |
| Ventricular extrasystoles | 0 (0.0) | 1 (8.3) |
| Viral infection | 0 (0.0) | 1 (8.3) |
| Viral upper respiratory tract infection | 1 (3.4) | 0 (0.0) |
| White blood cell count increased | 1 (3.4) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Guselkumab" and WGTGR1 = "< 70 kg" and SAFFL = Y (Guselkumab (< 70kg)); TRT01A = "Guselkumab" and WGTGR1 = ">= 70 kg" and SAFFL = Y (Guselkumab (>= 70kg)); TRTEMFL = "Y" (Adverse Events).

Therefore, given the deficiencies identified above, the [redacted] (b) (4) presentation [redacted] (b) (4) [redacted]. However, the safety and efficacy data support approval guselkumab for the treatment of moderate to severe plaque psoriasis in the pediatric population age 6 years to 17 years who also weigh ≥40 kg. Refer to Section 6.3.1 General Pharmacology and Pharmacokinetic Characteristics for a discussion of PK modeling to support fixed dosing in patients who weigh ≥40 kg. The Applicant will be required to develop an age-appropriate formulation/presentation to fully address the required assessment under PREA. Refer to

Section 8.2.8 Pediatrics and Assessment of Effects on Growth.

**Drug device combination products for the pediatric patients age 6 years and older who weigh ≥ 40 kg**

(b) (4), the Agency and Applicant discussed the options for the administration of guselkumab in the pediatric patients who weighed at least 40 kg (teleconference held on August 21, 2025) and for whom a fixed dosing of 100 mg is supported by modeling. The pre-filled syringe (PFS-U), One-Press patient-controlled injector (100 mg/ml) and Tremfya Pen (PFP: 100 mg/ml) are currently approved for self-administration of guselkumab by adults with moderate to severe plaque psoriasis.

Use of the prefilled syringe for self-administration in patients aged 10 years and older was supported by human factors study data[2]and extensive experience with self-administration of biologic products by children for indications (Concurrence with DRTM, DMEPA and Pediatrics teams).

The review team and Applicant considered the use of the approved devices (One-Press patient-controlled injector and Tremfya Pen) for administration in pediatric patients 6 years and older who also weigh ≥ 40 kg by healthcare provider or caregiver. The use of the One-Press patient-controlled injector and Tremfya Pen was discussed with the Office of Combination Products (OCP), DMEPA, DRTM and Pediatric team.

As recommended by OCP, the review team considered the differences in the drug-delivery performance characteristics as well as the potential information gaps in the determination of the appropriateness of the autoinjectors for administration of guselkumab to children. These considerations included:

1) lack of clinical use experience under the proposed conditions of use (e.g., to determine if the 3 injection sites are appropriate for the younger pediatric patients (age 6-12 years);
2) lack of clinical data to inform local adverse reactions using the Injector or the Pen in the proposed pediatric age and weight range; and
3) lack of PK profile comparison of the PFS-U vs the Injector vs. the Pen.
4) device differences. The devices have different needle lengths (PFS-U [12.7 mm]) and the One-Press Injector / Pen [8 mm]) with different angles of injection (PFS-U [45 degrees] versus 90 degrees [One-Press Injector / Pen]), respectively. These differences are based on the device design to reach the subcutaneous space (SC) space.

These considerations were discussed with other member of the review team.
In consultation with the pediatric and clinical pharmacology teams:

[2] Mena-Grillasca, C. Human Factors, Label, Labeling and Packaging Review for guselkumab. Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2017 May 12. BLA 761061.

- the designated injection sites in labeling for adult administration (anterior thighs, lower abdomen, posterior proximal arm) were deemed safe and appropriate for pediatric administration in patients 6 years and older who weigh ≥ 40kg. They reference their extensive experience with the administration of vaccines in the pediatric population.

- Local safety data from Trial CNTO1959PSO3011 in pediatric patients did not demonstrate differences in adverse reactions according to the device used ((b) (4) versus PFS-U). The approved devices (One-Press patient-controlled injector and Tremfya Pen) have the same needle gauge and contain the same volume and formulation as the PFS-U but different injection angles and needle lengths. It is expected that adverse reactions with use of One Press device and Tremfya Pen will be consistent with those observed during Trial CNTO1959PSO3011. Therefore, a new clinical trial will not be necessary. Moreover, use of the device with 90-degree angle of injection and shorter needle may be safer than the PFS-U with a 45-degree angle of injection and longer needle.

- The use of One-Press injector and Tremfya Pen are supported by the use of the PFS-U in the pediatric clinical trial which had the same dose, volume of injection, needle size and injection sites and the (b) (4) use in the pediatric trial supports the angle of injection.

- The clinical pharmacology review team stated that no PK data would be needed to support the use of the approved devices in the pediatric population because the data that supported approval in adults could be extrapolated to the pediatric population.

Other considerations raised by OCP included:

- The device performance characteristics and technical specifications (e.g., syringe size, syringe volume, needle size, needle length, injection force).
- The physicochemical properties of Tremyfa versus the approved biologic products.
- The user interface of the Tremfya pen versus the other approved pens.
- Device malfunction profile of Tremfya pen vs. the other approved pens

These considerations were discussed with other member of the review team including DPMH, CDRH and DMEPA:

The review team evaluated the **device performance characteristics** and technical specifications (e.g., syringe size, syringe volume, needle size, needle length, injection force) of the devices used to administer guselkumab in Trial CNTO1959PSO3011 ((b) (4) and PFS-U) compared to the devices approved for use in adults. All four devices have the same (b) (4). The PFS-U, One-Press injector and Tremfya Pen all share the same volume of injection (1 mL) and fixed dose (100 mg). While the PFS-U has a 12.7 mm needle length intended for a 45-

degree insertion angle, both One-Press injector and Tremfya Pen have an 8 mm needle length intended for a 90-degree insertion angle. The [redacted] has [redacted] mm needle length and [redacted]. The pediatric team had no safety concerns regarding the 8 mm needle length of the One-Press patient-controlled injector and Pen compared with the [redacted] mm needle length of the [redacted].

| Device presentation | Needle size and Needle length |
|---|---|
| Tremfya One-Press | 27 G; 8 mm |
| Tremfya Pen | 27 G; 8 mm |
| Tremfya PFS-U | 27 G; ½ inch (12.7 mm) |

| Device presentation | Insertion angle |
|---|---|
| Tremfya One-Press | 90 degree insertion |
| Tremfya Pen | 90 degree insertion |
| Tremfya PFS-U | 45 degree insertion with pinch prior to needle insertion |

**Other device specifications**

| Tremfya devices | Injection depth | Injection force |
|---|---|---|
| Prefilled syringe | 12.7 mm (~ 9 mm perpendicular distance at 45-degree insertion) | The injection force (glide force) specification is ≤ [redacted] N at [redacted] mm/min; this is a manual injection device, the users can inject at their comfortable speed; slower injection will have lower injection force |
| One-Press | 8 mm | The injection force (operation force) specification is ≤ [redacted] N at [redacted] mm/min; this is a manual injection device, the users can inject at their comfortable speed; slower injection will have lower injection force |
| Tremfya Pen | 8 mm | The force to activate injection (cover sleeve actuation force) specification is <= [redacted] N; this is an autoinjector. [redacted] The user must maintain the force until the injection is complete. |
| VarioJect | [redacted] | |

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- The Applicant provided a comparison of **injection force** between the four Tremfya devices which are ≤ (b) (4) N for the PFS-U, ≤ (b) (4) N for the One-Press injector, ≤ (b) (4) N for the (b) (4) at (b) (4) mm/min and ≤ (b) (4) N for the Tremfya Pen. Most of local AEs are due to the drug itself and not to the device. Given the same needle gauge, product volume/viscosity, route of injection, it is expected that local adverse reactions will be comparable even with a different injection force.

- To further support the use of Tremfya Pen in the pediatric population, the team evaluated the **device characteristics of other approved pens** (AI) that use a similar (b) (4) platform design. The (b) (4) Pen (approved (b) (4)) and the (b) (4) auto-injector (approved (b) (4)) are indicated for use in pediatric patients 6 years of age and older who weigh at least 35 kg for the (b) (4) Pen and 45 kg for the (b) (4) auto-injector. The (b) (4) pen uses a 29 G and 12.7 mm needle to administer 1 mL of drug product and the (b) (4) auto-injector uses a 27 G needle to inject 1.5 mL of drug product. Both devices are used at a 90-degree angle in the same injection sites as the Tremfya Pen and One-Press injector. Approval of these (b) (4) platform devices with similar performance characteristics and technical specifications for use in similar target populations (similar age and weight restrictions) supports the use of the Tremyfa Pen in pediatric patients ages 6 and older who weigh at least 40 kg with moderate to severe plaque psoriasis.

- CDRH compared the **device characteristics** of both the One-Press injector and the Tremfya Pen and found the dose accuracy/delivered volume is similar between the two device presentations.

- Regarding the **user interface**, DMEPA stated that there is sufficient human factors data to support the use of these two devices by caregivers or health care providers (HCPs) to administer the product to pediatric patients.

- To address the **device malfunction profile**, the FDA queried the Applicant regarding the post marketing safety data related to the 100mg/mL devices (One-Press patient-controlled injector and TREMFYA PEN.) Most of the data related to the One-Press patient-controlled injector because the TREMFYA PEN was only recently approved (March 2025). The Applicant reviewed medication errors and device related safety signals (Periodic Benefit Risk Evaluation Report: July 13, 2023, to July 12, 2024; SDN 1300). According to the Applicant, the most important MedDRA **PTs of interest** by frequency were Product dose omission issue (50.6%), Inappropriate schedule of product administration (17.8%), Accidental exposure to product (6.8%;), Needle issue (4.8%), Product storage error (4.1%), and Device malfunction (3.3%.)

  There were 12 cases that were serious that included 13 serious MedDRA PTs of interest. Of these 12 cases, 6 reported MedDRA PTs of interest only (device malfunction and product dose omission issue; expired product administered; product storage error; product dose omission issue, needle issue, and accidental exposure to product with

possible missed dose; product storage error, syringe issue, product label issue, and product dose omission issue) and no additional associated AEs. The most common associated serious adverse events were psoriasis, psoriatic arthropathy, condition aggravated, arthralgia, pneumonia, COVID-19 and hospitalization. Most serious and nonserious adverse events were potentially related to the drug and not the delivery system. However, there were single serious AE reports of injection site hemorrhage and drug ineffective.

Therefore, the review team including DPMH supports approval for the One-Press injector and Tremfya Pen for administration of guselkumab (100 mg/mL) to pediatric patients 6 years of age and older by caregivers or HCPs.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

The Applicant supported the approval of guselkumab for the treatment of moderate to severe psoriasis with a comprehensive nonclinical data package. In this submission, the Applicant provided no new nonclinical information. Therefore, sections 5.2, 5.3, 5.4, and 5.5 are not applicable to this review. For the analysis and discussion of the nonclinical data, refer to the Multi-disciplinary Review and Evaluation of BLA 761061 (Section 5 Nonclinical Pharmacology/Toxicology by Renqin Duan, PhD dated July 13, 2017).

# 6 Clinical Pharmacology

## 6.1. Executive Summary

Guselkumab (TREMFYA®) is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody that binds to the p19 protein subunit of human interleukin 23 (IL-23) and inhibits its interaction with IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune response. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

Guselkumab was approved for the treatment of adults with moderate to severe plaque PsO who are candidates for systemic therapy or phototherapy. The approved dose of guselkumab for the treatment of plaque PsO in adults is 100 mg, regardless of body weight, administered SC at Week 0, Week 4, and q8w thereafter. At the time of original approval for the indication of severe plaque PsO, one PREA post-marketing requirements (PMRs) were issued as shown below.

PMR 3225-1: Conduct a pharmacokinetics (PK), safety and efficacy study in pediatric subjects 6 years to <18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

The purpose of this efficacy supplement is to address PMR 3225-1 and extend the indication of the treatment of moderate-to-severe plaque PsO in subjects 6 years and older.

The safety and effectiveness guselkumab were assessed in a phase 3 trial in pediatric subjects 6 to <18 years of age with moderate-to-severe plaque PsO, with the goal to fulfill the PMR (PMR 3225-1). The doses investigated in phase 3, include 1.3 mg/kg for pediatric subjects <70 kg (using (b) (4) injections to administer the dose), and at 100 mg fixed dose for pediatric subjects ≥70 kg [administered using the prefilled syringe fitted with the UltraSafe Plus™ Passive Needle Guard device (PFS-U). Subjects were dosed at Week 0, Week 4, and q8w thereafter. In the current submission, Applicant proposed the following pediatric dose for guselkumab, to be given at Week 0, Week 4, and q8w thereafter (b) (4) for body weight ≥40 kg (at time of dose): 100 mg administered with the prefilled syringe (PFS-U).

The clinical pharmacology review evaluated pharmacokinetic (PK), exposure-response (E-R), Population PK (popPK), and immunogenicity data obtained from the phase 3 placebo- and active-controlled clinical trial (52- week analysis), CNTO1959PSO3011 (PROTOSTAR), of guselkumab in the treatment of chronic plaque PsO in pediatric subjects (≥6 to <18 years of age) to support the dose justification. In the phase 3 trial (PROTOSTAR), dose of 1.3 mg/kg was evaluated in subjects < 70 kg; however, the Applicant is seeking a flat dose of 100 mg in subjects ≥40 kg. In order to justify the proposed dose change, pediatric data were also compared with those previously observed in adults with moderate to severe plaque PsO in Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002, including specific analyses comparing data for adult participants <70 kg and those ≥70 kg, as well as modeling and simulation analyses.

On July 25, 2025, the Applicant (b) (4) Thus, this review is primarily focused on the PK, safety, and efficacy of recommended flat dose for pediatrics with BW ≥ 40 kg.

**Recommendation:**

The Office of Clinical Pharmacology (OCP) has reviewed this sBLA submission and found it acceptable for approval from a clinical pharmacology standpoint, provided that a mutually satisfactory agreement can be reached between the Applicant and Agency regarding the labeling language. Since the Applicant has (b) (4), OCP considers that the Applicant has partially fulfilled the Pediatric Research Equity Act (PREA) requirement (PMR 3225-1) in patients 6 to 17 years as it is not possible to dose subjects that weigh below 40 kg at this time. We recommend the issuance of a deferral extension through PeRC for the existing PREA PMR to allow the Applicant time to develop a new presentation which will enable dosing in subjects

below 40 kg bodyweight with emphasis on 6 to <12 years of age to better assess the safety and PK in this lower age group and including good proportion of patient population who are obese in this age range to assess the effect of obesity on the PK and safety. Thus, the Applicant cannot be released from the PMR 3225-1 and from a Clinical Pharmacology standpoint, PMR3225-1 is not considered as fulfilled.

## 6.2. **Summary of Clinical Pharmacology Assessment**

### 6.2.1. **Pharmacology and Clinical Pharmacokinetics**

MOA: Guselkumab is a human monoclonal IgG1 λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. It is believed that that the IL-23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune mediated diseases, including psoriasis. By binding to the p19 subunit of IL-23, guselkumab blocks IL-23-mediated intracellular signaling, activation and cytokine production.

Pharmacodynamic response: Serum levels of IL-17A, IL-17F, and IL-22 were reduced after receiving 100 mg (for > 70 kg BW) and 1.3 mg/kg (for < 70 kg BW patients) guselkumab treatment compared to pretreatment levels in subjects with moderate to severe plaque psoriasis. However, these observations were based on limited data in a subset of subjects. The relationship between these pharmacodynamic changes and the mechanism(s) by which guselkumab exerts its clinical effects is unknown.

Pharmacokinetics (PK) of guselkumab in the pediatric population ≥6 to <18 years of age: In the current submission, the Applicant evaluated efficacy, safety, and PK of SC administered guselkumab for the treatment of moderate to severe plaque PsO in pediatric participants ≥6 to <18 years of age in a phase 3 multicenter, randomized, placebo- and active comparator-controlled phase 3 trial (Study CNTO1959PSO3011).

Study CNTO1959PSO3011 was conducted at sites in the US, EU, Canada, and Australia. Guselkumab was dosed at 1.3 mg/kg for pediatric participants <70 kg (using (b) (4) injections to administer the dose), and at 100 mg fixed dose for pediatric participants ≥70 kg (administered using the PFS-U).

In Part 1 of Trial CNTO1959PSO3011, the mean and median serum guselkumab concentrations at Week 16 were slightly lower in the ≥6 to <12 years age group compared with the ≥12 to <18 years age group, but the ranges largely overlapped. Serum guselkumab concentrations were similar in participants <70 kg and ≥70 kg. Steady-state serum guselkumab concentrations were achieved by Week 20 and were maintained through Week 44. There was no apparent relationship between guselkumab exposure levels and efficacy outcomes. Furthermore, there was no apparent impact of the development of antibodies to guselkumab, or the titer of antibodies, on

guselkumab PK, efficacy, or safety. The systemic exposure of guselkumab in pediatric subjects were comparable to that seen in adult subjects with PsO. Treatment with guselkumab consistently resulted in greater clinical efficacy compared with the placebo group at Week 16, as demonstrated by significantly higher proportions of pediatric subjects achieving responses in both co-primary and major secondary clinical outcomes.

Overall, treatment with guselkumab had a favorable safety profile and was well tolerated in the pediatric population with moderate to severe PsO ≥6 to <18 years of age that was studied. The PK simulations based on the final PopPK model support guselkumab dose of (b) (4) 100 mg for pediatric subjects weighing ≥40 kg. Modeling and simulation results demonstrated comparable exposure in subjects ≥40 kg with a fixed dose of 100 kg to adults who received a flat dose of 100 mg, which support the proposed pediatric body weight cutoff for use of the 100 mg fixed dose of guselkumab to be lowered from 70 kg to 40 kg. Overall predicted systemic exposures (PK), immunogenicity, and E-R data of guselkumab from the phase 3 trial in pediatric subjects weighing ≥40 kg with PsO (study CNTO1959PSO3011) were consistent with those from the global phase 3 trials in adults with PsO (CNTO1959PSO3001 and CNTO1959PSO3002) are comparable to those in adult subjects with PsO across the full body weight range.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

In the current submission, the Applicant proposed dose recommendation for children and adolescents is different from that evaluated in Trial CNTO1959PSO3011 that was based on a 70kg weight limit. The recommended pediatric dose for guselkumab (Table 3), to be given at Week 0, Week 4, and q8w thereafter is as follow:

- (b) (4)
- Body weight ≥40 kg (at time of dose): 100 mg administered with the prefilled syringe (PFS-U) for pediatrics patients weighing ≥40 kg given at Week 0, 4, and q8w thereafter.

**Table 3: Recommended Dose of Guselkumab for Subcutaneous Injection in Pediatric Patients with Plaque PsO**

| Body Weight | Dose (mg)[a] |
|---|---|
| (b) (4) | |
| ≥40 kg | 100 |

PsO=psoriasis.
[a] (b) (4); the 100 mg dose is administered using the PFS-U (100 mg prefilled syringe fitted with the UltraSafe Plus™ Passive Needle Guard device).
Source: Summary of Clinical Pharmacology Studies, Table 1

(b) (4) this review is primarily focused on the PK, safety, and efficacy of recommended flat dose for pediatrics with BW ≥ 40 kg.

PK modelling and simulation supported flat dosing of 100 mg in subjects ≥40kg which demonstrated that systemic exposures were comparable to adult subjects that were administered a flat dose of 100 mg administered with the prefilled syringe (PFS-U). Hence, for pediatrics patients weighing ≥40 kg a flat dose of 100 mg administered at Week 0, 4, and q8w is acceptable from a Clinical Pharmacology perspective.

**Therapeutic Individualization:** Therapeutic individualization is not necessary for patients with BW ≥ 40 kg. Population PK analysis identified body weight as a significant covariate that impacted guselkumab exposure. However, efficacy data from the phase 3 trial indicated that the difference in treatment effect between guselkumab and placebo (i.e., IGA0/1 scores guselkumab minus placebo at Week 16) was consistent across all baseline weight quartiles; therefore, dose adjustment based on body weight ≥ 40 kg is not needed.

**Outstanding Issues:** The outstanding issue at the conclusion of this review is approval in subjects below 40 kg body weight. Due to this, PMR 3225-1 is not considered as fulfilled.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant evaluated the safety and effectiveness of guselkumab in the treatment of pediatric subjects ≥6 to <18 years of age with moderate to severe plaque PsO in Trial CNTO1959PSO3011 (PROTOSTAR). Trial CNTO1959PSO3011 was a phase 3 placebo- and active-controlled clinical trial.

The main trial (through Week 52) was conducted in 2 parts. Part 1 was randomized, placebo- and active comparator-controlled period to evaluate the efficacy, safety, and PK of guselkumab in pediatric subjects in two age group (Part 1a: ≥12 to <18 years of age; Part 1b: ≥6 to <12 years of age) until 16 weeks (primary endpoint). Part 1a subjects were randomized in a 2:1:1 ratio to guselkumab, placebo, and etanercept. Part 1b subjects were randomized in a 1:1:1 ratio to guselkumab, placebo, and etanercept (active comparator).

Part 1 was followed by an uncontrolled period of continuation of treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52 in Part 2, which was an open-label, single-arm period to collect additional efficacy, safety, and PK data with a continuous dose regimen of guselkumab. The active comparator used in the study was etanercept, which was administered SC weekly based on body weight (<63 kg: 0.8 mg/kg; ≥63 kg: 50 mg). All subjects who completed either Part 1 or Part 2 of the main study through Week 52 were offered the opportunity to participate in an open-label long term extension (LTE) phase which will be up to 1 year of treatment period and data will be presented in a separate LTE clinical study report (CSR.)

In this trial, guselkumab was dosed at 1.3 mg/kg for pediatric participants <70 kg BW, using (b) (4) injections to administer the weight-based dose; and at 100 mg fixed dose by PFS-U for pediatric participants ≥70 kg BW.

Of 41 subjects who were randomly assigned to guselkumab at Week 0 and received treatment with guselkumab through Week 16, 58.5% were male, 87.8% were White, with a median body weight of 56.7 kg (range: 26 to 119 kg) and a median age of 14.0 years (range: 6 to 17 years). The majority of subjects (67.4%) were adolescents (≥12 to <18 years) while 32.6% were younger children (≥6 to <12 years. A total of 29 (70.7%) subjects had a baseline body weight <70 kg and 12 (29.3%) subjects had a baseline body weight ≥70 kg. A summary of demographics and baseline characteristics for Part 1 (Study CNTO1959PSO3011) are presented in Table 4.

**Table 4: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3011 Part 1)**

| | Placebo | Guselkumab | Etanercept | Total |
|---|---|---|---|---|
| Analysis set: Full analysis set | 25 | 41 | 26 | 92 |
| Age (years) | | | | |
| N | 25 | 41 | 26 | 92 |
| Mean (SD) | 12.4 (3.63) | 13.4 (2.86) | 12.5 (3.29) | 12.9 (3.20) |
| Median | 13.0 | 14.0 | 12.5 | 13.0 |
| Range | (7; 17) | (6; 17) | (6; 17) | (6; 17) |
| IQ range | (9.0; 16.0) | (12.0; 16.0) | (10.0; 16.0) | (10.0; 16.0) |
| ≥12 to <18 years | 15 (60.0%) | 31 (75.6%) | 16 (61.5%) | 62 (67.4%) |
| ≥6 to <12 years | 10 (40.0%) | 10 (24.4%) | 10 (38.5%) | 30 (32.6%) |
| Sex | | | | |
| N | 25 | 41 | 26 | 92 |
| Male | 12 (48.0%) | 24 (58.5%) | 15 (57.7%) | 51 (55.4%) |
| Female | 13 (52.0%) | 17 (41.5%) | 11 (42.3%) | 41 (44.6%) |
| Undifferentiated | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 0 |
| Race | | | | |
| N | 25 | 41 | 26 | 92 |
| American Indian or Alaska Native | 0 | 0 | 0 | 0 |
| Asian | 1 (4.0%) | 1 (2.4%) | 2 (7.7%) | 4 (4.3%) |
| Black or African American | 2 (8.0%) | 1 (2.4%) | 1 (3.8%) | 4 (4.3%) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 |
| White | 20 (80.0%) | 36 (87.8%) | 22 (84.6%) | 78 (84.8%) |
| Other | 1 (4.0%) | 2 (4.9%) | 0 | 3 (3.3%) |
| Multiple | 0 | 1 (2.4%) | 1 (3.8%) | 2 (2.2%) |
| Not reported | 0 | 0 | 0 | 0 |
| Unknown | 1 (4.0%) | 0 | 0 | 1 (1.1%) |
| Weight, (kg) | | | | |
| N | 25 | 41 | 26 | 92 |
| Mean (SD) | 54.6 (24.82) | 59.4 (20.33) | 56.4 (19.15) | 57.3 (21.19) |
| Median | 51.1 | 56.7 | 51.8 | 55.5 |
| Range | (18; 128) | (26; 119) | (25; 99) | (18; 128) |
| IQ range | (39.4; 61.5) | (43.7; 71.6) | (42.9; 72.0) | (43.0; 70.9) |
| <70 kg | 20 (80.0%) | 29 (70.7%) | 19 (73.1%) | 68 (73.9%) |
| ≥ 70 kg | 5 (20.0%) | 12 (29.3%) | 7 (26.9%) | 24 (26.1%) |

Key: IQ = interquartile
Note: N's for each parameter reflect non-missing values.
Adapted from Attachment TSIDEM01 [TSIDEM01.RTF] [PROD/CNTO1959/PSO3011/DBR_WEEK_16/RE_WEEK_16/TSIDEM01.SAS] 01SEP2023, 10:50

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Table 6

Part 2 of the trial was an open-label, single-arm trial to collect additional efficacy, safety, and PK data for pediatric subjects with a continuous weight-based dose regimen of guselkumab at Weeks 0, 4, and q8w thereafter through Week 52. Part 2 enrolled only subjects aged ≥12 to <18 years. In Part 2, a total of 28 subjects (60.7% male, 100% white) with a median body weight of 67.6 kg (range: 36.2 to 122 kg) and a median age of 15.5 years (range: 12 to 17 years) were enrolled and treated with guselkumab through Week 44. Of these subjects, 16 (57.1%) subjects had a baseline body weight <70 kg and 12 (42.9%) subjects had a baseline body weight ≥70 kg. A summary of demographics and baseline characteristics for Part 2 (Study CNTO1959PSO3011) are presented in Table 5.

**Table 5: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study CNTO1959PSO3011 Part 2)**

| | Guselkumab |
|---|---|
| Analysis set: Full analysis set | 28 |
| Age, (years) | |
| N | 28 |
| Mean (SD) | 15.1 (1.59) |
| Median | 15.5 |
| Range | (12; 17) |
| IQ range | (14.0; 16.0) |
| ≥6 to <12 years | 0 |
| ≥12 to <18 years | 28 (100%) |
| Sex | |
| N | 28 |
| Male | 17 (60.7%) |
| Female | 11 (39.3%) |
| Undifferentiated | 0 |
| Unknown | 0 |
| Race | |
| N | 28 |
| American Indian or Alaska Native | 0 |
| Asian | 0 |
| Black or African American | 0 |
| Native Hawaiian or other Pacific Islander | 0 |
| White | 28 (100%) |
| Other | 0 |
| Multiple | 0 |
| Not reported | 0 |
| Unknown | 0 |
| Weight, (kg) | |
| N | 28 |
| Mean (SD) | 68.42 (17.288) |
| Median | 67.55 |
| Range | (36.2; 122.2) |
| IQ range | (58.90; 73.00) |
| <70 kg | 16 (57.1%) |
| ≥ 70 kg | 12 (42.9%) |

Key: IQ = interquartile

Adapted from Attachment TSIDEM21 [TSIDEM21.RTF]
[PROD/CNTO1959/PSO3011/DBR_WEEK_52/RE_WEEK_52/TSIDEM21.SAS] 01MAY2024, 11:23

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Table 7

All participants who completed either Part 1 or Part 2 of the main trial through Week 52 were offered the opportunity to participate in an open-label LTE, which is ongoing. Subjects were required to return to the study site q8w for safety and efficacy assessments in addition to study intervention administration.

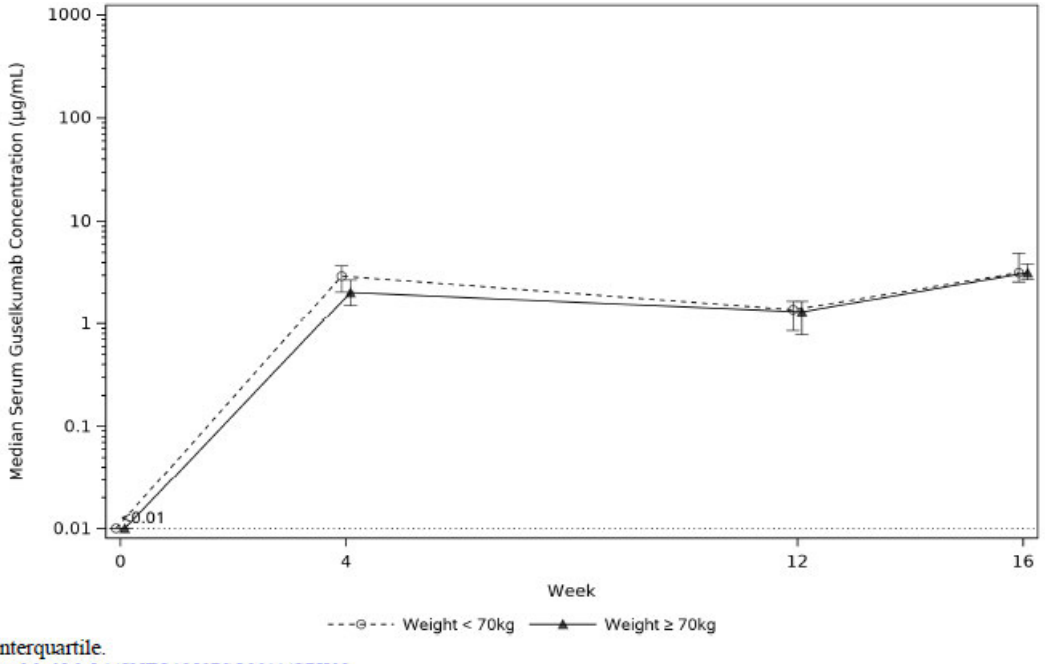
**Pharmacokinetic Results Part 1**:
The mean and median steady-state serum guselkumab concentrations at Week 16 were similar for the <70 kg subjects who received dose based on BW (1.3 mg/kg) and ≥70 kg subjects, who received a flat dose of 100 mg. A tabulated summary of observed serum guselkumab concentrations by baseline body weight (<70 kg who received dose based on BW, ≥70 kg, who received a flat dose of 100 mg) through Week 16 for subject who were treated with guselkumab

(Part 1 and Part 2) is presented in Table 6. For <70 kg group, mean and median serum guselkumab concentrations at Week 16 were 3.57 µg/mL and 3.2 µg/mL, respectively. For the ≥70 kg group, the mean and median serum guselkumab concentrations at Week 16 were 3.3 µg/mL and 3.1 µg/mL, respectively.

The comparison of median of serum concentration by baseline body weight shows that the PK of guselkumab is comparable in participants with BW <70 kg who were administered the 1.3 mg/kg dose and participants with BW ≥70 kg who were administered the 100 mg dose through week 16 as shown in Figure 1. A tabulated summary of serum guselkumab concentrations by baseline body weight (<70 kg who received dose based on BW, ≥70 kg, who received a flat dose of 100 mg) through week 16 is presented in Table 6.

The mean and median serum guselkumab concentrations at Week 16 were slightly lower in the ≥6 to <12 years group compared with the ≥12 to <18 years group, but the concentration ranges largely overlapped (Figure 2). For the subjects in the age group ≥6 to <12 years, the mean and median serum guselkumab concentrations at Week 16 were 2.83 µg/mL and 2.50 µg/mL, respectively. For subjects in the age group ≥12 to <18 years, the mean and median serum guselkumab concentrations at Week 16 were 3.61 µg/mL and 3.34 µg/mL, respectively. The steady-state serum guselkumab concentrations were achieved by Week 20 and were maintained through Week 44.

**Figure 1: The median and IQ range of serum concentration (ug/mL) by baseline body weight (<70 kg and ≥70 kg) through Week 16 (Part 1)**




IQ=interquartile.
Source: Mod5.3.5.1/CNTO1959PSO3011/GPK02

**Table 6: Summary of Observed Serum Guselkumab Concentrations (micrograms/mL) by Baseline Body Weight (<70 kg, ≥70 kg) Through Week 16 for Subjects Treated with Guselkumab (Part 1).**

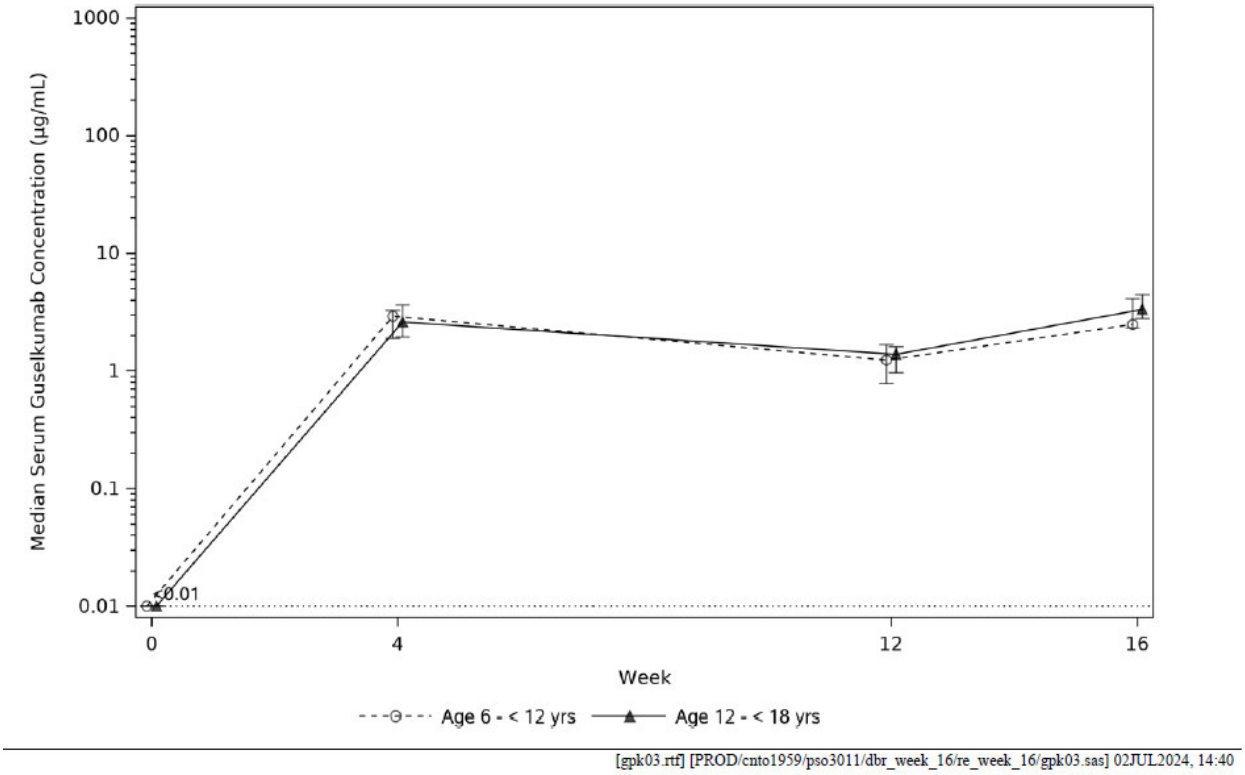
| | < 70 kg | ≥ 70 kg | Combined |
|---|---|---|---|
| Analysis set: Subjects Treated with Guselkumab[a] | 45 | 24 | 69 |
| Week 0 | | | |
| N | 44 | 23 | 67 |
| Mean (SD) | 0.046 (0.307) | 0.000 (0.000) | 0.030 (0.249) |
| Median | 0.000 | 0.000 | 0.000 |
| Range | (0.000, 2.035) | (0.000, 0.000) | (0.000, 2.035) |
| CV (%) | 663.325 | . | 818.535 |
| IQ range | (0.000, 0.000) | (0.000, 0.000) | (0.000, 0.000) |
| Week 4 | | | |
| N | 44 | 23 | 67 |
| Mean (SD) | 2.847 (1.309) | 2.552 (1.261) | 2.746 (1.291) |
| Median | 2.845 | 2.483 | 2.698 |
| Range | (0.180, 6.556) | (0.000, 5.171) | (0.000, 6.556) |
| CV (%) | 45.961 | 49.413 | 47.002 |
| IQ range | (2.141, 3.576) | (1.520, 3.246) | (1.928, 3.534) |
| Week 12 | | | |
| N | 42 | 23 | 65 |
| Mean (SD) | 1.526 (1.242) | 1.501 (0.896) | 1.517 (1.125) |
| Median | 1.233 | 1.429 | 1.347 |
| Range | (0.174, 7.481) | (0.000, 4.074) | (0.000, 7.481) |
| CV (%) | 81.401 | 59.677 | 74.118 |
| IQ range | (0.973, 1.630) | (0.900, 2.063) | (0.955, 1.674) |
| Week 16 | | | |
| N | 42 | 22 | 64 |
| Mean (SD) | 3.568 (1.581) | 3.296 (1.388) | 3.474 (1.512) |
| Median | 3.208 | 3.116 | 3.198 |
| Range | (0.016, 7.696) | (1.302, 6.674) | (0.016, 7.696) |
| CV (%) | 44.318 | 42.111 | 43.519 |
| IQ range | (2.637, 4.461) | (2.321, 3.884) | (2.512, 4.330) |

[a] Include subjects who were randomized to guselkumab at Week 0 and received guselkumab in Part 1 and subjects who received guselkumab in Part 2.

[tpk31b.rtf] [PROD/cnto1959/pso3011/dbr_week_52/re_week_52/tpk31b.sas] 11JUL2024, 21:41

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Table TPK31B (Page 360)

**Figure 2: Median and IQ Range of Serum Guselkumab Concentrations (ug/mL] by Age (6-<12, 12-<18 yrs) Through Week 16 (Part 1)**




Source: Mod5.3.5.1/CNTO1959PSO3011/GPK01

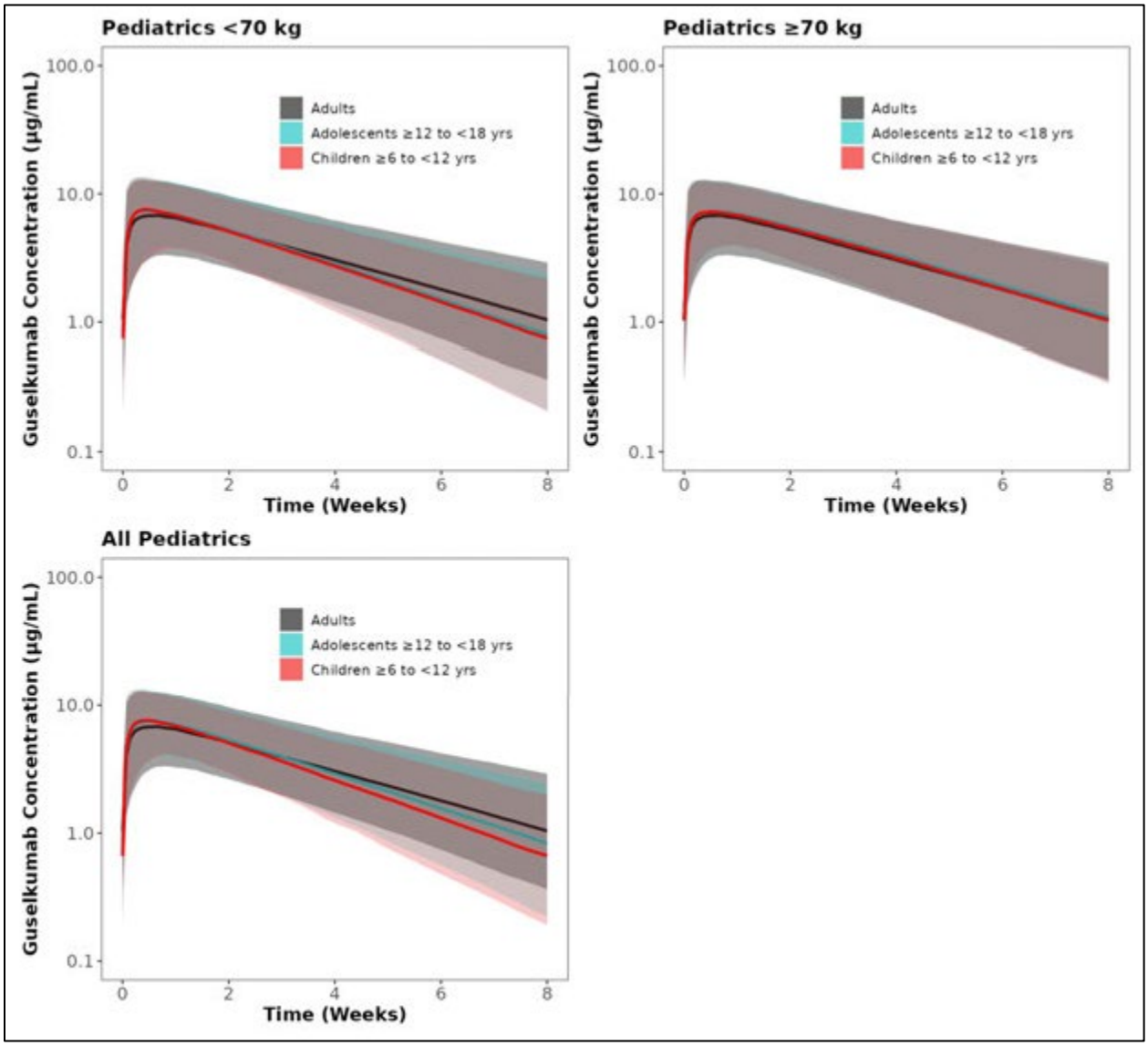
**Pharmacokinetic Results Part 2**:
Mean and median trough serum guselkumab concentrations were comparable at Week 20 (1.52 µg/mL and 1.33 µg/mL, respectively) and Week 28 (1.27 µg/mL and 1.17 µg/mL, respectively) suggesting that serum guselkumab concentrations achieved steady state by Week 20. The mean and median trough serum guselkumab concentrations were maintained at steady state through Week 44 (1.38 µg/mL and 1.36 µg/mL, respectively). There was no evidence of accumulation in serum guselkumab concentrations over time beyond Week 12, where the mean and median trough serum guselkumab concentrations were 1.52 µg/mL and 1.35 µg/mL respectively.

The mean and median steady-state trough serum guselkumab concentrations at Week 20 were similar for the <70 kg and ≥70 kg participants in Part 2. For the <70 kg group, mean and median steady-state trough serum guselkumab concentrations at Week 20 were 1.50 µg/mL and 1.29 µg/mL, respectively. For the ≥70 kg group, the mean and median steady-state trough serum guselkumab concentrations at Week 20 were 1.54 µg/mL and 1.47 µg/mL, respectively.

The model-predicted steady-state guselkumab exposure based on the population PK (popPK) modeling (details are in section 19.4.2 and 19.4.3) between pediatric subjects with BW < 70 kg who received 1.3 mg/kg dose and ≥ 70 kg subjects who received a flat dose of 100 mg when compared to adult subjects who received a flat dose of 100 mg, shows the median guselkumab

concentrations of adolescents and children overlapped and were well within the median and 90% prediction interval of the adult concentrations, despite a slight trend towards a lower steady-state $C_{trough}$ in children with body weight <70 kg (Figure 3).

**Figure 3: Comparison of model-predicted steady state exposures for adolescents (≥12 to <18 years), children (≥6 to <12 years), and adult virtual subjects who received the fixed dose of 100 mg, or a 1.3 mg/kg dose for pediatric subjects weighing <70 kg, as studied in CNTO1959PSO3011**

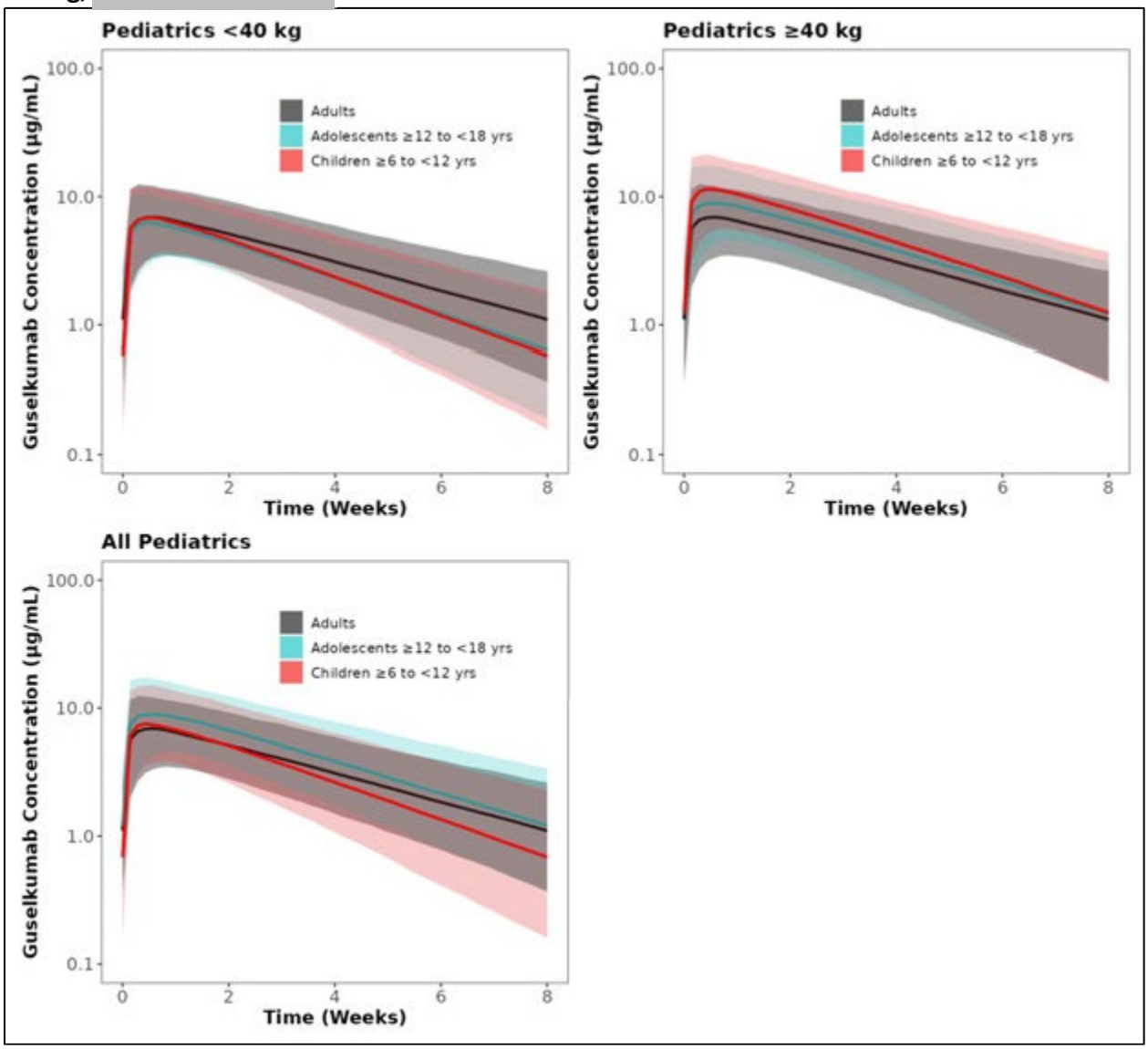



Source: Applicant, Population Pharmacokinetics and Exposure-Response Report, Figure E3

When the model predicted exposures in pediatric subjects with body weight ≥40 kg receiving the 100 mg fixed dose were compared to adult exposures who receive flat dose of 100 mg, the median exposure for this pediatric subset was numerically higher than for adults, however overall exposures were still within the 90% prediction interval of adult exposure.

For pediatric subjects with body weight ≥40 kg receiving the 100 mg fixed dose, the median exposure for this pediatric subset (BW ≥ 40 kg who received a flat dose of 100 mg) was numerically higher when compared to the adults exposure, however overall exposures were still within the 90% prediction interval of adult exposure (Figure 4). This slight increase in exposure in pediatric subjects ≥ 40 kg BW who received a flat dose of 100 mg has no meaningful impact on the exposure-response (ER) for efficacy (section 6.3.2) and safety (section 6.3.3), which support a flat dose of 100 mg down to 40 kg body weight in pediatric subjects. For pediatric subjects with body weight below 40 kg (receiving guselkumab 1.3 mg/kg with a maximum of 45 mg), Ctrough is lower than that of adults (all adult body weights combined).

**Figure 4: Comparison of model-predicted steady state exposures for adolescents (≥12 to <18 years), children (≥6 to <12 years), and adult virtual subjects who received the fixed dose of 100 mg in subjects weighing 40 kg and more, or a 1.3 mg/kg dose for pediatric subjects weighing <40 kg, (b) (4).**



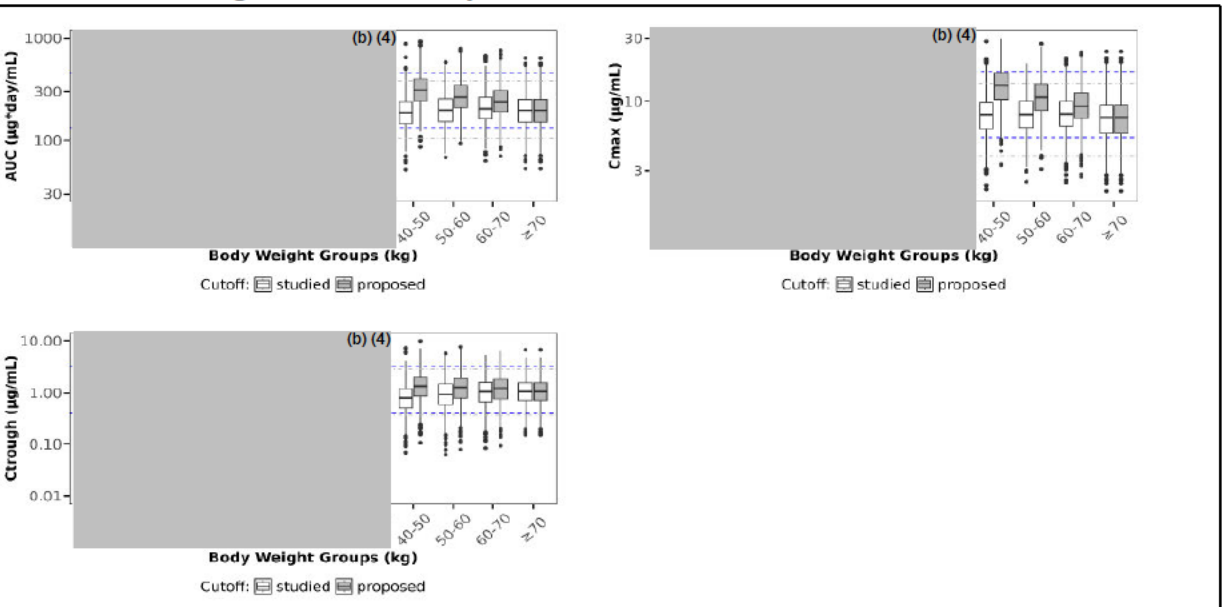

Source: Applicant, Population Pharmacokinetics and Exposure-Response Report, Figure E4

The comparison of model predicted steady state PK exposures metrics for pediatric subjects using "Studied" dosing which represents regimen based on 70 kg body weight cutoff for 100 mg flat guselkumab dose, when compared to "Proposed" dosing which represents regimen based on 40 kg body weight cutoff for 100 mg flat guselkumab dose is shown in Figure 5, where the 90% prediction interval of the overall adult subject exposures (gray dashed lines) and <70 kg adult subject exposures (blue dashed lines).

Note, in Figure 5, (b) (4) at Week 0, 4, and q8w thereafter which were different to that was clinically studied in Trial CNTO1959PSO3011.

The median and IQR of the steady-state exposure metrics $C_{trough}$, AUC, and $C_{max}$ for pediatric subjects in both body weight cutoff groups were within the 90% prediction intervals of the overall adult subject exposures (gray dashed lines) for all body weight groups except the 40 to 50 kg body weight group of the 40 kg body weight cutoff dosing regimen. IQR of steady-state AUC and $C_{max}$ for the 40 to 50 kg weight group were still within the 90% prediction intervals of the <70 kg adult subject exposures (blue dashed lines), which were also found to be safe in Studies CNTO1959PSO3001 and CNTO1959PSO3002. A lower steady-state $C_{trough}$ in children with body weight <70 kg is observed, where inter-quartile range doesn't not cover the 90% exposure observed in adults especially for (b) (4) age groups and is underpredicted in these age groups, when compared to 90% CI range with adult predictions (both overall and in adult participants with body weight cut off <70 kg).

**Figure 5: Simulated steady-state concentration-time profiles for children, adolescents, and adults across different weight categories (proposed 40 kg and studied 70 kg cutoff for the 100 mg fixed dose) compared with those in adults <70 kg that have received the 100 mg guselkumab dose regimen in P-3 study.**




AUC=area under the serum concentration-time curve; Cmax=maximum concentration; Ctrough=trough concentration; IQR=interquartile range; PK=pharmacokinetics. Note: "Studied" and "Proposed" represent regimen based on the 70 kg and 40 kg weight cutoffs. Adults received a 100 mg fixed dose. Note: Simulations consist of virtual participants (1,000/group). The grey dashed lines in each figure represent the 90% prediction intervals of the overall adult steady-state PK metric. The blue dashed lines in each figure represent the 90% prediction interval of the steady-state PK metric in adult participants with body weight <70 kg. Each boxplot represents the median and IQR for each simulated group. The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

Source: Applicant, Response to IR dated May 2, 2025, Figure 1.

Overall, the simulated systemic exposure for a 100 mg flat dose of guselkumab down to 40 kg body weight and between 40 kg to 70 kg in pediatric subjects is supported by the clinical data from Phase 3 trials in adults, especially in adult subjects below 70 kg body weight that were administered a 100 mg flat dose.

## Efficacy

1. **Part 1:** The co-primary efficacy endpoint of an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieved a PASI 90 response at Week 16, were significantly higher in the guselkumab group (65.9% and 56.1%, respectively) compared with the placebo group (16.0% and 16.0%, respectively; p<0.001 and p=0.003, respectively) as shown in Table 7. Furthermore, other co-primary endpoints as defined by the protocol was PASI 75 response at Week 16 and this was significantly higher in the guselkumab group (75.6%) compared with the placebo group (20.0%; p<0.001) as shown in Table 8.

**Table 7: Number of Subjects with an IGA Score of Cleared (0) or Minimal (1) and a PASI 90 Response at Week 16 (Main Analysis); Full Analysis Set (Study CNTO1959PSO3011 Part 1)**

| | Placebo | Guselkumab | Etanercept |
|---|---|---|---|
| Analysis set: Full analysis set | 25 | 41 | 26 |
| Subjects with IGA scores of cleared (0) or minimal (1) | 4 (16.0%) | 27 (65.9%) | 18 (69.2%) |
| Treatment difference (95% CI) | | 49.9 (25.9, 69.4) | 53.2 (27.1, 74.3) |
| p-value | | < 0.001 | < 0.001 |
| PASI 90 responders | 4 (16.0%) | 23 (56.1%) | 14 (53.8%) |
| Treatment difference (95% CI) | | 40.1 (15.6, 61.3) | 37.8 (11.8, 61.8) |
| p-value | | 0.003 | 0.009 |

Note 1: CIs are based on exact method
Note 2: P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled). The primary comparison is between guselkumab and placebo.
[TEFCP01F.RTF] [PROD/CNTO1959/PSO3011/DBR_WEEK_16/RE_WEEK_16/TEFCP01F.SAS] 01SEP2023, 10:49

Source: Applicant, Clinical Study Report CNTO1959PSO3011, Table 10

**Table 8: Number of Subjects with an IGA Score of Cleared (0) or Minimal (1) and a PASI 75 Response at Week 16 (Main Analysis); Full Analysis Set (Study CNTO1959PSO3011 Part 1)**

| | Placebo | Guselkumab | Etanercept |
|---|---|---|---|
| Analysis set: Full analysis set | 25 | 41 | 26 |
| Subjects with IGA scores of cleared (0) or minimal (1) | 4 (16.0%) | 27 (65.9%) | 18 (69.2%) |
| Treatment difference (95% CI) | | 49.9 (25.9, 69.4) | 53.2 (27.1, 74.3) |
| p-value | | <0.001 | <0.001 |
| PASI 75 responders | 5 (20.0%) | 31 (75.6%) | 18 (69.2%) |
| Treatment difference (95% CI) | | 55.6 (32.1, 74.0) | 49.2 (22.4, 71.1) |
| p-value | | <0.001 | <0.001 |

Note 1: CIs are based on exact method
Note 2: P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled). The primary comparison is between guselkumab and placebo.
[TEFCP01.RTF] [PROD/CNTO1959/PSO3011/DBR_WEEK_16/RE_WEEK_16/TEFCP01.SAS] 01SEP2023, 10:49

Source: Applicant, Clinical Study Report CNTO1959PSO3011, Table 9

Subgroup analysis based on demographics, baseline PsO disease characteristics, and previous PsO medication history, confirms the treatment differences (guselkumab vs placebo) in co-primary endpoints observed in the ≥12 to <18 years age group compared with the ≥6 to <12 years age group (IGA score of 0/1: 71% vs 6.7% in ≥12 to <18 years; 50% vs 30% in ≥6 to <12 years; PASI 75: 80.6% vs 13.3% in ≥12 to <18 years; 60% vs 30% in ≥6 to <12 years). A greater treatment differences (guselkumab vs placebo) in co-primary and major secondary endpoints were observed in the ≥12 to <18 years age group compared with the ≥6 to <12 years age group; however, any concreate conclusions could not be made due to limited number of subjects in this lower age group. A Summary of Primary and Major Secondary Endpoints at Week 16 by Age Group; Full Analysis Set (Study CNTO1959PSO3011 Part 1) is presented in Table 9 below.

**Table 9: Summary of Primary and Major Secondary Endpoints at Week 16 by Age Group; Full Analysis Set (Study CNTO1959PSO3011 Part 1)**

| | Placebo | | Guselkumab | | Etanercept | |
|---|---|---|---|---|---|---|
| | 6-<12 yrs | 12-<18 yrs | 6-<12 yrs | 12-<18 yrs | 6-<12 yrs | 12-<18 yrs |
| Analysis set: Full analysis set | 10 | 15 | 10 | 31 | 10 | 16 |
| IGA scores of cleared (0) or minimal (1) | 3 (30.0%) | 1 (6.7%) | 5 (50.0%) | 22 (71.0%) | 6 (60.0%) | 12 (75.0%) |
| IGA scores of cleared (0) | 1 (10.0%) | 0 | 3 (30.0%) | 13 (41.9%) | 2 (20.0%) | 5 (31.3%) |
| PASI 75 responders | 3 (30.0%) | 2 (13.3%) | 6 (60.0%) | 25 (80.6%) | 6 (60.0%) | 12 (75.0%) |
| PASI 90 responders | 3 (30.0%) | 1 (6.7%) | 5 (50.0%) | 18 (58.1%) | 4 (40.0%) | 10 (62.5%) |
| PASI 100 responders | 0 | 0 | 3 (30.0%) | 11 (35.5%) | 2 (20.0%) | 5 (31.3%) |
| CDLQI change from baseline | | | | | | |
| N | 10 | 15 | 10 | 31 | 9 | 15 |
| Mean (SD) | -4.40 (7.260) | 0.13 (5.083) | -3.00 (5.963) | -8.45 (7.715) | -6.00 (5.431) | -6.93 (5.910) |
| Median | -3.50 | 0.00 | -3.00 | -4.00 | -3.00 | -5.00 |
| Range | (-18.0; 4.0) | (-9.0; 10.0) | (-17.0; 6.0) | (-27.0; 3.0) | (-18.0; -2.0) | (-19.0; 4.0) |
| IQ range | (-8.00; 2.00) | (-2.00; 1.00) | (-5.00; 0.00) | (-14.00; -3.00) | (-8.00; -3.00) | (-13.00; -4.00) |

[TEFAGE.RTF] [PROD/CNTO1959/PSO3011/DBR_WEEK_16/RE_WEEK_16/TEFAGE.SAS] 01SEP2023, 10:49

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Table 15

2. **Part 2:** In the open-label uncontrolled Part 2 cohort, 92.9% of subjects achieved a PASI 75 response at Week 52, 82.1% of subjects achieved a PASI 90 response, and 53.6% of subjects achieved a PASI 100 response at Week 52, which was higher when compared to response at Week 16 for PASI 75 (82.1%), PASI 90 (64.3%), and PASI 100 (35.7%), respectively. The proportion of subjects achieving an IGA score of 0/1 was 89.3% at Week 16 and maintained through Week 52 at 85.7%. The proportion of subjects achieving an IGA score of 0 was 46.4% at Week 16 and 75.0% at Week 52.

   The results also showed that the BSA involvement improved from baseline through Week 52, with median BSA involvement decreasing from 24.0% at baseline to 3.0% at Week 16 and 0% at Week 52. Subjects with baseline Children's Dermatology Life Quality Index (CDLQI) scores greater than 1 showed improvements in CDLQI scores of 0 or 1 (indicative of no to minimal impact of skin disease on quality of life) through Week 52. The proportion of subjects achieving a CDLQI 0 or 1 (n=24) increased from 50.0% at Week 8 to 66.7% at Week 52, showing clinical meaningful incremental improvements over the treatment period for 52 weeks. Based on all the efficacy measures evaluated in CNTO1959PSO3011, including IGA scores and PASI responses at Week 16, the weight-based 1.3 mg/kg dose group ( (b) (4) ) and the 100 mg dose (PFS-U) generally demonstrated similar clinical response rates. For more details on Efficacy, refer to section 8.

**Safety results Part 1 and Part 2:** Similar proportions of subjects reported AEs across treatment arms and for both Part 1 and Part 2 of the study. Additionally, similar proportions of subjects reported AEs between age groups (6 to <12 years of age and 12 to <18 years of age). Through the 16-week, randomized, placebo- and active comparator-controlled period, the proportion of subjects experiencing one or more AEs was 41.5% in the guselkumab group, 57.7% in the etanercept group and 68.0% in the placebo group and 1 subject in the guselkumab group reported a SAE, no participants in the placebo or etanercept group reported SAEs. The proportion of subjects with AEs of severe intensity through Week 52 was low; only 1 (3.6%) of 28 subjects in

guselkumab treatment group reported a SAE. The summary of key safety findings in CNTOPSO3011 study is presented in Table 10.

**Table 10: Summary of Key Safety Findings in CNTOPSO3011 Study; Safety Analysis Set**

| | Through Week 16 | | | Through Week 52 | | | | |
|---|---|---|---|---|---|---|---|---|
| | Part 1 | | | Part 1 | | | Part 2 | |
| | Placebo | Guselkumab | Etanercept | Placebo -> Guselkumab | Guselkumab | Etanercept -> Guselkumab | Guselkumab | Combined |
| Analysis set: Safety analysis set | 25 | 41 | 26 | 23 | 41 | 22 | 28 | 114 |
| Avg duration of follow-up (weeks) | 16.3 | 16.4 | 16.1 | 33.6 | 50.1 | 31.7 | 50.8 | 43.4 |
| Subjects who discontinued study agent due to AEs | 1 (4.0%) | 0 | 0 | 0 | 1 (2.4%) | 0 | 1 (3.6%) | 2 (1.8%) |
| Subjects with 1 or more: | | | | | | | | |
| Adverse events | 17 (68.0%) | 17 (41.5%) | 15 (57.7%) | 16 (69.6%) | 33 (80.5%) | 13 (59.1%) | 23 (82.1%) | 85 (74.6%) |
| Serious adverse events | 0 | 1 (2.4%) | 0 | 1 (4.3%) | 1 (2.4%) | 0 | 1 (3.6%) | 3 (2.6%) |
| Any infections | 10 (40.0%) | 12 (29.3%) | 10 (38.5%) | 12 (52.2%) | 25 (61.0%) | 13 (59.1%) | 15 (53.6%) | 65 (57.0%) |
| Serious infections | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections requiring treatment | 3 (12.0%) | 1 (2.4%) | 0 | 5 (21.7%) | 3 (7.3%) | 3 (13.6%) | 1 (3.6%) | 12 (10.5%) |

Placebo → Guselkumab column includes AE events occurred after placebo subjects who crossed over to receive guselkumab.
Etanercapt → Guselkumab column includes AE events occurred after etanercept subjects who crossed over to receive guselkumab

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Source: Summary of Clinical Safety, Table 6

The proportion of subjects in Part 1 through Week 16 with 1 or more infections for guselkumab and etanercept was similar or somewhat comparable to placebo group. There was no observed exposure-response relationship to the AE of infections for guselkumab. The most common infections were nasopharyngitis (12.2% in the guselkumab group, 11.5 % in etanercept group, and 24.0% in the placebo group) and URTI (9.8% in the guselkumab group, 7.7% in the etanercept group, and 8.0% in the placebo group. The proportion of participants with infections were similar across age treatment groups of <12 years when compared to ≥12 years. For more details on safety, refer to section 8.2.

The subgroup analysis for 40 – 70 kg weight group, using pooled observed adult safety, efficacy, and PK data from trials CNTO1959PSO3001 and CNTO1959PSO3002 in adults who received 100 mg flat dose is compared with Trial CNTOPSO3011 in pediatric 40 – 70 kg weight group who received BW based dose of 1.3 mg/kg, for key safety events (AE, SAE, infections, and AE leading to discontinuation) showed that the proportion of subjects with key safety events were similar between adults and pediatric subjects in the 40-70 kg weight subset and are comparable with placebo through week 16 Table 11) and through week 52 (Table 12).

**Table 11: Comparison of safety parameters (TEAEs, SAEs, Infections, or AEs) Leading to Study Intervention Discontinuation Through Week 16 Among Subjects with Baseline Weight Between 40 - <70 Kg in Trial 3011 who received BW based dosing and 40 - <70 Kg in Trials 3001 and 3002 who received flat dosing.**

| | Pediatric Psoriasis | | Adult Psoriasis | |
|---|---|---|---|---|
| | CNTO1959PSO3011 (Part1) | | CNTO1959PSO3001/3002 | |
| | Placebo | Guselkumab | Placebo | Guselkumab |
| Analysis set: Safety analysis set | 13 | 23 | 78 | 125 |
| Avg duration of follow-up (weeks) | 16.1 | 16.4 | 16.2 | 15.9 |
| Participants with 1 or more adverse events | 5 (38.5%) | 9 (39.1%) | 31 (39.7%) | 69 (55.2%) |
| Participants with 1 or more serious adverse events | 0 | 0 | 0 | 2 (1.6%) |
| Participants with 1 or more infections | 4 (30.8%) | 5 (21.7%) | 15 (19.2%) | 31 (24.8%) |
| Participants who discontinued study intervention because of adverse events | 0 | 0 | 1 (1.3%) | 2 (1.6%) |

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Source: Applicant, IR dated May 21, 2025, Table 3

**Table 12: Number of subjects with 1 or More TEAEs, SAEs, Infections, or AEs Leading to Treatment Discontinuation Through 1 Year Among Subjects with Baseline Weight Between 40 - <70 Kg in 3011 who received BW based dosing and 40 - <70 Kg in Trials 3001 and 3002, who received Flat dosing.**

| | Pediatric Psoriasis (0-52 weeks) | | | | Adult Psoriasis (0-48 weeks) | | | |
|---|---|---|---|---|---|---|---|---|
| | CNTO1959PSO3011 (Parts 1& 2) | | | | CNTO1959PSO3001/3002 | | | |
| | Placebo→ guselkumab | Guselkumab | Etanercept→ guselkumab | Combined | Placebo→ guselkumab | Guselkumab | Adalimumab → guselkumab | Combined |
| Analysis set: Safety analysis set | 12 | 38 | 12 | 62 | 76 | 125 | 25 | 226 |
| Avg duration of follow-up (weeks) | 34.8 | 49.4 | 31.5 | 43.1 | 31.8 | 45.5 | 16.0 | 37.7 |
| Participants with 1 or more adverse events | 6 (50.0%) | 30 (78.9%) | 6 (50.0%) | 42 (67.7%) | 42 (55.3%) | 91 (72.8%) | 14 (56.0%) | 147 (65.0%) |
| Participants with 1 or more serious adverse events | 1 (8.3%) | 1 (2.6%) | 0 | 2 (3.2%) | 1 (1.3%) | 5 (4.0%) | 1 (4.0%) | 7 (3.1%) |
| Participants with 1 or more infections | 3 (25.0%) | 20 (52.6%) | 6 (50.0%) | 29 (46.8%) | 29 (38.2%) | 61 (48.8%) | 8 (32.0%) | 98 (43.4%) |
| Participants who discontinued study intervention because of adverse events | 0 | 2 (5.3%) | 0 | 2 (3.2%) | 0 | 2 (1.6%) | 0 | 2 (0.9%) |

Note: Placebo → Guselkumab column includes AE events occurred after placebo subjects who crossed over to receive guselkumab.
Note: Etanercapt → Guselkumab column includes AE events occurred after etanercept subjects who crossed over to receive guselkumab.
Note: Adalimumab → Guselkumab column includes AE events occurred after adalimumab subjects who crossed over to receive guselkumab.

[tscs16sub.rtf] [PROD/cnto1959/z_scs/dbr_2024_04/re_fda_may2025/tscs16sub.sas] 28MAY2025, 03:42

Source: Applicant response to IR dated May 21, 2025, Table 4

### 6.3.2. Exposure-response (efficacy) assessment Part 1 (Week 16) and Part 2 (week 52):

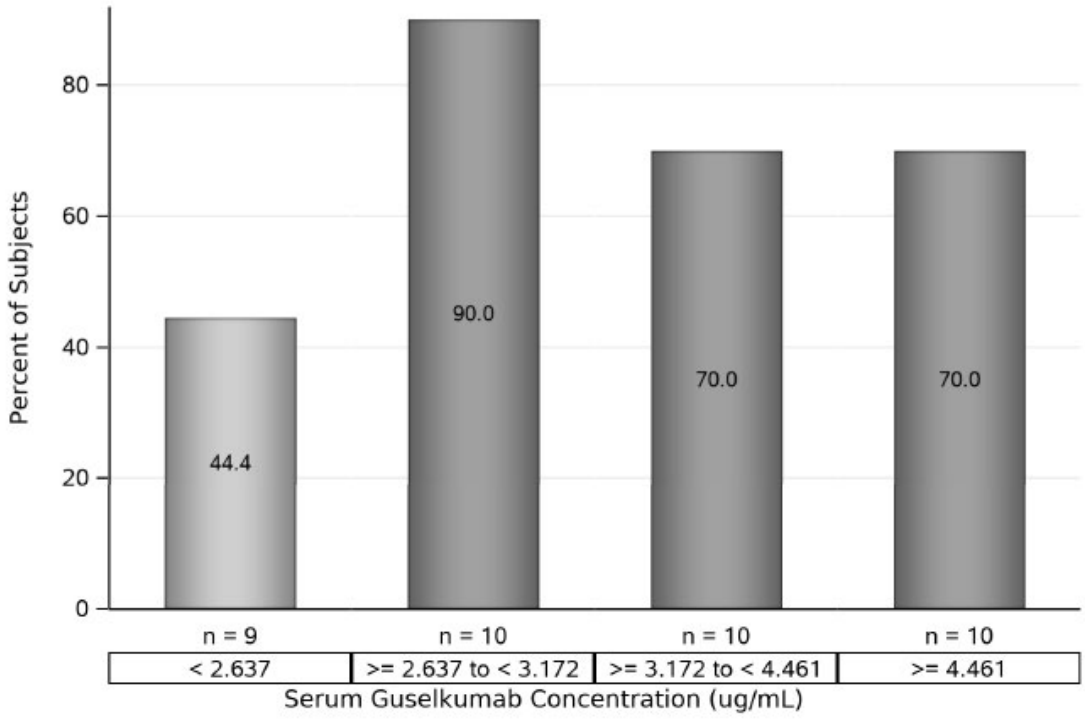
Graphical E-R analysis was performed to explore the relationship between guselkumab exposure and clinical efficacy endpoints to corroborate and supplement the evidence of guselkumab

efficacy in pediatric subjects with PsO. The relationship between systemic exposure to guselkumab and clinical efficacy (improvement in IGA score and PASI) such that the proportion of subjects who achieved an IGA score of 0/1 (IGA score of cleared (0) or minimal (1)), PASI 75 (≥75% improvement in PASI from baseline at Week 16), and PASI 90 (≥90% improvement in PASI from baseline at Week 16) responses at Week 16 were evaluated with respect to serum guselkumab concentration levels at Week 16 and to individual model-predicted $AUC_{week\ 0\text{-}16}$ based on actual subject dosing information for participants randomized to guselkumab at Week 0. The serum guselkumab concentrations at Week 16 were categorized into 4 different levels yielding approximately equal number of subjects in each of the 4 categories:

- First quantifiable level: <2.637 µg/mL
- Second quantifiable level: ≥2.637 µg/mL to <3.172 µg/mL
- Third quantifiable level: ≥3.172 µg/mL to <4.461 µg/mL
- Fourth quantifiable level: ≥4.461 µg/mL

The proportion of subjects who achieved an IGA score of 0/1 at Week 16 was high across concentration categories in subjects with serum guselkumab concentrations ≥2.637 µg/mL (70% to 90.0%), but lower for subjects with serum guselkumab concentrations of <2.637 µg/mL at Week 16 (44.4%). The percent of subjects achieving an IGA score of 0 or 1 at week 16 by serum guselkumab concentrations at eek 16 among subjects randomized to guselkumab at week 0 showed no apparent relationship between guselkumab exposure levels and subjects achieving an IGA score of 0 or 1 at week 16 (Figure 6).

**Figure 6: Percent of Subjects Achieving an IGA Score of 0 or 1 at Week 16 by Serum Guselkumab Concentrations at Week 16 Among Subjects Randomized to Guselkumab at Week 0**

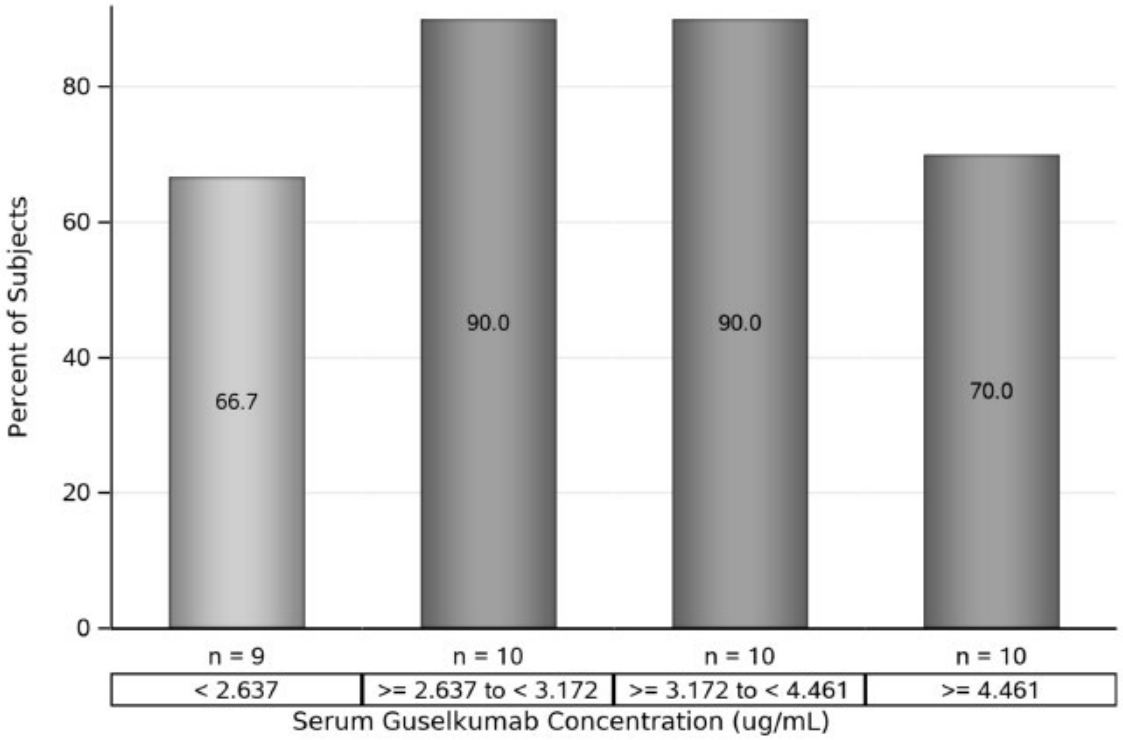



[gpk06.rtf] [PROD/cnto1959/pso3011/dbr_week_16/re_week_16/gpk06.sas] 20AUG2024, 05:06

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Figure 8

The proportion of subjects who achieved PASI 75 response at Week 16 was similar in subjects with serum guselkumab concentrations for the first and fourth quantifiable concentrations category (66.7% and 70.0%). The second and third quantifiable concentration category had a higher percent of subjects with PASI 75 response (90.0% each) when compared with subjects from other quantifiable concentration categories. Notably, PASI 75 response at Week 16 generally did not increase with increasing serum guselkumab concentration levels at Week 16 (Figure 7).

**Figure 7: Percent of Subjects Achieving PASI 75 Response at Week 16 by Serum Guselkumab Concentrations at Week 16 Among Subjects Randomized to Guselkumab at Week 0**




[gpk05.rtf] [PROD/cnto1959/pso3011/dbr_week_16/re_week_16/gpk05.sas] 20AUG2024, 05:06

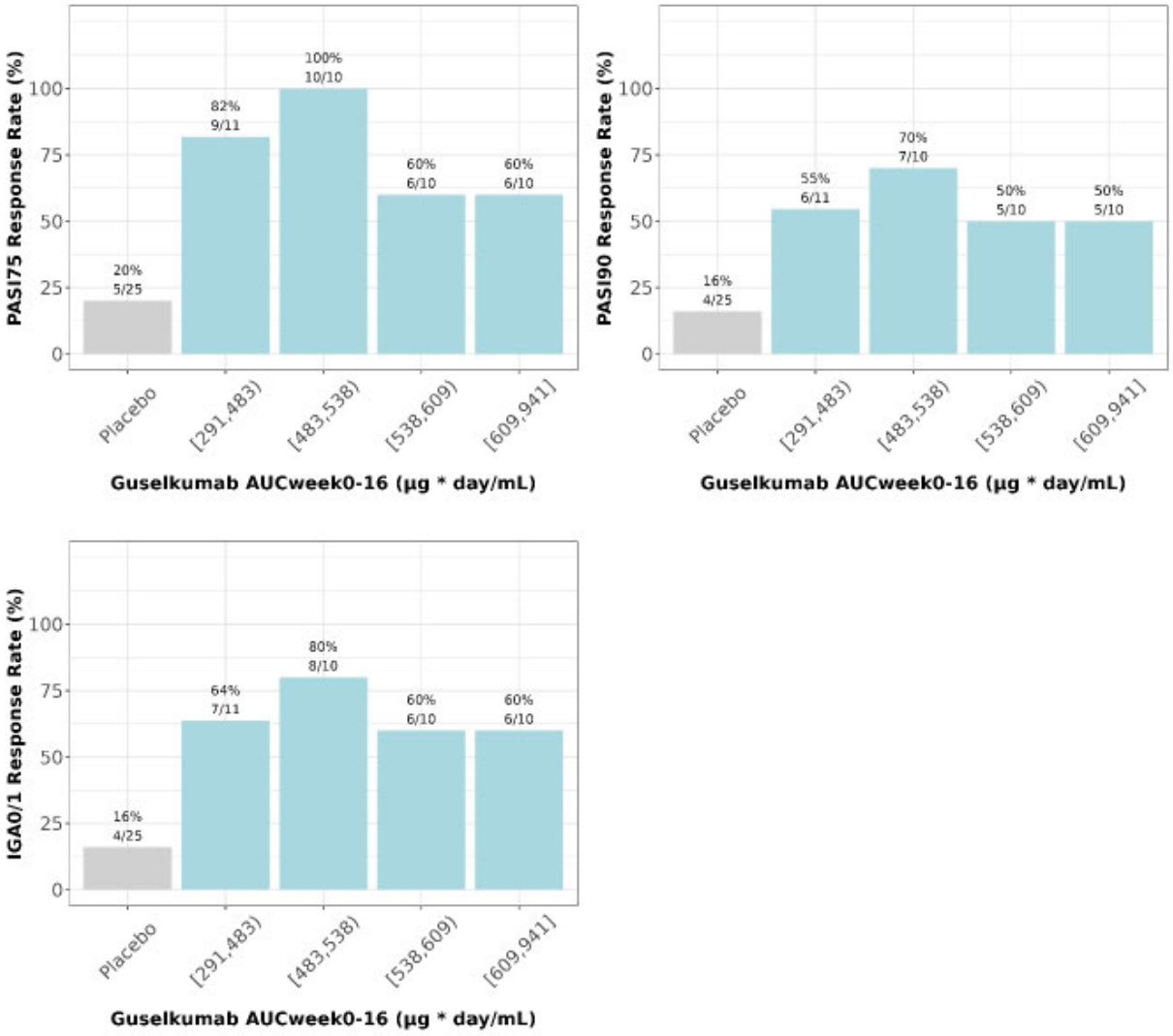
Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, Figure 9

A similar trend is observed for PASI 90 response at Week 16, which did not increase with increasing serum guselkumab concentration levels at Week 16. Overall, there was no apparent relationship between guselkumab exposure levels and efficacy outcomes in pediatric subjects which were comparable with the adult data, where the ER relationship was flat for all co-primary endpoints studied.

This is also evident from the graphical E-R relationships for the guselkumab exposure metric $AUC_{week\ 0\text{-}16}$ and all 3 selected key efficacy endpoints at Week 16, which includes PASI 75, PASI 90 and IGA 0/1 which indicate that there were generally no apparent positive E-R trends across the quartiles of systemic guselkumab AUCweek0-16 and the key efficacy endpoints (Figure 8). Based on all the efficacy measures evaluated in CNTO1959PSO3011, including IGA scores and PASI responses at Week 16, the weight-based 1.3 mg/kg dose group ( (b) (4) ) and the 100 mg dose (PFS-U) generally demonstrated similar clinical response rates.

Overall, there was no ER relationship observed with increase in guselkumab concentration, when compared to co-primary endpoints of PASI 75, PASI 90 and IGA 0/1 in pediatric subjects. It is noted that this behavior is consistent to that observed in adults (link). Since the number of pediatric subjects in each quartile were low, and these results should be interpreted with caution.

**Figure 8: Proportion of Pediatric Subjects Responders Across Efficacy Endpoints (PASI75, PASI 90 and IGA) at Week 16 by Serum Guselkumab AUC, Week 0-16 Quartiles**.




$AUC_{week0-16}$=area under the plasma concentration-time curve from Week 0 to 16; IGA=Investigator's Global Assessment; IGA0/1=IGA score of minimal or cleared; PASI=Psoriasis Area Severity Index; PASI75=75% improvement in PASI score; PASI90=90% improvement in PASI score.
Note: Pediatrics below 70 kg received a 1.3 mg/kg dose, and 70 kg or above received a 100 mg fixed dose.

Source: PopPK report, P-18, Figure E8

Based on the subgroup analyses for the 40 - 70 kg weight group, using pooled observed adult efficacy data from studies CNTO1959PSO3001 and CNTO1959PSO3002 where a flat dose of 100 mg is administered and comparing with the pediatric study CNTO1959PSO3011 data, where BW based dose of 1.3 mg/kg was administered are presented in Table 13.

**Table 13: Summary of PASI and IGA Responses at Week 16 Among Subjects with Baseline Weight Between 40 - <70 Kg in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Full Analysis Set**

| | Pediatric Psoriasis | | Adult Psoriasis | |
|---|---|---|---|---|
| | CNTO1959PSO3011 (Part 1) | | CNTO1959PSO3001/3002 | |
| | Placebo | Guselkumab | Placebo | Guselkumab |
| Analysis set: Full analysis set | 13 | 23 | 78 | 125 |
| IGA scores of cleared (0) or minimal (1) | 2 (15.4%) | 15 (65.2%) | 10 (12.8%) | 112 (89.6%) |
| % Difference (95% CI) [a] | | 49.8 (15.8, 76.2) | | 76.2 (66.8, 85.6) |
| IGA scores of cleared (0) | 1 (7.7%) | 9 (39.1%) | 2 (2.6%) | 67 (53.6%) |
| % Difference (95% CI) [a] | | 31.4 (-2.2, 61.4) | | 50.7 (41.1, 60.4) |
| PASI 75 responders | 3 (23.1%) | 19 (82.6%) | 10 (12.8%) | 116 (92.8%) |
| % Difference (95% CI) [a] | | 59.5 (26.4, 82.2) | | 79.3 (70.4, 88.2) |
| PASI 90 responders | 2 (15.4%) | 14 (60.9%) | 2 (2.6%) | 98 (78.4%) |
| % Difference (95% CI) [a] | | 45.5 (11.3, 72.6) | | 75.8 (67.6, 84.0) |
| PASI 100 responders | 0 | 8 (34.8%) | 2 (2.6%) | 53 (42.4%) |
| % Difference (95% CI) [a] | | 34.8 (1.1, 63.5) | | 39.6 (30.0, 49.1) |

Source: Response to IR dated May 21, 2025, Table 1

*Reviewer summary: Graphical E-R assessment for the IGA 0/1, PASI 75, and PASI 90 response rates in pediatric subjects showed no apparent E-R trend across quartiles of maximum concentration observed at week 16 and AUCweek0-16, when compared to key efficacy endpoints. Based on all the efficacy measures evaluated in CNTO1959PSO3011, including IGA scores and PASI responses at Week 16, the weight-based 1.3 mg/kg dose group (b) (4)) and the 100 mg dose (PFS-U) generally demonstrated similar clinical response rates. Since the number of subjects in each quartile was low, and these results should be interpreted with caution.*

### 6.3.3. Exposure-response (safety) assessment Part 1 (Week 16) and Part 2 (week 52):

Safety events in adults and pediatric subjects treated with guselkumab in the phase 3 trials were comparable to those of the placebo subjects, and there was no apparent exposure–safety relationship across quartiles of exposure metrics. Subgroup analyses for the 40 - 70 kg weight group, using pooled observed adult safety, data from Trials CNTO1959PSO3001 and CNTO1959PSO3002, who received 100 mg flat dose and the pediatric Trial CNTO1959PSO3011 data for the 40 - 70 kg weight group, who received BW based dosing of 1.3 mg/kg. The comparison of number of participants with 1 or more treatment-emergent adverse events, serious adverse events, infections, or adverse events leading to study intervention discontinuation through week 16 and through 1 year of treatment period among

subjects with baseline weight between 40 - <70 Kg in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies is shown in Table 14 and Table 15, respectively.

**Table 14: Number of Subjects with 1 or More TEAEs, SAEs, Infections, or AEs Leading to Drug Discontinuation Through Week 16 Among Subjects with Baseline Weight Between 40 - <70 Kg in Trials 3011, 3001 and 3002**

| | Pediatric Psoriasis | | Adult Psoriasis | |
|---|---|---|---|---|
| | CNTO1959PSO3011 (Part1) | | CNTO1959PSO3001/3002 | |
| | Placebo | Guselkumab | Placebo | Guselkumab |
| Analysis set: Safety analysis set | 13 | 23 | 78 | 125 |
| Avg duration of follow-up (weeks) | 16.1 | 16.4 | 16.2 | 15.9 |
| Participants with 1 or more adverse events | 5 (38.5%) | 9 (39.1%) | 31 (39.7%) | 69 (55.2%) |
| Participants with 1 or more serious adverse events | 0 | 0 | 0 | 2 (1.6%) |
| Participants with 1 or more infections | 4 (30.8%) | 5 (21.7%) | 15 (19.2%) | 31 (24.8%) |
| Participants who discontinued study intervention | 0 | 0 | 1 (1.3%) | 2 (1.6%) |
| because of adverse events | | | | |

Safety Analysis Set
Source: Response to IR dated May 21, 2025, Table 3

**Table 15: Number of Subjects with 1 or More TEAEs, SAEs, Infections, or AEs Leading to Drug Discontinuation Through 1 Year Among Subjects with Baseline Weight Between 40-<70 Kg in Trials 3011, 3001 and 3002**

| | Pediatric Psoriasis (0-52 weeks) | | | | Adult Psoriasis (0-48 weeks) | | | |
|---|---|---|---|---|---|---|---|---|
| | CNTO1959PSO3011 (Parts 1& 2) | | | | CNTO1959PSO3001/3002 | | | |
| | Placebo→ guselkumab | Guselkumab | Etanercept→ guselkumab | Combined | Placebo→ guselkumab | Guselkumab | Adalimumab → guselkumab | Combined |
| Analysis set: Safety analysis set | 12 | 38 | 12 | 62 | 76 | 125 | 25 | 226 |
| Avg duration of follow-up (weeks) | 34.8 | 49.4 | 31.5 | 43.1 | 31.8 | 45.5 | 16.0 | 37.7 |
| Participants with 1 or more adverse events | 6 (50.0%) | 30 (78.9%) | 6 (50.0%) | 42 (67.7%) | 42 (55.3%) | 91 (72.8%) | 14 (56.0%) | 147 (65.0%) |
| Participants with 1 or more serious adverse events | 1 (8.3%) | 1 (2.6%) | 0 | 2 (3.2%) | 1 (1.3%) | 5 (4.0%) | 1 (4.0%) | 7 (3.1%) |
| Participants with 1 or more infections | 3 (25.0%) | 20 (52.6%) | 6 (50.0%) | 29 (46.8%) | 29 (38.2%) | 61 (48.8%) | 8 (32.0%) | 98 (43.4%) |
| Participants who discontinued study intervention because of adverse events | 0 | 2 (5.3%) | 0 | 2 (3.2%) | 0 | 2 (1.6%) | 0 | 2 (0.9%) |

Note: Placebo → Guselkumab column includes AE events occurred after placebo subjects who crossed over to receive guselkumab.

Note: Etanercapt → Guselkumab column includes AE events occurred after etanercept subjects who crossed over to receive guselkumab.
Note: Adalimumab → Guselkumab column includes AE events occurred after adalimumab subjects who crossed over to receive guselkumab.
Safety Analysis Set
Source: Response to IR dated May 21, 2025, Table 4

### 6.3.4. **Assessment of Immunogenicity:**

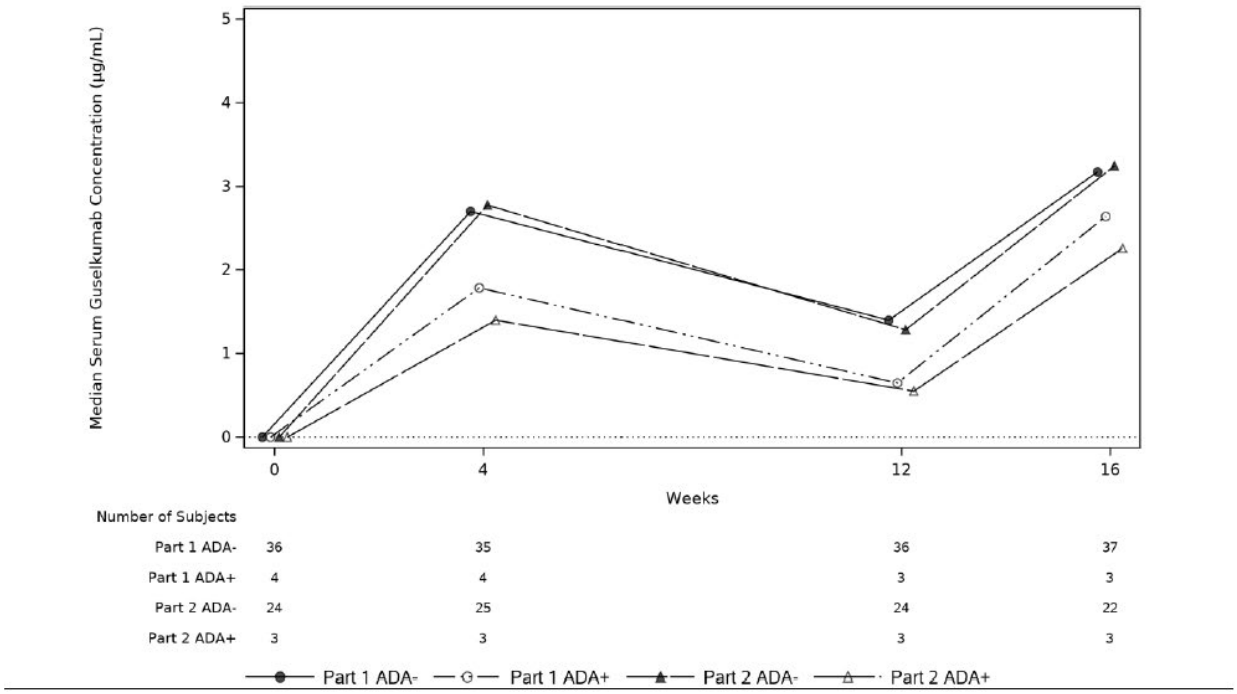
The Applicant has used 2 different validated and sensitive methods to evaluate the immunogenicity of guselkumab in human serum, including initial ECLIA method (referred to as the 'Original EIA method') and a revised DT-ECLIA method using the MSD platform that incorporated an acid dissociation step to improve detection of anti-guselkumab antibodies in the presence of excess guselkumab (referred to as the revised 'DT-EIA method'). The details for each method are summarized in section 19.4.1.

For subjects treated with guselkumab and with available immunogenicity samples (n=114), the overall incidence of anti-drug antibodies (ADA) to guselkumab through Week 44 was 18% (n=21), with titers of antibodies to guselkumab were generally low (80.0% had titer levels ≤1:160) (using the Original EIA method). The incidence in the pediatric study was reported to be somewhat higher with the revised ECLIA method (18.4% (n=21/114) at Week 44), and with the initial plus revised ECLIA methods combined (21.1% (n =24/114) at Week 44). All subjects who tested positive for ADA shows similar efficacy towards IGA score of 0/1, PASI 75 and PASI 90 on or after ADA detection, regardless of the antibody titer level. None of the 24 subjects who were positive for antibodies to guselkumab had antibodies that were able to neutralize (NAb) the bioactivity of guselkumab in vitro. The presence of antibodies to guselkumab and the titer of antibodies to guselkumab neither showed any substantial impact on the PK (based on comparisons of serum guselkumab concentrations between subjects who were positive for antibodies to guselkumab and subjects who were negative for antibodies to guselkumab), nor they were showed to be associated with a reduction in the clinical efficacy (based on the responders for IGA score of 0/1, PASI 75 and PASI 90 on or after ADA detection) of guselkumab. Due to limited number of subjects in the pediatric population studied, a definitive conclusion regarding the impact of antibody titer levels on the clinical efficacy of guselkumab cannot be drawn.

1) **Effect of Antibodies on Pharmacokinetics of Guselkumab:** A total of 4 subjects (9.8%) were postbaseline positive for antibodies to guselkumab through Week 16. The incidence of antibodies to guselkumab through Week 16 was comparable between the 2 baseline body weight groups (<70 kg: 10.3% [3 of 29 subjects]; ≥70 kg: 8.3% [1 of 12 subjects]) and between the 2 age groups (≥6 to <12 years: 10.0% [1 of 10 subjects]; ≥12 to <18 years: 9.7% [3 of 31 subjects]). The overall incidence of antibodies to guselkumab through Week 44 was 18.4% (n=24) for the revised ECLIA method and titers of antibodies to guselkumab were generally low (90% had titer levels ≤1:320 (using the revised DT-EIA method). The presence of antibodies to guselkumab and the titer of antibodies to guselkumab showed some impact on the PK (based on comparisons of serum guselkumab concentrations between subjects who were positive for antibodies to guselkumab and subjects who were

negative for antibodies to guselkumab), where the PK is lower in ADA positive subjects both in Part 1 and Part 2 as shown in Figure 9. None of the 24 subjects who were positive for antibodies to guselkumab at any time were positive for NAbs to guselkumab through Week 44. The impact of ADA formation on the efficacy is discussed in next section.

**Figure 9: Median Guselkumab Concentrations (micrograms/mL) by Treatment-emergent Antibody Status Through Week 16 with Drug Tolerant EIA Method; Pharmacokinetics Analysis Set (Study CNTO1959PSO3011 Part 1 and Part 2).**




Key: ADA+=positive for treatment-emergent anti-drug antibody; ADA -=negative for treatment-emergent anti-drug antibody
Note: Concentration values below LLOQ are considered as 0.
[gpkada41b.rtf] [PROD/cnto1959/pso3011/dbr_week_52/re_week_52/gpkada41b.sas] 19JUL2024, 03:34

Source: Applicant, Week 52 Clinical Study Report CNTO1959PSO3011, GPKADA41B

2) **Effect of Antibodies on Efficacy of Guselkumab:** The development of antibodies to guselkumab and the titer of antibodies to guselkumab with the EIA and DT-EIA assay were not associated with an apparent reduction in the clinical efficacy of guselkumab, as measured by IGA score of 0/1 response, PASI 75 response or PASI 90 response.

Of the 4 subjects in Part 1 that were positive for treatment-emergent antibodies to guselkumab with the DT-EIA assay through Week 16, 3 participants maintained or achieved clinical response (IGA score of 0/1, PASI 75 responders and 2 (50.0%) were PASI 90 responders) after antibodies were detected and showed similar clinical responses compared with the subjects that were antibody negative. One subject with treatment-emergent antibodies to guselkumab was a non-responder through Week 16 for all primary efficacy parameters and 2 participants with treatment-emergent antibodies

were non-responder through Week 16 for PASI 90 response. Overall, the % non-responders that were ADA+ve and ADA -ve were comparable.

For Part 1 and Part 2 through Week 44, a similar pattern was observed with both the EIA or DT-EIA assay, with most subjects in Parts 1 and 2 that were positive for antibodies to guselkumab being responders for IGA score of 0/1, PASI 75 and PASI 90 on or after ADA detection, regardless of the antibody titer level.

There was no observed impact on efficacy (IGA score of 0/1 response, PASI 75 response or PASI 90 response) by the development of antibodies to guselkumab or the titer levels of antibodies to guselkumab through Week 44 in Parts 1 and 2 of this study CNTO1959PSO3011. These finding are comparable to the Phase 3 studies in adult subjects (CNTO1959PSO3001 and CNTO1959PSO3002), where the development of antibodies to guselkumab was not associated with a reduction in the clinical efficacy of guselkumab through Weeks 44 to 52, although the incidence of antibodies to guselkumab in the adult studies was also low.

There is small number of subjects precludes drawing a definitive conclusion regarding the impact of antibody titer levels on the clinical efficacy of guselkumab in the pediatric population studied and the reason for this is not known.

### 6.3.5. Clinical Pharmacology Questions

**1) Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes, the co-primary efficacy endpoints (an IGA score of cleared (0) or minimal (1) and the proportion of participants who achieved a PASI 90 response at Week 16, were significantly higher in the guselkumab group (65.9% and 56.1%, respectively) compared with the placebo group (16.0% and 16.0%, respectively; $p<0.001$ and $p=0.003$, respectively). In addition to this, the protocol defined co-primary endpoints of PASI 75 response at Week 16 was also significantly higher in the guselkumab group (75.6%) compared with the placebo group (20.0%, $p<0.001$).

These finding are consistent with the findings at week 52, where 92.9% of subjects achieved a PASI 75 response, 82.1% of subjects achieved a PASI 90 response, and 53.6% of subjects achieved a PASI 100 response, which it was higher when compared to response at Week 16 for PASI 75 (82.1%), PASI 90 (64.3%), and PASI 100 (35.7%), respectively. The proportion of subjects achieving an IGA score of 0/1 was 89.3% at Week 16 and maintained through Week 52 at 85.7%. The proportion of subjects achieving an IGA score of 0 was 46.4% at Week 16 and 75.0% at Week 52.

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

In the current submission, the proposed dose recommendation for children and adolescents is different from that studied in CNTO1959PSO3011. The proposed pediatric dose for guselkumab, to be given at Week 0, Week 4, and q8w thereafter is:
Body weight ≥40 kg (at time of dose): 100 mg administered with the prefilled syringe (PFS-U); while the dose that was studied is 1.3 mg/kg administered using [redacted] (b) (4) in subjects <70 kg and 100 mg administered with PFS-U in subjects ≥ 70 kg body weight.

The proposed flat dose of 100 mg administered with the prefilled syringe (PFS-U) for pediatrics patients weighing ≥40 kg given at Week 0, 4, and q8w thereafter is acceptable from Clin Pharm prospective based on ER response analysis for efficacy and safety. See Section 6.3.2 and 6.3.3.

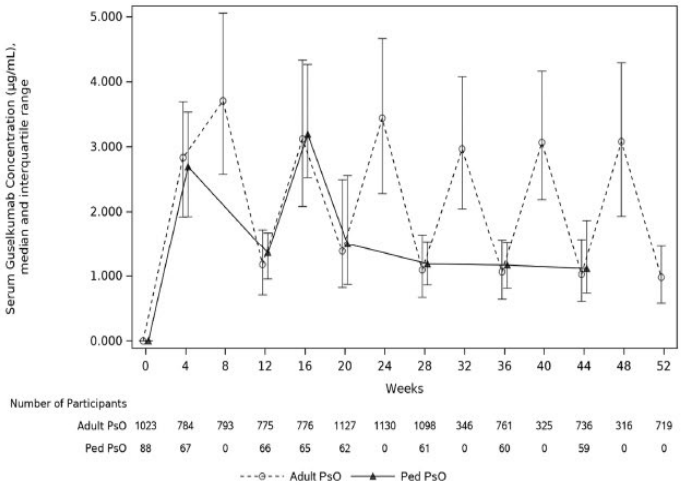
Based on the communication dated 25 July 2025, [redacted] (b) (4) this review is primarily focused on the PK, safety, and efficacy of recommended flat dose for pediatric population with BW ≥ 40 kg.

3) **Is the model predicted PK exposures for adolescents (≥12 to <18 years), children (≥6 to <12 years), and adult virtual participants comparable using Phase 3 dosing [redacted] (b) (4) ?**

PK of guselkumab was compared among subgroup by age (6 to <12 yrs., and 12 to < 18 yrs), showed comparable PK profile among 6 to <12 yrs., and 12 to < 18 yrs age groups using the phase 3 dosing as shown in Figure 2. The observed median serum guselkumab concentrations through Week 52 in adult subjects from CNTO1959PSO3001 and CNTO1959PSO3002, and through Week 44 in pediatric subjects from CNTO1959PSO3011, shows that at Weeks 16, 28, and 44, median serum guselkumab concentrations in pediatric subjects were similar to those in adult participants as shown in Figure 10. Steady state guselkumab concentrations were achieved by Week 12 in both the pediatric as well as the adult population. The steady state, median serum guselkumab concentrations in pediatric subjects ≥70 kg was similar to those in adult subjects ≥70 kg and for pediatric subjects <70 kg was similar to those in adult subjects <70 kg.

For [redacted] (b) (4) dosing, where subjects with BW >40 kg will be dosed with 100 mg flat dosing, and those with BW <40 kg were dosed 1.3 mg/kg BW, the model-predicted steady-state guselkumab exposure between pediatric and adult subjects, shows the median guselkumab concentrations of adolescents and children overlapped and were well within the median and 90% prediction interval of the adult concentrations, despite a slight trend towards a lower steady-state $C_{trough}$ in children with body weight <40 kg as shown in Figure 10.

**Figure 10: Median (IQ range) Serum Guselkumab Concentrations (µg/mL) Over Time in Adult PsO Participants (CNTO1959PSO3001 and CNTO1959PSO3002) and Pediatric PsO subjects (CNTO1959PSO3011)**




IQ=interquartile; N=number of participants; PASI=Psoriasis Area and Severity Index; Ped=pediatric; PK=pharmacokinetic(s); PsO=psoriasis.
Note: Adult PsO includes studies CNTO1959PSO3001 and CNTO1959PSO3002, and Ped PsO includes study CNTO1959PSO3011.
Note: CNTO1959PSO3001 and CNTO1959PSO3002: Participants randomly assigned to adalimumab at Week 0 are not considered. For CNTO1959PSO3002 only, participants who were randomly assigned to guselkumab but withdrew, due to being a PASI 90 responder at Week 28 and re-randomization to placebo, are excluded after guselkumab discontinuation (N=182).
Note: CNTO1959PSO3011: Participants randomly assigned to etanercept at Week 0 are not considered. Participants who were randomly assigned to guselkumab but withdrew treatment due to being a PASI 90 responder at Week 16, are excluded after guselkumab discontinuation (N=23).
Note: For all studies, participants randomly assigned to placebo at Week 0 who later received guselkumab are only included at visits where concentrations were collected after those participants received their first dose of guselkumab (N=20).

Source: Summary of Clinical Pharmacology Studies, Figure 12

**4) Is the proposed 40 kg weight cutoff value for pediatric participants to receive the 100 mg SC dose justified based on analysis of adult and pediatric data to yield comparable guselkumab exposure in pediatric patients?**

The proposed (b) (4) fixed dosing of 100 mg for pediatric subjects in the 40–70 kg body weight range, is supported by pharmacokinetic (PK), efficacy, and safety data pooled from the Applicant's observed data in adults with PsO (studies CNTO1959PSO3001 and CNTO1959PSO3002) and pediatric subjects with PsO (study CNTO1959PSO3011). Furthermore, ER analysis for both efficacy and safety helped justify the acceptability of the 100 mg flat dose in pediatric subjects 40 kg to 70 kg.

**5) Is there any impact of ADA on PK, efficacy, and safety in subjects 6 <18 years. Is this observed impact comparable with adults.**

In CNTO1959PSO3011, the incidence of antibodies to guselkumab was low in each treatment group, and the presence of antibodies to guselkumab did show some decrease in the systemic concentrations of guselkumab; however, there was no apparent impact of ADA status of efficacy and safety. The ADA titer was low and none of the subjects showed any nABs. See Section 6.3.4 for further details.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. **Table of Clinical Studies**

The primary evaluation of the efficacy of guselkumab SC injection in pediatric subjects 6 to < 18 years of age with severe plaque PsO is based on data from the phase 3, multicenter, randomized, placebo- and active comparator-controlled study, conducted at sites in the US, EU, Canada, and Australia, that evaluated the efficacy, safety, and PK of SC administered guselkumab for the treatment of moderate to severe plaque PsO in pediatric subjects ≥6 to <18 years of age. Details of clinical trial that evaluated guselkumab SC injection in pediatric subjects 6 to < 18 years of age with severe plaque PsO to support Supplement 0028 for BLA 761061 is presented in Table  below.

Refer to Appendix 19.4 for tables summarizing the assay validation parameters to support the pharmacologic evaluation. For the determination of serum guselkumab concentrations, the validated ECLIA method used in the clinical studies in support of the current application for pediatric patients with moderate to severe plaque PsO.

**Table 16: Listing of Clinical Trials Relevant to this BLA 761061 S028**

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| | | ***Controlled Studies to Support Efficacy and Safety*** | | | | | | |
| CNTO1959PSO3011 PROTOSTAR 2017-003053-42 | | Randomized placebo and active comparator controlled multicenter study | Guselkumab: 100 mg/mL sterile liquid (b) (4) Subjects received dose levels depending on their weight: Weight <70 kg: 1.3 mg/kg administered using the (b) (4). Weight ≥70 kg: 100 mg administered using the PFS-U. Placebo: Identical devices containing placebo were used to deliver a volume equivalent to that of active treatment for Subjects randomized to the placebo arm. Etanercept: 25 mg powder and solvent for solution for injection and 50 mg PFS. Participant received dose levels depending on their weight: <63 kg: 0.8 mg/kg once weekly using powder and solvent for solution for injection. ≥63 kg: 50 mg once weekly administered using a PFS.<br><br>Route: Formulations to support SC administrations: | To evaluate the efficacy and safety of guselkumab in pediatric subjects aged ≥6 through <18 years with chronic plaque PsO. | **PART 1** Week 0 through Week 16 (Placebo-Controlled Period):<br>Group I: Weight-based guselkumab dose up to 100 mg SC at Weeks 0, 4, and 12.<br>**Group II:** Weight-based placebo for guselkumab dose administered SC at Weeks 0, 4, and 12.<br>Group III: Weight-based open label etanercept dose up to 50 mg SC weekly through Week 15. Week 16 through Week 52 (Withdrawal and Retreatment Period):<br>**Group Ia**: Subjects randomized to guselkumab who were PASI 90 responders at Week 16 did not receive any additional doses of guselkumab until they lost ≥50% of their Week 16 PASI improvement, at which time they received a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and q8w thereafter through Week 52.<br>**Group Ib:** Subjects randomized to guselkumab who were PASI 90 non responders at Week 16 received a placebo SC injection at Week 16 and continued treatment with guselkumab SC q8w from Week 20 through Week 52.<br>Group IIa: Subjects randomized to placebo who were PASI 90 responders at Week 16 did not receive any additional | **Part 1**: Randomized: 92<br><br>Part 2: Enrolled: 28 | Pediatric Subjects (≥6 to <18 years of age) with a diagnosis of chronic plaque-type PsO (with or without PsA) | 9 countries: Belgium, Germany, Hungary, Italy, Netherlands, Poland Australia Canada, USA |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | doses of study intervention until they lost ≥50% of their Week 16 PASI improvement, at which time they received a weight-based guselkumab SC dose, followed by a dose 4 weeks later, and q8w thereafter through Week 52.<br>**Group IIb**: Subjects randomized to placebo who were PASI 90 nonresponders at Week 16 received a weight-based SC dose up to 100 mg guselkumab at Weeks 16 and 20, followed by q8w dosing thereafter through Week 52.<br>**Group III**: Subjects randomized to etanercept who elected to continue in the study received a weight-based guselkumab SC dose at Weeks 20 and 24, followed by q8w dosing thereafter through Week 48.<br>**Part 2:** Subjects enrolled in Part 2 of the study were to receive a weight-based dose of open-label guselkumab SC at Week 0, Week 4, and q8w thereafter through Week 52 | | | |

CSR=clinical study report; kg=kilogram; mg=milligram; PFS=pre-filled syringe; PFS-U=prefilled syringe assembled with the UltraSafe Plus™ Passive Needle Guard; PASI=Psoriasis Area and Severity Index; PsA=psoriatic arthritis; PsO=psoriasis; q8w=every 8 weeks; SC=subcutaneous; (b) (4)

### 7.2. **Review Strategy**

The sources of data used for the evaluation of the efficacy and safety of guselkumab for the proposed indication included clinical study reports submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

- Original submission: \\CDSESUB1\evsprod\BLA761061

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to Section 19.2 Financial Disclosure of this review for additional information.

## 8 Statistical and Clinical and Evaluation

### 8.1. **Review of Relevant Individual Trials Used to Support Efficacy**

#### 8.1.1. **Trial CNTO1959PSO3011**

##### **8.1.1.1. Trial Design**

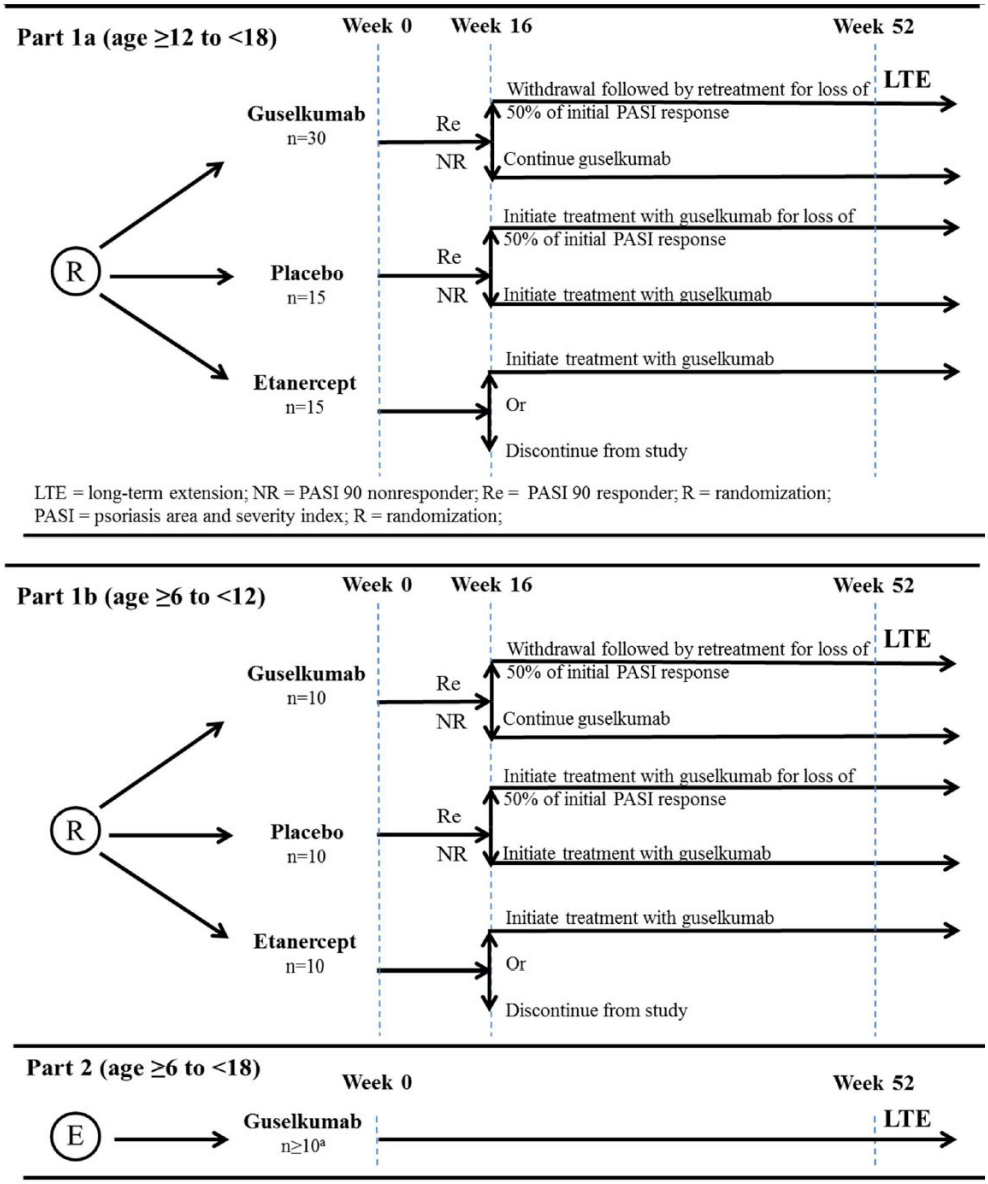
Trial CNTO1959PSO3011 was a multicenter, randomized, double-blind, placebo- and active-controlled, phase 3 trial to evaluate the efficacy, safety, and pharmacokinetics (PK) of subcutaneously administered guselkumab for the treatment of chronic plaque psoriasis in pediatric subjects. For enrollment, the protocol specified the following key inclusion criteria:

- Male or female; ≥6 to <18 years of age
- Subjects must have a diagnosis of chronic plaque-type psoriasis for at least 6 months (with or without psoriatic arthritis), prior to first administration of study intervention, defined as having at screening and baseline with:
  - Investigator's Global Assessment (IGA) score ≥3 (moderate) and
  - Psoriasis Area Severity Index (PASI) score ≥12 and
  - ≥10% body surface area (BSA) involvement and

  at least one of the following:
  - very thick lesions or
  - clinically relevant facial, genital, or hand/ foot involvement or
  - PASI ≥20 or
  - >20% BSA involvement or
  - IGA=4 (severe)

Figure 11 presents the schematic overview for Trial CNTO1959PSO3011. The trial was conducted in 2 parts. In Part 1, the efficacy, safety, and PK of guselkumab was evaluated in pediatric subjects during a 16-week randomized, placebo- and active-controlled period followed by an uncontrolled period of continued treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52.

**Figure 11: Schematic Overview for Trial CNTO1959PSO3011**




E = enrollment; LTE = long-term extension; NR = PASI 90 nonresponder; Re = PASI 90 responder; PASI = Psoriasis Area and Severity Index; R = randomization

[at] The number of subjects to be enrolled is dependent on the number of subjects in Part 1 who are treated with guselkumab and will range from at least 10 subjects to a sufficient number to ensure at least 100 subjects are exposed to guselkumab.

Source: page 14 of the protocol for Trial CNTO1959PSO3011

Part 1 of the trial was divided into Part 1a (≥12 to <18 years of age [i.e., adolescents]) and Part 1b (≥6 to <12 years of age). Part 1a was designed to enrolled and randomize at least 60 subjects in a 2:1:1 ratio to receive either guselkumab (n=30), placebo (n=15), or etanercept (n=15). Part 1b was designed to enrolled and randomize at least 30 subjects in a 1:1:1 ratio to receive either guselkumab (n=10), placebo (n=10), or etanercept (n=10). The protocol specified stratifying the randomization by age group (6 to <12 years and 12 to <18 years) and pooled region (North America [NA], Europe [EU]).

Subjects randomized to guselkumab received a dose based on body weight at Weeks 0, 4, and 12. Subjects received one of the following dose levels depending on their weight:

- Weight <70 kg: 1.3 mg/kg administered using the (b) (4).
- Weight ≥70 kg: 100 mg administered using the prefilled syringe assembled with the UltraSafe Plus™ Passive Needle Guard (PFS-U).

Subjects randomized to placebo received injections at Weeks 0, 4, and 12 with a volume determined using the same weight-base dose calculation and device as for guselkumab. Guselkumab and placebo administrations were given at the study site. Subjects randomized to open-label etanercept received a body weight-based etanercept dose of 0.8mg/kg up to a maximum of 50 mg subcutaneous weekly through Week 15. Subjects randomized to etanercept were given the option to self-administer or have their caregiver administer at home or have the study intervention administered at the study site.

From Week 16, subjects were treated as follows:

- Subjects initially randomized to guselkumab:
  - PASI 90 responders at Week 16 did not receive any additional doses of guselkumab until they lost ≥50% of their Week 16 PASI improvement, at which time they were retreated with guselkumab followed by a dose 4 weeks later, and then guselkumab every 8 weeks (q8w) thereafter through Week 52.
  - PASI 90 nonresponders at Week 16 received a placebo injection at Week 16 to maintain the blind and continued treatment with guselkumab q8w from Week 20 through Week 52.
- Subjects initially randomized to placebo:
  - PASI 90 responders at Week 16 did not receive any additional doses of study intervention until they lost ≥50% of their Week 16 PASI response, at which time they initiated treatment with guselkumab SC followed by a dose 4 weeks later, and q8w thereafter through Week 52.
  - PASI 90 non-responders-initiated treatment with guselkumab at Weeks 16 and 20, and q8w thereafter through Week 52.
- Subjects initially randomized to etanercept:
  - Initiated treatment with guselkumab at Week 20 followed by a dose 4 weeks later, and then q8w thereafter through Week 48.
  - Discontinued from study intervention administration.

Part 2 of the trial consisted of a single, open-label, treatment group, with the aim of collecting additional efficacy, safety, and PK data for pediatric subjects (6 to <18 years of age) with a continuous weight-based dose regimen of guselkumab at Weeks 0 and 4, and q8w thereafter through Week 52. Part 2 was designed to enroll enough additional subjects to achieve a total of at least 100 subjects exposed to guselkumab (i.e., at least 10 subjects in Part 2, with the total number dependent on the number of subjects randomized in Part 1 who were exposed to guselkumab).

Rescue Therapy:
The protocol specified that in Part 1 of the trial, subjects with a PASI score increase of ≥50% from their baseline PASI score at Week 8 or Week 12 will be allowed to use a topical steroid as rescue treatment, with the exception of ultra-high potency topical steroids (e.g., clobetasol propionate, halobetasol propionate) which are not allowed at any time. The protocol instructed those subjects to use no more than 60 grams of topical steroids per week. In addition, these subjects should be managed using the lowest possible potency and frequency of rescue topical steroid. Subjects were specified to discontinue the use of rescue topical steroids by Week 20 (should not initiate rescue topical steroids at or after Week 16).

#### 8.1.1.2. Endpoints

The protocol specified the following two co-primary efficacy endpoints:

- Proportion of subjects achieving an IGA score of 0 (cleared) or 1 (minimal) at Week 16.
- Proportion of subjects with a PASI 90 response (defined as subjects who achieved at least 90% reduction in the PASI composite score from baseline) at Week 16.

The protocol specified the following secondary efficacy endpoints (controlled for multiplicity):

- Proportion of subjects achieving a PASI 75 response at Week 16.
- Proportion of subjects achieving an IGA score of 0 (cleared) at Week 16.
- Proportion of subjects achieving a PASI 100 response at Week 16.
- Change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16.

**Investigator's Global Assessment (IGA) Scale**
The IGA is used to determine the subject's psoriasis lesions overall at a given time point. Overall lesions will be graded for induration, erythema, and scaling based on the scales below. The sum of the 3 scales will be divided by 3 to obtain a final IGA score.

**Induration (I)** (averaged over all lesions; use the National Psoriasis Foundation Reference card for measurement)

0 = no evidence of plaque elevation
1 = minimal plaque elevation, = 0.25 mm
2 = mild plaque elevation, = 0.5 mm
3 = moderate plaque elevation, = 0.75 mm
4 = severe plaque elevation, >1 mm

**Erythema (E)** (averaged over all lesions)

0 = no evidence of erythema, hyperpigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration

**Scaling (S)** (averaged over all lesions)

0 = no evidence of scaling
1 = minimal; occasional fine scale over less than 5% of the lesion

2 = mild; fine scale dominates
3 = moderate; coarse scale predominates
4 = severe; thick, scale predominates

**Total Average = (I + E + S) / 3**

**Investigator's Global Assessment based upon above Total Average**

0 = Cleared, except for residual discoloration
1 = Minimal - majority of lesions have individual scores for I + E + S / 3 that averages 1
2 = Mild - majority of lesions have individual scores for I + E + S / 3 that averages 2
3 = Moderate - majority of lesions have individual scores for I + E + S / 3 that averages 3
4 = Severe - majority of lesions have individual scores for I + E + S / 3 that averages 4

Note: Scores should be rounded to the nearest whole number. If total ≤1.49, score = 1; if total ≥1.50, score = 2.

**Psoriasis Area and Severity Index (PASI)**

The Psoriasis Area and Severity Index or PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) are: 0 = none, 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head.
b. The axillae and groin are part of the trunk.
c. The buttocks are part of the lower extremities.

The PASI formula is:

PASI = 0.1 (Eh + Ih + Sh) Ah + 0.3 (Et + It + St) At + 0.2 (Eu + Iu + Su) Au + 0.4 (El + Il + Sl) Al

Where E = erythema, I = induration, S = scaling, and A = area

**Children's Dermatology Life Quality Index (CDLQI)**

The CDLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a subject's quality of life. It is an adapted version of the Dermatology Life Quality Index (DLQI) for the pediatric population. The CDLQI, a 10-item instrument, has 4 item response options and a recall period of 1 week. The instrument is designed for use in children (i.e., subjects from 4 to 16 years of age), is self-explanatory and can be simply handed to the subjects who is asked to fill it in with the help of the child's parent or caregiver. In addition to evaluating overall quality of life, the CDLQI can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The CDLQI score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease.

#### 8.1.1.3. Statistical Analysis Plan

**Analysis Populations**

The pre-specified primary analysis population for efficacy was the full analysis set (FAS), defined as all randomized subjects in Part 1a and Part 1b. In the efficacy analyses, subjects were analyzed according to their assigned treatment group regardless of their actual treatment received. Of note, there were no subjects in Part 1 that were randomized but not treated.
The protocol and the statistical analysis plan (SAP) specified conducting supportive analyses using a per-protocol (PP) population. The PP population includes subjects in FAS except those:

- who did not meet the inclusion criterion 2 in the protocol as listed below:

  Have a diagnosis of chronic plaque-type psoriasis for at least 6 months (with or without PsA), prior to first administration of study intervention, defined as having at screening and baseline:
  - IGA ≥3 and
  - PASI ≥12 and
  - ≥10% BSA involvement and

  at least one of the following:
  - very thick lesions or
  - clinically relevant facial, genital, or hand/ foot involvement or
  - PASI≥20 or
  - >20% BSA involvement or
  - IGA=4
- who violated the exclusion diagnosis criteria 1 or 2:
  - Currently have nonplaque forms of psoriasis (e.g., erythrodermic, guttate, or pustular).
  - Have current drug-induced psoriasis (e.g., a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
- who violated the concomitant or previous psoriasis medical therapies-related exclusion criteria as listed below:
  - Has previously received guselkumab or etanercept.

  - Has received any anti-TNFα biologic therapy (with the exception of etanercept, see exclusion 9) within the previous 3 months before the first administration of study intervention.
  - Has received any therapeutic agent directly targeted to IL-12/23, IL-17, or IL-23 within 6 months of the first administration of study intervention (including but not limited to ustekinumab, tildrakizumab, secukinumab, ixekizumab, risankizumab, or brodalumab).
  - Has received natalizumab, efalizumab, or agents that deplete B or T cells (e.g., rituximab, alemtuzumab, abatacept, anakinra, or visilizumab) within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population.
  - Has received any systemic immunosuppressants (e.g., methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, hydroxyurea, and tacrolimus) within 4 weeks of the first administration of study intervention.
  - Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, oral or injectable corticosteroids, retinoids, 1,25-dihydroxy vitamin D3 and analogues, psoralens, sulfasalazine, hydroxyurea, fumaric acid derivatives, herbal treatments, or traditional Taiwanese, Korean, or Chinese medicines) within 4 weeks of the first administration of study intervention.
  - Has used topical medications/treatments that could affect psoriasis or IGA evaluations (including, but not limited to, corticosteroids, anthralin, calcipotriene, topical vitamin D derivatives, retinoids, tazarotene, methoxsalen, trimethylpsoralens, pimecrolimus, tacrolimus, or topical traditional Taiwanese, Korean, or Chinese medicines) within 2 weeks of the first administration of study intervention.
  - Is currently receiving lithium, antimalarials, or intramuscular (IM) gold, or has received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study intervention.
  - Has received an experimental antibody or biologic therapy within the previous 6 months or received any other experimental therapy or new investigational agent (topical or systemic) within 30 days or 5 half-lives (whichever is longer) of any study intervention administration or is currently enrolled in another study using an investigational agent or procedure.
- who did not complete the specified exposure to study agent as outline below
  - Subject randomized to guselkumab at Week 0 but did not receive all scheduled guselkumab administrations (i.e., Week 0, Week 4, and Week 12), or received one or more extra guselkumab administrations.
  - Subject randomized to etanercept at Week 0 but missed two or more scheduled etanercept administrations (weekly dose through Week 15) or received one or more extra etanercept administrations.

The SAP specified that subjects who discontinued the study intervention due to unsatisfactory therapeutic effect or an adverse event (AE) of worsening of psoriasis, or subjects who started prohibited medications and continued receiving study agents prior to Week 16 will be included in the per-protocol analysis. Subjects who used rescue medication will also be included in the per-protocol analysis.

**Estimands**

The protocol and SAP specified the following as the main estimands for the co-primary and key secondary efficacy endpoints (binary and continuous endpoints):

Binary Endpoints

- Treatment: guselkumab injection and placebo
- Population: FAS (all randomized subjects in Part 1a and Part 1b)
- Endpoint: a binary response at Week 16
- Intercurrent Events and Strategy for Handling: Composite strategy (non-responder imputation) for initiation of rescue treatment and meeting treatment failure (TF) criteria (discontinuation of study intervention due to lack of efficacy; or due to an AE of worsening of psoriasis; or initiation of a protocol-prohibited medication or therapy that could improve psoriasis).
- Population-level Summary Measure: difference in proportions between guselkumab and placebo

Continuous Endpoints

- Treatment: guselkumab injection and placebo
- Population: FAS (all randomized subjects in Part 1a and Part 1b)
- Endpoint: a continuous response at Week 16
- Intercurrent Events and Strategy for Handling: Composite strategy (imputed as zero change from baseline) for initiation of rescue treatment and meeting TF criteria (discontinuation of study intervention due to lack of efficacy; or due to an AE of worsening of psoriasis; or initiation of a protocol-prohibited medication or therapy that could improve psoriasis).
- Population-level Summary Measure: difference in least squares (LS) means between guselkumab and placebo.

**Analysis Methods**

The protocol and SAP specified the following analysis approaches for the co-primary and key secondary efficacy endpoints:

- Binary endpoints were analyzed using a 2-sided ($\alpha$=0.05) Fisher's exact test, stratified by age group (≥6 to <12 years, ≥12 to <18 years) and pooled region (NA, EU). The p-values and the differences in proportions with exact 95% confidence intervals (CIs) were presented. Missing data was imputed as non-response.
- Continuous endpoints were analyzed using the Mixed Model for Repeated Measures (MMRM) approach with factors of treatment group (guselkumab, placebo, and

etanercept), region (NA, EU), age group (6 - <12 years, 12- <18 years), baseline CDLQI score, visit week, an interaction of baseline CDLQI score and visit, and an interaction of treatment and visit; and with an unstructured (UN) variance-covariance matrix for repeated measures within a subject. The 95% CIs for the difference in LS means between the groups and p-values were presented. Missing data was imputed as zero (i.e., no change from baseline).

**Multiplicity Adjustment Plan**

The protocol specified using a fixed-sequence method to control the Type I error rate. The co-primary and key secondary efficacy endpoints were specified to be tested in the order listed below. Both co-primary efficacy endpoints were tested at a 2-sided α-level of 0.05. If one of the comparisons was not significant at the 2-sided α-level of 0.05, both co-primary efficacy endpoints were considered not significant. The key secondary efficacy endpoints were tested only if both co-primary efficacy endpoints were significant and were tested in the below pre-specified order. If a given key secondary efficacy endpoint was not significant at the 2-sided α-level of 0.05, the remaining key secondary efficacy endpoints in this sequence were considered not significant. The multiplicity adjustment plan is specifically for the comparison between guselkumab and placebo. The protocol and SAP specified producing nominal p-values for the comparisons between etanercept and placebo. The SAP stated that no formal comparison between etanercept and guselkumab will be performed.

Co-Primary Efficacy Endpoints

- Proportion of subjects achieving an IGA score of 0 (cleared) or 1 (minimal) at Week 16.
- Proportion of subjects with a PASI 90 response (defined as subjects who achieved at least 90% reduction in the PASI composite score from baseline) at Week 16.

Key Secondary Efficacy Endpoints

1. Proportion of subjects achieving a PASI 75 response at Week 16.
2. Proportion of subjects achieving an IGA score of 0 (cleared) at Week 16.
3. Proportion of subjects achieving a PASI 100 response at Week 16.
4. Change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16.

**Sensitivity and Supplementary Analyses**

The SAP pre-specified the following sensitivity analyses and supplementary analysis for the co-primary efficacy endpoints:

- Sensitivity Analysis 1: For subjects who had missing IGA or PASI score at Week 16, the score was not imputed. That is, the Fisher's exact test, stratified by age group and region, was performed using observed data after applying treatment failure and rescue treatment rules.
- Sensitivity Analysis 2: Used multiple imputations by fully conditional specification (MI FCS), after applying treatment failure rules and rescue treatment rules. The missing data of the IGA score of 0/1 and PASI 75 responses was imputed with FCS logistic regression with treatment group, region, and age group in the model with 500 imputation and seed = 36789. The proportion of IGA score of 0/1 and PASI 75 responses at Week 16 was

compared between the guselkumab and the placebo group combining the Mantel-Haenszel estimates stratified by region and age group obtained from the multiple imputation datasets using PROC MIANALYZE.

- Per-protocol Analyses: Performed for the co-primary efficacy endpoints; similar to the primary analyses but based on the PP population.

### 8.1.2. Trial Results

#### 8.1.2.1. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial CNTO1959PSO3011 enrolled and randomized a total of 92 subjects (41 to guselkumab, 26 to etanercept and 25 to placebo) from 29 sites. Table 17 presents the subject disposition for Part 1 of the trial. No subjects in the guselkumab group discontinued from the trial or discontinued treatment. The treatment discontinuation rates were higher in the placebo and etanercept groups compared to the guselkumab group.

**Table 17: Subject Disposition – Trial CNTO1959PSO3011**

| | Placebo | Guselkumab | Etanercept |
|---|---|---|---|
| Randomized Subjects | 25 | 41 | 26 |
| Discontinued from Trial, n (%)[1] | 0 | 0 | 2 (7.7%) |
| Withdrawal by parent/guardian | 0 | 0 | 2 (7.7%) |
| Discontinued Treatment, n (%)[1] | 1 (4.0%) | 0 | 3 (11.5%) |
| Adverse events | 1 (4.0%) | 0 | 0 |
| Withdrawal by subject | 0 | 0 | 1 (3.8%) |
| Withdrawal by parent/guardian | 0 | 0 | 2 (7.7%) |

[1] The percentages were calculated based on the number of subjects that were randomized.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); addisp.xpt.

The demographics and baseline disease characteristics were generally balanced across the three treatment groups and are presented in Table 18.

**Table 18: Demographics and Baseline Disease Characteristics – Trial CNTO1959PSO3011 (FAS[2])**

| | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 12.4 (3.6) | 13.4 (2.9) | 12.5 (3.3) |
| Median | 13 | 14 | 12.5 |
| Min, Max | 7, 17 | 6, 17 | 6, 17 |
| Categories, n (%) | | | |
| 6 to <12 years | 10 (40%) | 10 (24.4%) | 10 (38.5%) |
| 12 to <18 years | 15 (60%) | 31 (75.6%) | 16 (61.5%) |
| Sex, n (%) | | | |
| Female | 13 (52%) | 17 (41.5%) | 11 (42.3%) |
| Male | 12 (48%) | 24 (58.5%) | 15 (57.7%) |

| | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Race, n (%) | | | |
| White | 20 (80%) | 36 (87.8%) | 22 (84.6%) |
| Asian | 1 (4%) | 1 (2.4%) | 2 (7.7%) |
| Black or African American | 2 (8%) | 1 (2.4%) | 1 (3.8%) |
| Multiple[2] | 0 (0%) | 1 (2.4%) | 1 (3.8%) |
| Other | 1 (4%) | 2 (4.9%) | 0 (0%) |
| Unknown | 1 (4%) | 0 (0%) | 0 (0%) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 2 (8%) | 2 (4.9%) | 1 (3.8%) |
| Not Hispanic or Latino | 23 (92%) | 39 (95.1%) | 25 (96.2%) |
| Weight (kg) | | | |
| Mean (SD) | 54.6 (24.8) | 59.4 (20.3) | 56.4 (19.1) |
| Median | 51.1 | 56.7 | 51.8 |
| Min, Max | 18, 128.1 | 26, 119.1 | 25, 98.5 |
| Categories, n (%) | | | |
| < 70 kg | 20 (80%) | 29 (70.7%) | 19 (73.1%) |
| ≥ 70 kg | 5 (20%) | 12 (29.3%) | 7 (26.9%) |
| Categories, n (%) | | | |
| < 40 kg | 7 (28%) | 6 (14.6%) | 6 (23.1%) |
| ≥ 40 kg | 18 (72%) | 35 (85.4%) | 20 (76.9%) |
| Region, n (%) | | | |
| Europe | 20 (80%) | 32 (78%) | 21 (80.8%) |
| North America | 5 (20%) | 9 (22%) | 5 (19.2%) |
| History of psoriatic arthritis, n (%) | | | |
| Yes | 1 (4%) | 2 (4.9%) | 0 (0%) |
| No | 24 (96%) | 39 (95.1%) | 26 (100%) |
| Prior phototherapy or conventional systemic therapy, n (%) | | | |
| Yes | 4 (16%) | 15 (36.6%) | 10 (38.5%) |
| No | 21 (84%) | 26 (63.4%) | 16 (61.5%) |
| Prior biologic systemic therapy, n (%) | | | |
| Yes | 1 (4%) | 4 (9.8%) | 4 (15.4%) |
| No | 24 (96%) | 37 (90.2%) | 22 (84.6%) |
| IGA, n (%) | | | |
| Moderate | 20 (80%) | 31 (75.6%) | 21 (80.8%) |
| Severe | 5 (20%) | 10 (24.4%) | 5 (19.2%) |
| PASI | | | |
| Mean (SD) | 18 (4.4) | 19.9 (7) | 17.9 (5.9) |
| Median | 17.2 | 17.5 | 16.6 |
| Min, Max | 12, 31 | 13, 49 | 12, 37 |
| BSA | | | |
| Mean (SD) | 23.4 (9.8) | 25.9 (16.8) | 22.7 (10.4) |
| Median | 20 | 20 | 20 |
| Min, Max | 10, 46 | 10, 75 | 10, 52 |
| CDLQI | | | |
| Mean (SD) | 9.3 (6.6) | 9.4 (7) | 9.6 (6.6) |
| Median | 7 | 8 | 7 |

| | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Min, Max | 1, 24 | 0, 27 | 2, 23 |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b.

[2] Subjects who reported more than one race are categorized as Mixed race.

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adigai.xpt, adpasi.xpt and adcdlqi.xpt.

#### 8.1.2.2. Rescue Medication Use

Table **19** presents the intercurrent events (ICEs) that occurred during Part 1 of Trial CNTO1959PSO3011. No subjects in Part 1 received rescue medication.

**Table 19: ICEs During Part 1 – Trial CNTO1959PSO3011 (FAS[1])**

| ICEs | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Rescue treatment | 0 | 0 | 0 |
| Meeting treatment failure (TF) criteria | | | |
| Lack of efficacy | 0 | 0 | 0 |
| AE of worsening of PsO | 1 (4%) | 0 | 0 |
| Protocol-prohibited medication | 0 | 0 | 0 |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b.

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adtfl.xpt.

#### 8.1.2.3. Results of the Co-Primary Efficacy Endpoints

Table 20 presents the results of the primary efficacy endpoints in the FAS population for Trial CNTO1959PSO3011. In this trial, guselkumab was statistically superior to placebo on both co-primary efficacy endpoints (p-values ≤ 0.003). The results in the PP population (not shown) were similar to those obtained using the FAS.

**Table 20: Results of the Co-Primary Efficacy Endpoint – Trial CNTO1959PSO3011 (FAS[1])**

| | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Proportion of subjects achieving an IGA score of 0 (cleared) or 1 (minimal) at Week 16 | 4 (16.0%) | 27 (65.9%) | 18 (69.2%) |
| Difference (95% CI)[2] | | 49.9% (25.9%, 69.4%) | 53.2% (27.1%, 74.3%) |
| P-value[3] | | <0.001 | <0.001 |
| Proportion of subjects with a PASI 90 response at Week 16 | 4 (16.0%) | 23 (56.1%) | 14 (53.8%) |
| Difference (95% CI)[2] | | 40.1% (15.6%, 61.3%) | 37.8% (11.8%, 61.8%) |
| P-value[3] | | 0.003 | 0.009 |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as non-responders.

[2] CIs are based on exact method.

[3] P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled).

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adigai.xpt and adpasi.xpt.

There were no subjects in the guselkumab and placebo groups that had missing data at Week 16. Two subjects in the etanercept group had missing data at Week 16. Therefore, the results for the Applicant's sensitivity analyses for the handling of missing data were the same as the results for the main analysis (guselkumab vs. placebo).

#### 8.1.2.4. Results of the Key Secondary Efficacy Endpoints

Table 21 presents the results of the key secondary efficacy endpoints. Guselkumab was statistically superior to placebo on all key secondary efficacy endpoints (p-values ≤ 0.002) in Trial CNTO1959PSO3011.

**Table 21: Results of the Key Secondary Efficacy Endpoints – Trial CNTO1959PSO3011 (FAS[1])**

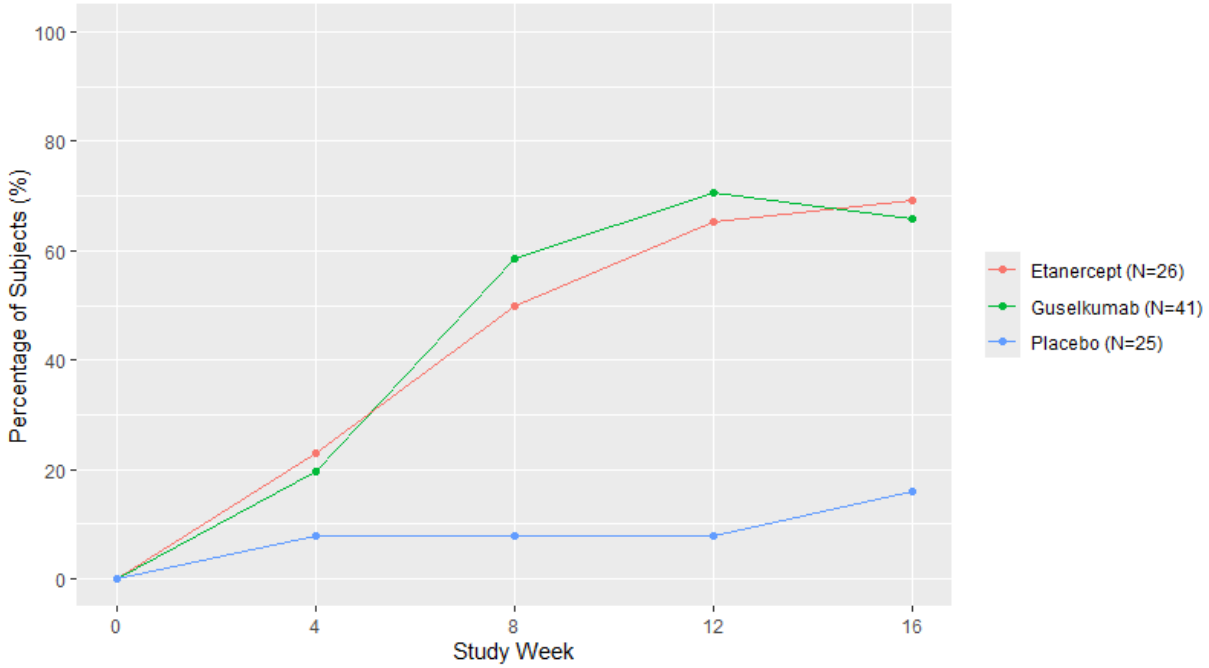
| Endpoint | Placebo (N=25) | Guselkumab (N=41) | Etanercept (N=26) |
|---|---|---|---|
| Proportion of subjects achieving a PASI 75 response at Week 16 | 5 (20%) | 31 (75.6%) | 18 (69.2%) |
| Difference (95% CI)[2] | | 55.6% (32.1%, 74.0%) | 49.2% (22.4%, 71.1%) |
| P-value[3] | | <0.001 | <0.001 |
| Proportion of subjects achieving an IGA score of 0 (cleared) at Week 16 | 1 (4%) | 16 (39%) | 7 (26.9%) |
| Difference (95% CI)[2] | | 35.0% (10.5%, 56.8%) | 22.9% (-3.9%, 48.4%) |
| P-value[3] | | 0.004 | 0.061 |
| Proportion of subjects achieving a PASI 100 response at Week 16 | 0 | 14 (34.1%) | 7 (26.9%) |
| Difference (95% CI)[2] | | 34.1% (9.7%, 56.1%) | 26.9% (0.1%, 51.8%) |
| P-value[3] | | 0.002 | 0.013 |
| Change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16[4] | | | |
| LS Mean | -1.9 | -7.3 | -6.1 |
| Difference (95% CI)[5] | | -5.4 (-7.7, -3.1) | -4.2 (-6.7, -1.6) |
| P-value[5] | | <0.001 | 0.002 |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as non-responders.
[2] CIs are based on exact method.
[3] P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled).
[4] The missing data was imputed as zero change from baseline after applying treatment failure rules and rescue treatment rules.
[5] Least squares (LS) means, confidence interval (CI), and p-value from mixed models for repeated measures (MMRM) model with factors of treatment group, region, age group, baseline CDLQI score, visit, baseline CDLQI score by visit and treatment by visit.
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adeff.xpt and adeffmi.xpt

#### 8.1.2.5. Efficacy over Time

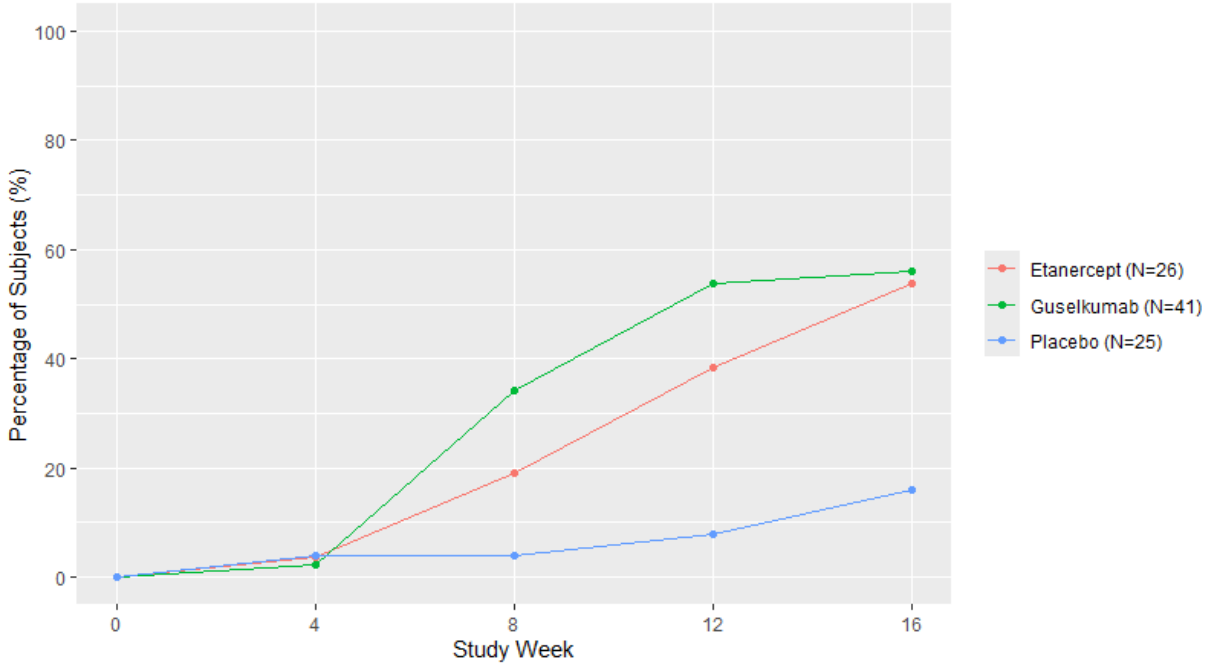
Figure 12 presents the proportion of IGA score of 0 (cleared) or 1 (minimal) by visit for the evaluated regimens. presents the PASI 90 response by visit for the evaluated regimens. For both assessments, the proportions of responders in the guselkumab group were higher than the proportions of responders in the placebo group throughout the trial.

**Figure 12: Results for IGA Score of 0 (Cleared) or 1 (Minimal) by Visit – Trial CNTO1959PSO3011 (FAS[1])**




[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as nonresponders.
Source: Statistical Reviewer's Analysis; adiga.xpt

**Figure 13: Results for PASI 90 Response by Visit – Trial CNTO1959PSO3011 (FAS[1])**




[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as non-responders.
Source: Statistical Reviewer's Analysis; adpasii.xpt

#### 8.1.2.6. Findings in Subgroup Populations

Results for the subgroup analyses by age, sex, race, ethnicity, baseline IGA score, and weight are presented in Table 22 and Table 23. For both co-primary endpoints, the treatment effects were larger in subjects with 12 to <18 years old compared with subjects with 6 to <12 years old, and the treatment effects were larger in subjects with moderate baseline IGA score compared with subjects with severe baseline IGA score. For race and ethnicity, the sample sizes for some of the subgroups were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

**Table 22: Result of IGA score of 0 (Cleared) or 1 (Minimal) at Week 16 by Demographics Subgroups – Trial CNTO1959PSO3011 (FAS[1])**

| Demographic/Subgroup ($N_P$, $N_G$)[2] | Placebo (N=25) | Guselkumab (N=41) | Difference (95% CI)[3] |
|---|---|---|---|
| **Age (years)** | | | |
| 6 to <12 years (10, 10) | 30% | 50% | 20.0% (-27.9%, 61.8%) |
| 12 to <18 years (15, 31) | 6.7% | 71.0% | 64.3% (37.3%, 84.8%) |
| **Gender** | | | |
| Female (13, 17) | 15.4% | 52.9% | 37.6% (0.9%, 66.4%) |
| Male (12, 24) | 16.7% | 75.0% | 58.3% (23.2%, 84.8%) |
| **Race** | | | |
| White (20, 36) | 20.0% | 63.9% | 43.9% (16.8%, 66.7%) |
| Asian (1, 1) | 0 | 100% | Not estimable |
| Black or African American (2, 1) | 0 | 100% | Not estimable |
| Multiple[4] (0, 1) | 0 | 100% | Not estimable |
| Other (1, 2) | 0 | 50% | 50% (-77.0%, 98.7%) |
| Unknow (1, 0) | 0 | 0 | Not estimable |
| **Ethnicity** | | | |
| Hispanic or Latino (2, 2) | 0 | 100% | 100% (-20.5%, 100%) |
| Non-Hispanic or Latino (23, 39) | 17.4% | 64.1% | 46.7% (21.9%, 67.3%) |
| **IGA** | | | |
| Moderate (20, 31) | 10.0% | 61.3% | 51.3% (24.8%, 72.8%) |
| Severe (5, 10) | 40.0% | 80.0% | 40.0% (-18.6%, 85.3%) |
| **Baseline Weight** | | | |
| < 70 kg (20, 29) | 15.0% | 65.5% | 50.5% (22.7%, 72.8%) |
| ≥ 70 kg (5, 12) | 20.0% | 66.7% | 46.7% (-8.6%, 85.3%) |
| **Baseline Weight** | | | |
| < 40 kg (7, 6) | 14.3% | 66.7% | 53.3% (-7.0%, 88.6%) |
| ≥ 40 kg (18, 35) | 16.7% | 65.7% | 49.1% (20.5%, 70.7%) |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as non-responders.
[2] $N_G$: number of subjects received Guselkumab in the category, $N_p$: number of subjects received placebo in the category.
[3] CIs are based on exact method.
[4] Subjects who reported more than one race are categorized as Mixed race.
Source: Statistical Reviewer's Analysis; adigai.xpt, adsl.xpt

**Table 23: Result of PASI 90 Response at Week 16 by Demographics Subgroups – Trial CNTO1959PSO3011 (FAS[1])**

| Demographic/Subgroup ($N_P$, $N_G$)[2] | Placebo (N=25) | Guselkumab (N=41) | Difference (95% CI)[3] |
|---|---|---|---|
| **Age (years)** | | | |
| 6 to <12 years (10, 10) | 30% | 50% | 20.0% (-27.9%, 61.8%) |
| 12 to <18 years (15, 31) | 6.7% | 58.1% | 51.4% (22.8%, 75.1%) |
| **Gender** | | | |
| Female (13, 17) | 15.4% | 52.9% | 37.6% (0.9%, 66.4%) |
| Male (12, 24) | 16.7% | 58.3% | 41.7% (5.2%, 72.3%) |
| **Race** | | | |
| White (20, 36) | 20.0% | 52.8% | 32.8% (5.3%, 57.1%) |
| Asian (1, 1) | 0 | 100% | Not estimable |
| Black or African American (2, 1) | 0 | 100% | Not estimable |
| Multiple[4] (0, 1) | 0 | 100% | Not estimable |
| Other (1, 2) | 0 | 50% | 50% (-77.0%, 98.7%) |
| Unknow (1, 0) | 0 | 0 | Not estimable |
| **Ethnicity** | | | |
| Hispanic or Latino (2, 2) | 0 | 100% | 100% (-20.5%, 100%) |
| Non-Hispanic or Latino (23, 39) | 17.4% | 53.9% | 36.5% (11.2%, 58.6%) |
| **IGA** | | | |
| Moderate (20, 31) | 10.0% | 54.8% | 44.8% (17.7%, 67.2%) |
| Severe (5, 10) | 40.0% | 60.0% | 20.0% (-37.2%, 71.6%) |
| **Baseline Weight** | | | |
| < 70 kg (20, 29) | 15.0% | 58.6% | 43.6% (15.4%, 66.4%) |
| ≥ 70 kg (5, 12) | 20.0% | 50.0% | 30.0% (-24.7%, 71.6%) |
| **Baseline Weight** | | | |
| < 40 kg (7, 6) | 14.3% | 50.0% | 35.7% (-22.9%, 78.8%) |
| ≥ 40 kg (18, 35) | 16.7% | 57.1% | 40.5% (11.4%, 64.3%) |

[1] Full Analysis Set (FAS): all randomized subjects in Part 1a and Part 1b. Subjects with missing data after application of ICEs were considered as non-responders.
[2] $N_G$: number of subjects received Guselkumab in the category, $N_p$: number of subjects received placebo in the category.
[3] CIs are based on exact method.
[4] Subjects who reported more than one race are categorized as Mixed race.
Source: Statistical Reviewer's Analysis; adpasii.xpt, adsl.xpt

### 8.1.2.7 Health Related Outcomes

(b) (4)

a consult review by Division of Clinical Outcome Assessments (DCOA review under IND 105004 Dated November 1, 2017) of these instruments raised several concerns and offered the following assessments:

> "Both the CDLQI and FDLQI may lack item relevancy. For instance, the CDLQI appears to include some concepts that might be relevant in the context of this drug development program (e.g., skin symptoms, embarrassment, social interactions, etc.), however there may be some important concepts that should be measured but are missing. Obtaining patient input would be helpful to ensure that this instrument is a comprehensive

assessment of plaque psoriasis among pediatric patients. The FDLQI measures caregivers' self-reported dermatology related quality of life impacts and caregiver burden. While the impact of plaque psoriasis on a caregiver's quality of life, including the burden of disease, are very important concepts to measure, these concepts do not directly or indirectly measure clinical benefit.

There are issues surrounding the content validity of both instruments. Specifically, the use of multi-barreled questions (questions measuring more than one concept, e.g., Questions 1-2, 5, and 8 for the CDLQI and Questions 1-2, 5-10 for the FDLQI) which can be problematic from a measurement standpoint. If the sponsor in interested in assessment of disease impacts, we encourage them to use a plaque psoriasis-specific instrument that evaluates the impacts of plaque psoriasis signs and symptoms on patients' daily life functioning in order to provide meaningful information on the clinical benefit of their product; we are open to consider any proposals the sponsor may offer."

(b) (4)

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The Applicant conducted Trial CNTO1959PSO3011 (3011) to expand the indication of guselkumab to include the pediatric population ages 6 years and older with moderate to severe psoriasis and to address PMR 3225-1. The safety analysis focused on data from the randomized controlled period of Trial CNTO1959PSO3011 from baseline to Week 16. To inform the long-term safety in the pediatric population, additional uncontrolled data from Week 16 to Week 52 with controlled data from Week 0 to 16 was compared to pooled data from the two phase 3 trials (CNTO1959PSO3001 and CNTO1959PSO3002) that was used to support the initial approval (July 2017) of guselkumab in adults with moderate to severe psoriasis. The Applicant provided additional supportive safety data from Week 52 through January 3, 2025, of Trial CNTO1959PSO3011 in the 120 Day Safety Update Report (SUR). Refer to Section 8.2.9 of this review.

Trial CNTO1959PSO3011 was a randomized double-blind, placebo- and active comparator-controlled trial. The study population included subjects ages 6 to <18 years with moderate to severe plaque psoriasis, defined as Psoriasis Area and Severity score (PASI) ≥12, Investigator Global Assessment score (IGA) ≥3 ("moderate"), and involved body surface area (BSA) ≥10% who were candidates for systemic therapy of phototherapy. The trial was conducted in two parts. In Part 1, subjects were randomized to etanercept, placebo or weight-based dosing of guselkumab from Week 0 to 16. Subcutaneous guselkumab was administered at 1.3mg/kg in subjects weighing <70 kg via (b) (4) and 100 mg in subjects weighing ≥70 kg via pre-filled syringe (PFS). At Week 16, subjects on guselkumab or placebo were re-assigned to or continued on guselkumab if they were PASI 90 non-responders. If they were PASI 90 responders, they

received no treatment until they lost ≥50% of their Week 16 PASI improvement after which they would resume or initiate treatment with guselkumab. All subjects on etanercept were either re-assigned to guselkumab or discontinued the trial. Part 2 was an open-label weight-based dosing of guselkumab SC at Week 0, 4 and every 8 weeks (Q8W) through Week 52. Refer to Section 8.1.1.1 for the trial schematic and details regarding the study population and study design.

The active comparator included in the phase 3 trial was EU-etanercept. (b) (4) an evaluation of comparative safety against the active comparators will be included in this review, (b) (4) .

The review team analyzed following types of data: exposure, demographics and baseline characteristics, treatment emergent adverse events (TEAEs), serious AEs (SAEs), AEs leading to discontinuation and adverse events of special interest (AESI) which included malignancy and active tuberculosis.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

A total of 114 subjects received treatment with guselkumab in Trial CNTO1959PSO3011. By comparison, 1367 subjects received treatment with guselkumab in Trials 3001 and 3002.

**Table 24: Summary of Extent of Exposure Through Week 16 in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002**

| | Pediatric Psoriasis | | Adult Psoriasis | |
|---|---|---|---|---|
| | CNTO1959PSO3011 | | CNTO1959PSO3001/3002 | |
| | Placebo | Guselkumab | Placebo | Guselkumab |
| Analysis set: Safety analysis set | 25 | 41 | 422 | 823 |
| Avg duration of follow-up (weeks) | 16.3 | 16.4 | 15.9 | 16.2 |
| Avg duration of exposure (weeks) | 12.0 | 12.3 | 14.6 | 12.0 |

Source: Table 3, Summary of Clinical Safety, page 17

Through Week 52, the average duration of follow-up for subjects who received guselkumab in Trial CNTO1959PSO3011 was 43.4 weeks. See the table below.

In Part 1 at Week 16, subjects in the placebo and etanercept groups crossed over to guselkumab, and those in guselkumab either continued or withdrew from treatment based on PASI response at Week 16.

- A total of 18 (43.9%) of 41 guselkumab-treated subjects were PASI 90 nonresponders at Week 16 and continued on maintenance guselkumab.
- A total of 23 (56.1%) of 41 guselkumab-treated subjects were PASI 90 responders

at Week 16 and were withdrawn from guselkumab. Four subjects withdrawn from guselkumab required retreatment with guselkumab prior to Week 52.

- Of the 24 (96.0%) of 25 placebo subjects who did not discontinue study intervention prior to Week 16, 20 were PASI 90 nonresponders that continued to receive guselkumab and 4 were PASI 90 responders who were withdrawn from treatment. Three subjects withdrawn from treatment required retreatment with guselkumab, and 1 subject did not require retreatment through Week 52.
- Of the 23 (88.5%) of 26 etanercept subjects who did not discontinue study intervention prior to Week 16, 1 ended study participation at Week 16 and 22 subjects crossed over to receive guselkumab.

In the open-label Part 2 of the study, 28 subjects were enrolled and received guselkumab.

**Table 25: Summary of Extent of Exposure Through 1 Year in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Safety Analysis Set**

| | Pediatric Psoriasis (0-52 weeks) CNTO1959PSO3011 | | | | | Adult Psoriasis (0-48 weeks) CNTO1959PSO3001/3002 - | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Part 1 | | | Part 2 | | | | | |
| | Placebo→ guselkumab | Guselkumab part 1 | Etanercept→ guselkumab | Guselkumab | Combined | Placebo→ guselkumab | Guselkumab | Adalimumab→ guselkumab | Combined |
| Analysis set: Safety analysis set | 23 | 41 | 22 | 28 | 114 | 398 | 823 | 146 | 1367 |
| Avg duration of follow-up (weeks) | 33.6 | 50.1 | 31.7 | 50.8 | 43.4 | 31.6 | 46.5 | 16.8 | 39.0 |
| Avg duration of exposure (weeks) | 25.9 | 28.9 | 27.6 | 42.7 | 31.4 | 19.0 | 37.4 | 9.9 | 29.1 |

Note: Extent of exposure through Week 52 in Trial CNTO1959PSO3011 and through Week 48 in Trials CNTO1959PSO3001 and CNTO1959PSO3002
Source: Table 4, Summary of Clinical Safety, page 18

**Adequacy of the safety database:**

The total subject exposure to guselkumab, 100 mg SC or weight-based dosing (1.3 mg/kg) at Weeks 0, 4, and q8 weeks thereafter for the treatment of moderate to severe plaque psoriasis in the pediatric population provides adequate data for the evaluation of safety. However, the review team identified deficiencies (b) (4) The demographics of the study population are sufficiently representative of the target population. The total exposures for up to one year are sufficient to characterize the safety of the product over longer treatment periods.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of guselkumab in the pediatric population. We evaluated data quality and fitness in conjunction with the Clinical Data Science (CDS) Team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant. However, (b) (4) . Refer to section 4.3 of this review.

**Categorization of Adverse Events**

The Applicant defined an adverse event per International Conference on Harmonisation [ICH] as "any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product."

This definition includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, were recorded using medical terminology in the source document and the case report form (CRF). Whenever possible, diagnoses were provided when signs and symptoms suggested a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators recorded in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management were recorded in the source document and reported according to instructions from the Sponsor.

The Applicant defined a serious AE (SAE) based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

- Is a suspected transmission of any infectious agent via a medicinal product.
- Is medically Important.

The investigator assessed the severity of each AE and SAE reported during the trial according to the following categories:

- **Mild:** Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** Sufficient discomfort is present to cause interference with normal activity.
- **Severe:** Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator assessed the relationship between the intervention and the occurrence of each AE or SAE according to the following categories:

- **Not Related:** An adverse event that is not related to the use of the intervention.
- **Doubtful:** An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible:** An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- **Probable:** An adverse event that might be due to the use of the intervention. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- **Very Likely:** An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

Safety events of interest that were considered for expedited reporting or safety evaluation included overdose, suspected abuse/misuse of the intervention, accidental or occupational exposure or medication error. Investigators recorded these events in the CFR.

All SAEs that had not resolved by the end of the trial or that had not resolved upon discontinuation of the subject were followed until the event resolved, stabilized returned to baseline, were attributed to other agents or the subject was lost to follow-up.

**Routine Clinical Tests**

Safety monitoring was similar to previous trials conducted to evaluate guselkumab in other

populations. However, because the target population included pediatric subjects ages 6 to 17 years old, safety monitoring also included assessments of growth and development. Physical examinations included Tanner staging and head circumference every 12 months to assess sexual maturity, a skin examination and vital signs with assessment of height and weight. Other safety assessments were a clinical evaluation of AEs, SAEs, clinical laboratory evaluation (chemistry, and hematology), and an evaluation of injection site reactions and injection site pain (using the Faces Pain Scale- Revised for children ≥6 to <12 years of age and the linear Injection Pain Visual Analog Scale for children ≥12 to <18 years of age). Safety assessments also included pregnancy testing at every visit. Because of the increased risk of depression and suicidal ideation and behavior among patients with psoriasis, investigators administered the Columbia Suicide Severity Rating Scale (C-SSRS) at screening and all visits. Investigators screened subjects for tuberculosis (TB) prior to enrollment using the QuantiFERON®-TB test and conducted an active assessment of signs and symptoms of TB throughout the trial.

### 8.2.4. Safety Results

**Deaths**

The Applicant reported no deaths in Trial CNTO1959PSO3011.

**Serious Adverse Events**

During the 16-week placebo-controlled period of Trial CNTO1959PSO3011, there was one serious adverse event (SAE) in the guselkumab group. During the open- label period of the trial, there was one SAE in the placebo-guselkumab group in Part 1 and one SAE in the open-label Part 2. The SAEs are presented in the table below.

**Table 26: Summary of Subjects with Serious TEAEs by PT During the DB Period: Week 0-52 (All Safety Subjects)**

| | Guselkumab | Etanercept | Etanercept -> Guselkumab | Placebo | Placebo -> Guselkumab |
|---|---|---|---|---|---|
| | N = 69 | N = 4 | N = 22 | N = 1 | N = 24 |
| Preferred Term | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any SAE | 2 (2.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) |
| Multiple injuries | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Radius fracture | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Chronic tonsillitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Guselkumab" and SAFFL = Y (Guselkumab); TRTSEQA = "Etanercept" and SAFFL = Y (Etanercept); TRTSEQA = "Etanercept->Guselkumab" and SAFFL = Y (Etanercept -> Guselkumab); TRT01A = "Placebo" and TRT02A = "<BLANK>" and SAFFL = Y (Placebo); TRTSEQA = "Placebo->Guselkumab" or "Placebo->Withdraw to Guselkumab" and SAFFL = Y (Placebo -> Guselkumab); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Narrative summaries for SAEs in subjects treated with guselkumab are presented below:

- **Guselkumab group**: A 9-year-old white male (Subject CNTO1959PSO3011-(b) (6)) who received guselkumab 50 mg (Week 0), 55 mg (Week 4) and 50 mg (Week 12) developed a left radius **fracture** after falling from a tree on **Day 78.** He was hospitalized and underwent a reposition fixation. The event was deemed to be severe in intensity and reported as resolved. No action was taken with guselkumab. The subject completed the trial. This reviewer agrees that the event was not related to guselkumab.

- **Placebo-guselkumab group**: A 17-year-old black female (Subject CNTO1959PSO3011-(b) (6)) who received guselkumab 75 mg (at Week 16), 80 mg (at Week 20) followed by 80 mg Q8W developed "worsening of chronic tonsilitis" on **Day 52**. Leukocyte, lymphocyte and neutrophil counts were within normal range. No treatment was reported at the time. On **Day 207**, the subject was hospitalized due to chronic **tonsilitis.** Evaluation by otorhinolaryngology revealed "tonsils to be small" and enlarged adenoids. The subject underwent bilateral adenoidectomy and tonsillectomy. The event was deemed to be moderate in intensity and reported as resolved. No action was taken with guselkumab. The subject completed the trial. Because of the mechanism of action of this product, a role for guselkumab in the onset or progression of infection cannot be excluded.

- **Guselkumab group**: A 17-year-old white female (Subject CNTO1959PSO3011-(b) (6)) who received guselkumab 80 mg Q8W developed multiple injuries after a fall on Day **248**. She was hospitalized with a broken right leg, torn ligaments and tendons in the knee, and damage of the popliteal artery with a comminuted **fracture** of the right "shinbone". She underwent reconstruction surgery of the popliteal artery with vein graft as well as open reduction and internal fixation of the right shin bone fracture. The events (except the peroneal nerve injury) were reported as resolved. No action was taken with guselkumab. This reviewer agrees that the event was not related to guselkumab.

**Dropouts and/or Discontinuations Due to Adverse Effects**

There were 2 treatment emergent adverse events (TEAEs) (2/69, 2.9%) in subjects who received guselkumab and 1 TEAE in a subject who received placebo that led to discontinuation of the study product. The TEAEs which led to discontinuation are presented below.

**Table 27: Summary of Subjects with TEAEs Leading to Drug Discontinuation by PT through Week 0-52**

| Preferred Term | Guselkumab N = 69 n (%) | Etanercept N = 4 n (%) | Etanercept -> Guselkumab N = 22 n (%) | Placebo N = 1 n (%) | Placebo -> Guselkumab N = 24 n (%) |
|---|---|---|---|---|---|
| Any AE | 2 (2.9) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |
| Pregnancy | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Suicidal ideation | 1 (1.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Psoriasis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Guselkumab" and SAFFL = Y (Guselkumab); TRTSEQA = "Etanercept" and SAFFL = Y (Etanercept); TRTSEQA = "Etanercept->Guselkumab" and SAFFL = Y (Etanercept -> Guselkumab); TRT01A = "Placebo" and TRT02A = "<BLANK>" and SAFFL = Y (Placebo); TRTSEQA = "Placebo->Guselkumab" or "Placebo->Withdraw to Guselkumab" and SAFFL = Y (Placebo -> Guselkumab); TRTEMFL = "Y" and AEACN = ("DRUG WITHDRAWN") (Adverse Events).

Narratives for subjects treated with guselkumab who discontinued the study product because of an AE are presented below:

- A 15-year-old white female (CNTO1959PSO3011-(b) (6)) who received guselkumab 75 mg at Weeks 0, 4, and 12 had a positive urine pregnancy test on Day 168 (Week 24). Guselkumab was permanently discontinued. The subject had an unremarkable **pregnancy** and had a spontaneous delivery at 40 weeks gestation. The newborn had no congenital malformations. The event was assessed as not related to guselkumab.

- A 17-year-old white female (CNTO1959PSO3011-(b) (6)) with no relevant medical history developed **suicidal ideation** on Day 10 after one dose of 75 mg of guselkumab. The subject did not report suicidal ideation on the Columbia-suicide severity rating scale (C-SSRS) at Screening or Day 1. On Day 10, the subject reported “non-specific suicidal thought” and “wished to be dead” on the C-SSRS. Concomitant medication included oral contraception with ethinylestradiol/levonorgestrel with unreported start date. The event was deemed as mild and resolving at the time of the report. The subject discontinued guselkumab permanently and did not complete a safety follow up. There is insufficient information regarding concomitant medication history, personal and social history to determine causality. See Section 8.2.5.2.

*Reviewer’s comments:*

*This clinical reviewer assessed these events in subjects who received guselkumab as not related to treatment with guselkumab.*

**Significant Adverse Events**

Refer to Section 8.2.5 of this review for a discussion of the Adverse Events of Special Interest (AESI).

**Treatment Emergent Adverse Events and Adverse Reactions**

Treatment Emergent Adverse Events:

During the 16-week double-blind, placebo- and active comparator-controlled period, the proportion of subjects who developed at least 1 TEAE was greater in the subjects who received placebo (17/25, 68%) than in subjects who received guselkumab (17/41, 41.5%). The system organ class (SOC) in which the most subjects had TEAEs was Infections and Infestations as presented in the table below.

**Table 28: Subjects with TEAEs Affecting ≥1% of the Guselkumab Group by SOC and PT: Week 0-16**

| System Organ Class<br>Preferred Term | Guselkumab<br>N = 41<br>n (%) | Etanercept<br>N = 26<br>n (%) | Placebo<br>N = 25<br>n (%) |
|---|---|---|---|
| Any AE | 17 (41.5) | 15 (57.7) | 17 (68.0) |
| **Infections and infestations** | **12 (29.3)** | **10 (38.5)** | **10 (40.0)** |
| Nasopharyngitis | 5 (12.2) | 3 (11.5) | 7 (28.0) |
| Upper respiratory tract infection | 4 (9.8) | 2 (7.7) | 2 (8.0) |
| Acarodermatitis | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Covid-19 | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Enterobiasis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Pharyngitis | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Rhinitis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Viral infection | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Viral upper respiratory tract infection | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Abscess | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Bacterial vulvovaginitis | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Bronchitis | 0 (0.0) | 2 (7.7) | 0 (0.0) |
| Chronic tonsillitis | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Lice infestation | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Tonsillitis | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Urinary tract infection | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| **Gastrointestinal disorders** | **3 (7.3)** | **3 (11.5)** | **2 (8.0)** |

| | | | |
|---|---|---|---|
| Abdominal pain | 2 (4.9) | 0 (0.0) | 0 (0.0) |
| Enteritis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Abdominal pain upper | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Aphthous ulcer | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Dental caries | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Nausea | 0 (0.0) | 1 (3.8) | 1 (4.0) |
| Vomiting | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Injury, poisoning and procedural complications** | **3 (7.3)** | **1 (3.8)** | **1 (4.0)** |
| Ligament sprain | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Muscle strain | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Radius fracture | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Foot fracture | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Nervous system disorders** | **3 (7.3)** | **1 (3.8)** | **0 (0.0)** |
| Headache | 3 (7.3) | 1 (3.8) | 0 (0.0) |
| Lethargy | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| **Investigations** | **2 (4.9)** | **1 (3.8)** | **0 (0.0)** |
| Blood alkaline phosphatase increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Blood glucose increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| White blood cell count increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Liver function test increased | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| **Cardiac disorders** | **1 (2.4)** | **0 (0.0)** | **0 (0.0)** |
| Ventricular extrasystoles | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| **Eye disorders** | **1 (2.4)** | **0 (0.0)** | **1 (4.0)** |
| Myopia | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Conjunctivitis allergic | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **General disorders and administration site conditions** | **1 (2.4)** | **4 (15.4)** | **2 (8.0)** |
| Injection site erythema | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Application site hematoma | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Fatigue | 0 (0.0) | 2 (7.7) | 0 (0.0) |
| Influenza like illness | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Injection site induration | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Injection site pruritus | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Pyrexia | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Musculoskeletal and connective tissue disorders** | **1 (2.4)** | **3 (11.5)** | **0 (0.0)** |
| Bone pain | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Arthralgia | 0 (0.0) | 2 (7.7) | 0 (0.0) |
| Myalgia | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| **Respiratory, thoracic and mediastinal disorders** | **1 (2.4)** | **0 (0.0)** | **1 (4.0)** |
| Asthma | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Rhinorrhea | 0 (0.0) | 0 (0.0) | 1 (4.0) |

| | | | |
|---|---|---|---|
| Tonsillar hypertrophy | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Skin and subcutaneous tissue disorders** | **1 (2.4)** | **0 (0.0)** | **3 (12.0)** |
| Acne | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Dermatitis contact | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Psoriasis | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Urticaria | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Blood and lymphatic system disorders** | **0 (0.0)** | **0 (0.0)** | **2 (8.0)** |
| Eosinophilia | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Lymphadenopathy | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Immune system disorders** | **0 (0.0)** | **0 (0.0)** | **1 (4.0)** |
| Seasonal allergy | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| **Psychiatric disorders** | **0 (0.0)** | **1 (3.8)** | **0 (0.0)** |
| Anxiety | 0 (0.0) | 1 (3.8) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Guselkumab" and SAFFL = "Y" (Guselkumab); TRT01A = "Etanercept" and SAFFL = "Y" (Etanercept); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

In both placebo and guselkumab groups, nasopharyngitis and upper respiratory tract infection were the most frequently observed TEAEs. In the guselkumab group, these TEAEs were followed in frequency by headache and abdominal pain.

This is displayed in the table below showing TEAEs affecting ≥1% of subjects in the guselkumab group and greater than the placebo group.

**Table 29: Summary of Subjects with TEAEs Affecting ≥1% of the Guselkumab Treatment Group with a ≥1% Difference Over Placebo by PT During the DB Period: Week 0-16**

| Preferred Term | Guselkumab N = 41 n (%) | Etanercept N = 26 n (%) | Placebo N = 25 n (%) |
|---|---|---|---|
| Any AE | 17 (41.5) | 15 (57.7) | 17 (68.0) |
| Nasopharyngitis | 5 (12.2) | 3 (11.5) | 7 (28.0) |
| Upper respiratory tract infection | 4 (9.8) | 2 (7.7) | 2 (8.0) |
| Headache | 3 (7.3) | 1 (3.8) | 0 (0.0) |
| Abdominal pain | 2 (4.9) | 0 (0.0) | 0 (0.0) |
| Acarodermatitis | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Acne | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Asthma | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Blood alkaline phosphatase increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Blood glucose increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Bone pain | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Covid-19 | 1 (2.4) | 0 (0.0) | 0 (0.0) |

| Preferred Term | Guselkumab N = 41 n (%) | Etanercept N = 26 n (%) | Placebo N = 25 n (%) |
|---|---|---|---|
| Any AE | 17 (41.5) | 15 (57.7) | 17 (68.0) |
| Enteritis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Enterobiasis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Injection site erythema | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Lethargy | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Ligament sprain | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Muscle strain | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Myopia | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Pharyngitis | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Radius fracture | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Rhinitis | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Ventricular extrasystoles | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Viral infection | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Viral upper respiratory tract infection | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| White blood cell count increased | 1 (2.4) | 0 (0.0) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Guselkumab" and SAFFL = "Y" (Guselkumab); TRT01A = "Etanercept" and SAFFL = "Y" (Etanercept); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Guselkumab ≥ 1%.

Adverse Reactions:

The review team evaluated the occurrence of adverse reactions in the placebo and active comparator-controlled period, Weeks 0-16. The table below shows that upper respiratory infections (URI), headaches and injection site reactions (ISR) were the most frequently occurring adverse reactions in the guselkumab group.

**Table 30: Summary of Subjects with Adverse Reactions: Week 0-16**

| Group Term<br>Preferred Term | Guselkumab N = 41 n (%) | Etanercept N = 26 n (%) | Placebo N = 25 n (%) |
|---|---|---|---|
| **URI** | **11 (26.8)** | **6 (23.1)** | **8 (32.0)** |
| Nasopharyngitis | 5 (12.2) | 3 (11.5) | 7 (28.0) |

| | | | |
|---|---|---|---|
| Upper respiratory tract infection | 4 (9.8) | 2 (7.7) | 2 (8.0) |
| Pharyngitis | 1 (2.4) | 1 (3.8) | 0 (0.0) |
| Viral upper respiratory tract infection | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| **Headache** | **3 (7.3)** | **1 (3.8)** | **0 (0.0)** |
| Headache | 3 (7.3) | 1 (3.8) | 0 (0.0) |
| **ISR** | **1 (2.4)** | **1 (3.8)** | **1 (4.0)** |
| Injection site erythema | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Application site hematoma | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Injection site induration | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Injection site pruritus | 0 (0.0) | 1 (3.8) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Guselkumab" and SAFFL = "Y" (Guselkumab); TRT01A = "Etanercept" and SAFFL = "Y" (Etanercept); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

The observed adverse reactions in Trial CNTO1959PSO3011 (shown below) are comparable to the adverse reactions occurring in ≥1% of subjects through Week 16 in current guselkumab labeling (see Table 31 below).

**Table 31: Summary of Adverse Reactions by Group Pooled Term: Week 0-16**

| Group Pooled Term | Guselkumab N = 41 n (%) | Placebo N = 25 n (%) |
|---|---|---|
| **URI** | 11 (26.8) | 8 (32.0) |
| **Headache** | 3 (7.3) | 0 (0.0) |
| **ISR** | 1 (2.4) | 1 (4.0) |

Source: Reviewer's Table

**Table 32: Adverse Reactions Occurring in ≥1% of Subjects with Plaque Psoriasis through Week 16 in PsO1 and PsO2**

| | TREMFYA * 100 mg N=823 n (%) | Adalimumab † N=196 n (%) | Placebo N=422 n (%) |
|---|---|---|---|
| Upper respiratory infections ‡ | 118 (14.3) | 21 (10.7) | 54 (12.8) |
| Headache § | 38 (4.6) | 2 (1.0) | 14 (3.3) |
| Injection site reactions ¶ | 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 # | 11 (1.3) | 4 (2.0) | 4 (0.9) |
| Tinea infections Þ | 9 (1.1) | 0 | 0 |
| Herpes simplex infections ß | 9 (1.1) | 0 | 2 (0.5) |

Source: Tremfya (guselkumab) labeling, Section 6.1 Clinical Trials Experience

* Subjects receiving 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter
† U.S. licensed adalimumab
‡ Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.
§ Headache includes headache and tension headache.
¶ Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.
# Gastroenteritis includes gastroenteritis and viral gastroenteritis.
Þ Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.
ß Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

The review team evaluated the adverse reactions Week 0-52, shown below. Overall, the etanercept to guselkumab group experienced a greater percentage of infections compared to the guselkumab and placebo to guselkumab groups.

**Table 33: Summary of Subjects with Adverse Reactions by SOC: Week 0-52**

| | Guselkumab | Placebo à Guselkumab | Etanercept à Guselkumab |
|---|---|---|---|
| Analysis set: Safety analysis set | 41 | 23 | 22 |
| Avg duration of follow-up (weeks) | 50.14 | 33.61 | 31.74 |

| | Guselkumab | Placebo à Guselkumab | Etanercept à Guselkumab |
|---|---|---|---|
| Avg exposure (number of administrations) | 4.78 | 4.70 | 4.95 |
| Subjects with 1 or more related AEs | 10 (24%) | 4 (17%) | 5 (23%) |
| Infections and infestations | 7 (17%) | 3 (13%) | 5 (23%) |
| General disorders and administration site conditions | 4 (10%) | 1 (4%) | 0 |
| Nervous system disorders | 2 (5%) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 (2%) | 1 (4%) | 0 |
| Blood and lymphatic system disorders | 1 (2%) | 0 | 0 |
| Eye disorders | 0 | 0 | 1 (5%) |

Source: Adapted from Applicant's Table TSFAE37 in the Complete Study Report for Trial CNTO1959PSO3011

Key: AE = adverse event, Avg = average. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

Long Term Safety:

The review team evaluated the exposure adjusted incidence rates (EAIRs) for TEAEs is subjects exposed to guselkumab through Week 52. TEAEs were most frequently reported in the SOCs of Infections and infestations. The proportion of subjects in the guselkumab group with Infections increased over the 52-week treatment period. The proportion of subjects with injection site reactions over the 52-week treatment period remained unchanged.

**Table 34: Summary of Exposure Adjusted Incidence Rate of All TEAEs Through 1 year in Trial CNTO1959PSO3011**

| | Guselkumab | | | | Etanercept --> Guselkumab | | | | Placebo --> Guselkumab | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **System Organ Class** | **N = 41** | | **PYE = 39.4** | | **N = 22** | | **PYE = 13.4** | | **N = 23** | | **PYE = 14.8** |
| Preferred Term | **n** | **(%)** | **EAIR** | **PYR** | **n** | **(%)** | **EAIR** | **PYR** | **n** | **(%)** | **EAIR** |
| Any AE | 33 | (80.5) | 169.7 | 19.5 | 13 | (59.1) | 153.7 | 8.5 | 16 | (69.6) | 207.3 |
| **Infections and infestations** | **25** | **(61.0)** | **99.9** | **25.0** | **12** | **(54.5)** | **130.3** | **9.2** | **12** | **(52.2)** | **125.0** |
| Nasopharyngitis | 12 | (29.3) | 37.1 | 32.4 | 4 | (18.2) | 32.5 | 12.3 | 8 | (34.8) | 68.7 |
| Upper respiratory tract infection | 8 | (19.5) | 23.4 | 34.2 | 3 | (13.6) | 24.4 | 12.3 | 0 | (0.0) | 0.0 |
| Pharyngitis | 3 | (7.3) | 7.8 | 38.3 | 1 | (4.5) | 7.6 | 13.2 | 1 | (4.3) | 7.0 |
| Rhinitis | 3 | (7.3) | 7.9 | 37.9 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Covid-19 | 2 | (4.9) | 5.2 | 38.5 | 1 | (4.5) | 7.7 | 13.1 | 0 | (0.0) | 0.0 |
| Viral infection | 2 | (4.9) | 5.2 | 38.6 | 1 | (4.5) | 7.8 | 12.9 | 0 | (0.0) | 0.0 |
| Viral upper respiratory tract infection | 2 | (4.9) | 5.2 | 38.2 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Acarodermatitis | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Bronchitis | 1 | (2.4) | 2.6 | 38.8 | 1 | (4.5) | 7.6 | 13.2 | 1 | (4.3) | 6.9 |
| Enterobiasis | 1 | (2.4) | 2.6 | 38.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Gastroenteritis | 1 | (2.4) | 2.6 | 39.0 | 2 | (9.1) | 15.6 | 12.9 | 0 | (0.0) | 0.0 |
| Gastroenteritis viral | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| Otitis externa | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Tonsillitis | 1 | (2.4) | 2.5 | 39.2 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Bacterial vulvovaginitis | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.0 |
| Chronic tonsillitis | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.0 |
| Conjunctivitis | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.8 |
| Ear infection | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.5 | 13.3 | 0 | (0.0) | 0.0 |
| Helminthic infection | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.1 |
| Lice infestation | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.0 |
| Molluscum contagiosum | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| Otitis media | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.8 | 12.9 | 0 | (0.0) | 0.0 |
| Tinea capitis | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| Vulvovaginal mycotic infection | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.8 |
| **Gastrointestinal disorders** | **6** | **(14.6)** | **16.7** | **35.9** | **2** | **(9.1)** | **15.4** | **13.0** | **0** | **(0.0)** | **0.0** |
| Abdominal pain | 3 | (7.3) | 7.9 | 37.8 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Abdominal pain upper | 1 | (2.4) | 2.6 | 38.8 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Dental caries | 1 | (2.4) | 2.6 | 39.0 | 1 | (4.5) | 7.5 | 13.3 | 0 | (0.0) | 0.0 |
| Enteritis | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Mouth ulceration | 1 | (2.4) | 2.6 | 39.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Vomiting | 1 | (2.4) | 2.6 | 39.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Dyspepsia | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.6 | 13.1 | 0 | (0.0) | 0.0 |
| **Nervous system disorders** | **6** | **(14.6)** | **16.9** | **35.5** | **2** | **(9.1)** | **16.1** | **12.5** | **2** | **(8.7)** | **14.1** |
| Headache | 6 | (14.6) | 16.9 | 35.5 | 2 | (9.1) | 16.1 | 12.5 | 2 | (8.7) | 14.1 |
| Hypoaesthesia | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Lethargy | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |

| System Organ Class | Guselkumab | | | | Etanercept --> Guselkumab | | | | Placebo --> Guselkumab | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N = 41 | | PYE = 39.4 | | N = 22 | | PYE = 13.4 | | N = 23 | | PYE = 14.8 |
| Preferred Term | n | (%) | EAIR | PYR | n | (%) | EAIR | PYR | n | (%) | EAIR |
| **General disorders and administration site conditions** | **5** | **(12.2)** | **13.4** | **37.2** | **1** | **(4.5)** | **7.7** | **12.9** | **2** | **(8.7)** | **14.1** |
| Fatigue | 1 | (2.4) | 2.5 | 39.2 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Influenza like illness | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| Injection site erythema | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Injection site hematoma | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Injection site swelling | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Pyrexia | 1 | (2.4) | 2.6 | 39.0 | 1 | (4.5) | 7.7 | 12.9 | 1 | (4.3) | 6.9 |
| **Respiratory, thoracic and mediastinal disorders** | **5** | **(12.2)** | **13.5** | **36.9** | **1** | **(4.5)** | **7.7** | **12.9** | **3** | **(13.0)** | **21.3** |
| Asthma | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Epistaxis | 1 | (2.4) | 2.6 | 39.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Oropharyngeal pain | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Rhinitis allergic | 1 | (2.4) | 2.6 | 38.8 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| Rhinorrhea | 1 | (2.4) | 2.6 | 39.0 | 1 | (4.5) | 7.7 | 12.9 | 1 | (4.3) | 6.9 |
| Cough | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.8 |
| **Skin and subcutaneous tissue disorders** | **5** | **(12.2)** | **13.5** | **36.9** | **1** | **(4.5)** | **7.7** | **12.9** | **1** | **(4.3)** | **7.1** |
| Acne | 3 | (7.3) | 8.0 | 37.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Lichen planus | 1 | (2.4) | 2.6 | 39.1 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Pruritus | 1 | (2.4) | 2.6 | 39.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Psoriasis | 1 | (2.4) | 2.6 | 39.2 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Night sweats | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.1 |
| Rash | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.7 | 12.9 | 0 | (0.0) | 0.0 |
| **Injury, poisoning and procedural complications** | **4** | **(9.8)** | **11.0** | **36.4** | **1** | **(4.5)** | **7.6** | **13.1** | **0** | **(0.0)** | **0.0** |
| Ligament sprain | 2 | (4.9) | 5.3 | 38.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Joint dislocation | 1 | (2.4) | 2.6 | 38.7 | 1 | (4.5) | 7.6 | 13.1 | 0 | (0.0) | 0.0 |
| Ligament rupture | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Muscle strain | 1 | (2.4) | 2.6 | 38.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Radius fracture | 1 | (2.4) | 2.6 | 38.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| **Investigations** | **3** | **(7.3)** | **8.0** | **37.6** | **0** | **(0.0)** | **0.0** | **0.0** | **1** | **(4.3)** | **6.9** |
| Blood alkaline phosphatase increased | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Blood glucose increased | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Cardiac murmur | 1 | (2.4) | 2.5 | 39.4 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| White blood cell count increased | 1 | (2.4) | 2.6 | 38.5 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Alanine aminotransferase increased | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| **Musculoskeletal and connective tissue disorders** | **3** | **(7.3)** | **7.9** | **37.8** | **1** | **(4.5)** | **7.6** | **13.2** | **0** | **(0.0)** | **0.0** |
| Arthralgia | 2 | (4.9) | 5.3 | 38.0 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Arthritis | 1 | (2.4) | 2.5 | 39.3 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Bone pain | 1 | (2.4) | 2.6 | 38.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Ligament laxity | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Musculoskeletal discomfort | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.6 | 13.2 | 0 | (0.0) | 0.0 |
| **Blood and lymphatic system disorders** | **1** | **(2.4)** | **2.6** | **39.2** | **0** | **(0.0)** | **0.0** | **0.0** | **1** | **(4.3)** | **6.9** |
| Leukopenia | 1 | (2.4) | 2.6 | 39.2 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Eosinophilia | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| **Cardiac disorders** | **1** | **(2.4)** | **2.6** | **38.6** | **0** | **(0.0)** | **0.0** | **0.0** | **0** | **(0.0)** | **0.0** |
| Ventricular extrasystoles | 1 | (2.4) | 2.6 | 38.6 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| **Eye disorders** | **1** | **(2.4)** | **2.6** | **38.7** | **1** | **(4.5)** | **7.8** | **12.8** | **2** | **(8.7)** | **13.8** |
| Myopia | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| Blepharitis | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.5) | 7.8 | 12.8 | 1 | (4.3) | 6.8 |
| Conjunctivitis allergic | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 6.9 |
| **Metabolism and nutrition disorders** | **1** | **(2.4)** | **2.6** | **38.7** | **0** | **(0.0)** | **0.0** | **0.0** | **0** | **(0.0)** | **0.0** |
| Malnutrition | 1 | (2.4) | 2.6 | 38.7 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| **Pregnancy, puerperium and perinatal conditions** | **1** | **(2.4)** | **2.5** | **39.4** | **0** | **(0.0)** | **0.0** | **0.0** | **0** | **(0.0)** | **0.0** |
| Pregnancy | 1 | (2.4) | 2.5 | 39.4 | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 |
| **Psychiatric disorders** | **0** | **(0.0)** | **0.0** | **0.0** | **0** | **(0.0)** | **0.0** | **0.0** | **1** | **(4.3)** | **7.0** |
| Attention deficit hyperactivity disorder | 0 | (0.0) | 0.0 | 0.0 | 0 | (0.0) | 0.0 | 0.0 | 1 | (4.3) | 7.0 |

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRTSEQA = "Guselkumab->Withdraw to Guselkumab" or "Guselkumab->Guselkumab" and SAFFL = "Y" (Guselkumab); TRTSEQA = "Etanercept->Guselkumab" and SAFFL = "Y" (Etanercept --> Guselkumab); TRTSEQA = "Placebo->Guselkumab" and SAFFL = "Y" (Placebo --> Guselkumab); TRTEMFL = "Y" and ACOL52 = "Placebo-Guselkumab" or "Etanercept-Guselkumab" or "Guselkumab" (Adverse Events).

Patient years of exposure (PYE) was calculated as the difference between the treatment end date and start date for the period during which the subject received guselkumab.

The review team compared EAIRs for key safety findings through Week 52 for Trial CNTO1959PSO3011 versus pooled data through Week 48 for Trial 3001 and Trial 3002 conducted in adults with PsO. The results are displayed in the table below.

**Table 35: Summary of Exposure Adjusted Incidence Rate of Key Safety Findings Through 1 year in Trials CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002**

| | Pediatric Psoriasis (0-52 weeks) | | | | | Adult Psoriasis (0-48 weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | CNTO1959PSO3011 | | | | | CNTO1959PSO3001/3002 | | | |
| | Part 1 | | | Part 2 | | - | | | |
| | Placebo→ guselkumab | Guselkumab part 1 | Etanercept→ guselkumab | Guselkumab | Combined | Placebo→ guselkumab | Guselkumab | Adalimumab → guselkumab | Combined |
| Analysis set: Safety analysis set | 23 | 41 | 22 | 28 | 114 | 398 | 823 | 146 | 1367 |
| Total subject-years of follow-up | 14.8 | 39.4 | 13.4 | 27.3 | 94.9 | 240.7 | 733.8 | 47.0 | 1021.5 |
| Median subject-years of follow-up | 0.69 | 1.00 | 0.62 | 1.00 | 0.99 | 0.62 | 0.92 | 0.38 | 0.91 |
| Exposure-adjusted incidence rates of adverse events | | | | | | | | | |
| Adverse events | | | | | | | | | |
| Common adverse event* | | | | | | | | | |
| Nasopharyngitis | 0.684 (8/11.7) | 0.370 (12/32.4) | 0.325 (4/12.3) | 0.299 (7/23.4) | 0.389 (31/79.7) | 0.290 (64/221.0) | 0.269 (175/650.5) | 0.540 (23/42.6) | 0.287 (262/914.1) |
| Upper respiratory tract infection | 0 | 0.234 (8/34.2) | 0.244 (3/12.3) | 0.076 (2/26.4) | 0.148 (13/87.6) | 0.138 (32/231.5) | 0.134 (92/687.1) | 0.221 (10/45.2) | 0.139 (134/963.8) |
| Headache | 0.142 (2/14.1) | 0.169 (6/35.5) | 0.160 (2/12.5) | 0.078 (2/25.7) | 0.137 (12/87.7) | 0.038 (9/237.3) | 0.076 (53/701.9) | 0.107 (5/46.6) | 0.068 (67/985.7) |
| COVID-19 | 0 | 0.052 (2/38.5) | 0.076 (1/13.1) | 0.242 (6/24.8) | 0.099 (9/91.2) | | | | |
| Acne | 0 | 0.080 (3/37.6) | 0 | 0.116 (3/25.8) | 0.066 (6/91.6) | 0.013 (3/239.5) | 0.010 (7/730.7) | 0 | 0.010 (10/1017.3) |
| Pharyngitis | 0.070 (1/14.3) | 0.078 (3/38.3) | 0.076 (1/13.2) | 0.037 (1/27.2) | 0.065 (6/93.0) | 0.021 (5/239.0) | 0.023 (17/725.5) | 0.021 (1/46.8) | 0.023 (23/1011.3) |
| Serious adverse events | 0.069 (1/14.4) | 0.026 (1/38.6) | 0 | 0.037 (1/26.9) | 0.032 (3/93.3) | 0.042 (10/236.5) | 0.057 (41/716.7) | 0.021 (1/46.8) | 0.052 (52/1000.0) |
| Any infections | 1.237 (12/9.7) | 0.996 (25/25.1) | 1.512 (13/8.6) | 0.777 (15/19.3) | 1.037 (65/62.7) | 0.841 (157/186.6) | 0.733 (385/524.9) | 1.020 (40/39.2) | 0.775 (582/750.7) |
| Serious infections | 0 | 0 | 0 | 0 | 0 | 0.008 (2/239.9) | 0.010 (7/731.4) | 0 | 0.009 (9/1018.3) |
| Infections requiring treatment | 0.394 (5/12.7) | 0.079 (3/37.8) | 0.246 (3/12.2) | 0.037 (1/27.2) | 0.133 (12/89.9) | 0.258 (57/220.8) | 0.212 (142/669.4) | 0.130 (6/46.2) | 0.219 (205/936.4) |
| Malignancy | 0 | 0 | 0 | 0 | 0 | 0.013 (3/239.2) | 0.008 (6/732.2) | 0 | 0.009 (9/1018.5) |

Source: Table 22, Response to Information Request from the FDA Dated 05 March 2025, Page 26.
(Exposure-adjusted incidence rates = number of subjects with adverse events/total subject-years at risk. Total subject-years at risk is the sum of time to the first event of interest or follow-up period if no event occurred for a given subject.)

The review team noted small imbalances in the EAIRs for headache, acne, pharyngitis and any infections (not serious infections) in the pediatric population. Some preferred terms (e.g. acne, pharyngitis) were reported with greater frequency in the pediatric population compared with the adult population as expected. Based on the limited sample size, these imbalances are not considered to be clinically meaningful. The safety findings in the pediatric safety population from Trial CNTO1959PSO3011 are comparable to that of the adult safety population from pooled Trials CNTO1959PSO3001 and CNTO1959PSO3002.

**Laboratory Findings**

During the development program for guselkumab, evaluation of systemic safety included assessment of clinical laboratory data, hematology, serum chemistry, and urinalysis.

Hematology

The review team evaluated shift tables and TEAEs related to hematologic parameters for Weeks 0 to 16. Limited changes were observed in leukocytes, hemoglobin, and platelet counts through Week 16. There were no meaningful imbalances between treatment groups. No values of Common Terminology Criteria for Adverse Events (CTCAE) ≥2 were reported in the guselkumab treatment group through Week 16. There were no clinically meaningful changes in hematology parameters through Week 52.

Serum Chemistry

The review team evaluated shift tables and TEAEs related to serum chemistry parameters for Week 0 to 16. Through Week 16, 3 (7.3%) subjects in the guselkumab treatment group had laboratory values of CTCAE toxicity grade 2 of increased total bilirubin. Through Week 52, there was 1 case of grade 3 aspartate aminotransferase (AST) elevation and no cases of ≥ grade 2 alanine aminotransferase (ALT) elevation. The narrative for the subject with grade 3 AST elevation is provided below.

Select Narrative for Subject with Abnormal Liver Chemistry

- A 17-year-old white female (CNTO1959PSO3011-(b) (6)) with no history of alcohol use or smoking who received guselkumab 65 mg at Week 16, 20, 28, 36, 44, developed elevated AST of 265 U/L and elevated ALT of 66 U/L on Day 260. AST was normal at 23 U/L and ALT decreased to 38 U/L on Day 266 without intervention. Alkaline phosphatase and total bilirubin were within normal limits. The subject was asymptomatic but reported participation in strenuous exercise. Dosage of guselkumab was not changed. The subject completed the trial. This reviewer assesses the relationship of this TEAE to guselkumab as doubtful.

No serious adverse events of drug-induced liver injury (DILI) were observed in the trial.

**Vital Signs**

The safety evaluation by the Applicant included periodic assessments of vital signs. The review team evaluated summary tables for vital sign changes over time. No meaningful changes from baseline were observed for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature) across treatment groups in the trial.

**Electrocardiograms (ECGs)**

The Applicant did not conduct ECGs during the pediatric trial. However, during the development program for guselkumab for use in adults, the Applicant conducted routine cardiac safety monitoring during all the core trials in subjects with moderate to severe psoriasis. The QT Interdisciplinary Review Team (QT-IRT) evaluated the ECG data submitted to the ECG warehouse (Review dated February 10, 2017). Per Dr. Christine Garnett, the QT-IRT reviewer, "The nonclinical and clinical data reviewed do not suggest a potential for QTc prolongation. To further support the clinical assessment, an outlier analysis was conducted, which does not support a potential for QTc prolongation for guselkumab." The reviewer evaluated all postbaseline ECG abnormalities and concluded that "there is little evidence of a treatment effect for the observed ECG abnormalities".

**QT**

The ICH E14 guidance document regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (2005) does not specifically address QT assessments for biologic agents. A thorough QT study was not performed during the development program for moderate to severe psoriasis. Because of their large size and high target specificity, monoclonal antibodies (mAbs) such as guselkumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

**Immunogenicity**

Because therapeutic proteins have the potential to elicit an immune response, the Applicant evaluated for the presence of anti-drug antibodies (ADAb) during the pediatric development program for moderate to severe psoriasis. The clinical pharmacology team evaluated the immunogenicity data obtained from phase 3 Trial CNTO1959PSO3011. The overall incidence of antibodies to guselkumab through Week 44 was 18% (n=21), with generally low titers of antibodies to guselkumab (80.0% had titer levels ≤1:160). Per clinical pharmacology review, there was no apparent impact of the development of antibodies to guselkumab, or the titer of antibodies, on guselkumab PK, efficacy, or safety. None of the 24 subjects who were positive

for antibodies to guselkumab had antibodies that were able to neutralize the bioactivity of guselkumab in vitro. Refer to section 6 of this review.

### 8.2.5. **Analysis of Submission-Specific Safety Issues**

The review team evaluated the data in this submission for evolving safety concerns (suicidal ideation and behavior), serious safety issues conveyed in Warnings and Precautions sections of labeling (hypersensitivity and serious infections including tuberculosis) and adverse events of special interest (malignancy and active tuberculosis). Safety concerns of increasing interest and evolving understanding include hepatotoxicity which is being described in biologic products that target IL23. Because the literature support an increased risk of depression and suicidal ideation among patients with chronic diseases, including psoriasis, this remains a focus of submission-specific safety analysis especially in the adolescent population.

#### 8.2.5.1. Hepatotoxicity

In the current submission that evaluated the use of guselkumab in the pediatric population ages 6 to 17 years, there were no significant transaminase elevations or cases that met the criteria for Drug Induced Liver Injury (DILI). However, in the development program for psoriasis, mild liver transaminase elevations (<3 times the Upper Limit of Normal (ULN)) were seen at guselkumab dosages of 100 mg every 4 weeks or higher. More significant elevations (alanine aminotransferase (ALT) >5x ULN) or cases satisfying the biochemical criteria for Hy's Law were confounded by concomitant medications, alcohol use, and/or concurrent diagnoses or medical history (Periodic Benefit-Risk Evaluation Report [PBRER] - 9). The original approved labeling included elevated liver enzymes under Section 6 Adverse Reactions.

In the ulcerative colitis (UC) development program (approved September 11, 2024, by Division of Gastroenterology [DG]), the Drug Induced Liver Injury (DILI) Team found that "Case level data analyses did not yield any cases meeting Hy's Law or having cholestatic DILI with jaundice." However, there was no requirement for a baseline assessment of liver enzymes. During the development program for UC, a case of drug-induced liver injury (DILI) meeting Hy's law occurred when a subject in a phase 2 trial for CD was exposed to guselkumab at a higher than labeled dose. The DILI team suspected that Hy's law case was due, in part, to the higher dose.

During the review of the data to support the sBLA for Crohn's Disease (CD: approved March 20, 2025, by DG), the DILI team evaluated the data regarding hepatotoxicity including the previously identified case meeting Hy's Law. However, a dose response for liver injury was not demonstrated in the aggregated study data. Therefore, the potential for guselkumab to cause idiosyncratic DILI cannot be excluded. Because the occurrence of idiosyncratic DILI depends on individual susceptibilities that have not yet been characterized, all patients who receive treatment with guselkumab are at increased risk for hepatotoxicity.

In addition, the post marketing data from the Applicant's Periodic Safety Reports and the FDA Adverse Event Reporting System (FAERS) database (received by the FDA Sept 2, 2021, through April 10, 2024) in patients with psoriasis and psoriatic arthritis identified case reports submitted by healthcare providers of elevated liver enzymes and liver toxicity (hepatic cytolysis/ DILI) that were assessed as possibly related to guselkumab. The following are few cases of hepatic cytolysis/DILI:

**22791325 – 1**
A 43-year-old female with a history of Grave's disease, acute pancreatitis, and Crohn's disease developed "hepatic cytolysis" after one dose of guselkumab for ankylosing spondylitis. No concomitant medications reported. No lab data provided. Patient was recovering from **hepatic cytolysis**.

**22746955 – 2**
A 34-year-old male with no reported medical history developed "**increase of hepatic cytolysis**" after 14 weeks of guselkumab 100 mg unknown frequency for psoriasis. No concomitant medications reported. No lab data provided. Guselkumab dose was not changed or discontinued. Condition was not recovered.

**20865353 -1**
A 57 -year-old male with a history of psoriasis, developed **cytolytic hepatitis.** Treatment with guselkumab was stopped.

Additionally, cases of elevated transaminases, suspected drug-induced hepatitis, hepatic function disorder, liver damage, and cirrhosis were reported. Despite the inherent limitations of post marketing data to assess causality, this data provides support for a signal of hepatotoxicity across populations. (For additional information, refer to separate review by Dr. Elisabeth Daniel).

Labeling changes associated with the approval of guselkumab for the treatment of adult patients with moderately to severely active Crohn's disease (Approval March 20, 2025) included the addition of a Warning and Precaution under Section 5.4 for Hepatotoxicity and instructions "to evaluate liver enzymes and bilirubin at baseline, for at least 16 weeks of treatment, and periodically thereafter" in patients with Crohn's disease or ulcerative colitis. Based on the totality of the data and our inability to exclude the potential for guselkumab to cause idiosyncratic DILI, labeling should convey the risk of hepatotoxicity to all patient populations treated with guselkumab and provide instructions for testing of hepatic enzymes at baseline and periodically throughout the course of treatment. Therefore, the review team recommends the following changes to the Warnings and Precautions section of labeling.

2 **DOSAGE AND ADMINISTRATION**
2.1 Recommended Evaluations and Immunizations Prior to Treatment Initiation

For the treatment of plaque psoriasis or psoriatic arthritis, if clinically indicated, evaluate liver enzymes and bilirubin prior to initiating treatment with TREMFYA.

5.4 **Hepatotoxicity**

In patients with plaque psoriasis or psoriatic arthritis, if clinically indicated, evaluate liver enzymes and bilirubin at baseline, periodically thereafter according to routine patient management.

8.2.5.2. Suicidal Ideation and Behavior

Patients with psoriasis have a greater risk of the development of psychiatric disorders than the general population (Picardi, 2013). The Division of Psychiatry (DP) evaluated the neuropsychiatric adverse events (AEs) in collaboration with the review team (See Review by Cathy Southammakosane, MD dated April 8, 2025).

Trial CNTO1959PSO3011 evaluated a pediatric population that excluded subjects with history or current symptoms of severe, progressive, or uncontrolled psychiatric disease; a substance abuse problem in the past 12 months; and unstable suicidal ideation and behavior (SI/B) as determined by the following:

- Subjects ages >12 to <18 years- "yes" response to C-SSRS item 4 or 5 or non-suicidal self-injurious behavior in the past 6 months OR suicidal behavior ever (lifetime) OR item 1, 2, or 3 in the past 6 months and determined to be at risk by the Investigator in discussion with medical monitor.
- Subjects ages >6 to <12 years- "yes" response to C-SSRS item 4 or 5 or suicidal behavior or self-injurious behavior ever (lifetime) OR item 1, 2, or 3 ever (lifetime) and determined to be at risk by the Investigator in discussion with medical monitor.

The Columbia-Suicide Severity Rating Scale (C-SSRS) was administered at Screening and at all study visits. Subjects with a "yes" response to C-SSRS items 1 through 3 were further assessed by the Investigator; subjects with a "yes" response to items 4 or 5 or with any suicidal or self-injurious behavior were further assessed and referred to a mental health professional. Study treatment was to be paused or discontinued in the case of adjudicated risk.

Five psychiatric adverse events (AE) were reported: anxiety in a subject taking etanercept; attention deficit hyperactivity disorder in a subject taking guselkumab in the open-label phase (randomized to placebo in the double-blind treatment phase); and suicidal ideation (SI) and depression in two subjects in Part 2 of the study. Dr. Southammakosane summarized the relevant cases with her assessment below.

- "Subject CNTO1959PSO3011-(b) (6): a 17-year-old female with psoriasis but no other reported medical history reported an SI AE 1.5 weeks after her first and only dose of guselkumab. The AE was characterized as mild, non-serious, and doubtfully related to study drug. Her baseline C-SSRS was negative. Nearly 3 weeks later she endorsed on

specific suicidal thought and wish to be dead on the C-SSRS so was discontinued from study treatment. Although the SI event was reported as resolving, her C-SSRS responses were unchanged 1 month later, and she did not complete a safety follow-up visit thereafter. The subject did not report any other AEs. She denied alcohol use but used cigarettes (approximately one pack weekly). The only concomitant medication listed was oral contraception.

*Reviewer Comment: Newly reported SI 1.5 weeks after initiation of guselkumab may be associated with study treatment; however, because the event narrative is lacking in further detail (e.g., associated mood symptoms or psychosocial factors), a causal relationship cannot be determined.*

- Subject CNTO1959PSO3011-(b) (6): a 14-year-old female with psoriasis but no other reported medical history reported AEs of SI (based on C-SSRS responses) at baseline and depression on Day 14. The subject's SI was characterized as moderate, non-serious, and not related to study drug, and psychological support was initiated in response. The depression AE was characterized as moderate, non-serious, and unrelated to study intervention and resolved on Day 202. On the C-SSRS, the subject reported non-specific suicidal thought or wish to be dead at baseline and at each visit up to Day 113, but her C-SSRS was negative thereafter. These AEs did not lead to change in study treatment. The subject's other reported AEs were dysmenorrhea, headache, injection site hematoma, musculoskeletal chest pain, and oropharyngeal pain. Concomitant medications were amylmetacresol, dichlorobenzyl alcohol, and levomenthol; COVID-19 vaccine; topical emollient; and ibuprofen.

*Reviewer Comment: Given the subject's baseline SI and without further description of the SI and depression AEs (e.g., psychosocial factors), a causal relationship with guselkumab cannot be determined.*

The review by DP concluded that subject enrollment criteria and SI/B monitoring throughout the study were appropriate. There were no reports of AEs related to SI/B in the controlled phase of the trial, Part 1. The review states, "The two reported cases of SI in the Part 2, open-label phase of the study are insufficient to conclude that there is a causal association between guselkumab and SI/B, particularly in the absence of a control arm. Given the absence of an established safety signal, no regulatory action in labeling or in the post-marketing space is recommended."

#### 8.2.5.3. Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported with post-market use of TREMFYA. Some cases required hospitalization. Analysis of the safety data in the pediatric population showed one adverse event of urticaria in a subject who received guselkumab.

There were no reported cases of anaphylaxis, angioedema, urticaria or serum sickness-like reactions in subjects who received guselkumab in Trial CNTO1959PSO3011. There was one report of urticaria in a subject who received placebo.

Injection Site Reactions

An injection site reaction (ISR) was defined as an "unfavorable or unintended sign" (e.g. pain, erythema, or induration) that occur at the site of injection. ISRs were reported by 1 subject in each treatment group through Week 16. All reactions were reported as mild in severity. All preferred terms (PTs) were reported by single subjects. The reported ISRs are shown in the table below.

**Table 36: Summary of Subjects with ISR During the DB Period: Week 16**

| Group Term<br>Preferred Term | Guselkumab<br>N = 41<br>n (%) | Etanercept<br>N = 26<br>n (%) | Placebo<br>N = 25<br>n (%) |
|---|---|---|---|
| **ISR** | **1 (2.4)** | **1 (3.8)** | **1 (4.0)** |
| Injection site erythema | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Injection site swelling | 1 (2.4) | 0 (0.0) | 0 (0.0) |
| Application site hematoma | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| Injection site induration | 0 (0.0) | 1 (3.8) | 0 (0.0) |
| Injection site pruritus | 0 (0.0) | 1 (3.8) | 0 (0.0) |

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Guselkumab" and SAFFL = "Y" (Guselkumab); TRT01A = "Etanercept" and SAFFL = "Y" (Etanercept); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

#### 8.2.5.4. Tuberculosis

In the Warnings and Precautions section of labeling for TREMFYA, providers are advised to evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA. In clinical trials of TREMFYA in subjects with Crohn's disease, active TB was reported. In Trial CNTO1959PSO3011, the entry criteria excluded subjects who had a history of latent or active granulomatous infection, including TB or had persistently indeterminate QuantiFERON-TB test results.

To date, the Applicant has not identified adverse events of active TB in the pediatric population with moderate to severe psoriasis in Trial CNTO1959PSO 3011.

#### 8.2.5.5. Serious Infections

Based on the mechanism of action (immunomodulation via cytokine blockade), patients who receive TREMFYA may have an increased risk of infection. The Warnings and Precautions section of labeling (section 5.2) advise that "Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated." In Trial CNTO1959PSO3011, the entry criteria excluded subjects who had a history of chronic or recurrent infectious disease, history of serious infection or hospitalization/ intravenous antibiotics for infection within 2 months prior to screening, history of opportunistic infection, or a documented history of immune deficiency.

Most commonly reported infections were nasopharyngitis and upper respiratory tract infection. No events of opportunistic (herpes zoster and eczema herpeticum, candidiasis) or serious infections including active tuberculosis were reported in either treatment group in Trial CNTO1959PSO3011 through Week 52.

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

This BLA submission did not include any clinical outcome assessments (COAs) to inform safety/ tolerability. However, the Applicant did conduct COAs to characterize treatment benefit. Refer to section 8.1 of this review.

### 8.2.7. Safety Analyses by Demographic Subgroups

During the review of the initial BLA, the review team conducted additional analyses to evaluate the safety of guselkumab in different populations. The results showed that there were no substantial differences in the risk of adverse reactions in demographic subgroups. However, the review team noted that the trials were not powered for these analyses. Therefore, the data must be interpreted with caution. In the data to support the original application for guselkumab, a slightly greater proportion of females who received either guselkumab or placebo reported adverse reactions of upper respiratory infection, headache, injection site reaction, arthralgia and diarrhea than males. Approximately 95% of subjects enrolled in the phase 3 trials were adults ≤ 64 years of age; therefore, because of the limited number of subjects age >65 years, it was difficult to detect any differences in safety compared with younger subjects. The data for safety by race was difficult to interpret due to the relatively small sample sizes of the non-White subgroups. The safety findings across the two weight subgroups (≤90 kg and >90 kg) were similar although a greater percentage of subjects in the >90 kg subgroup experienced elevated liver enzymes.

Subgroup analyses were performed of the pediatric data to evaluate potential variations in treatment effects across different demographic groups. However, the size of study population and subgroups limited interpretability of analyses of adverse event data by preferred term.

Therefore, overall categories of TEAEs were evaluated by subgroup [age (12 - <18 years, and 6 - < 12 years), sex, weight (≥ 70 kg, and < 70 kg) and race (White and non-White)] and presented in the table below for comparison. In the guselkumab treated group, there were no meaningful differences in overall TEAEs or infections by age group or gender. A greater proportion of subjects who weighed less than 70kg had one or more TEAEs. Because most subjects were White, any comparison of categories of TEAEs was not meaningful.

**Table 37: Summary of Key Safety Findings Week 0- 16 by Age, Gender, Weight, and Race**

| | Guselkumab N=41 (%) | Etanercept N=26 (%) | Placebo N=25 (%) |
|---|---|---|---|
| **Age 12 - < 18 years** | 31 (75.6) | 16 (61.5) | 15 (60.0) |
| **Subjects with 1 or more TEAEs** | 13 (31.7) | 10 (38.5) | 10 (40.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 1 (4.0) |
| **Subjects with Serious TEAEs** | 0 | 0 | 0 |
| **Any Infection TEAEs** | 8 (19.5) | 6 (23.1) | 7 (28.0) |
| **Age 6 - < 12 years** | 10 (24.4) | 10 (38.5) | 10 (40.0) |
| **Subjects with 1 or more TEAEs** | 13 (31.7) | 10 (38.5) | 10 (40.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 1 (4.0) |
| **Subjects with Serious TEAEs** | 0 | 0 | 0 |
| **Any Infection TEAEs** | 8 (19.5) | 6 (23.1) | 7 (28.0) |
| **Gender Male** | 24 (58.5) | 15 (57.7) | 12 (48.0) |
| **Subjects with 1 or more TEAEs** | 9 (22.0) | 9 (34.6) | 7 (28.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 1 (4.0) |
| **Subjects with Serious TEAEs** | 1 (2.4) | 0 | 0 |
| **Any Infection TEAEs** | 6 (14.6) | 6 (23.1) | 4 (16.0) |
| **Gender Female** | 17 (41.5) | 11 (42.3) | 13 (52.0) |
| **Subjects with 1 or more TEAEs** | 8 (19.5) | 6 (23.1) | 10 (40.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 0 |
| **Subjects with Serious TEAEs** | 0 | 0 | 0 |
| **Any Infection TEAEs** | 6 (14.6) | 4 (15.4) | 6 (24.0) |
| **Baseline Weight >= 70 kg** | 12 (29.3) | 7 (26.9) | 5 (20.0) |
| **Subjects with 1 or more TEAEs** | 4 (33.3) | 5 (71.4) | 5 (100.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 1 (20.0) |
| **Subjects with Serious TEAEs** | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| **Any Infection TEAEs** | 4 (33.3) | 4 (57.1) | 3 (60.0) |
| **Baseline Weight < 70 kg** | 29 (70.7) | 19 (73.1) | 20 (80.0) |
| **Subjects with 1 or more TEAEs** | 13 (44.8) | 10 (52.6) | 12 (60.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 0 |
| **Subjects with Serious TEAEs** | 1 (3.4) | 0 | 0 |
| **Any Infection TEAEs** | 8 (27.6) | 6 (31.6) | 7 (35.0) |
| **Race - White** | 36 (87.8) | 22 (84.6) | 20 (80.0) |
| **Subjects with 1 or more TEAEs** | 15 (36.6) | 14 (53.8) | 12 (48.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 1 (4.0) |
| **Subjects with Serious TEAEs** | 1 (2.4) | 0 | 0 |
| **Any Infection TEAEs** | 11 (26.8) | 9 (34.6) | 6 (24.0) |
| **Race - Other (pooled)** | 5 (12.2) | 4 (15.4) | 5 (20.0) |
| **Subjects with 1 or more TEAEs** | 2 (4.9) | 1 (3.8) | 5 (20.0) |
| **Subjects who Discontinued Study Drug due to TEAEs** | 0 | 0 | 0 |
| **Subjects with Serious TEAEs** | 0 | 0 | 0 |
| **Any Infection TEAEs** | 1 (2.4) | 1 (3.8) | 4 (16.0) |

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = “Y”; Column Variable 1: TRT01A (Actual Treatment for Period 01).
Age >= 12 years - Dataset: Demographics; Filter: AGEGR1 = '12 to <18 years'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AGEGR1 = '12 to <18 years'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', AGEGR1 = '12 to <18 years'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', AGEGR1 = '12 to <18 years'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', AGEGR1 = '12 to <18 years'.
Age < 12 years - Dataset: Demographics; Filter: AGEGR1 = '6 to <12 years'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AGEGR1 = '12 to <18 years'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', AGEGR1 = '12 to <18 years'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', AGEGR1 = '12 to <18 years'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', AGEGR1 = '12 to <18 years'.
Gender Male - Dataset: Demographics; Filter: SEX = 'M'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', SEX = 'M'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', SEX = 'M'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', SEX = 'M'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', SEX = 'M'.
Gender Female - Dataset: Demographics; Filter: SEX = 'F'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', SEX = 'F'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', SEX = 'F'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', SEX = 'F'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', SEX = 'F'.
Baseline Weight >= 70 kg - Dataset: Demographics; Filter: WGTGR1 = '>= 70 kg'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '>= 70 kg'.

Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '>= 70 kg'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '>= 70 kg'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '>= 70 kg'.
Baseline Weight < 70 kg - Dataset: Demographics; Filter: WGTGR1 = '< 70 kg'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '< 70 kg'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '< 70 kg'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '< 70 kg'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y' and Dataset: Demographics; Filter: WGTGR1 = '< 70 kg'.
Race - White - Dataset: Demographics; Filter: RACEGR1 = 'WHITE'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', RACE = 'WHITE'.
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', RACE = 'WHITE'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', RACE = 'WHITE'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', RACE = 'WHITE'.
Race - Other (pooled) - Dataset: Demographics; Filter: RACEGR1 = 'OTHER' or 'BLACK OR AFRICAN AMERICAN' or 'ASIAN' or 'MULTIPLE' or 'NOT REPORTED' or 'UNKNOWN'.
Subjects with 1 or more TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', RACE = 'OTHER' or 'ASIAN' or 'MULTIPLE' or 'BLACK OR AFRICAN AMERICAN' or 'UNKNOWN'
Subjects who Discontinued Study Drug due to TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', TRDISCFL = 'Y', RACE = 'ASIAN' or 'MULTIPLE' or 'BLACK OR AFRICAN AMERICAN' or 'UNKNOWN' or 'OTHER'.
Subjects with Serious TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AESER = 'Y', RACE = 'OTHER' or 'MULTIPLE' or 'BLACK OR AFRICAN AMERICAN' or 'ASIAN' or 'UNKNOWN'.
Any Infection TEAEs - Dataset: Adverse Events; Filter: TRTEMFL = 'Y', AEINF = 'Y', RACE = 'ASIAN' or 'OTHER' or 'MULTIPLE' or 'BLACK OR AFRICAN AMERICAN' or 'UNKNOWN'.
Safety Population

Although imbalances in certain ARs between demographic subgroups were noted, because of the small subgroup sample sizes, the review team did not conclude that these differences are clinically meaningful. In this submission, the limited subgroup sample sizes prohibit meaningful comparisons and conclusions.

The review team conducted a comparison of TEAEs in subjects receiving guselkumab who weighed < 70 kg ( (b) (4) users) versus ≥ 70 kg (pre-filled syringe [PFS] users) to evaluate differences that may be related to device presentation (Refer to Section 4.4).

**Specific Safety Studies/Clinical Trials**

To provide context for the findings in the pediatric population, the Applicant submitted supportive safety data from the pooled phase 3 trials that supported the original approval of guselkumab for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (approved July 13, 2017). Because this data was previously reviewed, it will not be discussed in detail in this review. Refer to the Multi-disciplinary Review and Evaluation of BLA 761061 dated July 13, 2017.

### 8.2.8. Additional Safety Explorations

**120 Day Safety Update**

No new safety signals were identified in the 120 Day Safety Update (SDN 1463 dated March 26, 2025). The Applicant submitted data from the long-term extension from Week 52 through January 3, 2025. A total of 94 subjects entered the long- term extension trial. This submission includes an additional 194 total subject-years of follow-up for subjects who received guselkumab in Trial CNTO1959PSO3011 with an average additional duration of follow-up of 107.76 weeks.

**Table 38: Summary of Duration of Follow-up from Week 52 Through 03 January 2025 (Trial 3011 Part 1 and Part 2)**

| | Part 1 | | Part 2 | | |
|---|---|---|---|---|---|
| | Placebo → Guselkumab | Guselkumab | Etanercept → Guselkumab | Guselkumab | Combined |
| Analysis set: Subjects treated with guselkumab and did not terminate study participation prior to Week 52 | 20 | 32 | 18 | 24 | 94 |
| Average duration of follow-up (weeks) | 118.28 | 102.91 | 133.38 | 86.25 | 107.76 |
| Total subject-years of follow-up | 45.3 | 63.1 | 46.0 | 39.7 | 194.2 |

Source: 120-Day Safety Update, page 8

The key safety events in guselkumab-treated subjects that are discussed in this report are deaths, SAEs, AEs resulting in discontinuation of study intervention, AESIs (active TB and malignancies), and AEs of interest.

**Deaths:** none

**SAEs:** one event each of peritonsillar abscess, tonsillitis, syncope and influenza.

All SAEs were moderate to severe in intensity and considered as <u>not related</u> to guselkumab by the investigator. All subjects recovered within 2 to 6 days without changes in dosing. However, because of the mechanism of action of this product, a role for guselkumab in the onset or progression of infection cannot be excluded.

- 16-year-old male ([(b) (6)]) with a history of chronic tonsillitis, developed difficulty swallowing, sore throat, and fever and on Day 1527 (Etanercept->Guselkumab 100mg/ total dose 1480mg) and was diagnosed with right peritonsillar abscess of severe intensity. The subject was hospitalized and underwent an emergency tonsillectomy. The subject received treatment with pregabalin/ methylcobalamin and amoxicillin/clavulanic acid for peritonsillar abscess. On Day 1529, the SAE of peritonsillar abscess resolved and the subject was discharged from the hospital.

- 14-year-old female ((b) (6)) with a history of tonsillitis developed pharyngitis and fever on Day 712 (Placebo- >Guselkumab 55mg/ total dose 696 mg), was diagnosed with tonsillitis of moderate intensity. On the following day, the subject was hospitalized. Treatment for the tonsillitis included diclofenac sodium and intravenous hydration. On Day 714, the subject was discharged from the hospital and on Day 717, the SAE of tonsillitis resolved.

- 15-year-old male ((b) (6)) with no relevant medical history developed fever and abdominal pain on Day 871 (guselkumab 70mg/total dose 818mg) and was hospitalized with an SAE of influenza of severe intensity. The subject received treatment with cefuroxime, ibuprofen, paracetamol, and oseltamivir and on Day 874 the SAE of influenza resolved and the subject was discharged from the hospital.

- 16-year-old female ((b) (6)) with a history of syncope, ate and drank very little and then experienced an episode of syncope of moderate intensity on Day 852 (guselkumab 85mg/total dose of 816mg). The subject was hospitalized the same day and received an intravenous hydration. On Day 853 the SAE of syncope resolved and the subject was discharged from the hospital.

There were no AEs leading to discontinuation of guselkumab, no pregnancies no hypersensitivity reactions, thrombotic events, severe depression/suicidal ideation and behavior, or LFT elevations and no AESIs of active TB or malignancy. There were no clinically meaningful changes in laboratory values that support an impact of guselkumab on hematology and clinical chemistry parameters per Applicant (data not submitted).

**Human Carcinogenicity or Tumor Development**

Monoclonal antibodies are large proteins, that are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. Guselkumab will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression, and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of guselkumab. Refer to the Multi-disciplinary Review and Evaluation of BLA 761061 section 5.5.3 (dated July 13, 2017) for a discussion of the carcinogenicity risk from a Pharmacology/ Toxicology perspective.

Data from the nonclinical and clinical development programs does not support the conclusion that chronic administration of guselkumab is associated with increased risk of carcinogenesis. However, the limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency period such as malignancy. Therefore, an

ongoing post marketing study will inform the long-term risk of malignancy in patients with psoriasis receiving guselkumab (PMR 3225-4; Final Report Submission: 12/2031).

**Human Reproduction and Pregnancy**

Requirements for females of childbearing potential who were enrolled in guselkumab development program included the use of effective forms of contraception, negative pregnancy tests at screening and urine pregnancy testing at all study visits. Subjects who became pregnant withdrew from treatment and, where feasible, were followed until delivery. Pregnancy outcomes such as spontaneous abortion, stillbirth, and congenital anomalies were reported as SAEs. In addition, because the applicant did not evaluate the effect of the study drug on sperm, they also reported pregnancies in partners of male subjects who were included in the trials.

The review team evaluated the pregnancy data and related labeling in collaboration with the Maternal Health Team. There was one maternal pregnancy reported in Trial 3011 through Week 52 in a subject who received guselkumab. A brief narrative is below.

- A 15-year-old White female ([redacted] (b) (6)) reported pregnancy at Week 12 (total dose 225 mg). The subject discontinued treatment per protocol. The pregnancy was uncomplicated. The subject delivered a full-term, healthy newborn.

**Applicant data**

The Applicant identified a total of 139 reports of pregnancy in ongoing and completed interventional clinical trials evaluating guselkumab that included unblinded data through July 12, 2024. These clinical trials included subjects who received guselkumab across a large number of different indications (PsA, PsO, Crohn's disease, UC, PPP, hidradenitis suppurativa) as well as healthy volunteers. There were 73 pregnancies in female subjects exposed to guselkumab and 66 partner pregnancies. No subjects reported fetal abnormalities or congenital malformations. The outcomes are summarized in the tables below.

**Table 39: Pregnancy Outcomes for Guselkumab Treated Subjects in Clinical Studies: Maternal Exposure Pregnancies, Cumulatively Through 12 July 2024 (n=73)**

| Pregnancy Outcomes | Interventional Clinical Studies Indications | | | | | | |
|---|---|---|---|---|---|---|---|
| | PSO | PsA | UC | CD | Other Indications[a] | Healthy Participants | Total |
| Live birth | 16 | 0 | 2 | 6[b] | 0 | 0 | **24** |
| Premature birth | 1[c] | 0 | 0 | 0 | 0 | 0 | **1** |
| Spontaneous abortion | 2[d] | 0 | 2 | 2 | 0 | 3 | **9** |
| Elective abortion | 6 | 1 | 1 | 4 | 2 | 0 | **14** |
| Ectopic pregnancy | 1 | 0 | 1 | 0 | 1 | 0 | **3** |
| NR/continuing | 11 | 1 | 3 | 4 | 1 | 2 | **22** |
| **Total** | **37** | **2** | **9** | **16** | **4** | **5** | **73** |

a: Included cases reporting indications of palmoplantar pustulosis (3) and hidradenitis suppurativa (1).
b: Included 1 case reporting emergency C-section due to fetal brachycardia.
c: This case reported live birth via spontaneous method of delivery at 35 weeks gestation period (coded as premature delivery) without adverse events.
d: Included 1 case of missed abortion.

Source: Summary of Clinical Safety page 41, Table 11

**Table 40: Pregnancy Outcomes for Guselkumab Treated Subjects in Clinical Studies: Paternal Exposure Pregnancies, Cumulatively Through 12 July 2024 (n=66)**

| Pregnancy Outcomes | Interventional Clinical Studies Indications | | | | | | |
|---|---|---|---|---|---|---|---|
| | PSO | PsA | UC | CD | Other Indications | Healthy Participants | Total |
| Live birth | 18 | 3 | 1 | 8 | 0 | 1 | **31** |
| Premature birth | 0 | 0 | 0 | 1[a] | 0 | 0 | **1** |
| Spontaneous abortion | 6 | 0 | 0 | 1 | 0 | 0 | **7** |
| Elective abortion | 1 | 0 | 0 | 1 | 0 | 0 | **2** |
| Ectopic pregnancy | 1[b] | 0 | 0 | 0 | 0 | 0 | **1** |
| NR/continuing | 16 | 1 | 3 | 4 | 0 | 0 | **24** |
| **Total** | **42** | **4** | **4** | **15** | **0** | **1** | **66** |

a: This case reported that the baby was born at 36 weeks without reported complications.
b: This case reported induced abortion due to ectopic pregnancy.
**Source**: guselkumab IB

Source: Summary of Clinical Safety page 41, Table 12

**Ongoing Assessments to address Postmarketing Requirements under 505(o)**

Because the available safety data regarding guselkumab use during pregnancy are limited, there are ongoing Postmarketing Requirements under 505(o).

Per approval letter (dated July 13, 2017):

> 3225-2 A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to guselkumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including neonatal deaths, infections in the first 6 months of life, and effects on postnatal growth and development, will be assessed through at least the first year of life.
>
> Final Protocol Submission: 01/2018
> Study Completion: 12/2025
> Final Report Submission: 12/2026
>
> 3225-3 Conduct a retrospective cohort study using claims or electronic medical record data or a case control study to assess adverse pregnancy outcomes such as major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, neonatal deaths, and infant infections in women exposed to guselkumab during pregnancy compared to an unexposed control population.
>
> Final Protocol Submission: 07/2018
> Study Completion: 12/2024
> Final Report Submission: 12/2025

**DPMH Recommendations**

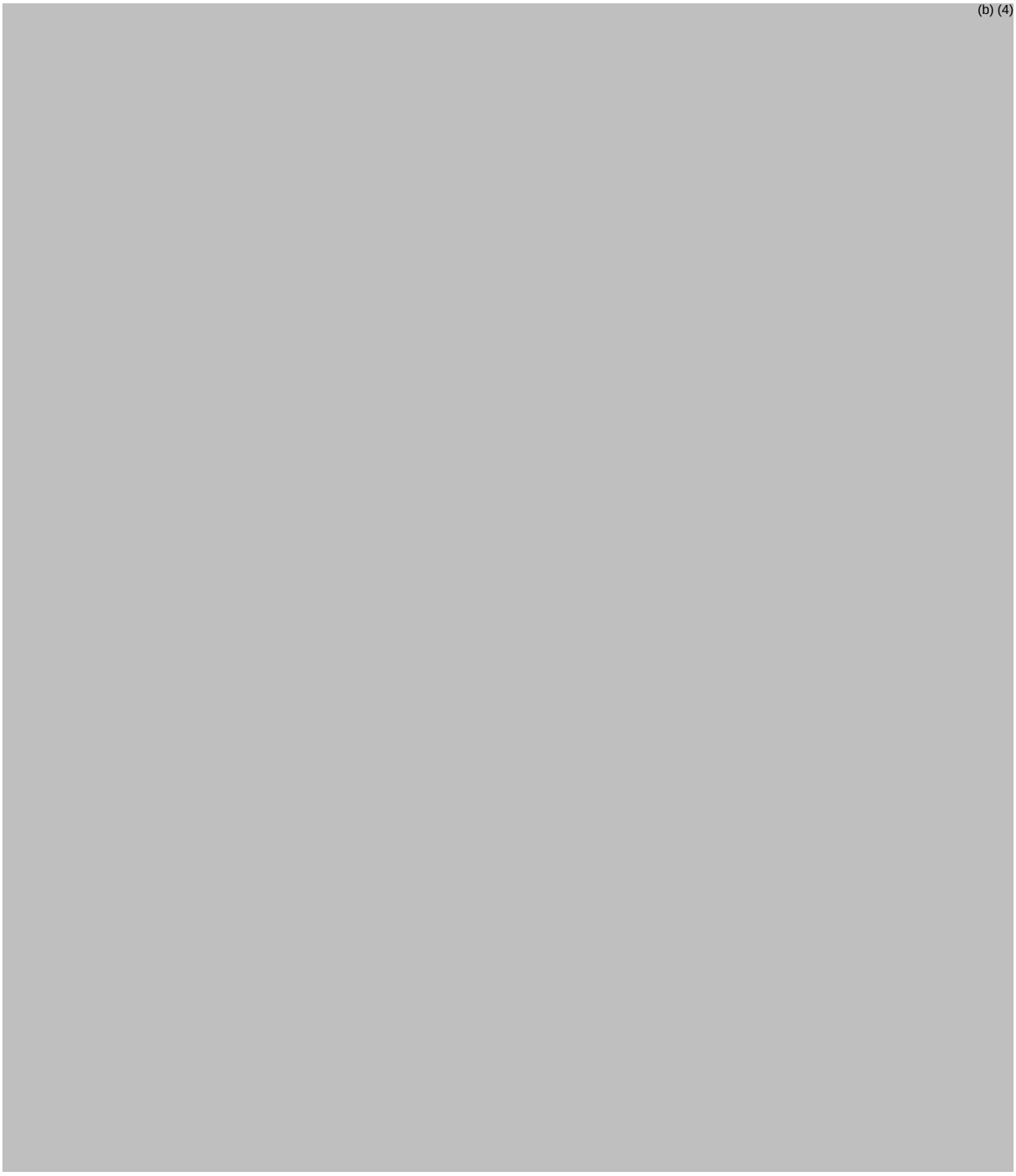
The Maternal Health Division of Pediatrics and Maternal Health (DPMH) team is participating in ongoing assessments of guselkumab in multiple target populations (S026, S028 and S029). In a review dated July 22, 2025, Kerry R. Shaab, MD, provides recommended language for subsection 8.1 Pregnancy, Clinical Considerations, Fetal/Neonatal Adverse Reactions and section 17 and the scientific rationale and regulatory requirements.

DPMH states

> "Based on regulatory labeling requirements for subsection 8.1, Clinical Considerations, Fetal/Neonatal Adverse Reactions, if it is known or anticipated that treatment of a pregnant woman may increase the risk of an adverse reaction in the fetus or neonate, the characteristics of the potential risk must be described. Based on what is known about the structure and function of guselkumab, placental transfer is expected; and there is mechanistic plausibility for immunosuppressive effects on the fetus and neonate, and persistence of immunosuppressive effects into infancy… Available data from published literature on placental transfer and infant outcomes of select IgG-based therapeutic products are difficult to interpret due to the small number of reported cases. Moreover,

DPMH did not identify any published data on postnatal immune function within utero exposure to guselkumab. DPMH concludes that the data are insufficient to label a broadly applicable finding and instead, labeling should communicate that the potential clinical impact of in utero guselkumab exposure should be considered on a case-by-case basis. Additionally, guselkumab labeling should require the HCP to advise the pregnant woman to communicate the history of in utero exposure to the infant's healthcare providers."

(b) (4)



The reviewer noted that **DG modified the language** for section 17 as follows:

> Advise patients treated with TREMFYA during pregnancy to inform the infant's healthcare providers about any history of in utero exposure [see Use in Specific Populations (8.1)].

At this time, the review team determined that this proposed language will not be included in section 17 of labeling for TREMFYA because the communication of "the history of in utero exposure" would not change the management of the infant by the healthcare provider.

**Pediatrics and Assessment of Effects on Growth**

Approval of guselkumab (July 13, 2017) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggered the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) as a new active ingredient. The Applicant received a partial waiver for studies in the pediatric population from birth to less than 6 years of age as "Necessary studies are impossible or highly impracticable because the number of patients in these age groups is small" (Section 505B (a)(4)(B)(i) of the Act). The FDA acknowledged that although the epidemiologic data is limited regarding the pediatric population with moderate to severe plaque psoriasis, the prevalence of plaque psoriasis generally increases with age.

In addition, the Applicant received a deferral of studies in the pediatric population from age 6 years to <18 years "until additional safety or effectiveness data have been collected in adults (Section 505B (a)(3)(A)(ii) of the Act)." The current pediatric plan is consistent with the agreed initial pediatric study plan (iPSP, agreement letter dated November 21, 2014) and the timeline granted with the deferred extension request (Pediatric Review Committee [PeRC] discussion August 8, 2023).

The data from Trial CNTO1959PSO3011 is intended to support the safe use of guselkumab in the pediatric population with moderate to severe psoriasis at exposures matching those in adults. The target population had sufficient severity (moderate-to-severe PsO defined by IGA ≥3, PASI ≥12, and a BSA ≥10, and at least 1 of the following: very thick lesions, clinically relevant facial, genital, or hand and foot involvement, PASI ≥20, BSA >20, or IGA=4) to support a positive benefit risk assessment. The study design and safety monitoring were similar to other phase 3 trials with the addition of assessments to evaluate the potential impact of guselkumab on growth and development. Relevant assessments included height and weight at Weeks 0 and 52, Tanner Staging at Screening and Week 52, and head circumference at Screening and Week 52 in subjects ≥6 years old to < 12 years old. The Division of Pediatrics and Maternal Health (DPMH) assisted in the review of this data. (Review by Karen Fratantoni, MD dated July 24, 2025.) The reviewer concluded:

> "A review of weight and height data for patients 6 years old to <18 years old enrolled in a 52-week trial of Tremfya for treatment of moderate to severe plaque psoriasis did not

identify concerns for weight loss or a decrease in height velocity." (from Pediatrics consult memo dated July 24, 2025).

In addition, DRTM issued PREA PMR 3899-1 to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (jPsA) in children 5 to 17 years of age. The extrapolation-based approach would be supported by completed and ongoing trials in adults with PsA, as well as data from the completed trial of guselkumab in pediatric subjects with psoriasis (Trial CNTO1959PSO3011). In S-029, the Applicant submitted their rationale to support the use of SC guselkumab for the treatment of jPsA in patients ≥40kg. Based on the submitted rationale, DRTM concluded that it was "reasonable to extrapolate the efficacy of guselkumab from adult PsA and PsO to juvenile psoriatic arthritis based on the similarity of conditions, exposure-responses, and responses to treatment." (PeRC Assessment Template)

On August 12, 2025, the Division discussed the results of the pediatric assessment with PeRC. In view of the (b) (4) from the S-028 (letter dated July 25, 2025), the PeRC agreed with the Division and initially recommended the following strategy to address the PREA PMR (meeting minutes dated September 5, 2025):

"Tremfya (guselkumab) Partial Waiver/Assessment & Deferral Extension

- Proposed indication: Treatment of moderate to severe plaque psoriasis in pediatric patients 6 years and older who are candidates for systemic therapy or phototherapy (final indication pending adjudication).
- The original approval for guselkumab is dated July 13, 2017, and the Applicant received a partial waiver for studies in the pediatric population from birth to less than 6 years of age as necessary studies are impossible or highly impracticable because the number of patients in this age groups is small. The Agency deferred the assessment of guselkumab in the pediatric population ages 6 years to less than 18 years because the product was ready for approval for use in adults and the pediatric study had not been completed. The Division issued the following PREA PMR with the initial adult approval of guselkumab:
- 3225-1 Conduct a PK, Safety and Efficacy Study in pediatric subjects 6 years to less than 18 years of age with moderate to severe plaque psoriasis (with a duration of exposure to guselkumab of at least one year).

  Initial Protocol Submission: 10/2017
  Final Protocol Submission: 04/2018
  Trial Completion: 10/2023
  Final Report Submission: 04/2024

  The Applicant submitted an efficacy supplement (S-028) to extend the indication to "the treatment of adult patients and in pediatric patients (6 years of age and older) with moderate to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy." Trial 3011 enrolled and randomized a total of 92 subjects from 29 sites. No new safety signals were identified. The results demonstrated that guselkumab was efficacious in the pediatric population. (b) (4)

(b) (4)
from S- 028 on July 25, 2025. Based on PK modeling, the clinical pharmacology team determined that the 100 mg dose in subjects ≥ 40 kg resulted in similar exposures when compared to subjects weighing 70 kg. The Division has concluded that these data demonstrate superior efficacy for guselkumab compared to placebo and identified no new safety signals regardless of the device used.

- The Division recommends that the PMR #3225-1 be considered partially fulfilled in pediatric patients who weigh at least 40 kg and a DE for the existing PREA PMR be issued to extend the final report submission due date to July 2027 to allow the Applicant time to develop a new presentation for patients weighing < 40 kg. The PeRC agreed.

*PeRC Recommendations:*

- The PeRC agreed that PREA PMR 3225-1 is partially fulfilled for pediatric patients weighing ≥ 40 kg based on the results from Trial 2011…
- The PeRC agreed to grant a deferral extension for PREA PMR 3225-1 to July 2027 to allow the Applicant to develop a device presentation for use in patients weighing < 40kg."

The Office of the Chief Counsel (OCC), Office of Regulatory Operations (ORO) and DPMH agreed with the regulatory approach of granting a deferral extension for PREA PMR 3225-1 to July 2027 to enable the Applicant to propose or develop an age-appropriate formulation/presentation to administer guselkumab to patients 6 years of age and older who weigh less than 40 kg. Another regulatory option that was considered in order to address the need for an adequate device to administer guselkumab to this population was to release the Applicant from the current PMR and reissue with a new PMR that includes the requirement to propose or develop a new device.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

Overdose

Because there were no reports of overdosage in the development programs to date Section 10 OVERDOSE is not included in labeling for guselkumab.

Drug Abuse Potential/ Withdrawal and Rebound

There is no data to support an association of monoclonal antibodies including guselkumab with the potential for addiction, abuse, or withdrawal. The applicant did not evaluate abuse potential but did document any potential cases of rebound that were reported during clinical trials. The protocol defined rebound as "an event of new erythrodermic or pustular psoriasis or a PASI of ≥125% of the baseline PASI (i.e., a worsening of PASI by 25% or greater from baseline) that occurred after subjects were withdrawn from active treatment with guselkumab at Week 28."

The Applicant reported one case of rebound in a subject who participated in Trial CNTO1959PSO3002. A subject ((b) (6)) initially randomized to guselkumab at Week 0 who was a

PASI 90 responder at Week 28 and rerandomized to placebo, developed rebound of psoriasis (PASI of ≥125% of baseline) at Day 309 of the trial. This event occurred approximately 16 weeks after withdrawal of guselkumab. No additional cases were reported.

### 8.2.9. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

The Applicant states that no new safety signals have been identified for guselkumab with respect to AEs, SAEs, mortality, and malignancy in the post marketing data. According to the Applicant, the estimated cumulative global exposure to guselkumab from launch through June 30, 2024, was (b) (4) person-years. The Applicant states that "the evaluation of postmarketing data is part of the Applicant's comprehensive safety surveillance program, which also includes review of data from ongoing clinical studies and registries. Periodic Safety Update Reports generated for guselkumab reflect ongoing postmarketing safety surveillance, as well as assessments of all important identified and potential risks."

As part of their monitoring of the long-term safety of guselkumab, the Applicant utilizes the **PSOLAR registry** (Protocol C0168Z03), an international, multicenter, prospective, observational registry for monitoring the long-term safety experience and clinical status of patients with moderate to severe psoriasis (PsO) who are ≥18 years of age and eligible to receive or are actively receiving any systemic therapies for PsO. In March 2018, the PSOLAR protocol was amended (Amendment 6, dated March 26, 2018; also referred to as PSOLAR 2) to allow enrollment of patients receiving treatment with guselkumab or an IL-17 inhibitor (e.g., secukinumab, ixekizumab, brodalumab) as part of a postmarketing commitment to health authorities for guselkumab.

Enrollment in PSOLAR 2 has closed. In the guselkumab cohort, a total of 2,198 patients with PsO are enrolled in PSOLAR 2 cumulatively through July 12, 2024. Of these, 65 patients have completed an enrollment visit only; 68 patients have completed a 6- month follow-up visit, 91 patients have completed a 1-year follow-up visit, 259 patients have completed a 1.5-year follow-up visit, 391 patients have completed a 2-year follow-up visit, and 1,324 patients have completed a 2.5- to 5.5-year follow-up visit.

The Applicant states:

> "Using the ever-exposed definition of exposure, the cumulative unadjusted incidence rates for reported cardiac disorders was similar for guselkumab cohort versus IL-17 cohort. The overall cumulative unadjusted incidence rate for AEs contained within the neoplasms SOC was numerically lower in the guselkumab cohort versus IL-17 cohort; incidence rates for individual PTs contained within the SOC were numerically similar between the guselkumab and IL-17 cohorts. Using the 91-day exposure definition, the cumulative unadjusted incidence rates for infections/infestations were numerically lower in the guselkumab versus IL-17 cohorts… The data analyses conducted for the

current reporting interval (cumulative through 12 July 2024) did not identify any new safety signals for guselkumab with respect to AEs and SAEs, or any specific AESIs."

The **German registry**, Treatment of PsoBest (Protocol [CNTO1959PSO4001]), is a prospective observational study designed to examine the long-term safety and effectiveness of systemic therapies, including biologics, available to treat adults with moderate to severe plaque PsO or psoriatic arthritis (PsA) in Germany. The cumulative number of patients included in the guselkumab cohort is 1,435 (1,816.80 patient years); median age and duration of illness were 48 years and 14 years, respectively. There were 924 SAEs and 812 AEs from December 13, 2007, to December 31, 2023 in the guselkumab cohort. Among the SAEs reported, the most frequently reported MedDRA PTs were in the following SOCs: Surgical and medical procedures (n=239) and Injury, poisoning and procedural complications (n=81). During this period, 29 patients exposed to guselkumab reported 39 malignancy SAEs (SOC Neoplasm benign, malignant and unspecified [incl cysts and polyps]). A total of 11 all-cause deaths were reported in the guselkumab cohort during this period. Comparative analyses of rates of SAE and AEs among systemic products are planned.

The Applicant stated that neither of these registries, **PSOLAR or PsoBest,** have identified any new safety signals.

In addition, the **OTIS** registry is a North American based, observational pregnancy registry designed to monitor planned or unplanned pregnancies exposed to guselkumab to treat an approved indication (PsO or PsA), and to collect follow-up information on the health status of the infants through approximately 1 year of age. Through May 31, 2024, 13 patients were enrolled with outcomes collected on 10 pregnancies. Outcomes included 6 live born infants, 3 spontaneous abortions and 1 lost to follow-up. There were no reports of major malformations. Three pregnancy outcomes are still pending at the time of this submission.

In support of BLA 761061/S-021 (guselkumab for adults with moderately to severely active ulcerative colitis [UC]), the Division of Pharmacovigilance (**DPV)** performed reviews of available postmarketing data (2024 and 2025). To identify signals, the Division of Pharmacovigilance (DPV) focused on unlabeled adverse events with the potential for serious outcomes, labeled adverse events with unexpected characteristics such as an increase in severity, and other important findings that inform the safety of the product. The review (dated February 24, 2025) identified no new safety signals and recommended no revisions to Section 6 of the USPI, Postmarketing Experience (Division of Pharmacovigilance review memos by Suraj Rajasimhan, PharmD dated June 28, 2024, and February 24, 2025 under BLA 761061).

**Expectations on Safety in the Postmarket Setting**

The proposed dosing regimen in the pediatric population with moderate to severe plaque psoriasis weighing ≥ 40 kg is 100 mg SC at Weeks 0, 4, and q8wks thereafter. The systemic

exposure in this pediatric population is comparable to the exposure in the adult population. The safety profile of guselkumab at the proposed dosing regimen in the pediatric population was consistent with the established safety profile of guselkumab in the adult population with moderate to severe plaque psoriasis. As such, based on the available safety data, we expect that the postmarketing safety experience for pediatric patients with moderate to severe psoriasis will be similar to that of adult patients with psoriasis for which guselkumab is approved.

### 8.2.10. **Integrated Assessment of Safety**

The safety profile for guselkumab in the pediatric population age 6 to < 18 years old was adequately characterized during the drug development program. The primary review of safety of the drug product for the treatment of adults and children ages 6 years and older with moderate to severe psoriasis who weigh ≥ 40 kg relied on the evaluation of safety data from the phase 3 Trial CNTO1959PSO 3011. A total of 120 eligible subjects enrolled in Trial CNTO1959PSO 3011 and were randomized in a 2:1:1 ratio to receive either guselkumab, placebo, or etanercept. The Applicant provided supportive safety data from the phase 3 development program in adults for comparison.

There were no deaths in Trial CNTO1959PSO3011. Three subjects who received guselkumab developed SAEs. In Part 1, two SAEs were reported among subjects who received guselkumab (2.9%) and none in subjects who received placebo (0%) or etanercept (0%). One SAE occurred during the controlled, double-blind period (fracture); one SAE occurred during the maintenance period in a subject originally randomized to placebo (tonsillitis.) One SAE occurred in the open-label Part 2 (1.4%, fracture). Three SAEs occurred were deemed unrelated to guselkumab by the review team (refer to Section 8.2.4 of this review).

The review team evaluated the data in the submission for evolving safety concerns associated with the disease (suicidal ideation and behavior), serious safety issues conveyed in Warnings and Precautions sections of labeling (hepatotoxicity, hypersensitivity and serious infections including tuberculosis) and adverse events of special interest (malignancy and active tuberculosis). There were no SAEs or adverse reactions related to suicidal ideation and behavior, hypersensitivity, serious infection including tuberculosis (refer to Section 8.2.5 of this review). Malignancy is a potential risk with a long latency period associated with chronic immunosuppression. No cases of malignancy were observed in Trial 3011 to date.

The most common adverse reactions (ARs) were upper respiratory infections (26.8%), headache (7.3%), injection site reactions (2.4%). These ARs are already included in Section 6 (Adverse Reactions) of guselkumab labeling. Despite the limitations of evaluating a small sample size,

the analysis by the review team reveals that the safety profile of pediatric subjects treated with guselkumab is comparable to that of adult subjects.

No new safety signals were identified. The safety data currently available demonstrate that guselkumab is safe for the treatment of adults and pediatric patients 6 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy.

## 8.3. **Statistical Issues**

There were no statistical issues identified in the review of this supplement.

## 8.4. **Conclusions and Recommendations**

To establish the effectiveness of guselkumab for the treatment of moderate to severe psoriasis in the pediatric population, the Applicant submitted data from an adequate and well-controlled clinical Trial CNTO1959PSO3011. The trial was a randomized, multicenter, double-blind, placebo and active-controlled trial that evaluated a total of 120 subjects ages 6 to < 18 years with moderate to severe psoriasis. The protocol-specified definition for moderate to severe psoriasis was an IGA score ≥3 (moderate), PASI score ≥12, ≥10% body surface area (BSA) involvement and at least one of the following [very thick lesions, clinically relevant facial, genital, or hand/ foot involvement, PASI ≥20, >20% BSA involvement or IGA=4 (severe)]).

Part 1 of the trial was divided into Part 1a (≥12 to <18 years of age [i.e., adolescents]) and Part 1b (≥6 to <12 years of age). Part 1a was designed to enrolled and randomize at least 60 subjects in a 2:1:1 ratio to receive either guselkumab (n=30), placebo (n=15), or etanercept (n=15). Part 1b was designed to enrolled and randomize at least 30 subjects in a 1:1:1 ratio to receive either guselkumab (n=10), placebo (n=10), or etanercept (n=10). The protocol specified stratifying the randomization by age group (6 to <12 years and 12 to <18 years) and pooled region (North America [NA], Europe [EU]).

The protocol specified co-primary efficacy endpoints were:

- Proportion of subjects achieving an IGA score of 0 (cleared) or 1 (minimal) at Week 16.
- Proportion of subjects with a PASI 90 response (defined as subjects who achieved at least 90% reduction in the PASI composite score from baseline) at Week 16.

The protocol specified secondary efficacy endpoints (controlled for multiplicity) were:

- Proportion of subjects achieving a PASI 75 response at Week 16.
- Proportion of subjects achieving an IGA score of 0 (cleared) at Week 16.
- Proportion of subjects achieving a PASI 100 response at Week 16.
- Change from baseline in Children's Dermatology Life Quality Index (CDLQI) at Week 16

Guselkumab was statistically superior to placebo on both co-primary efficacy endpoints (p-values ≤ 0.003) and all key secondary efficacy endpoints (p-values ≤ 0.002) in Trial CNTO1959PSO3011.

The Applicant conducted a comprehensive assessment of the safety of guselkumab in the target population. The size of the safety database and the safety evaluations were adequate to permit substantive review of the data and identify local injection site reactions and systemic treatment-emergent adverse reactions. The safety findings were limited by the size of the safety database but were comparable to the findings in the adult population. The safety and efficacy data submitted by the Applicant support approval of this sBLA for guselkumab for the treatment of adult and pediatric patients 6 years of age and older who also weigh ≥ 40 kg with moderate-to-severe plaque psoriasis and who are candidates for systemic therapy or phototherapy. However, (b) (4) the Applicant will be required to propose or develop an age-appropriate formulation and delivery system (presentation) for the pediatric age group weighing less than 40 kg in order to fulfill PMR 3225-1.

## 9 Advisory Committee Meeting and Other External Consultations

The Agency held no Advisory Committee Meeting regarding this application because the safety profile in the pediatric population was expected to be comparable to that of the adult population. There were no issues that warranted an advisory committee discussion.

## 10 Pediatrics

Refer to the following sections of this review for the proposed development program for guselkumab in the pediatric population:

- Section 3.2 Presubmission Regulatory History and 8.2.8 Pediatrics and Assessment of Effects on Growth for a discussion regarding the Pediatric Study Plan (PSP) and Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA)
- Section 13 Postmarketing Requirements and Commitments for additional deferred pediatric assessments, that are required to fulfill the PMR under the PREA (21 CFR 314.55(b) and 601.27(b)).

## 11 Labeling Recommendations

### 11.1. Prescription Drug Labeling

**Prescribing information**

The Applicant submitted proposed Tremfya prescribing information (PI) and Medication Guide for TREMFYA® (guselkumab) injection. The review team provided recommendations regarding the PI which are provided throughout this review. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed proposed Tremfya PI, Medication Guide (MG), Instructions for Use (IFU), container label, and carton labeling. The reviewer did not identify areas of vulnerability that may lead to medication errors in the original S-028 (submitted November 27, 2024) and the amended S-028 (submitted July 25, 2025) (b) (4) Refer to the labeling review by Madhuri R. Patel, PharmD dated August 21, 2025.

The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI. Refer to the OPDP review by Montherson Saint Juste, PharmD, MS dated September 11, 2025. The following table provides the location of the labeling discussion for each section.

**Table 41: Summary of Significant Labeling Changes**

| Summary of Significant High Level Labeling Changes | |
|---|---|
| **Section** | **Location of Reviewer Comments on Proposed Labeling** |
| 1 INDICATIONS AND USAGE | Section 1.1, 8.2.5.3 |
| 2 DOSAGE AND ADMINISTRATION | Section 4.4, 6.2.2 |
| 3 DOSAGE FORMS AND STRENGTHS | Section 4.4 |
| 4 CONTRAINDICATIONS | N/A |
| 5 WARNINGS AND PRECAUTIONS | Section 8.2.5 |
| 6 ADVERSE REACTIONS | Section 8.2.4 |
| 7 DRUG INTERACTIONS | N/A |
| 8 USE IN SPECIFIC POPULATIONS | Section 5.5.4, 8.2.9, 19.3 |
| 12 CLINICAL PHARMACOLOGY | Section 6.2, 6.3, 19.4 |
| 13 NONCLINICAL TOXICOLOGY | N/A |
| 14 CLINICAL STUDIES | Section 8.1 |
| 17 PATIENT COUNSELING INFORMATION | Reflects the data in other sections of labeling, Sections 4, 5, 6, 7 and 14. |

Source: Reviewer's Table

Labeling negotiations are ongoing at the time of this review, the key changes proposed by the review teams are discussed in the relevant sections as summarized above.

**Patient Labeling**

The Applicant submitted a proposed Medication Guide (MG), Instructions for Use (IFU) for TREMFYA (guselkumab) injection and carton and container labels. The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments regarding the MG and IFU. These comments are reflected in final labeling. Refer to the DMPP/OPDP review by Sharon Williams, MSN, BSN, RN and Montherson Saint Juste, PharmD, MS dated September 12, 2025.

## 12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and a Medication Guide are not required at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects.

## 13 Postmarketing Requirements and Commitment

(b) (4)

The Applicant has completed the trial. However, the Applicant has not completed the assessment in the pediatric population as required under PREA which also includes the development of an acceptable formulation and presentation for all pediatric age groups. (b) (4) , the Applicant will be required to propose or develop an age-appropriate presentation for the administration of guselkumab to pediatric patients weighing <40 kg. Fixed dosing of 100 mg in patients weighing ≥ 40 kg rather than ≥ 70 kg as specified in Trial CNTO1959PSO3011 was based on PK modeling. The clinical pharmacology team determined that similar exposures resulted from administration of the 100 mg dose of guselkumab to subjects who weigh ≥ 40 kg and subjects who weigh ≥ 70 kg.

The regulatory approach recommended by OCC, ORO and DPMH was to consider PMR 3225-1 as partially fulfilled. The internal Pediatric Review Committee (PeRC) meeting was held on August 12, 2025. PeRC agreed with the proposal to grant a deferral extension request to propose or develop an age-appropriate formulation/ presentation for use in the pediatric

population ages 6 to 17 years who weigh less than 40 kg. The PeRC also agreed with a milestone date of July/2027.

## 14 Division Director (DHOT) Comments

Not Applicable.

## 15 Division Director (OCP) Comments

Not Applicable.

## 16 Division Director (OB) Comments

Not Applicable.

## 17 Division Director (Clinical) Comments

None.

## 18 Office Director (or designated signatory authority) Comments

Not Applicable.

# 19 Appendices

## 19.1. References

Barlow R., et al. (2023). Suicide and Suicidality in Children and Adolescents with Chronic Skin Disorders: A Systematic Review. Acta Derm Venereol, 103.

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## 19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for guselkumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3) (i-iv).

The covered clinical study as defined in 21 CFR 54.2(e) was, phase 3 Trial CNTO1959PSO3011. The Applicant stated that “There were no investigators with disclosable financial interest/arrangements. There were no investigators requiring certification of due diligence. There are no investigators that are Sponsor employees (including full-time or part-time employees).”

**Table 42: Covered Clinical Study: CNTO1959PSO3011 (3011)**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ |
| Total number of investigators identified: 226 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ N/A | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ N/A | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ N/A | No ☐ (Request explanation from Applicant) |

## 19.3. Nonclinical Pharmacology/Toxicology

Not applicable.

## 19.4. OCP Appendices (Technical documents supporting OCP recommendations)

### 19.4.1. Summary of bioanalytical methods

For the determination of serum guselkumab concentrations, the validated ECLIA method used in the clinical studies in support of the current application for pediatric patients with moderate to severe plaque PsO. The pharmacokinetic validation summary parameters for adults (Study CNTO1959PSO3001 and CNTO1959PSO3002) and pediatric subjects (study CNTO2919PSO3011)

are listed in Table 43. The lowest quantifiable serum concentration of the PK assay was 0.01 µg/mL.

**Table 43: Pharmacokinetic validation summary parameters for CNTO1959PSO3001, CNTO1959PSO3002, and CNTO2919PSO3011**

| | |
|---|---|
| **Validation Report** | CP2014V-027 |
| **Validation Dates:** | 03 Jun 2014 to 24 Jun 2014 (original report) |
| **Assay Type:** | Electrochemiluminescence-Based Immunoassay (ECLIA) |
| **Standard Curve Fit:** | Wagner (log-log Quadratic) regression with no weighting in Watson LIMS |
| **Standard Curve Range:** | 0.064000 µg/mL to 0.00100 µg/mL define the standard curve limits of quantification with anchoring points for curve fitting at 0.12800 and 0.00050 µg/mL |
| **Minimum Required Dilution:** | 1:10 |
| **Lowest Quantifiable Concentration in a Sample:** | 0.01000 µg/mL at a 1:10 dilution |
| **Selectivity:** | Normal: Acceptable recovery in 10 out of 10 individuals, all results for all unspiked individuals below LLOQ<br>Psoriasis: Acceptable recovery in 9 out of 10 individuals, results for 9 out of 10 unspiked individuals below LLOQ<br>Psoriatic Arthritis: Acceptable recovery in 8 out of 10 individuals, results for 9 out of 10 unspiked individuals below LLOQ<br>Ulcerative Colitis: Acceptable recovery in 10 out of 10 individuals, all results for all unspiked individuals below LLOQ<br>Palmoplantar Pustulosis: Acceptable recovery in 9 out of 10 individuals, all results for all unspiked individuals below LLOQ (A7)<br>Crohn's Disease: Acceptable recovery in 8 out of 10 individuals, 9 out of 10 results for all unspiked individuals below LLOQ (A15)<br>Hidradenitis Suppurativa: Acceptable recovery in 9 out of 10 individuals, all results for all unspiked individuals below LLOQ (A16)<br>Familial Adenomatous Polyposis: Acceptable recovery in 9 out of 10 individuals, all results for all unspiked individuals below LLOQ (A22)<br>Systemic Sclerosis: Acceptable recovery in 9 out of 9 individuals, all results for all unspiked individuals below LLOQ (A34)<br>Systemic Lupus Erythematosus: Acceptable recovery in 9 out of 10 individuals, all results for all unspiked individuals below LLOQ (A34)<br>Giant Cell Arteritis: Acceptable recovery in 9 out of 10 individuals, all results for all unspiked individuals below LLOQ (A34) |
| **Maximum Acceptable Dilution:** | 1:5,000; no hook effect present at 1:10 dilution of a 20.00000 µg/mL spike |
| **Overlapping Area of the Range of Quantitation:** | 0.57000 µg/mL had acceptable range between 1:10 and 1:500 dilutions<br>28.50000 µg/mL had acceptable range between 1:500 and 1:5000 dilutions |
| **Specificity:** | Presence of polyclonal anti-drug antibodies at 200 and 500 ng/mL does not affect recovery of CNTO1959 at MQC and LLOQ concentrations.<br>Presence of non-neutralizing antibodies at 200 and 500 ng/mL does not affect recovery of CNTO1959 at MQC concentrations.<br>Presence of non-neutralizing antibodies at 200 and 500 ng/mL does affect recovery of CNTO1959 at LLOQ concentrations.<br>Presence of IL-23 affects CNTO1959 at 0.01000 µg/mL when tested at molar ratios of 20:1, 10:1, 2:1 and 1:1.<br>CNTO 1959 recovery is not impacted by the presence of JNJ-64304500 at 124.36509 µg/mL (A23) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | CNTO 1959 recovery is not impacted by the presence of Etanercept at 10.00000 µg/mL (A23)<br>CNTO 1959 recovery is not impacted by the presence of Risankizumab at 150.00000 µg/mL. (A29)<br>CNTO 1959 recovery is not impacted by the presence of Remicade at 189.00000 µg/mL (A36)<br>CNTO 1959 recovery is not impacted by the presence of Entyvio at 14.00000 µg/mL (A36) | | | | | |
| **Accuracy and Precision:** | **Control (µg/mL)** | **Diluted Concentration (µg/mL)** | **Dilution** | **% Bias** | **Inter-assay %CV** | **% Total Error** |
| | ULOQ (0.64000) | 0.06400 | 10 | 1.38 | 3.92 | 5.30 |
| | HQC (24.00000) | 0.04800 | 500 | 0.77 | 6.58 | 7.35 |
| | MQC (4.00000) | 0.00800 | 500 | -0.75 | 5.21 | 5.96 |
| | LQC (1.50000) | 0.00300 | 500 | -1.33 | 4.70 | 6.03 |
| | LLOQ (0.01000) | 0.00100 | 10 | -1.00 | 7.81 | 8.81 |
| **Batch Size:** | 20 plates | | | | | |
| **Ruggedness/Robustness:** | Biotinylated-CNTO2254 solution and Sample/Controls/Standard Curve can incubate for a minimum of 60 minutes and up to a maximum of 120 minutes.<br>SulfoTag-CNTO5203 can incubate for a minimum of 50 minutes and up to a maximum of 70 minutes. | | | | | |
| **Assay Quality Control Sample Stability:** | CNTO 1959 in Human Serum:<br>Freeze/Thaw: 8 cycles<br>Room Temperature: 24 hours<br>4°C: up to 6 months (A39,Appendix 1)<br>-20°C: up to 4 weeks<br>-70°C: up to 7 years (A41) | | | | | |
| **Standard Curve Calibrator and QC Stability in a 1 mL 96 Deep Well:** | 4°C: up to 1 week | | | | | |
| **Standard Curve Calibrator Stability in a Tube:** | 4°C: up to 1 week | | | | | |

Abbreviations: CV=coefficient of variation; ECLIA=electrochemiluminescent immunoassay; HQC=higher quality control; IL-23=interleukin 23; LIMS=laboratory information management system; LLOQ=lower limit of quantitation; LQC=lower quality control; MQC=middle quality control; QC=quality control; ULOQ=upper limit of quantitation

There were 2 methods for the determination of immunogenicity. The initial ECLIA method was used in previous registrations of PsA and PsO in adults and was used in CNTO1959PSO3001 and CNTO1959PSO3002. An updated ECLIA method, with improved drug tolerance, was developed and validated. In CNTO1959PSO3011, both methods were used for the detection of ADAs, and only the updated method was used for the detection of NAbs. The ADA assay validation parameters for CNTO1959PSO3001, CNTO1959PSO3002, and the first interim of CNTO2919PSO3011 are presented in Table 44.

**Table 44: ADA Assay Validation Parameters for CNTO1959PSO3001, CNTO1959PSO3002, and the First Interim of CNTO2919PSO3011**

| | |
|---|---|
| **Validation Report #** | CP2010V-008 |
| **Validation Period** | 19 Feb 2010 to 09 Mar 2010 (original report) |
| **Report Title** | Validation of an Assay to Detect Antibodies to CNTO 1959 in Human Serum Samples |
| **Report Effective Date** | 08 Jun 2010 |
| **Assay Type** | ECLIA |
| **Assay Result Type** | Normalized ECL Value (NV) |
| **Minimum Dilution** | 1/10 |
| **Sensitivity (A3)** | Maximum sensitivity was observed for an ADA (CNTO 8820) at a serum concentration of 3.1 ng/mL.<br>Maximum sensitivity was observed for a cynomolgus monkey polyclonal ADA at a serum concentration of 6.2 ng/mL. |
| **Specificity** | CNTO 1959 competitively inhibited an ADA control. |
| **Selectivity (Recovery)** | 102.2% and 102.7% for 15 ng/mL and 250 ng/mL of a CNTO 1959 specific monoclonal ADA, respectively, in human serum. (A4)<br>106.4% and 103.4% for 1/50,000 and 1/5,000 of a CNTO 1959 specific polyclonal ADA, respectively, in human serum.<br>104.4% to 130.8% for 1/50,000 of a CNTO 1959 specific polyclonal ADA, in human serum from psoriasis subjects and in hemolyzed and lipemic serum samples from normal healthy individuals (A5). |
| **Interference (A7)** | Drug tolerance:<br>Sample Description / Maximum Drug Concentration Tolerated<br>100 ng/mL CNTO 8820 in nNHS: 6.25 µg/mL<br>250 ng/mL CNTO 8820 in nNHS: 12.50 µg/mL<br>500 ng/mL CNTO 8820 in nNHS: 25.00 µg/mL<br>100 ng/mL MO1468 in nNHS: 12.50 µg/mL<br>250 ng/mL MO1468 in nNHS: 25.00 µg/mL<br>500 ng/mL MO1468 in nNHS: 25.00 µg/mL<br>Unrelated ADA tolerance: Pre-incubation with up to 50,000 ng/mL CNTO 9192 did not cause interference in the assay.<br>The drug tolerance of the assay in the presence of 10 µg/mL Etanercept was determined to be 6.25 µg/mL of CNTO 1959 for the 100 ng/mL and 250 ng/mL CNTO 8820, and 12.50 µg/mL for the 500 ng/mL CNTO 8820 (A9). |
| **Study Phase Bioanalysis Acceptance Criteria for Controls** | Consistency Controls for screening, titration, and specificity methods:<br>Diluent consistency control: Criteria not applicable as this control is used to calculate criteria for controls on same plate<br>Naive serum consistency control: <2.91 NV<br>Low monoclonal ADA consistency control in nNHS: 5.29 to 34.69 NV, inclusive.<br>High monoclonal ADA consistency control in nNHS: ≥89.15 NV.<br>Low polyclonal ADA consistency control in nNHS: 5.45 to 14.87 NV, inclusive.<br>High polyclonal ADA consistency control in nNHS: ≥42.63 NV.<br><br>Additional controls for the specificity method:<br>Uninhibited monoclonal ADA specificity control (250 ng/mL CNTO 8820): ≥2.91 NV.<br>Inhibited monoclonal ADA specificity control (250 ng/mL CNTO 8820): ≥48.5% inhibition after incubation with CNTO 1959 and <2.91 NV.<br>Uninhibited polyclonal ADA specificity control (1/5,000 MO1468): ≥2.91 NV. |

| | |
|---|---|
| | Inhibited polyclonal ADA specificity control (1/5,000 MO1468): ≥48.5% inhibition after incubation with CNTO 1959 and <2.91 NV.<br>Uninhibited IL-23 specificity control (2.5 µg/mL IL-23): 2.04 to 55.44 NV.<br>Inhibited IL-23 specificity control (2.5 µg/mL IL-23): ≥48.5% inhibition after incubation with CNTO 856. |
| **Cut Points (Normal, Psoriasis and Psoriatic Arthritis Populations) (A8)** | *Screening Method:<br>Normal Subjects: ≥1.20 NV Psoriasis Subjects: ≥1.20 NV Psoriatic Arthritis: ≥1.42 NV<br>*Note: The acceptance interval of the FPR of negative samples for a new disease population or a clinical study's PsO or normal pre-dose baseline is 2.06% to 40.9% based on the union of the two-sided 99% CI of the PsO and normal validation populations. The acceptance interval of the FPR of negative samples for a clinical study's PsA pre-dose baseline is 2.07% to 31.7% based on the two-sided 99% CI of the PsA validation population.<br><br>Titration Method: ≥1.55 NV<br><br>Specificity Method:<br><br>Samples from normal and psoriasis subjects are classified as specific for ADA to CNTO 1959 if:<br>In the absence of CNTO 1959 uninhibited sample signal ≥1.20 NV and<br>In the presence of CNTO 1959, the sample signal is inhibited by ≥30.4%<br><br>Samples from psoriatic arthritis subjects are classified as specific for ADA to CNTO 1959 if:<br>In the absence of CNTO 1959 uninhibited signal ≥1.42 NV and<br>In the presence of CNTO 1959, the sample signal is inhibited by ≥30.4% |
| **Dilutability** | Serial 1/2 dilutions of ADA resulted in a decline in the assay signal without prozone effects, and justified relevance of the titration method. |
| **Precision** | Assay results:<br>Intra-assay CV: 2.4 to 2.6% for the low monoclonal ADA consistency control<br>Inter-assay CV: 17.3 to 27.5% for the low monoclonal ADA consistency control<br><br>Specificity method (% inhibition):<br>Inter-assay CV: 0.4% for ADA controls inhibited by CNTO 1959<br>Inter-assay CV: 5.3% for IL-23 control inhibited by CNTO 856 |
| **Robustness** | Incubation periods that produced acceptable results for the low positive consistency control:<br>Sample + master mix in dilution tubes: 45 to 75 minutes<br>Samples + master mix in assay wells: 45 to 75 minutes<br>Acid Treatment of samples: 10 to 30 minutes<br>Read buffer incubation: 5 to 15 minutes<br>Acceptable results were obtained from plate lots Z0020568 and Z0020605 |

| | |
|---|---|
| **Stability** | Freeze/thaw:<br>At least 5 freeze/thaw cycles when thawed overnight at 4°C<br>At least 1 freeze/thaw cycle when thawed for 5 minutes at 37°C<br>Storage:<br>At least 3 months at -20°C, and 4°C<br>At least 36 months at -70°C<br>At least 2 days at 25°C |
| **Sensitivity of Screening Methods at Spring House Laboratory (SH) and (b) (4) (b) (4) (A6)** | Acceptable:<br><br>Sensitivity at (b) (4) for polyclonal ADA control MO1468 is 12.3 ng/mL compared to 6.2 ng/mL at SH. |
| **Interference due to drug in Screening Methods at SH and (b) (4) (A6)** | Acceptable:<br>Highest concentration of CNTO 1959 associated with a positive result at (b) (4) was 0.78 µg/mL compared to 3.13 µg/mL at SH. |
| **ADA Classification of Mock Samples using Screening and Specificity Methods at SH and (b) (4) (A6)** | Data from mock samples with known components demonstrate that Screening and Specificity Method at (b) (4) is comparable to Screening and Specificity Method at SH:<br><br>Screening Method at SH: 8/8 samples identified as potentially positive<br>Specificity Method at SH: 4/8 samples classified as positive for ADA to CNTO 1959<br>Method at SH classified the ADA status correctly for 8 out of 8 samples<br>Screening Method at (b) (4) 4/8 samples identified as potentially positive<br>Specificity Method at (b) (4) 4/4 samples classified as positive for ADA to CNTO 1959<br>Method at (b) (4) classified the ADA status correctly for 8 out of 8 samples |

Abbreviations: ADA=anti-drug antibody; CV=coefficient of variation; ECL=electrochemiluminescence; ECLIA=electrochemiluminescent immunoassay; FPR=false positive rate; (b) (4) IL-23=interleukin-23; nNHS=naïve normal human serum; NV=normalized ECL value; SH=Spring House Laboratory

ADA and Nab assay validation parameters for CNTO2919PSO3011 are presented in the tables below.

**Table 45: ADA Assay Validation Parameters for CNTO2919PSO3011**

| | |
|---|---|
| **Validation Report #** | CP2019V-068 |
| **Original Validation Period** | 27 Aug 2019 to 14 Nov 2019 (original report) |
| **Assay Type** | ECLIA |
| **Liquid Handling Procedure** | Manual |
| **Assay Result Type** | Normalized ECL value (by the naïve consistency control) |
| **Minimum Dilution** | 1/11.25 |
| **Replicates** | N=4 for the naïve serum consistency control. N=2 for all other controls and samples. |
| **CV Criteria** | ≤20% for all controls and samples (ECL counts) Appendix 3. |
| **Sensitivity** | Sample Description / Sensitivity in serum<br>CNTO 8820 in nNHS Screening Method / 0.77 ng/mL<br>CNTO 8820 in nNHS Specificity Method / 0.77 ng/mL<br>MO1468 in nNHS Screening Method / 0.77 ng/mL<br>MO1468 in nNHS Specificity Method / 0.77 ng/mL |
| **Specificity** | CNTO 1959 competitively inhibited an ADA control. |
| **Selectivity (Recovery)** | Screening Method: 122.1% recovery for 5 ng/mL of CNTO 8820 ADA in human serum.<br>Specificity Method: 5 out of 5 samples in each series tested above specificity cut point.<br><br>Five out of the five samples tested from individuals with Colorectal Cancer (COR), Hidradenitis Suppurativa (HDS) and Celiac disease (CLD) met the specificity method cut point (Appendix 5Appendix 5).<br><br>Five out of the five samples tested from individuals with Lupus Nephritis (LUN) and Giant Cell Arteritis (GCA) met the specificity method cut point (Appendix 7).<br><br>Four out of the five samples tested from individuals with Systemic Sclerosis (SSC) met the specificity method cut point (Appendix 7). |
| **Interference** | Drug tolerance in screening method:<br>Sample Description / Maximum Drug Concentration Tolerated<br>100 ng/mL CNTO 8820 in nNHS / 1,000 µg/mL<br>250 ng/mL CNTO 8820 in nNHS / 1,000 µg/mL<br>500 ng/mL CNTO 8820 in nNHS / 1,000 µg/mL<br>100 ng/mL MO1468 in nNHS / 1,000 µg/mL<br>250 ng/mL MO1468 in nNHS / 1,000 µg/mL<br>500 ng/mL MO1468 in nNHS / 1,000 µg/mL<br><br>Tolerance to unrelated ADA: Pre-incubation with 100 µg/mL of an unrelated ADA did not cause interference in the assay.<br>Tolerance to Etanercept (Enbrel): Pre-incubation with 10 µg/mL of Etanercept did not cause interference in the assay (Appendix 3).<br>Tolerance to Risankizumab (Skyrizi™): Pre-incubation with 10 µg/mL of risankizumab and 100 µg/mL of risankizumab ADAs did not cause interference in the assay (Appendix 5).<br><br>Tolerance to Stelara (ustekinumab): Pre-incubation with 200 µg/mL of ustekinumab and 100 µg/mL of ustekinumab ADA did not cause interference in the assay (Appendix 9).<br><br>Drug tolerance in specificity method:<br>Sample Description / Maximum Drug Concentration Tolerated |

| | |
|---|---|
| | 100 ng/mL CNTO 8820 in nNHS: 1,000 µg/mL<br>250 ng/mL CNTO 8820 in nNHS: 1,000 µg/mL<br>500 ng/mL CNTO 8820 in nNHS: 1,000 µg/mL<br>100 ng/mL MO1468 in nNHS: 1,000 µg/mL<br>250 ng/mL MO1468 in nNHS: 1,000 µg/mL<br>500 ng/mL MO1468 in nNHS: 1,000 µg/mL |
| **Study Phase Bioanalysis Acceptance Criteria for Controls** | Consistency Controls (CC) for screening, titration, specificity methods:<br>• Diluent CC: ≤1.55 NV<br>• Naive serum CC: ≤113 ECL<br>• Low ADA CC (5 ng/mL CNTO 8820 in nNHS): 1.85 to 4.38 NV, inclusive<br>• High ADA CC (1,000 ng/mL CNTO 8820 in nNHS): ≥236.31 NV and must be greater than the acceptable Low ADA CC on the same plate.<br><br>Additional controls for the specificity method:<br>• Uninhibited low ADA specificity control (5 ng/mL CNTO 8820 in nNHS): 1.85 to 4.38 NV, inclusive<br>• Inhibited low ADA specificity control (5 ng/mL CNTO 8820 in nNHS): ≥ 17.7% inhibition after incubation with 50 µg/mL CNTO 1959.<br>• Uninhibited high ADA specificity control (1,000 ng/mL CNTO 8820 in nNHS): ≥236.31 NV<br>• Inhibited high ADA specificity control (1,000 ng/mL CNTO 8820 in nNHS): ≥ 17.7% inhibition after incubation with 50 µg/mL CNTO 1959.<br><br>Note: The low and high ADA consistency controls can also be used as the uninhibited ADA specificity control on the same plate. |
| **Cut Points** | Validation supported the application of this assay for the following populations: Normal, CD, Psoriasis, UC, and PsA Populations. This assay may be used to support other populations by performing subsequent validation experiments or in-study cut point assessments. (b) (4) (b) (4)<br><br>Screening Method for Normal, Crohn's, and Ulcerative Colitis Populations: ≥ 1.03 NV*<br><br>*If the screening method cut point is applied to negative baseline samples of a clinical study of normal, Crohn's, or UC populations and the observed FPR is 3.06% to 25.33% or if the sample size (N) is less than 30 and a FPR is equal to 0%, the validated screening method cut point of 1.03 NV cut point and the 17.7% specificity cut point is suitable without additional statistical analysis if the median NV is greater than or equal to the NV specified by Table 01 below.<br><br>Screening Method for Psoriasis Populations: ≥0.99 NV*<br><br>*If the screening method cut point is applied to negative baseline samples of a clinical study of Psoriasis population and the observed FPR is 3.35% to 24.01% or if the sample size (N) is less than 30 and a FPR is equal to 0%, the validated screening method cut point of 0.99 NV cut point and the 17.7% specificity cut point is suitable without additional statistical analysis if the median NV is greater than or equal to the NV specified in Table 01 below.<br>Screening Method for Psoriatic Arthritis Populations: ≥ 1.06 NV* |

*If the screening method cut point is applied to negative baseline samples of a clinical study of Psoriatic Arthritis population and the observed FPR is 2.60% to 22.49 or if the sample size (N) is less than 30 and a FPR is equal to 0%, the validated screening method cut point of 1.06 NV cut point and the 17.7% specificity cut point is suitable without additional statistical analysis if the median NV is greater than or equal to the NV specified in Table 01 below.

Note: The "negative" qualifier before "drug-naïve" means to include the data only from samples that test negative by either the screening or specificity method. Remove samples that test positive by both the screening and specificity methods from all the statistics.

Table 01: Minimum median negative drug naïve sample to accept validated screening method cut points without further statistical analysis if the FPR is 0 and N<30.

| Psoriasis disease state population | | Normal, CD, and UC disease state populations | | PA disease state population | |
|---|---|---|---|---|---|
| N | Median NV ≥ | N | Median NV ≥ | N | Median NV ≥ |
| 1 | 0.70 | 1 | 0.71 | 1 | 0.73 |
| 2 | 0.73 | 2 | 0.74 | 2 | 0.76 |
| 3-4 | 0.75 | 3 | 0.76 | 3 | 0.78 |
| 5 | 0.76 | 4 | 0.77 | 4 | 0.79 |
| 6-7 | 0.77 | 5 | 0.78 | 5 | 0.80 |
| 8-11 | 0.78 | 6-7 | 0.79 | 6-7 | 0.81 |
| 12-18 | 0.79 | 8-10 | 0.80 | 8-10 | 0.82 |
| 19-29 | 0.80 | 11-18 | 0.81 | 11-18 | 0.83 |
| | | 19-29 | 0.82 | 19-29 | 0.84 |

Titration Method: ≥ 1.56 NV

Specificity Method:
All population samples are classified *ADA POSITIVE* to CNTO 1959 if the following conditions are met:

- Inhibited sample: signal is inhibited by ≥ 17.7% in the presence of 50 µg/mL CNTO 1959.

**Dilutability**

Serial 1/2 dilutions of ADA resulted in a decline in the assay signal, and justified relevance of the titration method.

Specificity method testing may be repeated using a greater dilution of sample if the NV of the sample, in the absence of CNTO 1959, is ≥625.43 NV and the %INH result is <17.7%. If the NV is ≥625.43 NV and the inhibition result is ≥17.7%, the result is acceptable.

**Precision**

Screening method:

- Intra-assay CV: 2.3% for the low ADA consistency control
- Inter-assay CV: 16.9% for the low ADA consistency control
- Intra-assay CV from 6 replicates of each control on the same plate (Appendix 3):
  - Diluent consistency control ranged from 0.0 to 2.6% (mean 1.6%)
  - Naïve serum consistency control ranged from 2.7 to 6.3% (mean 3.7%)
  - Low positive CNTO 8820 consistency control ranged from 0.3 to 1.9% (mean 1.0%)
  - High positive CNTO 8820 consistency control ranged from 0.2 to 4.1% (mean 2.3%)

Specificity method (% inhibition):

- Inter-assay CV: 4.8% for the low ADA specificity controls inhibited by 50 µg/mL CNTO 1959.

| | |
|---|---|
| | • Intra-assay CV from 6 replicates of the specificity controls on the same plate (Appendix 3):<br>○ 11.4% for low ADA specificity controls inhibited by 50 µg/mL CNTO 1959.<br>○ 0.1% for high ADA specificity controls inhibited by 50 µg/mL CNTO 1959. |
| **Robustness** | • Batch size: up to 10 MSD plates<br>• Plate dry time (prior to read buffer addition): within 5 minutes<br>• Read buffer incubation: within 10 minutes<br>• Plate blocking: 30-90 minutes<br>• Plate lot: Z0021501, Z0021544 |
| **Sample Stability** | Freeze/thaw:<br>• Up to 5 freeze/thaw cycles when thawed overnight at 4°C<br>• Up to 1 freeze/thaw cycle when thawed for 5 minutes at 37°C<br>Storage:<br>• At least 21 days at -70°C, -20°C, and 4°C<br>• At least 8 days at 25°C (Appendix 10)<br>• At least 3 months at 4°C for NCC and LCC 01<br>• At least 3 months at -20°C for LCC 01<br>• At least 25 months at -70°C for LCC 01 (Appendix 8) |
| **Method Comparison** | The anti-CNTO 1959 Enhanced DT Clinical ADA method demonstrated greater sensitivity and superior drug tolerance (Appendix 2) than the previously validated anti-CNTO 1959 Clinical ADA method (CP2010V-008). |
| **Approved Lab Locations** | Method validated for use at following laboratory locations:<br>• Janssen Spring House (SH) Laboratories (main report sections 1-14).<br>• Janssen Beerse Bioanalysis Laboratories (JBBL) Appendix 1.<br>(b) (4) Appendix 4 |

Abbreviations: %INH=percent inhibition; ADA=anti-drug antibody; CC=Consistency Controls; CD-Crohn's Disease; CV=coefficient of variation; ECL=electrochemiluminescence; ECLIA=electrochemiluminescent immunoassay; FPR=false positive rate; hIL-23=human interleukin 23; LCC=low consistency control; MSD=Meso Scale Discovery; NAb=neutralizing antibody; NHS=normal human serum; NV=normalized ECL value; UC=ulcerative colitis

**Table 46: NAb Assay Validation Parameters for CNTO1959PSO3011**

| | |
|---|---|
| **Validation Report Number** | CP2020V-071 |
| **Validation Duration** | 17 Jun 2020 to 13 Oct 2020 (original report) |
| **Assay Type** | A non-cell-based electrochemiluminescence (ECL) NAb assay method (MSD format) |
| **Assay Result Type** | Percent inhibition (%INH) of the assay signal derived from the Normalization Control:<br>%INH=[1 – (Mean ECL_Sample – Mean ECL_Background Control)/(Mean ECL_Normalization Control – Mean ECL_Background Control)]X100 |
| **Minimum Required Dilution** | 1:10 dilution |
| **Cut Point** | %INH ≥24.80% indicates that the test sample is NAb positive. |
| **Study Phase Bioanalytical Acceptance Criteria for the Assay Controls and Inter-replicate CV** | Acceptance ranges for the assay controls:<br>• High Positive Consistency Control: 58.20%INH to 92.66%INH, inclusive<br>• Low Positive Consistency Control: 24.80%INH to 61.97%INH, inclusive<br>• The %INH of the High Positive Consistency Control should be higher than the %INH of the Low Positive Consistency Control.<br>• Negative Consistency Control: less than 24.80%INH<br>• Normalization Control: 48968 and 339692 ECL units, inclusive<br>• Ratio of Normalization Control ECL/Background Control ECL: ≥16.17<br><br>Inter-replicate CV cut-off: less than or equal to 20% |
| **Sensitivity** | 265.36 ng/mL / 632.42 ng/mL in neat serum as determined by the monoclonal positive NAb controls CNTO 8820 and CNTO 4610, respectively. |
| **Specificity** | Five ADAs specific to other monoclonal antibody therapeutics generated negative results in the NAb assay. |
| **Selectivity** | Drug tolerance limit for NAb controls:<br>• 1 µg/mL of the monoclonal positive NAb control CNTO 8820 could be detected in the presence of exogenous CNTO 1959 at the maximum concentration of 4.14 µg/mL in neat human serum.<br>• 0.5 µg/mL of the monoclonal positive NAb control CNTO 4610 could be detected in the presence of exogeneous CNTO 1959 at the maximum concentration of 63.07 µg/mL in neat human serum.<br>• 1 µg/mL of the monoclonal positive NAb control CNTO 4610 could be detected in the presence of exogeneous CNTO 1959 at the maximum concentration of 125.21 µg/mL in neat human serum. |

| | |
|---|---|
| | Target tolerance limit<br>• The assay tolerated a maximum of 9.49 µg/mL of human soluble IL-23 in neat serum.<br>Matrix interference<br>• Recovery of the Low Positive Consistency Control spiked into lipemic and hemolyzed sera at the Low Positive Control concentration was within the acceptance range. |
| **Precision** | Intra-assay CVs:<br>• 2.83% mean CV for the High Positive Consistency Control<br>• 7.51% mean CV for the Low Positive Consistency Control<br>Inter-assay CVs:<br>• 4.17% CV for the High Positive Consistency Control<br>• 10.04% CV for the Low Positive Consistency Control |
| **Robustness** | (1) The CNTO 1959 NAb assay remained reproducible when different lots of critical reagents or different MSD plate readers were used in the assay.<br><br>(2) The NAb assay could tolerate changes in assay incubation time at the following steps:<br>• Acid treatment of test samples (between 20 minutes and 40 minutes)<br>• Duration of incubating the bound Ru-IL-23/Biotin-CNTO 1959 complexes in 2X assay read buffer for up to 30 minutes |
| **Stability** | Freeze/thaw stability:<br>Compared to the fresh preparation, the %Restoration for the freeze/thaw consistency controls with thawing at room temperature for 30 minutes:<br>• High Positive Consistency Control ranges from 86.16% to 102.64%.<br>• Low Positive Consistency Control ranges from 75.79% to 103.60%.<br><br>Compared to the fresh preparation, the %Restoration for the freeze/thaw consistency controls with thawing at 4°C overnight:<br>• High Positive Consistency Control ranges from 90.56% to 98.44%.<br>• Low Positive Consistency Control ranges from 77.10% to 109.94%.<br><br>Storage at 4°C for up to 55 days:<br>Compared to the fresh preparation, the %Restoration for the 4°C stored consistency controls:<br>• High Positive Consistency Control 98.93%.<br>• Low Positive Consistency Control is 111.03%. |
| Cross/partial validation | The assay sensitivity and drug tolerance in Spring House and Beerse sites are comparable (Appendix 1)<br>The assay sensitivity and drug tolerance in Spring House and (b) (4) sites are comparable (Appendix 7) |

| | |
|---|---|
| Impact of CNTO 148 on CNTO 1959 NAb Assay Sensitivity | No interference detected<br>A range of CNTO 148 drug combined with CNTO 1959 High and Low Positive Controls generated %INH within the respective acceptance ranges. CNTO 148 combined with the CNTO 1959 Negative Control generated %INH below assay cut point (Appendix 3). |
| Impact of CNTO 1275 on CNTO 1959 NAb Assay Sensitivity | No impact was detected.<br>A various concentration of CNTO 1275 drug combined with CNTO 1959 high and low positive controls generated %INH within the respective acceptance criteria. CNTO 1275 combined with the CNTO 1959 negative control generated %INH below the assay cut point (24.80%INH) (Appendix 5). |
| Impact of ENBREL on CNTO 1959 NAb Assay Sensitivity | No impact was detected.<br>Various concentrations of ENBREL combined with CNTO 1959 high and low positive controls generated %INH within the respective acceptance criteria. ENBREL combined with the CNTO 1959 negative control generated %INH below the assay cut point (24.80%INH) (Appendix 6). |

Abbreviations: %INH=percent inhibition; ADA=anti-drug antibody; CV=coefficient of variation; ECL=electrochemiluminescence; IL-23=interleukin 23; LCC=low consistency control; MSD=Meso Scale Discovery; NAb=neutralizing antibody; NHS=normal human serum; Ru-IL-23=Ruthenylated interleukin

Source: Appendix 9, 10, 11 and 13, Module 2.7.1, Summary of Biopharmaceutics

### 19.4.2. Population Pharmacokinetics (PopPK) Modeling Analysis

#### 19.4.2.1. Executive Summary

The FDA's Assessment
The objective of this review is to evaluate the adequacy of the Applicant's Population Pharmacokinetics (PopPK) modeling analysis and to evaluate the impact of intrinsic and extrinsic factors on the PK of guselkumab in pediatrics age range from ≥6 to <18 years, who weigh more the 40 kg. The key findings include:

- The population PK model adequately described PK data of guselkumab in pediatrics age range from ≥6 to <18 years. The observed serum concentration-time data of guselkumab in pediatric subjects ≥6 to <18 years of age were described by a 1-compartment linear PopPK model with first-order absorption and first-order elimination.
- The following covariate-PK relationships were found to have statistically significant effects on guselkumab PK: baseline body weight, race, and diabetes comorbidity on CL and baseline body weight on Vc. Among those, the impact of body weight is clinically meaningful, which supports weight-tiered dosage in pediatrics.
- Simulated guselkumab exposures in virtual pediatric subjects were aligned with the median and within the 90% prediction interval of those of adults for both children (≥6 to <12 years) and adolescents (≥12 to <18 years) when compared with adults (≥18 years).
- The median (range) of BMI studied in children (≥6 to <12 years) is 19.4 (14.5, 29.1) kg/$m^2$ and in adolescents (≥12 to <18 years) is 21.7 (15.7, 52.6) kg/$m^2$ whereas median (range) of BMI studied in adults is 28.6 (16.6, 66.4) kg/$m^2$. The safety for obese participants aged ≥6 and <12 yeas who weigh ≥ 40 and <70 kg and expected to get a flat dose of 100 mg has not been established.
- The proposed decrease in body weight cutoff for the 100 mg fixed dose from 70 kg to 40 kg was supported by the simulations which showed comparable exposures between pediatric subjects weighing ≥40 kg and adults with a fixed dose of 100 mg.

#### 19.4.2.2. PopPK Assessment Summary

The dataset for PopPK analysis consisted of serum guselkumab concentration values, actual dose amounts, dose administration times, scheduled and actual times of PK measurements, and other relevant information such as demographic information, laboratory measures, disease characteristics, and concomitant medications. Following Week 16, the records of subjects who switched from placebo to guselkumab were included for analysis in the final dataset. Missing serum concentration values were treated as missing and were not imputed. Guselkumab BQL concentrations were treated as missing data and were excluded from the analysis because the total number of BQL data points was less than 10% of the total number of observed guselkumab serum concentrations. A total of 13,529 PK samples from 1,545 subjects including 91 pediatrics and 1,454 adults are included in the analysis. The observed serum concentration-time profiles of guselkumab were described by a 1-compartment linear PopPK model with first-order absorption

and first-order elimination. The random effects due to IIV were included on CL/F, V/F, and ka, while the residual error was described by a combined additive and proportional error model. The final PopPK model including fixed allometric scaling factors of 0.75 and 1 for the body weight exponents on CL/F and V/F, respectively, was stable. There was a slight underprediction in pediatric serum concentrations, but no apparent systematic deviations or trends noticed in the diagnostic plots for both pediatric and adult data.

The final PopPK model parameters were well described with RSEs within 20% for the structural PK and covariate effect parameter estimates. Reasonable shrinkage was estimated for the IIV of CL/F and V/F, but not for ka (75%). The higher shrinkage in Ka may be due to the reason that most of the data used for model development were sparse and consists of Ctrough samples, which make it hard to adequately estimate the variability in the Ka parameter.

In the final PopPK model, the covariate effects of baseline body weight, race, and diabetes comorbidity were retained on guselkumab CL/F. Body weight was also identified as a statistically significant covariate on V/F. For non-Caucasian subjects and those with diabetes comorbidity, the associated CL/F was 7% and 18% higher, respectively.

The simulated result was consistent for both pediatrics subjects weighing > 40 and ≤70 kg when administered a flat dose of 100 mg when compared with observed exposures after weight based dose of 1.3 mg/kg and are within the range of 90% CI of observed exposures in adults (≥18 years) who received a flat dose of 100 mg (Figure 5). These simulations results in similar exposures (AUC, Cmax and Ctrough) in subjects weighing > 40 and ≤70 kg when administered with flat dose of 100 mg when compared with observed exposures in CNTO1959PSO3011 (1.3 mg/kg for subjects weighing <70 kg and a fixed dose of 100 mg for subjects weighing ≥70 kg) and were within the 90% prediction intervals of the overall adult participant exposures for all body weight groups except the 40 to 50 kg body weight group of the 40 kg body weight cutoff dosing regimen. IQR of steady-state AUC and Cmax for the 40 to 50 kg weight group were still within the 90% prediction intervals of the <70 kg adult participant exposures, which were also found to be safe in Studies CNTO1959PSO3001 and CNTO1959PSO3002.

The summary of final population PK model for guselkumab are presented in Table 47. The guselkumab PopPK parameters were estimated with an adequate precision. Diagnostic plots generally show a good agreement between predictions and observations (Figure 14). The visual predictive check plots do indicate a higher exposure in pediatrics but were comparable to the observed values as shown in Figure 15.

**Table 47: Summary of PopPK Assessment**

| **General Information** | |
|---|---|
| Objectives of PopPK Analysis | • To characterize the PK of guselkumab in pediatric subjects aged ≥6 to <18 years with plaque PsO. |

| | | |
|---|---|---|
| | | • To confirm the similarity of guselkumab exposure between pediatric and adult subjects with plaque PsO.<br>• To assess the appropriateness of decreasing the pediatric body weight cutoff from 70 kg to 40 kg for use of the 100 mg fixed dose of guselkumab.<br>• To extrapolate guselkumab exposure to pediatric subjects aged ≥5 to <18 years in support of the jPsA dose recommendation.<br>• To assess the relationship between guselkumab exposure metrics and clinical efficacy measures in pediatric subjects aged ≥6 to <18 years with plaque PsO |
| Study Included | | The integrated PK data were based on the PK analysis sets from each study that included all randomized subjects who received at least 1 dose of guselkumab and had at least 1 valid postbaseline PK measurement.<br>• CNTO1959PSO3011 (Phase 3 -Pediatrics)<br>• CNTO1959PSO2001 [X-PLORE] (Phase 2 - Adults)<br>• CNTO1959PSO3001 [VOYAGE 1] (Phase 3 - Adults)<br>• CNTO1959PSO3002 [VOYAGE 2] - (Phase 3 - Adults) |
| Dose(s) Included | | 100 mg fixed for subjects > 70 kg and 1.3 mg/kg for subjects <70 kg |
| Population Included | | PSO |
| Population Characteristics | General | 1,454 adult subjects (data up to Week 52) from Phase 2 study (CNTO1959PSO2001 [X-PLORE]), and 2 Phase 3 studies (CNTO1959PSO3001 [VOYAGE 1], CNTO1959PSO3002 [VOYAGE 2]) is included in the final PopPK model. |
| | Organ Impair-ment | Not applicable |
| | Pediatrics (if any) | 91 pediatric subjects (data up to Week 44; excluding subjects who received etanercept) and 1,454 adult subjects (data up to Week 52)<br>Age median (range) of children and adolescents were 9 (6 – 11) and 15 (12 to 17) years.<br>Weight at baseline (range) is 18.0 to 80.6 kg for children and 36.2 to 128 kg for adolescents.<br>Sex: Male 7/19 (36.8%), Female 12/19 (63.2%) in children (6<12 years) and<br>Male 43/72 (59.7%) and Female 29/72 (40.3%) in adolescents (12<18 years)<br>Race: Children (6<12 years): White, Not Hispanic or Latino (15/19 [78.9%]), White, Hispanic or Latino (1/19 [5.3%]), Asian (1/19 |

| | | | |
|---|---|---|---|
| | | [5.3%]), Other - Not Reported or Unknown (1/19 [5.3%]) and missing ((1/19 [5.3%]).<br>Adolescents (12<18 years): White, Not Hispanic or Latino (63/72 [87.5%]), Black, of African heritage or African American (3/72 [4.2%]), White, Hispanic or Latino (1/72 [1.4%]), Asian (1/72 [1.4%]), Other - Not Reported or Unknown (3/72 [4.2%]) and Missing (1/72 [1.4%]). | |
| Number of Subjects, PK Samples, and BLQ | | A total of 1545 subjects [91 pediatrics 6 to <18 years, whom 19 were children (≥6 to <12 years) and 72 were adolescents (≥12 to <18 years)] with 13,529 PK samples for guselkumab concentrations available, | |
| Sampling Schedule | Sparse Sampling | PK samples in study CNTO1959PSO2001 were collected before dosing at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 52.<br>PK samples in study CNTO1959PSO3001 were collected before dosing at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 36, 44, and 48.<br>PK samples in study CNTO1959PSO3002 were collected before dosing at Weeks 0, 4, 8, 12, 16, 20, and 24 in the active comparator-controlled period, at weeks 28, 32, 36, 40, 44, 48, 52, and 72 in randomized withdrawal and retreatment period and at weeks 76, 100, 124, 148, and 160 in the open label treatment period.<br>PK samples in study CNTO1959CRD3011 were collected before dosing at baseline (Week 0) and 4, 8, 12, 16, 20, 28, 36, and 44 weeks after the start of guselkumab treatment. | |
| | In the Intent-to-treat Population | The subjects included in the final analysis dataset had to have received at least 1 dose of guselkumab and have at least 1 valid postbaseline PK measurement (PK analysis population). | |
| Covariates Evaluated | Continuous | Body weight, age, height, BMI, BSA, Creatinine clearance, Albumin, AST, ALT, Alkaline phosphatase, White blood cells, PASI, and Serum creatinine (Table 48: ) | |
| | Categorical | Race, gender, past/current history of Diabetes Mellitus, Body weight group, past/current history of Hypertension, past/current history of Hyperlipidemia (<br>Table 49) | |
| | Time-varying | Not applicable | |
| **Final Model** | | **Summary: The final model is acceptable from PM perspective** | **Acceptability** |

| | | [FDA's comments] |
|---|---|---|
| Software and Version | NONMEM v7.4<br>Perl-speaks-NONMEM (PsN) v4.2<br>R v3.6 | Acceptable |
| Model Structure | The observed serum concentration-time data of guselkumab in pediatric and adult subjects with PsO was described by the re-estimated 1-compartment linear PK model with first-order absorption and first-order elimination and allometric components for CL/F and V/F fixed to 0.75 and 1.0, respectively. | Acceptable |
| Model Parameter Estimates | See Table 50 | |
| Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) | All the structure model parameters for the guselkumab were estimated precisely; the RSEs did not exceed 1.16% for CL/F and V/f, whereas 11.6% for Ka. The covariate effects parameters for the guselkumab were also estimated precisely; RSE did not exceed 2.58%.<br>The IIV was low for guselkumab main PK parameters CL/F (0.36), $V/F_c$ (0.285), and Ka (1.31) respectively.<br>Shrinkage was generally low (<16%) for most PK parameters, except for Ka (75%) | Acceptable |
| BLQ for Parameter Accuracy | The serum guselkumab concentration samples from the source dataset included 661/16,026 (4.1%) samples with BQL concentrations, of which 10/661 were from children and 20/661 were from adolescents amongst the 708/16,026 total samples obtained from pediatrics. Missing serum concentration values were treated as missing and were not imputed. Guselkumab BQL concentrations were treated as missing data and were excluded from the analysis because the total number of BQL data points was less than 10% of the total number of observed guselkumab serum concentrations | Acceptable |
| GOF, VPC | GOF plots (Figure 14)<br>VPC plots (Figure 15)<br>The final model adequately described the PK data. | Acceptable |
| Significant Covariates and Clinical Relevance | Baseline body weight, race, and diabetes comorbidity were retained on guselkumab CL/F. Body weight was also identified as a statistically significant covariate on V/F. For non-Caucasian subjects and those with diabetes comorbidity, the | Acceptable |

| | | |
|---|---|---|
| | associated CL/F was 7% and 18% higher, respectively. The PopPK analysis concluded that no dose adjustment was warranted in subjects with PsO, who are greater than 70 kg receiving the 100 mg dose and who are >40 and <70 kg receiving 1.3 mg/kg dose regardless of the covariates tested (eg, body weight, diabetes, and race on CL, and BW on V/F). | |
| Analysis Based on Simulation (optional) | See Figure 3 and Figure 4: Simulations were carried out to assess the appropriateness of lowering the pediatric body weight cutoff from 70 kg (which was studied in Study CNTO1959PSO3011) to 40 kg for use of the adult 100 mg fixed guselkumab dose. The results show that for pediatrics with body weight below 40 kg (receiving guselkumab 1.3 mg/kg with a maximum of 45 mg), PK profiles did not exceed those of adults. For pediatric subjects with body weight ≥40 kg receiving the 100 mg fixed dose, the median exposure for this pediatric subset is numerically higher than adults, however overall exposures were still within the adult 90% prediction interval. The overall results support the lowering of the pediatric body weight cutoff for the 100 mg fixed dose from 70 kg to 40 kg, to be aligned with the adult dose regimen, does not lead to clinically relevant differences guselkumab exposures in pediatrics weighing ≥ 40 when compared with exposures in adult subjects. | Body weight-based dosing appears acceptable. However, a flat dose was proposed for patients with WT ≥ 40 kg. For details, please refer to the FDA reviewer's assessment . |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.3 PK | (b) (4) [redacted] | (b) (4) [redacted] the drug label was not discussed. |

(b) (4)

(b) (4)

Metabolism

The exact pathway through which guselkumab is metabolized has not been characterized. As a human IgG monoclonal antibody, guselkumab is (b) (4) into small peptides and amino acids via catabolic pathways.

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.

No specific trials have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of guselkumab.

Adult subjects comprised 1,454/1,545 (94%) of the total number of subjects included in the final PK dataset, with a median age of 44.0 years (range: 18 to 82 years) and median body weight of 87.1 kg (range: 44.9 to 198 kg) and were primarily Caucasian (1,218/1,454 [83.8%]) and male (1,030/1,454 [70.8%]). Compared to the pediatric subjects, more of the adult subjects had a comorbidity of diabetes (129/1,454 [8.9%]), and 224/1,454 (15.4%) had a past or current history of hyperlipidemia.

Pediatric subjects treated with guselkumab comprised 91/1,545 (5.9%) of the total number of subjects included in the final PK dataset. The median ages of children and adolescents were 9 years (range: 6 to 11 years) and 15 years (range: 12 to 17 years), respectively. The body weight at baseline ranged from 18.0 to 80.6 kg for children and 36.2 to 128 kg for adolescents, with an overall median of 58.5 kg. Of the children, 1/19 (5.3%) subjects had baseline body weight ≥70 kg, 6/19 (31.6%) had baseline body weight ≥40 to <70 kg, and 12/19 (63.2%) had baseline body weight <40 kg. For the adolescents, 26/72 (36.1%) subjects had baseline body weight ≥70 kg, 44/72 (61.1%) had baseline body weight ≥40 to <70 kg, and 2/72 (2.8%) had baseline body

weight <40 kg. The majority of the children were Caucasian (16/19 [83.2%]) and female (12/19 [63.2%]), while the majority of the adolescents were Caucasian (63/72 [87.5%]) and male (43/72 [59.7%]). Descriptive statistics of the baseline continuous and categorical demographics of subjects in the final dataset are presented in Table 48and Table 49 respectively.

**Table 48: Summary of Demographic and Baseline Characteristics of Pooled Study Data (Continuous Covariates) for PopPK Analysis, Stratified by Study**

| Variable | Labels | Pediatric Study (CNTO1959PSO3011) | | Adult Studies (CNTO1959PSO2001, CNTO1959PSO3001, CNTO1959PSO3002) | |
|---|---|---|---|---|---|
| | | Children ≥6 to <12 y | Adolescents ≥12 to <18 y | Adults ≥18 y | Total |
| N | | 19 | 72 | 1454 | 1545 |
| Baseline weight (kg) | Mean (SD) | 39.6 (16.0) | 66.2 (19.2) | 89.3 (21.2) | 87.6 (22.2) |
| | Median | 38.2 | 62.2 | 87.1 | 85.8 |
| | Range | (18.0; 80.6) | (36.2; 128) | (44.9; 198) | (18.0; 198) |
| Age (years) | Mean (SD) | 8.89 (1.49) | 14.9 (1.67) | 43.9 (12.4) | 42.1 (14.0) |
| | Median | 9.00 | 15.0 | 44.0 | 43.0 |
| | Range | (6.00; 11.0) | (12.0; 17.0) | (18.0; 82.0) | (6.00; 82.0) |
| Baseline height (cm) | Mean (SD) | 139 (14.8) | 168 (11.5) | 173 (9.43) | 173 (10.4) |
| | Median | 138 | 167 | 173 | 173 |
| | Range | (110; 166) | (145; 194) | (142; 206) | (110; 206) |
| Body mass index (kg/m$^2$) | Mean (SD) | 19.7 (4.58) | 23.1 (5.88) | 29.7 (6.42) | 29.2 (6.61) |
| | Median | 19.4 | 21.7 | 28.6 | 28.2 |
| | Range | (14.5; 29.1) | (15.7; 52.6) | (16.6; 66.4) | (14.5; 66.4) |
| Baseline body surface area (m$^2$) | Mean (SD) | 1.22 (0.293) | 1.74 (0.263) | 2.06 (0.27) | 2.04 (0.292) |
| | Median | 1.23 | 1.71 | 2.06 | 2.04 |
| | Range | (0.74; 1.89) | (1.22; 2.45) | (1.37; 3.09) | (0.74; 3.09) |
| Creatinine clearance (mL/min) | Mean (SD) | 89.6 (12.3) | 85.4 (15.9) | 134 (40.3) | 131 (40.8) |
| | Median | 89.4 | 85.4 | 129 | 126 |
| | Range | (68.6; 115) | (57.2; 142) | (48.0; 431) | (48.0; 431) |
| Albumin (g/dL) | Mean (SD) | 4.79 (0.199) | 4.73 (0.236) | 44.5 (3.46) | 42.2 (9.95) |
| | Median | 4.80 | 4.70 | 45.0 | 45.0 |
| | Range | (4.40; 5.20) | (4.30; 5.40) | (29.0; 57.0) | (4.30; 57.0) |
| Aspartate transaminase (U/L) | Mean (SD) | NA (4.85) | NA (5.66) | NA (10.1) | NA (9.96) |
| | Median | 22.0 | | 22.0 | |
| | Range | (15.0; 35.0) | (11.0; 40.0) | (10.0; 9.00) | (10.0; 9.00) |
| | N missing (%) | 0 (0) | 0 (0) | 1 (0.1) | 1 (0.1) |
| Alanine transaminase (U/L) | Mean (SD) | 15.4 (5.32) | 15.3 (7.73) | 28.1 (17.2) | 27.3 (17.0) |
| | Median | 15.0 | 14.0 | 23.0 | 23.0 |
| | Range | (7.00; 32.0) | (5.00; 62.0) | (5.00; 250) | (5.00; 250) |
| Alkaline phosphatase (U/L) | Mean (SD) | 230 (46.1) | 141 (93.4) | 75.3 (22.8) | 80.3 (37.2) |
| | Median | 222 | 98.0 | 73.0 | 73.0 |
| | Range | (162; 333) | (35.0; 417) | (27.0; 248) | (27.0; 417) |
| White blood cells (×10$^9$ L) | Mean (SD) | 6.46 (1.92) | 6.59 (1.60) | 6.97 (1.92) | 6.95 (1.91) |
| | Median | 6.31 | 6.40 | 6.74 | 6.71 |
| | Range | (2.64; 10.6) | (2.47; 10.4) | (2.78; 15.5) | (2.47; 15.5) |
| | N missing (%) | 1 (5.3) | 0 (0) | 2 (0.1) | 3 (0.2) |
| Baseline PASI | Mean (SD) | 16.8 (5.11) | 20.7 (7.24) | 21.6 (8.77) | 21.5 (8.68) |
| | Median | 14.9 | 19.5 | 18.8 | 18.8 |
| | Range | (12.6; 30.6) | (12.9; 51.9) | (11.7; 68.4) | (11.7; 68.4) |
| Serum creatinine (µmol/L) | Mean (SD) | 44.4 (8.20) | 64.9 (14.3) | 77.0 (15.1) | 76.1 (15.6) |
| | Median | 44.0 | 64.5 | 77.5 | 76.0 |
| | Range | (35.0; 66.0) | (42.0; 111) | (39.0; 212) | (35.0; 212) |

Source: Population PK Report, Table 2

**Table 49: Summary of Demographic and Baseline Characteristics of Pooled Study Data (Categorical Covariates) for PopPK Analysis, Stratified by Study (Applicant Table 3)**

| Variable | Labels | Pediatric Study (CNTO1959PSO3011) | | Adult Studies (CNTO1959PSO2001, CNTO1959PSO3001, CNTO1959PSO3002) | |
|---|---|---|---|---|---|
| | | Children ≥6 to <12 y | Adolescents ≥12 to <18 y | Adults ≥18 y | Total |
| N | | 19 | 72 | 1454 | 1545 |
| Race, n (%) | White, Not Hispanic or Latino | 15 (78.9) | 63 (87.5) | 1131 (77.8) | 1209 (78.3) |
| | Black, of African heritage or African American | 0 (0) | 3 (4.2) | 26 (1.8) | 29 (1.9) |
| | White, Hispanic or Latino | 1 (5.3) | 1 (1.4) | 87 (6) | 89 (5.8) |
| | Asian | 1 (5.3) | 1 (1.4) | 177 (12.2) | 179 (11.6) |
| | Native Hawaiian or Other Pacific Islander | 0 (0) | 0 (0) | 6 (0.4) | 6 (0.4) |
| | American Indian or Alaskan Native | 0 (0) | 0 (0) | 3 (0.2) | 3 (0.2) |
| | Other - Not Reported or Unknown | 1 (5.3) | 3 (4.2) | 24 (1.7) | 28 (1.8) |
| | Missing | 1 (5.3) | 1 (1.4) | 0 (0) | 2 (0.1) |
| Gender, n (%) | Male | 7 (36.8) | 43 (59.7) | 1030 (70.8) | 1080 (69.9) |
| | Female | 12 (63.2) | 29 (40.3) | 424 (29.2) | 465 (30.1) |
| Past/Current History Diabetes Mellitus, n (%) | No | 19 (100) | 71 (98.6) | 1325 (91.1) | 1415 (91.6) |
| | Yes | 0 (0) | 1 (1.4) | 129 (8.9) | 130 (8.4) |
| Body Weight Group, n (%) | <40 kg | 12 (63.2) | 2 (2.8) | 0 (0) | 14 (0.9) |
| | ≥40 to <70 kg | 6 (31.6) | 44 (61.1) | 240 (16.5) | 290 (18.8) |
| | ≥70 kg | 1 (5.3) | 26 (36.1) | 1214 (83.5) | 1241 (80.3) |
| Past/Current History Hypertension, n (%) | No | 19 (100) | 71 (98.6) | 1068 (73.5) | 1158 (75) |
| | Yes | 0 (0) | 1 (1.4) | 386 (26.5) | 387 (25) |
| Past/Current History of Hyperlipidemia, n (%) | No | 19 (100) | 70 (97.2) | 1230 (84.6) | 1319 (85.4) |
| | Yes | 0 (0) | 2 (2.8) | 224 (15.4) | 226 (14.6) |

n=number of participants; N=number of participants included in the analysis; PopPK=population pharmacokinetics; y=years.

Source: Population PK Report, Table 3

The final model was based on the previously developed adult PopPK model, where the PK of guselkumab was described by 1-compartment linear model with first-order absorption and first-order elimination with IIV on $k_a$, CL/F, and V/F. Additionally, correlation terms were confirmed among CL/F and V/F (Ω block). Effects of body weight (variable: BWT) on CL/F and V/F, and diabetes comorbidity (variable: DIAB) and race (Caucasian versus non-Caucasian) on CL/F were identified as significant covariates on guselkumab PK exposure. The adult data from Studies CNTO1959PSO2001, CNTO1959PSO3001, and CNTO1959PSO3002 and was applied to re-estimate all the model parameters except the allometric exponents, which were fixed to 0.75 and 1 for the body weight effect on CL/F and V/F, respectively. External validation was performed with the updated PopPK model using the pediatric data from Study CNTO1959PSO3011. The PK parameters from the final model were presented in Table 50.

**Table 50: Parameter Estimates and SE from the Applicant's Final Population PK Model.**

| Parameter, unit | Estimate (RSE%)[a] | 95th CI | Magnitude of Change[b] |
|---|---|---|---|
| CL/F (L/day)[c] | 0.517 (1.16) | 0.505 to 0.529 | - |
| Baseline body weight (BWT) on CL/F | 0.75 (-) | - | -10.8% to 10.9% |
| Diabetes (DIAB) on CL/F | 1.18 (2.58) | 1.12 to 1.24 | 18% |
| Non-Caucasian (RACE) on CL/F | 1.07 (1.70) | 1.03 to 1.11 | 7% |
| V/F (L)[d] | 13.5 (1.04) | 13.2 to 13.8 | - |
| Baseline body weight on V/F | 1.00 (-) | - | -14.1% to 14.8% |
| $k_a$ (1/day) | 1.13 (11.6) | 0.873 to 1.39 | - |
| IIV of CL/F (%) | 36.1% (6.4) [4] | 33.7 to 38.2 | - |
| IIV of V/F (%) | 28.5% (9.5) [16] | 25.7 to 31.1 | - |
| IIV of $k_a$ (%) | 131% (20.2) [75] | 102 to 155 | - |
| Correlation between IIV of CL/F and V/F | 0.813 | - | - |
| Proportional residual error (CV%) | 20.0% (2.42) | 19.0 to 21.0 | - |
| Additive residual error (µg/mL) | 0.00289 (-) | - | - |
| OFV | -17332.962 | - | - |
| Condition number | 180.79 | - | - |

BWT=baseline body weight; CI=confidence interval; CL/F=apparent clearance; CV=coefficient of variation; DIAB=diabetes comorbidity; IIV=inter-individual variability, calculated as (variance)$^{1/2}$*100%; $k_a$=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling; OFV=objective function value; PK=pharmacokinetics; PopPK=population pharmacokinetics; RSE=relative standard error; V/F=apparent volume of distribution.

[a] Mean (RSE%) [Shrinkage%] estimates by NONMEM from the final PK dataset.

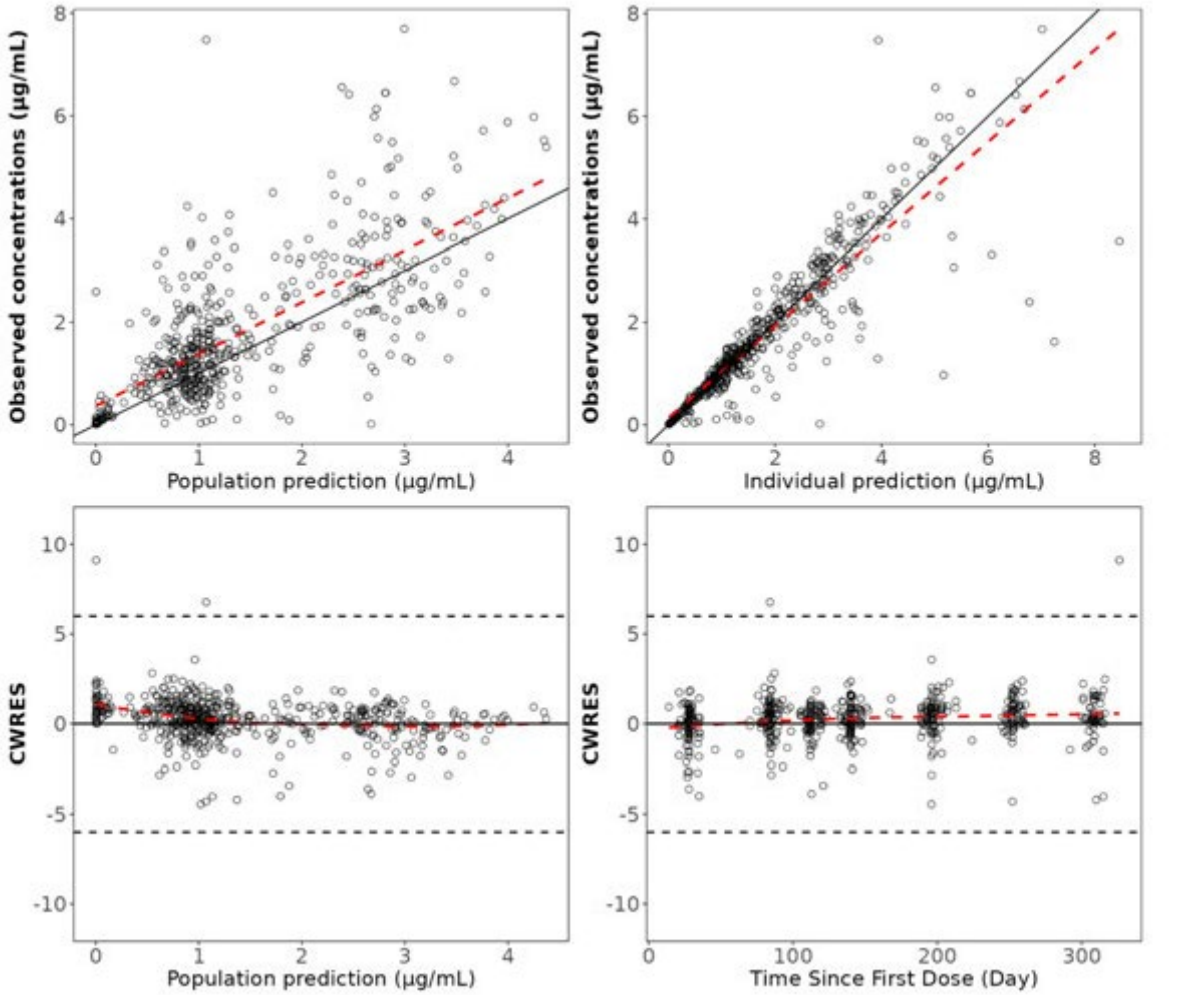
[b] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from the 25th to the 75th percentile of the population.

[c] $$CL/F = 0.517 \times (\frac{BWT}{87.1})^{0.75} \times 1.18^{DIAB} \times 1.07^{RACE}$$

[d] $$V/F = 13.5 \times (\frac{BWT}{87.1})^{1.0}$$

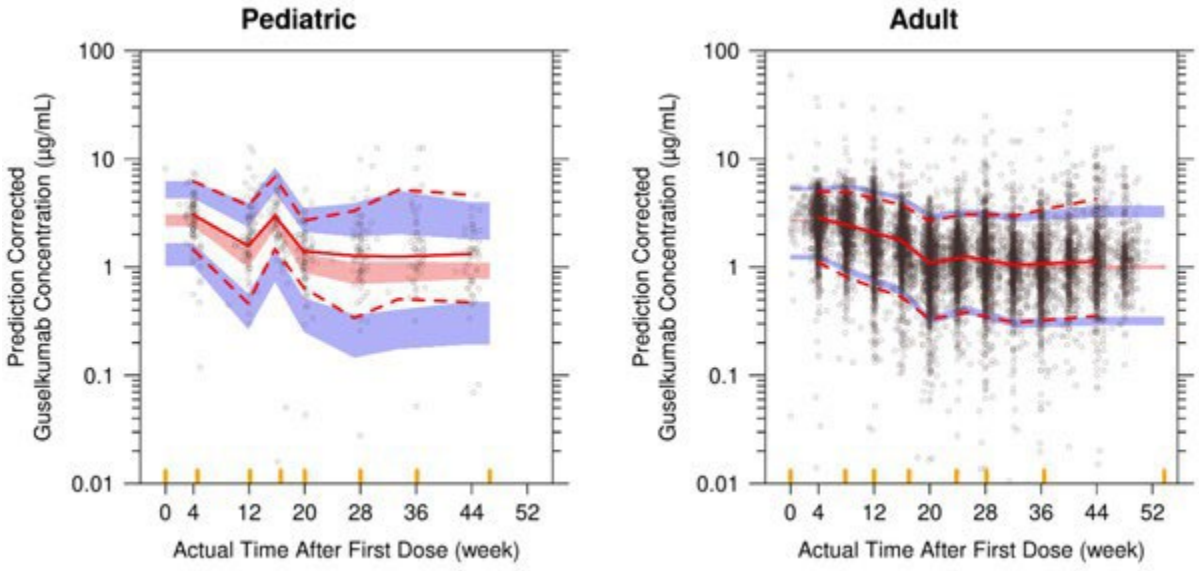
Source: Population PK Report, Table 5

**Figure 14: Goodness-of-fit Plots of the Guselkumab Final PopPK Model for Pediatric Subjects (CNTO1959PSO3011) (OBS-PRED/IPRED, CWRES-TIME/PRED).**




Source: Population PK Report Figure E1.

**Figure 15: Visual Predictive Checks of Final PopPK Model Stratified by Population (Pediatric [CNTO1959PSO3011], Adults [CNTO1959PSO3001, CNTO1959PSO3002]) (Applicant - Figure E2)**




Source: Population PK Report Figure E2.

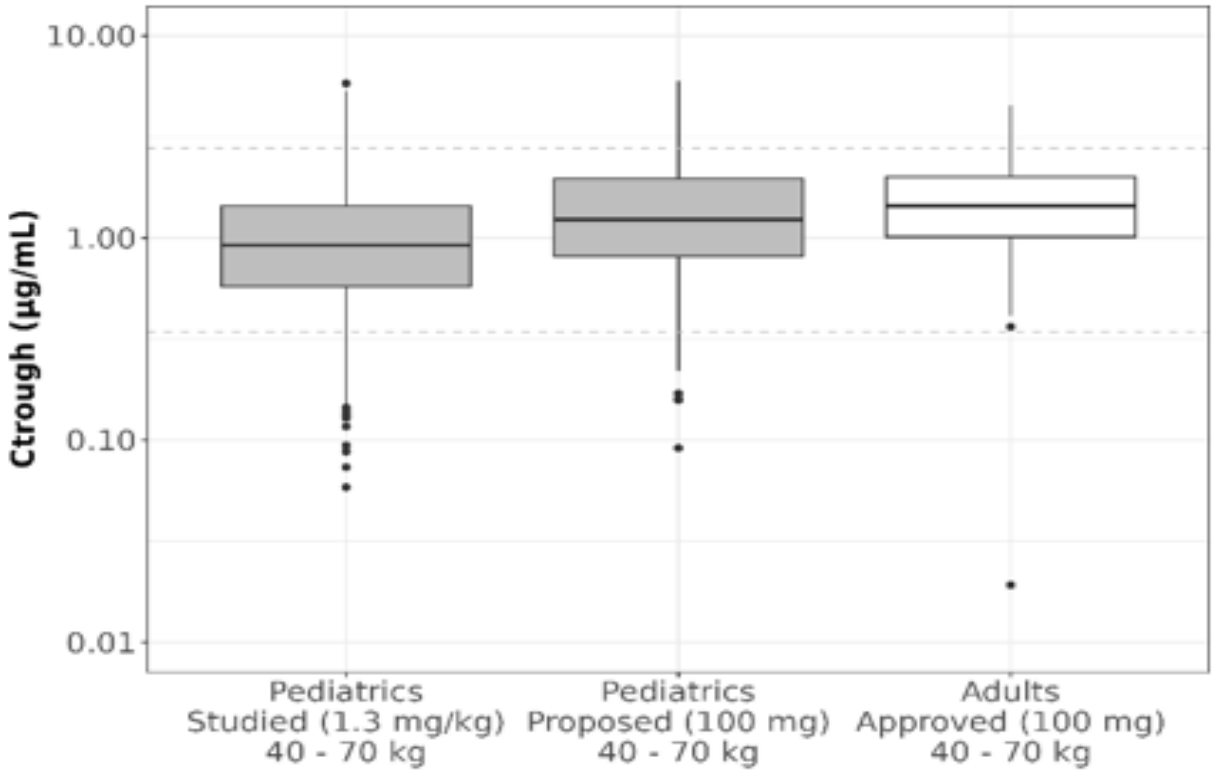
19.4.3. Evaluation of Appropriate Body Weight Cutoff for Use of the 100 mg Fixed Dose of Guselkumab in Pediatric Subjects

In CNTO1959PSO3011, children and adolescents with body weight ≥70 kg received a guselkumab 100 mg dose, and children and adolescents with body weight <70 kg received a guselkumab 1.3 mg/kg dose. For adults, the recommended guselkumab dose is 100 mg, regardless of body weight, and adults with body weight as low as 37 kg have received the 100 mg dose in CNTO1959PSO3001/CNTO1959PSO3002. This change in the dosing regimen based on the BW cut off was carried out by simulations to assess the appropriateness of lowering the pediatric body weight cutoff from 70 kg (which was studied in Study CNTO1959PSO3011) (Figure 3) to the proposed body weight cutoff for 40 kg for use of the adult 100 mg fixed guselkumab dose (Figure 4) respectively. In our analysis, we compare the PK, efficacy, and safety among 40 to 70 kg BW among adults who received 100 mg flat dose, with the simulated and observed data available from pediatric study (CNTO1959PSO3011).

The summary of model-predicted guselkumab serum concentrations for 100 mg dose compared to observed serum concentrations for 1.3 mg/kg dose in 40–70 kg pediatric subjects at Weeks 16 and Week 28 is given in Table 51. The predicted median concentrations were higher but with less than 2-fold variation compared to observed concentrations for subjects receiving 1.3 mg/kg, with a large overlap for the [redacted](b) (4).

Model-predicted pediatric steady-state guselkumab trough concentrations (1.3 mg/kg and 100 mg guselkumab dose) are comparable with week 28 guselkumab trough concentrations in adults weighing 40 – 70 kg, as shows in Figure 16.

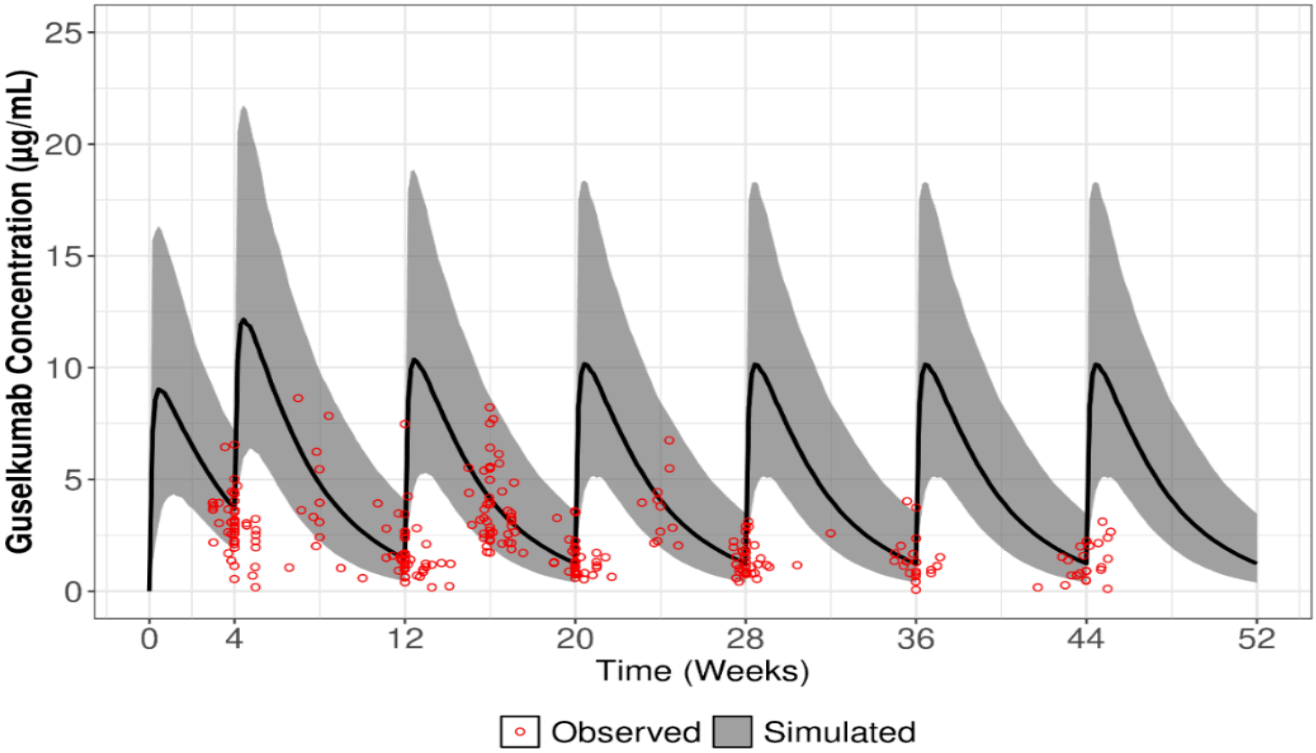
**Figure 16: Comparison of Model-predicted Pediatric Steady-State Guselkumab Trough Concentrations (1.3 mg/kg and 100 mg Guselkumab Dose) and Week 28 Guselkumab Trough Concentrations in Adults Weighing 40 – 70 kg, Semi-log Plot.**




Source: Applicant, IR response dated 21 May 2024, Figure 1

For pediatric subjects with body weight ≥40 kg receiving the 100 mg fixed dose, the median exposure for this pediatric subset at week 16 and week 28 was numerically higher than for adults, however overall exposures were still within the 90% prediction interval of adult exposure (Figure 5). The model-predicted time course of guselkumab concentrations in subjects weighing 40–70 kg who will receive a fixed dose of 100 mg, overlaid with the observed concentrations in pediatric subjects from the CNTO1959PSO3011 study for the same weight group is shown in Figure 17.

**Figure 17: Model-Predicted Serum Concentration-Time Profile (Linear and Log-scale) for Subjects Weighing 40–70 kg Administered a 100 mg Dose, Overlaid with Observed Serum Concentrations in Pediatric 40–70 kg Subjects Receiving a 1.3 mg/kg Dose.**




Source: IR response dated 21 May 2025, Figure 3.

**Table 51: Summary of Model-predicted Guselkumab Serum Concentrations for 100 mg Dose Compared to Observed Serum Concentrations for 1.3 mg/kg Dose in 40–70 kg Pediatric Subjects at Weeks 16 and Week 28.**

| | Observed after 1.3 mg/kg dose | | Model simulated after 100 mg flat dose | |
|---|---|---|---|---|
| Concentration (µg/mL) | Week 16 (N=35) | Week 28 (N=21) | Week 16 (N=1000) | Week 28 (N=1000) |
| Mean (SD) | 3.82 (1.47) | 1.22 (0.753) | 4.60 (2.06) | 1.50 (0.972) |
| Median (Range) | 3.28 (1.71; 7.70) | 1.097 (0.00; 2.89) | 4.15 (0.852 - 14.0) | 1.24 (0.0914 - 6.00) |

Source: IR response dated 21 May 2025, Table 5

This proposed change in dosing is further supported by the safety of 100 mg guselkumab fixed dose which was shown to be similar in the adult <70 kg bodyweight group and the ≥70 kg

bodyweight group at week 16 and through 1 year as given in 52 and Table 53 respectively, despite an approximately 40% higher exposure in the lower weight subgroup. These additional subgroup analyses support the lack of an exposure – safety relationship for guselkumab in adults where doses resulting in higher exposures were studied, and the comparable safety between pediatrics and adults with PsO, and further support the safety in the 40–70 kg pediatric group with a fixed 100 mg dose is expected to be comparable to that observed in the CNTO1959PSO3011 study and that observed in adults with PsO.

**Table 52: Number of Subjects with 1 or More Treatment-emergent Adverse Events, Serious Adverse Events, Infections, or Adverse Events Leading to Study Intervention Discontinuation Through Week 16 by Baseline Weight in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Safety Analysis Set**

| | Pediatric Psoriasis | | | | Adult Psoriasis | | | |
|---|---|---|---|---|---|---|---|---|
| | CNTO1959PSO3011 (Part 1) | | | | CNTO1959PSO3001/3002 | | | |
| | Placebo | | Guselkumab | | Placebo | | Guselkumab | |
| | 40 – <70 kg | ≥70 kg | 40 – <70 kg | ≥70 kg | 40 – <70 kg | ≥70 kg | 40 – <70 kg | ≥70 kg |
| Analysis set: Safety analysis set | 13 | 5 | 23 | 12 | 78 | 344 | 125 | 698 |
| Avg duration of follow-up (weeks) | 16.1 | 15.5 | 16.4 | 16.3 | 16.2 | 15.8 | 15.9 | 16.2 |
| Participants with 1 or more adverse events | 5 (38.5%) | 5 (100.0%) | 9 (39.1%) | 4 (33.3%) | 31 (39.7%) | 166 (48.3%) | 69 (55.2%) | 336 (48.1%) |
| Participants with 1 or more serious adverse events | 0 | 0 | 0 | 0 | 0 | 6 (1.7%) | 2 (1.6%) | 14 (2.0%) |
| Participants with 1 or more infections | 4 (30.8%) | 3 (60.0%) | 5 (21.7%) | 4 (33.3%) | 15 (19.2%) | 75 (21.8%) | 31 (24.8%) | 160 (22.9%) |
| Participants who discontinued study intervention because of adverse events | 0 | 1 (20.0%) | 0 | 0 | 1 (1.3%) | 3 (0.9%) | 2 (1.6%) | 9 (1.3%) |

Source: IR response dated 18 July 2025, Table 3

**Table 53: Number of Subjects with 1 or More Treatment-emergent Adverse Events, Serious Adverse Events, Infections, or Adverse Events Leading to Study Intervention Discontinuation Through 1 year by Baseline Weight in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Safety Analysis Set.**

| | Pediatric Psoriasis (0-52 weeks) | | Adult Psoriasis (0-48 weeks) | |
|---|---|---|---|---|
| | CNTO1959PSO3011 (Parts 1& 2) | | CNTO1959PSO3001/3002 | |
| | Guselkumab | | Guselkumab | |
| | 40 – <70 kg | ≥70 kg | 40 – <70 kg | ≥70 kg |
| Analysis set: Safety analysis set | 62 | 33 | 226 | 1140 |
| Avg duration of follow-up (weeks) | 43.1 | 45.9 | 37.7 | 39.3 |
| Participants with 1 or more adverse events | 42 (67.7%) | 26 (78.8%) | 147 (65.0%) | 732 (64.2%) |
| Participants with 1 or more serious adverse events | 2 (3.2%) | 0 | 7 (3.1%) | 45 (3.9%) |
| Participants with 1 or more infections | 29 (46.8%) | 20 (60.6%) | 98 (43.4%) | 483 (42.4%) |
| Participants who discontinued study intervention because of adverse events | 2 (3.2%) | 0 | 2 (0.9%) | 22 (1.9%) |

Source: IR response dated 18 July 2025, Table 4

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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.**

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/s/

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MELINDA L MCCORD
09/25/2025 10:10:11 AM
Signing for myself and Dr. Elizabeth Daniel

RAKESH GOLLEN
09/25/2025 10:14:13 AM

CHINMAY SHUKLA
09/25/2025 10:23:59 AM

YE XIONG
09/25/2025 10:46:57 AM

MEIRUO XIANG
09/25/2025 10:51:01 AM

MATTHEW W GUERRA
09/25/2025 10:51:34 AM

GORDANA DIGLISIC
09/25/2025 10:53:32 AM