BLA Multi-Disciplinary Review and Evaluation

Application Type	Prior approval efficacy supplement
Application Number(s)	BLA 761061 S-029
Priority or Standard	Standard
Submit Date(s)	November 27, 2024
Received Date(s)	November 27, 2024
PDUFA Goal Date	September 27, 2025
Division/Office	Division of Rheumatology and Transplant Medicine (DRTM)
Review Completion Date	See electronic time stamp
Established/Proper Name	Guselkumab
(Proposed) Trade Name	Tremfya
Pharmacologic Class	IL-23 inhibitor
Code name	Tremfya
Applicant	Janssen Biotech, Inc.
Dosage form	Subcutaneous injection
Applicant proposed Dosing Regimen	Pre-filled syringe: ≥40 kg 100 mg SC injection at Week 0, Week 4, and every 8 weeks thereafter
Applicant Proposed Indication(s)/Population(s)	For treatment of pediatric patients 5 years of age and older with active psoriatic arthritis (PsA)
Recommendation on Regulatory Action	Approval for age 6 years of age and older weighing ≥40 kg; not approved in 5 years age group
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of pediatric patients 6 years of age and older who also weigh at least 40 kg with active psoriatic arthritis
Recommended Dosing Regimen	100 mg by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter. TREMFYA may be administered alone or in combination with a conventional disease-modifying antirheumatic drug (e.g., methotrexate).

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OPQ=Office of Pharmaceutical Quality
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OSE= Office of Surveillance and Epidemiology
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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	body surface area involvement
BW	body weight
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDLQI	Children's Dermatology Life Quality Index
CDRH	Center for Devices and Radiological Health
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
DDD	Division of Dermatology and Dentistry
DRTM	Division of Rheumatology and Transplant Medicine
DMC	data monitoring committee
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 Council for Harmonization
IGA	Investigator Global Assessment
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JPsA	juvenile psoriatic arthritis

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
PASI	Psoriasis Area and Severity Index
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PFS	prefilled syringe
(b) (4)	
PFS-U	prefilled syringe assembled with UltraSafe Plus Passive Needle Guard
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSA	psoriatic arthritis
PSO	psoriasis
PSUR	Periodic Safety Update report
Q8W	every 8 weeks
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Guselkumab (Tremfya®) is a recombinant human immunoglobulin G1 lambda monoclonal antibody that binds to the p19 protein subunit of human interleukin-23 (IL-23). IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23 mediated intracellular signaling and release of proinflammatory cytokines and chemokines. It is approved in the United States for the treatment of adult patients with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy (BLA 761061), for the treatment of adult patients with active psoriatic arthritis (PsA, sBLA 761061/S-007), for the treatment of adults with Crohn's disease (sBLA 761061/S-024), and for the treatment of adults with ulcerative colitis (sBLA 761061/S-021).

The approved dosage is 100 mg administered by subcutaneous (SC) injection at Week 0, Week 4 and every 8 weeks thereafter for both PsO and PsA and comes in a single-dose prefilled syringe, a single-dose One-Press patient-controlled injector, and a single dose prefilled pen (TREMFYA Pen). Approved dosing for ulcerative colitis includes intravenous (IV) induction dose of 200 mg IV at Week 0 and Week 4, and every 8 weeks thereafter, or alternatively, maintenance dosing can be SC 100 mg at Week 16 and every 8 weeks thereafter, or 200 mg SC at Week 12 and every 4 weeks thereafter. Approved dosing for Crohn's disease includes IV induction dose of 200 mg at Week 0, Week 4, and every 8 weeks thereafter, or alternatively, SC induction dose of 400 mg at Week 0, Week 4, and Week 8. After either IV or SC induction, maintenance dosing is 100 mg SC at Week 16 and every 8 weeks thereafter, or 200 mg SC at Week 12 and every 4 weeks thereafter.

Janssen Biotech, Inc. has submitted supplement 29 to Biological Licensing Application (BLA) 761061 for the treatment of pediatric patients aged 5 years and older with active juvenile PsA (JPsA). The proposed dose was 100 mg/dose for weight ≥40kg. (b) (4) [redacted] Supplement 29 includes only dosing for JPsA patients 6 to 17 years of age weighing ≥40 kg using the previously approved 100 mg/dose prefilled syringe. (b) (4) [redacted]

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval of Supplement 29 for SC guselkumab via prefilled syringe, OnePress, or Tremfya Pen at 100 mg/dose at Week 0, Week 4, and every 8 weeks thereafter for the treatment of pediatric patients 6 years of age and older and also weighing ≥ 40 kg with active PsA.

Juvenile psoriatic arthritis is a subtype of juvenile idiopathic arthritis that is characterized by arthritis and psoriasis, or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, or psoriasis in a first degree relative. Juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA. Currently, treatment options for JPsA include abatacept, etanercept, golimumab, ustekinumab, secukinumab, upadacitinib, and apremilast. A full description of JPsA and its diagnosis, treatment, and prognosis, which are all highly similar to adults PsA, can be found in Section 2.1 and 2.2.

No clinical studies have been conducted with guselkumab in JPsA. The recommendation for approval for the treatment of active PsA in pediatric patients 6 years of age and older and also weighing 40 kg is based on the PK/exposure-matching based extrapolation of efficacy established in adult PsA and leveraging the safety information from pediatric patients with PsO, as well as supportive safety data from adequate and well controlled trials in adult PsA and PsO and postmarketing data. Studies CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSA3001, and CNTO1959PSA3002 have been used to establish efficacy and safety in the adult PsO and PsA patients, and safety data from the PROTOSTAR study in pediatric PsO patients are leveraged to support safety in the closely related condition of JPsA.

The PROTOSTAR study was a phase 3 study to assess the PK, safety, and efficacy of guselkumab for the treatment of pediatric participants ≥6 to <18 years of age with chronic plaque type psoriasis designed to evaluate safety and efficacy of guselkumab through two parts: Part 1 of PROTOSTAR was a 16-week placebo-controlled period and Part 2 of the study evaluated the safety and efficacy of guselkumab through 1 year of treatment. Overall, the safety of guselkumab in pediatric patients with PsO is consistent with adult patients, and no new safety signals have been identified that warrant discussion of the data contained in this submission at a public advisory committee meeting or an updated of the Warnings and Precautions section of the current label. Supportive safety data from this study is detailed below in Section 8.2**.**

The recommendation of approval for the treatment of pediatric patients with active PsA 6 years of age and older and weighing ≥40 kg is based on the following aspects that were considered for the extrapolation of efficacy:

- The disease similarity between adult patients with PsA and pediatric patients with PsA
- The similarity in systemic exposure of guselkumab between adults with PsO and adults with PsA
- PK bridging of guselkumab in adult patients with PsA and pediatric patients with PsA
- Efficacy extrapolation from adult patients with PsA to pediatric patients with PsA

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Juvenile psoriatic arthritis (JPsA) is a chronic progressive inflammatory arthritis associated with psoriasis that can result in permanent joint damage and disability; it is a subtype of the broader group of childhood inflammatory arthritides that comprise juvenile idiopathic arthritis (JIA). Juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA, and it has a calculated annual incidence of ~3 per million children. Without appropriate treatment, JIA, including JPsA, can lead to significant disability. Although there are 7 FDA-approved treatments for JPsA (golimumab, secukinumab, ustekinumab, etanercept, abatacept, upadacitinib, and apremilast), there remains an unmet need for therapeutic options in this population since not all patients respond to the approved treatments.

Guselkumab is a fully human IgG1 monoclonal antibody that binds to the p19 subunit of IL-23 with high specificity and affinity, thereby acting as an IL-23 inhibitor. Subcutaneous guselkumab was approved for the treatment of adults with active PsA on July 13, 2020 (sBLA761061/S-007). At the time of approval, the Agency issued a PMR under PREA (PMR 3899-1) to provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of active PsA in pediatric patients 5 to 17 years of age. The Applicant has submitted BLA 716016/S-029 and study to address this PMR. However, submission of this study only partially fulfills this PMR; see Section 10 for details.

No clinical trials or dedicated pharmacokinetic studies were conducted in pediatric patients with PsA in support of BLA 761061/S-029. The efficacy of guselkumab in pediatric subjects with active PsA was extrapolated from adults with active PsA where efficacy has been previously demonstrated in adequate and well-controlled clinical trials. The initial submission of supplement 29 was to support treatment of pediatric patients with active PsA aged 5 to 17 years of age (b) (4) approval in pediatric patients with active PsA could only be granted using the existing approved presentation of SC guselkumab, which is a 100 mg/dose pre-filled syringe that supported use only in patients weighing ≥40 kg. Modelling was used to establish that the exposure in pediatric patients weighing ≥40 kg would be similar to exposure in adults. Adult PsO and PsA and pediatrics PsO trial data were used to establish PK-bridging to JPsA subjects, and with the establishment of this scientific bridge and given the significant disease similarity between adult and pediatric patients with PsA, it is scientifically justifiable to extrapolate the efficacy established in adults with PsA to pediatric patients with PsA.

The safety of guselkumab in JPsA patients is supported by the safety in pediatric patients with PsO, observed in the PROTOSTAR study. The

relevance of the safety data is supported by the high degree of similarity between pediatric PsO and JPsA and overall, the safety profile of guselkumab in pediatric psoriasis was generally consistent with the safety observed in the adult PsO and PsA populations. No new safety signals were identified and no new updated to the Warnings and Precautions section on current labeling for guselkumab were warranted.

The Applicant has provided adequate information to inform the benefit-risk assessment of SC guselkumab for the treatment of JPsA patients and to support the expansion of the indication for guselkumab for the treatment of JPsA patients weighing ≥40 kg. Approval of guselkumab will provide an additional treatment option in the United States for pediatric patients with PsA. Therefore, we recommend approval of guselkumab for pediatric patients 6 years and older and weighing ≥40 kg with active JPsA.

PMR 3899-1 is only partially fulfilled by the data submitted in this application and further development will be needed in order to fully fulfill the PREA PMR, as the Applicant has not provided a suitable administration method for pediatric patients 6 years and older and weighing less than 40 kg. Additionally, approval will not be granted in the 5 years age group because no safety data in 5 years old subjects is available in the PROTOSTAR study to leverage to JPsA patients. A deferral extension is granted to the existing PMR to allow time for development of an age-appropriate formulation/presentation for use in the pediatric population ages 6 to 17 years who weigh less than 40 kg; see Section 10 for further details.

Conclusion:
The benefit-risk profile for guselkumab is favorable for the treatment of JPsA in pediatric patients 6 years and older and also weighing ≥40 kg. This approval will provide an important treatment option for this pediatric population with high unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Juvenile psoriatic arthritis, or JPsA, is a subtype of JIA and comprises between 2 and 11% of children with JIA. Clinical manifestations of pediatric PsA are similar to adult PsA and include peripheral and axial arthritis, enthesitis, dactylitis, and cutaneous and nail changes.	• JPsA is a serious disabling form of JIA with significant impact on quality of life for patients and families. Pediatric PsA and adult PsA share similar disease manifestations, disease progression, and similar response to treatment, supporting the similarity of the diseases to support the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		extrapolation of efficacy from adult PsA to pediatric PsA based on exposure matching.
Current Treatment Options	• Recommendations for treatment are based on Expert Consensus Treatment Guidelines, and treatment is determined based on active disease manifestations. • Standard-of-care treatments for pediatric patients with pediatric patients with PsA is similar to treatment in adult patients and includes initial treatment with NSAIDs, followed by the addition of non-biologic DMARDs, and/or TNF-inhibitors in patients with persistent disease activity.	Despite 7 FDA-approved therapies for the treatment of JPsA in the United States, there remains an unmet need for safe and effective therapies since not all patients with JPsA respond to currently approved treatments.
Benefit	• No clinical studies of guselkumab in JPsA patients were submitted in this application. The efficacy of guselkumab in JPsA was assessed via a full efficacy extrapolation approach from existing efficacy and PK data in adults with PsA and/or PsO. • The efficacy of guselkumab in adults with PsA was demonstrated previously in adequate and well-controlled studies (CNTO1959PSA3001 and CNTO1959PSA3002) that supported the approval of guselkumab for adults with active PsA. • To support PK bridging between adults and children with PsA, PK data from adults with PsO and PsA were compared. Systemic exposures were matched between adults with PsA, adults with PsO, and pediatric patients with pediatric PsO, supporting the similarity of exposures in adult and pediatric patients with PsA.	• Efficacy of guselkumab in pediatric subjects weighing 40 kg with active JPsA is based on PK-based exposure matching in pediatric subjects with PsO and extrapolation of established efficacy of guselkumab in adults with PsA and/or PsO. This approach is justified based of the disease similarities between pediatric and adults PsA, as well as the consistent exposure-response in adults with PsA and pediatric patients with JPsA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Pediatric psoriasis and JPsA are highly similar diseases. Therefore, it is reasonable to leverage safety data from pediatric PsO to JPsA. • The safety database (N=92) from the PROTOSTAR study is sufficient to provide a risk assessment for guselkumab in the JPsA population and is further supported by additional safety data from the Applicant's clinical development program for adult PsO and PsA. • In the PROTOSTAR study, there were no deaths. • There were no new safety signals identified in PROTOSTAR. • Additionally, in additional data contained in the 120-DSUR, no new safety signals were identified.	• Pediatric PsO and JPsA are highly similar diseases with similar clinical manifestations and responses to treatment. Therefore, it is reasonable to leverage safety data from the pediatric PsO study, PROTOSTAR, to the JPsA patient population. • The overall safety profile of guselkumab in pediatric psoriasis patients aged 6 to 17 years was generally consistent with the safety observed in adult PsO and PsA. • There were no new safety signals. • The safety of guselkumab in JPsA is expected to be similar to that that of patients with pediatric PsO. • Additional development will be necessary to further explore dose administration in younger populations, given that this application supports the dosing of guselkumab only in JPsA patients weighing ≥40kg; PMR 3899-1 has not been fully fulfilled with this study.

1.4. Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

Juvenile psoriatic arthritis (JPsA) can also be referred to as pediatric psoriatic arthritis or psoriatic juvenile idiopathic arthritis (JIA). For this review, psoriatic arthritis in children will be referred to as juvenile psoriatic arthritis. The ILAR criteria classify JPsA as subtype of JIA characterized by arthritis and psoriasis or arthritis and at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative (Petty 2004). Exclusions to a classification of PsA include arthritis in an HLA-B27 positive male after age 6; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome (reactive arthritis), acute anterior uveitis, or a history of one of these in a first degree relative; presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart; and presence of systemic JIA (Petty 2004). The Vancouver Criteria for juvenile psoriatic arthritis define definite juvenile psoriatic arthritis by the presence of 2 major criteria (arthritis and psoriasis) or arthritis plus 3-4 minor criteria (dactylitis, nail pitting, family history of psoriasis in first or second degree relative, psoriasis-like lesion) (Southwood 1989). Notably, the presence of skin rash is not required for classification based on either criterion. Juvenile psoriatic arthritis comprises between 2 to 11% of children with JIA (Stoll 2011; Ravelli 2007).

Aside from a difference in the timing of psoriasis and arthritis onset, pediatric PsA and adult PsA share many of the same disease characteristics and clinical manifestations, suggesting that they may be a spectrum of the same disease (Brunello 2022). Table 1 presents a detailed comparison of the clinical manifestations of PsA in children and adults. There are also data suggesting that the pathogenesis of pediatric and adult PsA are similar based on elevated levels of the pro-inflammatory cytokines IL-17, IL-23, and tumor necrosis factor observed in patients with these diseases (Carvalho 2021).

In children, the age of onset of JPsA has a biphasic distribution with a peak between ages 2 to 4 years and a second peak at 9 to 11 years of age. Younger patients are more commonly female with a positive ANA, while older children are more likely to have axial disease and enthesitis (Stoll 2006; Zisman 2017). In general, the initial presentation is a monoarthritis or oligoarthritis, and the most commonly involved joints are knee and ankle, with hip joint disease in up to 20% to 30% of patients (Nigrovic 2024). In the absence of effective therapy, the arthritis will often progress to polyarticular disease. Juvenile psoriatic arthritis can affect the axial skeleton in 10% to 30% of patients (Stoll2006). Sacroiliitis is more frequent in patients with older age at onset, who are often positive for the HLA-B27 antigen. Approximately 60% of children in the older subgroup of pediatric PsA have enthesitis, as compared to 22% of younger patients (Southwood 1989). Dactylitis is observed in 20 to 40% of patients (Southwood 1989). Chronic painless uveitis occurs in 10 to 15% of children with pediatric PsA and more commonly in younger patients with a positive ANA (Stoll 2006). Psoriasis occurs in 40 to 60% of patients with pediatric psoriatic arthritis, and nail changes are observed in 50 to 80%.

Table 1. Similarities and Differences Between PsA in Adults and Children

Clinical Feature	Adults	Children
Timing of psoriasis and arthritis onset	Psoriasis prior to arthritis	Arthritis prior to psoriasis
Peripheral arthritis		
Oligoarticular	20-55%	45-55%
Polyarticular	20-60%	35-55%
Oligo-extended	7-40%	15-38%
Axial arthritis	7-40%	10-30%
Radiological damage	47%	25%
Enthesitis	30-50%	12-45%
Dactylitis	40-50%	17-37%
Nail involvement	41-93%	37-57%
Uveitis	8%	8-13%
HLA-B27 positive	40-50%	10-25%
ANA positive	16%	40-46%

Adapted from Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, et al., 2022, New insights on juvenile psoriatic arthritis. *Front Pediatr*, 10:884727.

2.2. Analysis of Current Treatment Options

Table 2 lists the therapies currently approved for pediatric patients with JPsA. Seven (7) therapies are currently approved. Intravenous golimumab was approved September 29, 2020, for age 2 years and older; secukinumab was approved December 22, 2021, for age 2 years and older; ustekinumab was approved July 29, 2022, for age 2 years and older; etanercept was approved October 19, 2023, for age 2 years and older; subcutaneous abatacept was approved October 31, 2023, for age 2 years and older; upadacitinib was approved April 26, 2024 for ages 2 and older who have had an inadequate response or intolerance to one or more TNF-blockers; and apremilast was approved July 23, 2025 for ages 6 years and older and weighing at least 20 kg. All of these approvals were based on a PK matching and efficacy extrapolation methodology except for secukinumab, which was approved based on a randomized withdrawal study.

In additional, similar to pJIA, NSAIDs (celecoxib, naproxen, ibuprofen, rofecoxib, meloxicam, and tolectin) and glucocorticoids approved for the treatment of JIA and JRA are used as off-label treatments for JPsA.

Table 2 FDA-Approved Treatments for Pediatric Psoriatic Arthritis

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Abatacept	Pediatric patients with active PsA	2005/2003	SC formulation: 10 to <25 kg dose is 50 mg weekly 25 to <50 kg dose is 87.5 mg weekly ≥50 kg dose is 125 mg weekly	PK extrapolation using data from adult PsA	Similar to safety profile in adults
Etanercept	Pediatric patients with active PsA	1998/2003	SC formulation: 0.8 mg/kg weekly (maximum 50 mg weekly)	PK extrapolation using data from adult PsA	Similar to safety profile in adults
Golimumab	Pediatric patients with active PsA	2009/2020	Children ≥2 years: IV formulation: 80 mg/m^2 IV over 30 minutes at Wks 0 and 4, and then q8w thereafter	PK extrapolation using data from pJIA study	Similar to safety profile in adults
Ustekinumab	Pediatric patients with active PsA	2009/2022	SC formulation: <60 kg dose is 0.75 mg at Wks 0 and 4 and then q12w thereafter ≥60 mg dose is 45 mg at Wks 0 and 4 and then q12w thereafter >100 kg with co-existent moderate-to-severe plaque psoriasis 90 mg at Wks 0 and 4 and then q12w thereafter	PK extrapolation using data from adult PsA	Similar to safety profile in adults

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Secukinumab	Pediatric patients with active PsA	2016/2021	Children ≥2 years: ≥15 kg to <50 kg dose is 75 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter ≥50 kg dose is 150 mg SC at Wks 0, 1, 2, 3, and 4 and then q4w thereafter	RW study with fewer flares vs PBO	Similar to safety profile in adults
Upadacitinib	Pediatric patients with active PsA who have had inadequate response or intolerance to 1 or more TNF inhibitors	2024	Children ≥2 years and ≥10kg: 10kg to <20kg dose is 3mg tablet or 3mL oral solution (Rinvoq LQ) twice daily 20kg to <30kg: 4mg tablet or 4mL oral solution (Rinvoq LQ) twice daily ≥30kg: 6mg tablet or 6mL oral solution (Rinvoq LQ) twice daily	PK extrapolation using data from adult PsA	Similar to safety profile in adults
Apremilast	Pediatric patients with active PsA 6 years and older weighing at least 20 kg	2025	Initial dosing: Per Dosage Titration Schedule on USPI Maintenance dosing Patients weighing ≥50kg: Maintenance dose of 30 mg twice a day Patients weighing 20kg to <50kg: Maintenance dose of 20 mg twice a day	PK extrapolation using data from adult PsA	Similar to safety profile in adults

Abbreviations: CPK=phosphokinase; DB=double-blind; IV=intravenous; JRA=Juvenile Rheumatoid Arthritis; PBO=placebo; PC=placebo-controlled; PhGA=Physician Global Assessment; PK=pharmacokinetic; R=randomized; RW=randomized withdrawal; SC=subcutaneous; WKs= weeks

Similar to other ILAR subgroups of JIA including pJIA, pediatric PsA patients also are generally managed via expert, consensus-driven, treatment regimens recommended for JIA that were updated in 2019 by the American College of Rheumatology/Arthritis Foundation (Ringold 2019). Initial treatment regimens are based on a patient's level of disease activity (amount of peripheral joint involvement and the presence/absence of axial skeletal involvement and/or systemic manifestations). The treatment regimens are also similar to those used to treat pediatric patients with other subtypes of JIA and adults with PsA. Juvenile PsA patients with oligoarthritis without axial or systemic involvement or who have low disease activity are typically treated with NSAIDs and intra-articular injections of glucocorticoids that can be escalated to include a nonbiologic DMARD (methotrexate, sulfasalazine) as second-line treatment for persistent disease activity. Initiation of treatment with a biological DMARD

(bDMARD) is generally reserved for patients who are intolerant or who are considered conventional DMARD failures because of persistent or progressing underlying disease activity. Short courses of oral glucocorticoids may be used in such cases as bridging therapy until non-biologic or bDMARD therapy becomes effective. Juvenile PsA patients who have dactylitis that fails to respond to local glucocorticoid injection or who have sacroiliac and/or axial involvement are typically treated with a bDMARD along with an NSAID for symptomatic relief. Physical therapy to maintain range of motion, to prevent deformities, and to minimize loss of function of affected joints is an integral component of the treatment and management of children with PsA.

Although these guidelines included anti-TNF biologics, tocilizumab, abatacept, and rituximab, they did not include biologics with other mechanisms of action (e.g., anti-IL-17 and anti-IL-12/23 inhibition) due to a lack of published studies in pediatrics at the time. Notably, these most recent treatment guidelines were published in 2019, prior to the approval dates of golimumab, secukinumab, ustekinumab, etanercept, upadacitinib, abatacept, and apremilast for pediatric patients with PsA.

Although the above treatment options are available, administration of these treatments is not always uniformly effective. Additionally, long-term treatment with some of these options can be associated with side-effects that lead to medication discontinuation or long-term damage. The approval of SC guselkumab for the treatment of JPsA will hopefully result in improvement of treatment outcomes for patients, but there remains an unmet need for more efficacious treatments for JPsA.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Guselkumab was initially approved in the United States on July 13, 2017 for patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy and subsequently, guselkumab was approved on July 13, 2020 (sBLA761061/S-007) for the treatment of adults with active PsA. The following postmarketing study was required with the approval of guselkumab for the treatment of PsA:

PMR 3899-1: Provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (JPsA) in children 5 to 17 years of age.
- Study/Trial Completion: 10/2023
- Final Report: April 2024

Guselkumab was subsequently approved for the following additional indications:

- adult patients with moderately to severely active ulcerative colitis (September 11, 2024). This supplement also included three new drug presentations: 200 mg/20mL (10 mg/mL) single dose vial, 200 mg/20mL single dose prefilled pen (Tremfya pen), and 200 mg/2mL single dose prefilled syringe.

- adult patients with moderately to severely active Crohn's disease (March 20, 2025)

3.2. Summary of Presubmission/Submission Regulatory Activity

As part of the approval action on July 13, 2020 for BLA 761061 S-007 as treatment for adult patients with active PsA, the Agency required a pediatric postmarketing assessment (PMR 3899-1) of guselkumab SC under PREA as follows:

> *Provide PK and safety information to support the pediatric assessment of guselkumab for the treatment of juvenile psoriatic arthritis (JPsA) in children 5 to 17 years of age.*

On November 14, 2022 (under IND 124177), the Applicant submitted a draft initial Pediatric Study Plan (iPsP) which outlined their plans for the pediatric clinical development of guselkumab (SC (b) (4)) for JPsA. In this iPsP, the Applicant proposes request of a waiver for the study of guselkumab in pediatric patients <6 years of age with JPsA and a deferral of the required pediatric assessment until the time of the submission of the adult sBLA.

February 9, 2023 - written responses only

- The Agency noted that there was insufficient information about efficacy or safety of guselkumab (b) (4) dosing in adults with PsA to determine appropriate pediatric assessment. If the benefit-risk in adults was found to be favorable, a PK-based approach to support extrapolation of efficacy, with appropriate justification, would be reasonable.
- Additionally, the Applicant would need to provide support for the safety of guselkumab (b) (4) in the pediatric population, which could be provided by a PK and safety study

March 30, 2023 – agreed iPsP submitted by Applicant.

June 29, 2023, PREA PMR Deferral Extension Communication:

- The Applicant requested a deferral extension to the pediatric final report submission date for PMR 3899-1 (initial Study completion date was October 2023)
- Rationale for the deferral extension request was that as agreed in the Agency's July 2, 2020 communication, the required PK and safety information could be supported based on information of disease similarity between adult and juvenile psoriatic arthritis, justification that PK would be similar in pediatric psoriasis and JPsA, rationale for PK bridging between adult PsA and JPsA, and justification of relevance of PK and safety data from pediatric PsO to JPsA.
- The extrapolation-based approach described above would be supported by

completed and ongoing adult PsA studies, as well as data from a completed pediatric study of guselkumab in pediatric psoriasis (CNTO1959PSO3011). PMR timelines were aligned with the timeline of the PREA PMR for pediatric plaque psoriasis PMR 3225-1; study CNTO1959PSO3011 under IND 105004). Despite efforts to increase enrollment into this study, actual enrolment averaged below initial projections.

- The last safety follow-up visit for the last participant was anticipated to occur in June 2024, and therefore the Applicant requested extension of both the pediatric PsO and JPsA PMR's.
- The new proposed final report submission date, December 2024, was accepted by the Agency.

May 21, 2024, Type B Meeting

- The Applicant requested a Type B pre-sBLA meeting to discuss whether the Agency concurred with the Applicant's plan to submit the guselkumab sBLA for the pediatric PsA indication in parallel with the submission for the sBLA for the pediatric PsO indication; the Agency's response was that the timing of submissions was at the Applicant's discretion, but the submission for the JPsA indication should include all referenced safety and pharmacokinetic data needed to support filing at the time of the submission.

August 8, 2025, Response to Advice Letter

- Following communications to the Applicant from the DDD and DRTM teams (teleconference on June 26, 2025 and Agency Advice Letter on June 18, 2025), the Applicant chose to (b) (4) from S-028 and S-029.
- In this letter, the Applicant proposes (b) (4)
- Additionally, the Applicant proposed (b) (4) , supported by modeling and simulation data.
- (b) (4)

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

4.1. Office of Study Integrity and Surveillance (OSIS)

An analytical site inspection was requested for Study CNTO1959PSO3011. OSIS conducted an inspection for the analytical site in March 2023. The inspection was conducted under another IND. OSIS declined to conduct an on-site inspection and concluded that data from the reviewed studies were reliable.

4.2. OSE/DEMPA

(b) (4)

(b) (4)

(b) (4)

, Janssen is opting to use the currently approved Tremfya 100 mg prefilled syringe (PFS) to support the pediatric PsO and jPsA indications in patients ≥40 kg.

On November 16, 2016, Janssen submitted HF validation study results for the Tremfya 100 mg PFS that included pediatric participants. OSE/DEMPA reviewed the HF validation study result report at that time and found it acceptable. As such, we determine 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), we have no additional HF comments and recommendations.

5 Clinical Pharmacology

5.1. Executive Summary

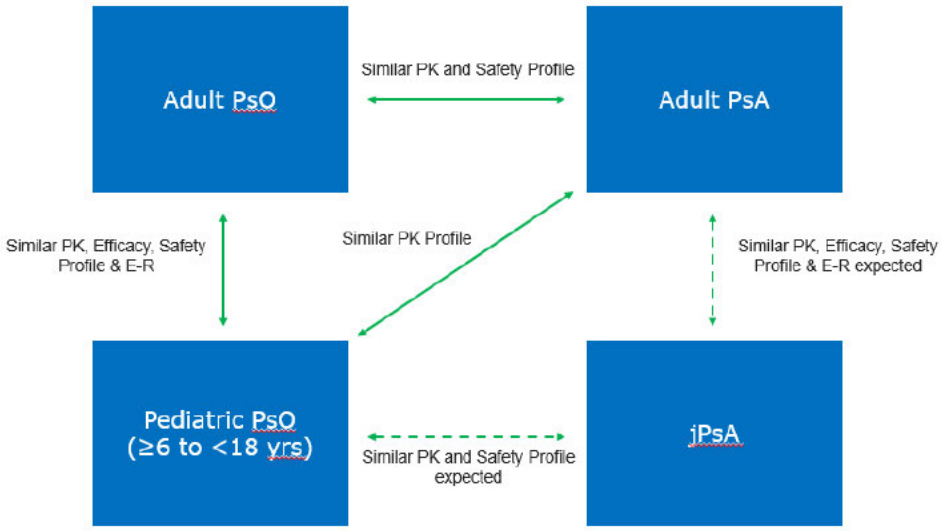
The Applicant is seeking the approval of TREMFYA® (guselkumab) for the treatment of patients 5 years of age and older with active psoriatic arthritis (PsA) and fulfilling PMR 3899-1. However, submission of this study only partially fulfills this PMR; see Section 10 for details.

No clinical trials or dedicated PK studies were conducted in pediatric patients with active PsA in support of BLA 761061/S-029. The Applicant relied on an extrapolation approach to establish the safety and efficacy in the jPsA patient population 5 years of age and older. The Applicant claims that extrapolation of efficacy from the adult to the pediatric patient population is most plausible when disease and treatment response are highly similar between these populations.

The data from participants with pediatric PsO as well as data from adult participants with PsO and/or PsA form the basis for extrapolation approach for this application (Figure 1 below).

- The disease similarity between adults with PsA and children with JPsA
- The similarity in systemic exposure of guselkumab between adults with PsO and adults with PsA
- PK bridging of guselkumab in adults with PsA and children with PsA
- Efficacy extrapolation from adults with PsA to pediatrics with PsA

Figure 1: Extrapolation of Data from Clinical Studies in Adults and Related Pediatric Populations



Source: Clinical Overview, Figure 1, page 18.

The original submission of supplement 29 was to support treatment of JPsA patients aged 5 to 17 years of age [redacted] (b) (4)

(b) (4)

approval in jPsA could only be granted using the existing approved presentation of SC guselkumab, which is a 100 mg dose pre-filled syringe (PFS) that supported use only in patients weighing ≥40kg. Modelling was used to establish that the exposure in patients weighing ≥40 kg would be similar to exposure in adults. Adult PsO and PsA trial data were used to establish PK-bridging to JPsA subjects, and with the establishment of this scientific bridge and given the significant disease similarity between adult and pediatric patients with PsA, it is scientifically justifiable to extrapolate the efficacy established in adults with PsA to pediatric patients with PsA.

Recommendations

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under sBLA 761061 and finds the sBLA approvable for 6 years of age and older with active psoriatic arthritis (PsA).

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

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

Steady-state serum concentrations of guselkumab were achieved by Week 20 in pediatric subjects 6 to 17 years of age with moderate-to-severe plaque psoriasis.

Overall, the observed guselkumab trough concentrations in pediatric subjects with plaque psoriasis were within range of those observed for adult subjects with plaque psoriasis and adult subjects with psoriatic arthritis after administration of TREMFYA.

The recommended dosing regimen for TREMFYA results in similar predicted serum guselkumab exposure in pediatric subjects as compared to adults across the body weight range.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose of guselkumab in adult subjects and pediatric patients 6 years of age and older and weighing at least 40 kg with active PsA is 100 mg administered by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter.

Therapeutic Individualization

Therapeutic individualization is not necessary for patients with body weight ≥ 40 kg. Population PK analysis identified race and diabetes comorbidity as a significant covariate that impacted

guselkumab exposure but were considered not clinically meaningful; therefore, dose adjustment based on race and diabetes comorbidity is not needed.

Outstanding Issues

The data submitted to this sBLA 761061/S-029 are inadequate to fully fulfill PREA PMR 3899-1; this submission partially fulfills PMR 3899-1, as the required study has been conducted and submitted, but the Applicant has not developed a suitable dose strength and dosing regimen for delivery of guselkumab to pediatric patients weighing <40 kg.
A deferral extension is granted to the existing PMR to allow time for development of an age-appropriate formulation/presentation for use in the pediatric population ages 6 to 17 years who weigh less than 40 kg; see Section 10 for further details.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

Guselkumab exhibited linear pharmacokinetics in healthy subjects and subjects with plaque psoriasis following subcutaneous injections. In subjects with plaque psoriasis, following subcutaneous administration of 100 mg of TREMFYA at Weeks 0 and 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.
The pharmacokinetics of guselkumab in subjects with psoriatic arthritis was similar to that in subjects with plaque psoriasis. Following subcutaneous administration of 100 mg of TREMFYA at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.
Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks or 200 mg TREMFYA every 4 weeks in subjects with ulcerative colitis, mean steady-state trough serum guselkumab concentrations were approximately 1.4 mcg/mL and 10.7 mcg/mL, respectively.

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose. The absolute bioavailability of guselkumab following a single 100 mg subcutaneous injection was estimated to be approximately 49% in healthy subjects.
Following the recommended intravenous induction dose regimen of TREMFYA 200 mg at Weeks 0, 4, and 8, mean (± SD) peak serum guselkumab concentration at Week 8 was 68.3 ± 17.3 mcg/mL in subjects with ulcerative colitis.

Distribution

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

Elimination

Apparent clearance in subjects with plaque psoriasis was 0.516 L/day. Mean half-life of guselkumab was approximately 15 to 18 days in subjects with plaque psoriasis across trials.
The apparent clearance in subjects with ulcerative colitis was 0.531 L/day. Mean half-life of guselkumab was approximately 17 days in subjects with ulcerative colitis.

Metabolism

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

5.3.2. Clinical Pharmacology Questions

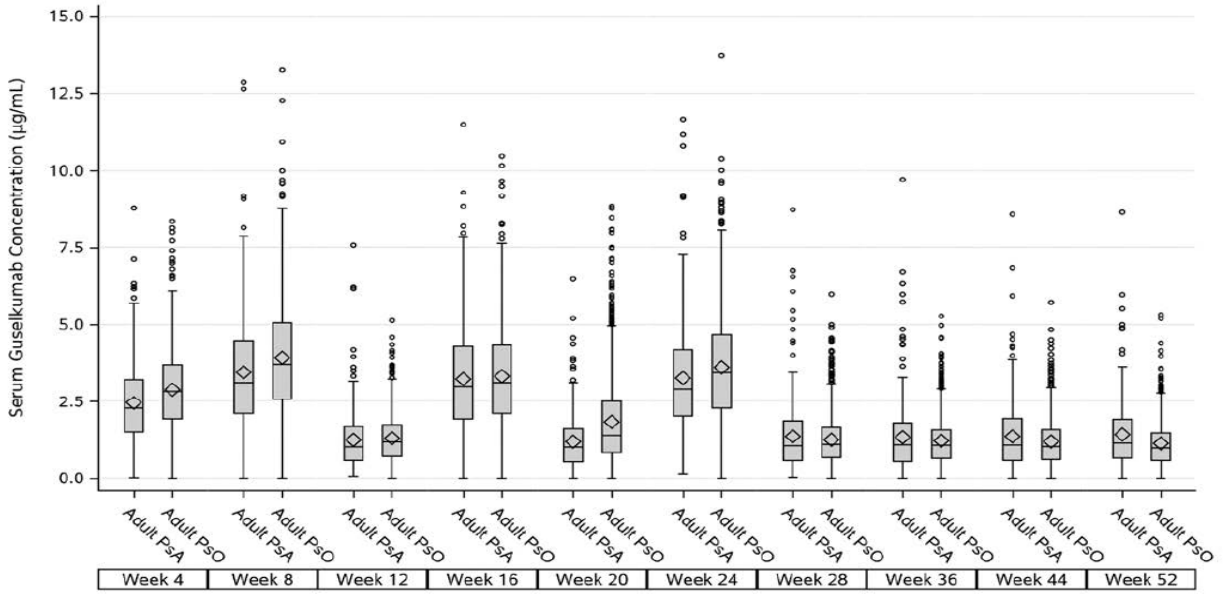
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. This sBLA for PsA in pediatrics is supported a PK matching based efficacy extrapolation approach. This supplement S029 is relying on the following considerations in an extrapolation approach for jPsA:

- The disease similarity between adult patients with PsA and pediatric patients with PsA
- The similarity in systemic exposure of guselkumab between adults with PsO and adults with PsA
- PK bridging of guselkumab in adult patients with PsA and pediatric patients with PsA
- Efficacy extrapolation from adult patients with PsA to pediatric patients with PsA

In general, the serum guselkumab concentrations in adults with active PsA were in the same range as adult patients with PsO (**Figure 2**). This comparison suggested that disease (PsO vs PsA) have no impact on guselkumab PK. Therefore, the observed PK data in pediatric patients with PsO are relevant to pediatric patients with active PsA.

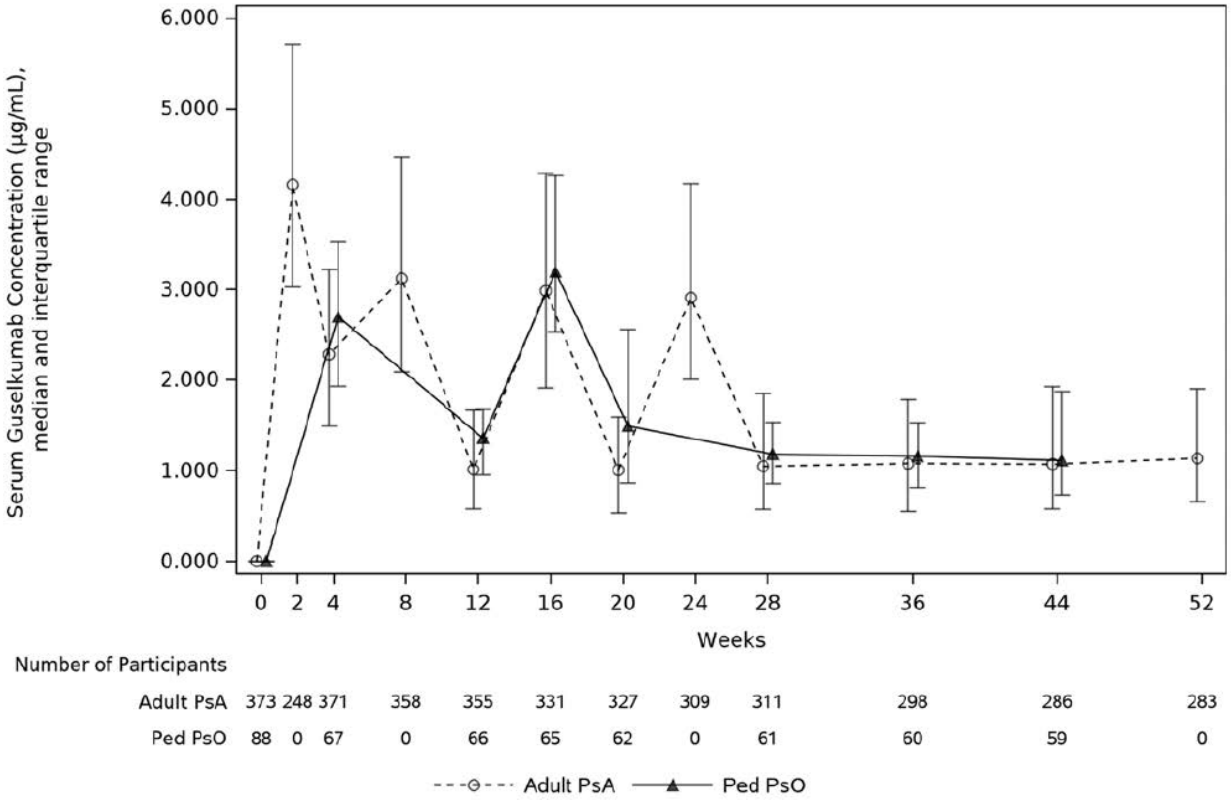
Figure 2: Boxplot of Serum Guselkumab Concentrations in Adult PsA Participants (CNTO1959PSA3001 and CNTO1959PSA3002) and Adult PsO Participants (CNTO1959PSO3001 and CNTO1959PSO3002



Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the first and third quartiles. The upper and lower whiskers represent the location of the maximum and minimum within the first and third quartiles +/-1.5 times the interquartile range. The circles represent outliers. Note: CNTO1959PSA3001 and CNTO1959PSA3002: Only participants assigned to guselkumab 100 mg q8w and who received the dose are considered. Note: CNTO1959PSO3001 and NTO1959PSO3002: Participants randomized to adalimumab at Week 0 are not considered. Participants randomized 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=389). For CNTO1959PSO3002 only, participants who were randomized to guselkumab but withdrew, due to being a PASI 90 responder at Week 28 and rerandomization to placebo, are excluded after withdrawal from guselkumab (n=182).
Source: Clinical Overview, Figure 3, page 25.

To evaluate the similarity in PK between pediatric PsA and adult PsA, the medians (with IQRs) of guselkumab concentrations over time were compared between pediatric participants with PsO(with or without jPsA) (CNTO1959PSO3011) and adult participants with PsA who received the adult dosage (100 mg at Week 0, 4 then every 8 weeks, CNTO1959PSA3001 and CNTO1959PSA3002, Figure 3). In general, at all common time points, serum guselkumab concentration-time profiles in pediatric participants with PsO were similar to those in adult participants with PsA.

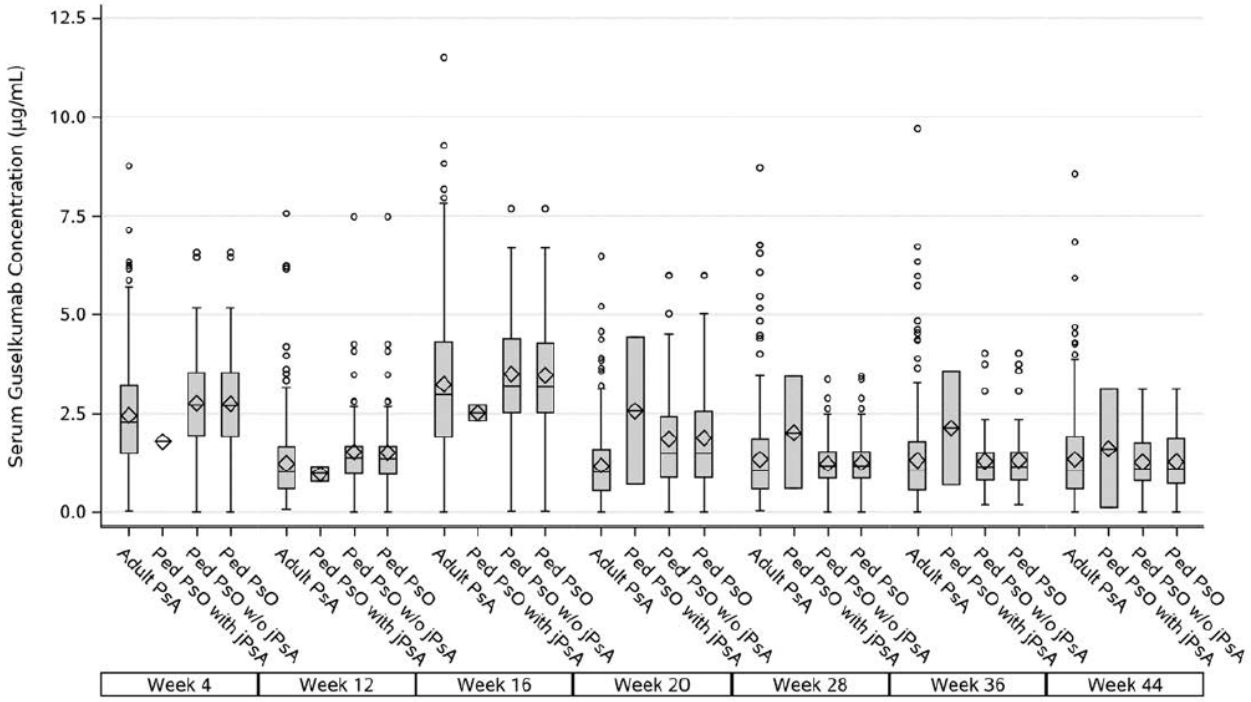
Figure 3: Line Plot of Median (IQ range) Serum Guselkumab Concentrations (µg/mL) Over Time in Adult PsA Participants (CNTO1959PSA3001 and CNTO1959PSA3002) and Pediatric PsO Participants (CNTO1959PSO3011).



Note: Adult PsA includes studies CNTO1959PSA3001 and CNTO1959PSA3002, and Ped PsO includes study CNTO1959PSO3011.
Note: CNTO1959PSA3001 and CNTO1959PSA3002: Only participants assigned to guselkumab 100 mg q8w and who received the dose are considered. Note: CNTO1959PSO3011: Participants randomized to etanercept at Week 0 are not considered. Participants randomized 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 at Week 16 (n=20). Participants who were randomized to guselkumab but withdrew, due to being a PASI 90 responder at Week 16, are excluded after withdrawal from guselkumab (n=23).
Source: Clinical Overview, Figure 4, page 27.

In the pediatric PsO study CNTO1959PSO3011, there were 3 PsO participants with jPsA that were compared with the rest of the pediatric PsO patients as well as with adult PsA participants from CNTO1959PSA3001 and CNTO1959PSA3002 (Figure 4). Although the number of pediatric PsO participants with jPsA is small, the overlapping steady-state trough serum guselkumab concentrations through Week 52 further support that the PK is similar with the pediatric PsA and adult PsA patients.

Figure 4: Box Plot of Serum Guselkumab Concentrations in Adult PsA Participants (CNTO1959PSA3001 and CNTO1959PSA3002) and Pediatric PsO Participants with and without jPsA (CNTO1959PSO3011).



Note: The line inside the box represents the median value. The symbol inside the box represents the mean value. The outer box borders represent the first and third quartiles. The upper and lower whiskers represent the location of the maximum and minimum within the first and third quartiles +/-1.5 times the interquartile range. The circles represent outliers. Note: Adult PsA includes studies CNTO1959PSA3001 and CNTO1959PSA3002, and Ped PsO with and w/o jPsA includes study CNTO1959PSO3011. Note: CNTO1959PSA3001 and CNTO1959PSA3002: Only participants assigned to guselkumab 100 mg q8w and who received the dose are considered. Note: CNTO1959PSO3011: Participants randomized to etanercept at Week 0 are not considered. Participants randomized 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 at Week 16 (n=20). Participants who were randomized to guselkumab but withdrew, due to being a PASI 90 responder at Week 16, are excluded after withdrawal from guselkumab (n=23). Source: Clinical Overview, Figure 4, page 27.

In summary, similar systemic exposure between pediatric patients with active PsA and adult patients with PsA are supported by 1) the similar systemic exposure between adult patients with PsO and adult patients with PsA; 2) the similar systemic exposure between pediatric patients with PsO and adult patients with PsA.

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

No. In the current submission, the recommended dose for pediatric patients with active PsA is different from that studied in CNTO1959PSO3011 and proposed by the Applicant.

The Applicant originally proposed dosing regimen in pediatric patients with active PsA for guselkumab is to be given at Week 0, Week 4, and q8w thereafter:
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 (b) (4) in subjects <70 kg and 100 mg administered with PFS-U in subjects ≥ 70 kg body weight.

(b) (4)

(b) (4)

a flat dose of 100 mg was proposed for pediatrics with body weight ≥ 40 kg.

Population PK modelling and simulation supported flat dosing of 100 mg in subjects ≥40 kg which demonstrated that systemic exposures were comparable to adult subjects that were administered a flat dose of 100 mg administered with the 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.

Refer to the pharmacometrics review in Appendix 15.3 for details on the population PK analysis.

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

No. The statistically significant covariates (race, body weight, and diabetes comorbidity) included in the PsA final population PK model are discussed in pharmacometrics review in section 15.3. It should be noted that neither of these factors warrant dose adjustment in pediatric patients 6 years and older and weighing at least 40 kg with PsA.

What Was the Impact of Immunogenicity on guselkumab Exposure?

There are 3 pediatric PsO participants with jPsA in study CNTO1959PSO3011. None of these 3 children developed antibodies against guselkumab up to Week 44. This number was too small to evaluate the overall incidence of antibodies to guselkumab in this population.

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

Validated sensitive ECLIA methods on the MSD® platform were used to determine serum guselkumab concentrations antibodies to guselkumab and neutralizing antibodies to guselkumab in pediatric study CNTO1959PSO3011. The same bioanalytical assay for serum guselkumab concentrations was used in the adult Phase 3 PsO studies (CNTO1959PSO3001, CNTO1959PSO3002) and PsA studies (CNTO1959PSA3001, CNTO1959PSA3002). Serum concentrations of guselkumab in the PsA studies were determined with a validated ECLIA method on the MSD platform. This is the same method that was used in the guselkumab PsO clinical development program. A description of the method and its revisions and addendums were included and reviewed as part of the original BLA submission for psoriasis. Please refer to the archived unireview (Reference ID: 4123785).

6 Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

Clinical support for guselkumab for JPsA was based on an extrapolation approach to establish safety and efficacy from the adult to the pediatric patient population, supported primarily by data generated from the phase 3 CNTO1959PSO3011/PROTOSTAR study in pediatric psoriasis and supported by 2 completed pivotal phase 3 studies in adults with plaque PsO (CNTO1959PSO3001/VOYAGE 1 and CNTO1959PSO3002/VOYAGE 2) and 2 completed pivotal phase 3 studies in adults with psoriatic arthritis (CNTO1959PSA3001/DISCOVER 1 and CNTO1959PSA3002/DISCOVER 2). These clinical studies are detailed below:

Table 3. Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety						
CNTO1959PSO3001	Phase 3, R, DB, placebo and active comparator-controlled study to assess efficacy and safety	• GUS 100 mg SC at W0, 4, and 12, and q8W thereafter • PBO at W0, 4, and 12, with crossover to GUS 100 mg SC at W16 followed by q8W • Adalimumab 80 mg SC at W0 and 40 mg at W1, 3, and 5, followed by 40 mg Q2W	Co-primary endpoints: • Proportion of patients who achieved and IGA score of cleared (0) or minimal (1) • Proportion of patients who achieved PASI 90 response at W16	16-week placebo-controlled period, W0 through 48 active comparator-controlled period, and open-label extension period from W48 through W264	N=837	Adults with mod to severe plaque-type psoriasis
CNTO1959PSO3002	Phase 3, R, DB, placebo and active comparator-controlled study to assess the efficacy and safety after randomized withdrawal and retreatment	• GUS 100 mg SC at W0, 4, 12, and 20 <u>- At W28:</u> - PASI 90 NR continued GUS 100 mg SC q8w. -PASI 90 responders were rerandomized to GUS 100 mg SC q8w or placebo. Upon loss of ≥50% of PASI improvement at W28, subjects receiving PBO were retreated with GUS 100	Co-primary endpoints: • Proportion of patients who achieved and IGA score of cleared (0) or minimal (1) • Proportion of patients who achieved PASI 90 response at W16	W0 thought W16 PBO-controlled period, W0 through 2 active-comparator controlled period, and blinded randomized withdrawal and retreatment period from W28 to W72	N=992	Adults with mod to severe plaque-type psoriasis

		mg SC, followed by dosing 4 weeks later, and then q8W. • PBO SC at W0, 4, and 12, followed by GUS at W16 and 20 <u>-At W28:</u> -PASI 90 NR continued GUS 100 mg SC q8W -PASI 90 responders received PBO until loss of ≥50% of PASI improvement at Week then retreated with GUS 100 mg SC q8W • Adalimumab 80 mg SC at W0 then 40 mg at W1 and q2W thereafter At W28: -PASI 90 NR initiated GUS 100 mg SC, followed by dosing 4 weeks later, and then q8W -PASI 90 responders received placebo. Upon loss of ≥50% of PASI improvement at W28, subjects initiated				

		guselkumab 100 mg SC, followed by dosing 4 weeks later, and then q8W				
CNTO1959PSA3001	Phase 3, multicenter, R, DB, placebo-controlled study to assess efficacy and safety At W24, PBO crossed over to GUS 100 mg SC q4W until W48	• GUS 100 mg SC q4 weeks • GUS 100 mg SC at W0, 4, and q8W thereafter	• ACR20 at W24 • Psoriasis IGA, HAQ-DI, and SF-36 PCS	60 weeks	N=381 •GUS 100 mg SC q4 weeks, N=128 •GUS 100 mg SC at Weeks, 0, 4, and q8W thereafter, N=127 •PBO n=126	Adults with active PsA, including those exposed to anti TNF agents
CNTO1959PSA3002	Phase 3, MC, R, DB, PC study to assess efficacy and safety At W24, PBO crossed over to GUS 100 mg SC q4W until W100	• GUS 100 mg SC q4 weeks • GUS 100 mg SC at Weeks, 0, 4, and q8W thereafter	ACR20 at W24 Psoriasis IGA, HAQ-DI, modified vdH-S, SF-36 PCS, SF-36 MCS, dactylitis, and enthesitis	100 weeks	N=739 • GUS q4w n=245 • GUS q8w n=248 • PBO n=246	Biologic-naïve adults with active PsA
Studies to Support Safety						
CNTO1959PSO3011	Phase 3, multicenter, R, DB, PC study to assess PK, safety, and efficacy	Dosing at W0, W4, and q8W thereafter: • Weight <70kg: 1.3mg/kg SC Weight ≥70kg: 100 mg/dose SC	Co-primary endpoints: • Proportion of patients who achieved and IGA score of cleared (0) or minimal (1) • Proportion of patients who achieved PASI 90 response at W16	16-week placebo-controlled portion (Part 1) and through 1 year of treatment (Part 2)	N=92	Pediatric subjects age ≥6 to <18 years with chronic plaque type PsO

-						

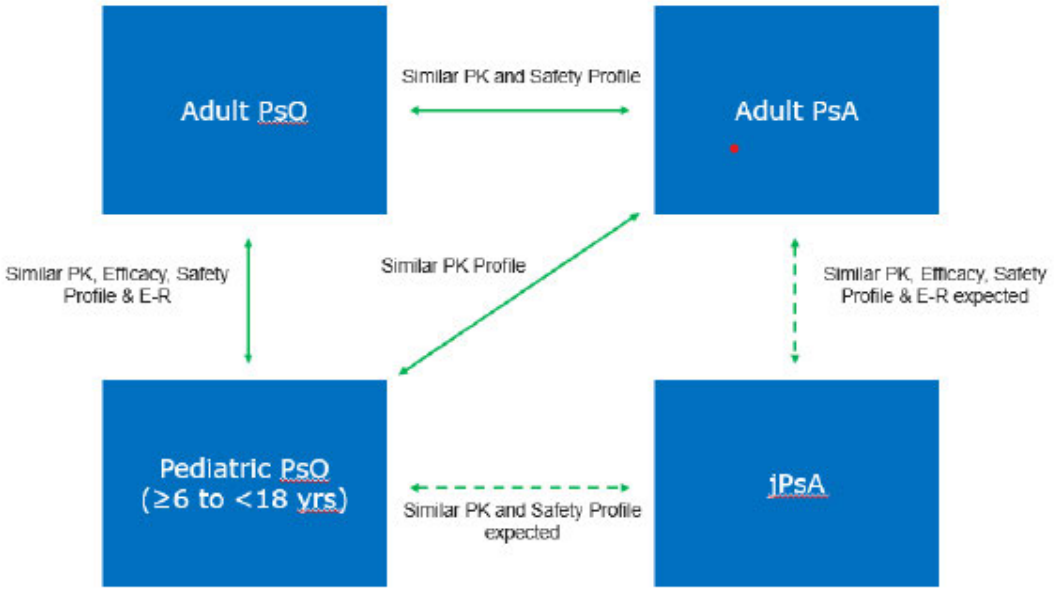
R=randomized, DB=double-blinded, PC=placebo-controlled, MC=multicenter, PsA= psoriatic arthritis, PsO=psoriasis, SC=subcutaneous, GUS=guselkumab, PASI=Psoriasis Area and Severity Index, IGA=Investigator Global Assessment, HAQ-DI=Health Assessment Questionnaire Disability Index, SF-36 PCS=36-item Short Form Health Survey Physical Component, vdH-S=van der Heijde=Sharp; SF-36 MCS=36-item Short Form Health Survey Mental Component

6.2. Review Strategy

There were no clinical studies of guselkumab SC conducted in pediatric subjects with active JPsA submitted in support of this application. As permitted under 21 CFR 314.55 and per the agreed Pediatric Study Plan (PsP), as assessment of guselkumab SC treatment in children with active JPsA was conducted via extrapolation approach from existing efficacy, safety, and PK data in children with PsO, adults with active PsA, and adults with PsO. The Applicant provided the following information in order to support the proposed PK-matching approach to the extrapolation of the efficacy in adult PsA to patients with JPsA:

- The disease similarity between adults with PsA and children with JPsA
- The similarity in systemic exposure of guselkumab between adults with PsO and adults with PsA
- PK bridging of guselkumab in adults with PsA and children with PsA
- Efficacy extrapolation from adults with PsA to pediatrics with PsA

Figure 5 Extrapolation of Data from Clinical Studies in Adults and Related Pediatric Populations



Source: Applicant's Clinical Overview, Section 1.4 Extrapolation Framework for Juvenile Psoriatic Arthritis

As the efficacy and safety of guselkumab in adults with active PsO and PsA has been previously established, these data will not be reviewed here again.

- Data from the studies CNTO1959PSO3001 and CNTO1959PSO3002 were submitted under original BLA 761061 to support the approval of guselkumab SC for the treatment of adults with moderate to severe PsO who are candidates for systemic therapy or phototherapy. See the review dated July 13, 2017, for details.

- Data from the studies CNTO1959PSA3001 and CNTO1959PSA3002 were submitted under BLA 761061/S-007 and (b) (4) (supplement 7 for the treatment of adults with active PsA at doses of 100mf SC at Week 0, Week 4, and q8 weeks thereafter, and (b) (4)) to support the approval of guselkumab SC for the treatment of adults with active PsA. See the review dated July 13, 2020, for details.

To support safety, data from clinical study CNTO19593011 (PROTOSTAR), which was a study in the pediatric psoriasis population using guselkumab SC, was leveraged since pediatric PsO is considered to be a closely related disease to JPsA. This study included 3 subjects with a diagnosis of JPsA.

7 Statistical and Clinical and Evaluation

7.1. Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study CNTO1959PSO3011/PROTOSTAR

Overview and Objective

CNTO1959PSO3011, or PROTOSTAR as it will be referred to in this section, is a phase 3 study to assess the PK, safety, and efficacy of guselkumab for the treatment of pediatric participants ≥6 to <18 years of age with chronic plaque type psoriasis designed to evaluate safety and efficacy of guselkumab through two parts. Three subjects in this study had a diagnosis of JPsA; there were no differences in efficacy or safety observed in these patients, as compared to the pediatric psoriasis subjects.

Trial Design

Part 1 of PROTOSTAR was a 16-week placebo-controlled period, and Part 2 of the study evaluated the safety and efficacy of guselkumab through 1 year of treatment.

Subjects in Part 1 were randomized to 1 of 3 treatment group through Week 16:

- Group 1: weight-based guselkumab dose up to 100 mg SC at Weeks 0, 4 and 12
- Group 2: weight-based placebo for guselkumab dose administered SC at Week 0, 4, and 12
- Group 3: weight-based open-label etanercept dose up 50 mg SC weekly through Week 15

Part 1 of the study was further divided into 2 age cohorts: Part 1a (12 to <18 years of age) and Part 1b (≥6 to <12 years of age) and enrolled a minimum of 90 subjects. Part 1a enrolled at least 60 subjects randomized 2:1:1 to guselkumab (n=30), placebo (n=15), and etanercept (n=15). Part 1b enrolled at least 30 subjects randomized in a 1:1:1 ratio to guselkumab (n=10), placebo (n=10), and etanercept (n=10).

At Week 16, depending on PASI response, the subjects would stay in the respective study arm or crossover to another arm, as detailed below:

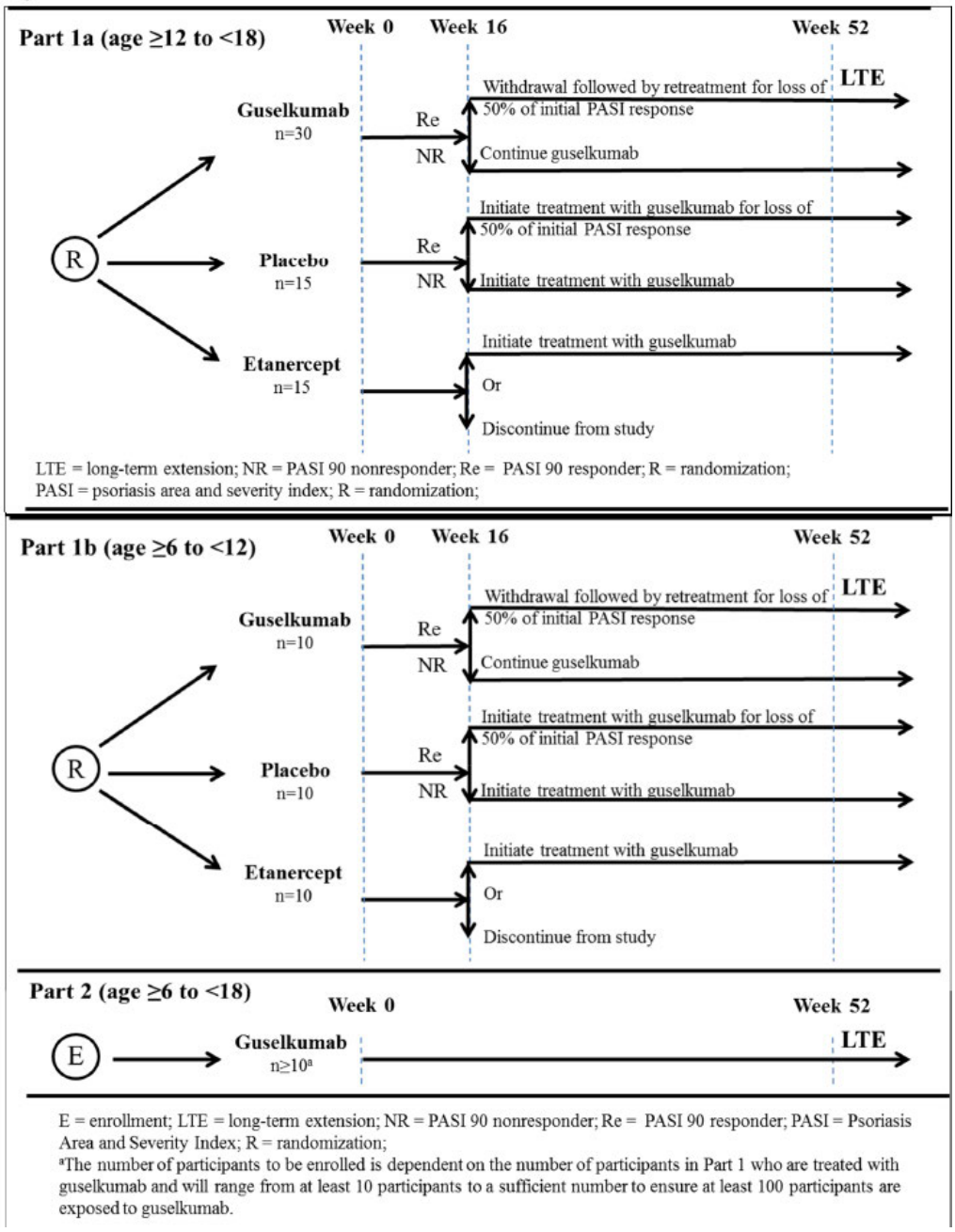
- Group 1a, randomized to guselkumab, who achieved a PASI 90 response at Week 16 were withdrawn from study intervention and then retreated upon loss of ≥50% of their Week 16 PASI improvement (dosed at the time of retreatment, 4 weeks later, and q8 weeks thereafter through Week 52).
- Group 1b, randomized to guselkumab, who did not achieve at PASI 90 response at Week 16 were given placebo at Week 16 and guselkumab q8W from Week 20 to Week 52.
- Group 2a, randomized to placebo, who achieved PASI 90 response at Week 16 were withdrawn from study intervention and then initiated on guselkumab treatment upon loss of ≥50% of their Week 16 PASI improvement.

- Group 2b, randomized to placebo, who did not achieve a PASI 90 response at Week 16 was treated with guselkumab at Week 16 and then q8W from Week 20 through Week 52.
- Group 3, randomized to etanercept, who elected to continue in the study were treated with guselkumab doses at Week 20 and 24, then q8W thereafter through Week 48.

Guselkumab and placebo were provided as a 100 mg 1mL single use prefilled syringe PFS-U and a (b) (4) for SC injection. Subjects randomized to guselkumab received a body weight-based dose: for weight <70 kg, 1.3 mg/kg was administered using the (b) (4) and for weight ≥70 kg, 100 mg was administered using the PFS-U. Commercially available etanercept was supplied and administered using approved pediatric body weight based dosing.

The study population was boys and girls who had a diagnosis of chronic plaque-type psoriasis, defined as having an IGA ≥3, a PASI ≥12, a BSA ≥10, and at least 1 of the following; very thick lesions, clinically relevant genital, facial, or hand and foot involvement, PASI ≥20, BSA >20, or IGA=4. Subjects were also required to be a candidate for phototherapy or systemic treatment of plaque PsO and have plaque PsO considered to be inadequately controlled with phototherapy and/or topical therapy after and adequate dose and duration of therapy.

Figure 6 Schematic of PROTOSTAR



Source: Applicant's Week 52 CSR for Study CNTO1959PSO3011, page 28, Figure 1

This study was conducted at 29 sites across 9 countries (Belgium, Germany, Hungary, Italy, Netherlands, Poland, Australia, Canada, and USA).

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 extension (OLE); those who participated were required to return to the study site q8W for safety and efficacy assessments in addition to study intervention administration.

Major Inclusion Criteria:

- Age ≥6 to <18 years old
- IGA ≥3 AND PASI ≥12 AND ≥10% BSA involvement AND at least one of the following:
  - Very thick lesions OR
  - Clinically relevant facial, genital, and/or hand/foot involvement OR
  - PASI ≥20 OR
  - >20% BSA involvement OR
  - IGA=4
- Be a candidate for phototherapy or systemic treatment of plaque psoriasis (either naïve or history of previous treatment)
- Have plaque psoriasis considered by the investigator to be inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration
- Be considered a suitable candidate to receive etanercept, according to the country's approved ENBREL labeling.
- Female not of childbearing potential OR for male participants and females of childbearing potential, must use highly effective contraception consistent with local regulations
- Up to date with vaccinations, and must agree to not to receive a live virus/bacterial vaccination at least 3 months prior to the first administration of study drug or within 3 months after the last administration
- Screening laboratory test results within the defined parameters

Major Exclusion Criteria:

- Nonplaque forms of psoriasis or drug-induced psoriasis
- Pregnant, nursing, or planning a pregnancy
- Has previously received guselkumab or etanercept
- Has received any anti-TNF biologic therapy within the previous 3 months
- Has contraindication to anti-TNF therapy
- Has received any therapeutic agent targeting IL-12/23, IL-17, or IL-23 within the previous 6 months
- Has received any agents that deplete B or T cells within the previous 12 months, or has received any systemic immunosuppressants within 4 weeks of the first administration of study drug
- Has received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations within 4 weeks of first administration of study drug
- Has used topical medications that could affect psoriasis or IGA evaluation within 2 weeks of first administration of study drug
- History of or current signs of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurological, cerebral, or psychiatric disease
- Transplanted organ (other than corneal transplant >3 months prior to first administration of study drug)

- Major surgery within 8 weeks
- Unstable suicidal ideation or behavior
- Has history of chronic or recurrent infections or serious infection within the previous 2 months

Study Objectives

The primary study objective was to evaluate the efficacy and safety of guselkumab in pediatric subjects aged ≥6 to <18 years with chronic plaque PsO. Secondary objectives included to evaluate the PK and immunogenicity of guselkumab in the study population, to evaluate the effect of guselkumab on the dermatologic HRQoL in the study population, to evaluate maintenance of response in subjects who had active treatment withdrawn, to evaluate the safety and efficacy of retreatment of retreatment with guselkumab, and to generate clinical usability data and use experience with the (b) (4) in pediatric subjects with a body weight <70 kg.

Study Endpoints

For the primary objective of evaluating safety and efficacy of guselkumab in pediatric subjects aged 6 to <18 years old with chronic plaque PsO in Part 1 of the study, the co-primary endpoints were the proportion of subjects achieving an IGA score of cleared (0) or 1 (minimal) at Week 16 and the proportion of patients was a PASI 75 response at Week 16 (for US-FDA, this co-primary endpoint was a PASI 90 response).
Major secondary endpoints for Part 1 of the study were (1) the proportion of subjects achieving a PASI 90 response at Week 16 (for US-FDA, this major secondary endpoint was a PASI 75 response), (2) the proportion of subjects achieving an IGA score of cleared (0) at Week 16, and (3) the change from baseline in CDLQI at Week 16.
Safety endpoints for Part 1 and 2 were the proportion of subjects with AE, SAE, AESI, AEs leading to discontinuation, infections, and injection-site reactions (including assessment of pain) at Week 16 and Week 52, assessment of safety laboratory (hematology, chemistry, and immunoglobulins) over time, and assessment of vital signs, growth, and development parameters over time.

7.2. Integrated Assessment of Effectiveness

The 2 pivotal trials CNTO1959PSA3001 and CNTO1959PSA3001 established the efficacy of guselkumab SC in adults with PsA. These studies were previously reviewed under BLA 761061/S-007 and (b) (4) (supplement 7 for the treatment of adults with active PsA at doses of 100 mg SC at Week 0, Week 4, and q8 weeks thereafter, and (b) (4)); see review dated July 13, 2020, for full details. The 2 pivotal trials CNTO1959PSO3001 and CNTO1959PSA3002 established the efficacy of guselkumab SC in adults with PsO, a closely related disease to PsA, and these studies were previously reviewed under the original BLA 761061; see review dated July 13, 2017, for full details.

The extrapolation of efficacy for guselkumab SC from adults with active PsA to children (ages 6 years to 17 years of age) is based on the similarity of disease between adult PsA and JPsA (Section 2). In addition, the Application provided adequate justification of the PK bridge from adults with PsA to children with JPsA based on comparable PK data from adults with PsO and PsA and children with PsO, as reviewed above in Section 4.5. With the guselkumab phase 3 study in pediatric PsO, a closely related disease to JPsA, there is an adequate amount of guselkumab data in pediatric subjects and adequate knowledge about systemic exposures and exposure-response to support extrapolation.

8 Review of Safety

8.1. Safety Review Approach

The safety of guselkumab SC in pediatric patients with JPsA is leveraged from the safety of guselkumab SC in pediatric psoriasis as demonstrated in the PROTOSTAR study.

The Applicant has referenced safety data from the following clinical trials:

- PROTOSTAR (CNTO1959PSO3011) - phase 3, multicenter, randomized, placebo and active comparator controlled study evaluation the efficacy, safety, and PK of SC guselkumab for the treatment of chronic plaque psoriasis in pediatric subjects aged 6 to less than 18 years of age; the primary evidence to support the safety of guselkumab SC in patients with JPsA is leveraged from this study in pediatric PsO, designed to evaluate safety and efficacy of guselkumab through a 16-week placebo-controlled period and through 1 year of treatment. For full review, refer to review under BLA 761061/Supplement-028 dated September 25, 2025.

Since the safety data from the adult PsO and PsA studies were previously reviewed in support of the marketing approval of guselkumab SC as treatment for adults with active PsO and PsA, these data will not be re-presented here. There were no clinical trials conducted in JPsA for this submission; however, a clinical study in pediatric PsO was conducted and a general overview of that safety data is presented in Section 8.4.

8.2. Review of the Safety Database

Overall Exposure

In the PROTOSTAR study, a total of 92 subjects were randomized in Part 1 of the study as follows: guselkumab= 41 subjects, etanercept= 26 subjects, and placebo= 25 subjects. Forty-one subjects in the guselkumab group and 26 subjects in the etanercept group received at least 1 administration of study intervention. In Part 2 of the study, a total of 28 subjects enrolled in

the open-label guselkumab group received at least 1 administration of study intervention. Among these 92 subjects, 3 subjects had a diagnosis of juvenile psoriatic arthritis.
In a 12-Day Safety Update report, additional information from Week 52 through January 3, 2025 was provided; this data represented 94 subjects who did not terminate the main study and entered the LTE. These data represented an additional 194 total subject-years of follow up for subjects who received guselkumab, with an average duration of follow up of 107.76 weeks.

For Part 1 of PROTOSTAR, safety data through Week 16 are summarized by treatment groups (placebo, guselkumab, and etanercept) to allow for intergroup safety comparisons and safety data through Week 52 were summarized by treatment groups as follows:

- Subjects randomized to placebo who crossed over at Week 16 to receive treatment with guselkumab (placebo → guselkumab)
- Subjects randomized to and treated with guselkumab
- Etanercept subjects who crossed over at Week 16 to receive treatment with guselkumab (etanercept → guselkumab)
- All subjects treated with guselkumab through Week 52

For Part 2 of PROTOSTAR, the safety analyses include all subjects enrolled and treated with at least 1 study intervention administration of guselkumab in Part 2 and are presented though Week 52.

Relevant Characteristics of the Safety Population

In Part 1 of the study, demographic characteristics were comparable across treatment groups, more than half of the subjects were male (55.4%) and white (84.8%) and the mean age was 12.9 (SD 3.20, range 6 to 17 years) with 67.4% adolescents (≥12 to <18 years) and 32.6% younger children (≥6 to <12 years). In Part 2 of the study, demographic characteristics were generally comparable to those in Part 1. Nearly two-thirds of the subjects were male (60.7%), and all subjects were white. Mean age was 15.1 years (SD 1.59, range 12 to 17 years). Clinical disease characteristics at baseline were generally similar across treatment groups in Part 1 and 2 and the proportions of subjects receiving previous therapies in each PsO medication category were generally comparable across treatment groups and between Part 1 and 2. The Applicant has also provided adequate justification for the applicability of foreign data to the U.S. population.

Adequacy of the Safety Database

The safety database for this application relies primarily of the observed safety in the PROTOSTAR study as reported in the CSR and the 120-Day Safety Update report (SUR). Safety data from PROTOSTAR includes 92 subjects who were randomized, with 41 subjects receiving guselkumab, 26 receiving etanercept, and 25 subjects receiving placebo in Part 1, as well as 28 subjects receiving guselkumab in Part 2 of the study. Demographic and disease characteristic

information is detailed above in Section 8.2.2.; in general, the subjects appear to adequately represent the US population of patients with JPsA and the Applicant's rationale for applicability of foreign data to the U.S. population is also reasonable.
Additionally, data provided in the 120-Day Safety Update report represents 94 subjects who entered the LTE, providing longer term safety data.

8.2.1. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No important concerns regarding data integrity and the quality of the overall submission were identified to impact the safety review.

Categorization of Adverse Events

Per ICH standard definitions, an adverse event (AE) was defined as any untoward medical occurrence in a clinical study participant administered in a medicinal product. A serious adverse event (SAE) was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization, or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, in a congenital anomaly, is a suspected transmission of any infectious agent via a medicinal product, or is medically important.
Assessment of severity grade was made using the following general categorical descriptors:

- 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.

All AEs and SAEs were reported from the time a signed and dated ICF was obtained until completion of the subject's last study-related procedure. SAEs, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, were to be reported using a Serious Adverse Event Form. SAEs were to be reported to the Applicant's contact person by study-site personnel within 24 hours of their knowledge of the event.

AEs, SAEs, and adverse events of special interest (AESIs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. Adverse events of special interest (AESIs) were based on safety concerns reported from other clinical development programs, mechanism of action, and guselkumab data from preclinical studies and were classified per standard MedDRA queries. For PROTOSTAR, the AESIs specified were as follows:

- Any newly identified malignancy
- Any case of active TB occurring after the administration of study intervention

Routine Clinical Tests

Clinical laboratory tests measures during the study period included routine hematology, blood chemistry, liver enzymes, urine pregnancy testing for females of childbearing age, and serum IgG, IgM, and IgA levels were assessed through Week 52 in the main study. Infectious screening serologies (QuantiFERON, hepatitis B and C serologies, serum varicella, measles, mumps, and rubella antibody titers, and HIV antibody testing) were done at screening. A guideline algorithm was created for the management of abnormal liver enzymes (ALT or AST >3 times the upper limit of normal), which determined how frequently laboratory assessments should be done to re-assess for improvement or normalization, or whether the subject should be permanently discontinued from the study.

8.2.2. Safety Results

The safety of guselkumab is well characterized in numerous clinical studies, including in adult patients with PsO and PsA. In this pediatric psoriasis program, no new safety signals were identified in the pediatric patients compares to the known adverse event profile of guselkumab in adult patients. The observed safety profile of guselkumab in children with JPsA was consistent with the known safety profile of guselkumab.

Currently labeled Warnings and Precautions for guselkumab include hypersensitivity reactions, infections, tuberculosis, hepatotoxicity, and avoidance of live vaccines. As hepatoxicity has been noted in adult psoriasis and inflammatory bowel disease studies, modification to the hepatotoxicity portion in labeling will include language to monitor liver enzymes for all patients receiving guselkumab per routine patient management. No new safety issues will be added to the Warnings and Precautions section in the labeling for this submission.

Table 4 Summary of Safety Findings Through Placebo-Controlled Portion in Study CNTO1959PSO3011 (PROTOSTAR)

	Placebo	**Guselkumab**
Safety analysis set	25	41
Avg duration of follow up (weeks)	16.3	16.4
Subjects with 1 or more:		
Common Adverse Event (≥5% incidence)	8 (32.0%	11 (26.8%)
Nasopharyngitis	7 (28.0%)	5 (12.2%)
Upper respiratory tract infection	2 (8.0%	4 (9.8%)
Headache	0	3 (7.3%)
Serious Adverse Event	0	1 (2.4%)
Treatment difference		2.4 (-22.0, 26.6)
Any Infections	10 (40.0%	12 (29.3%)
Serious infections	0	0
Treatment difference		--
Infections requiring treatment	3 (12.0%)	1 (2.4%)
Malignancy	0	0
Treatment difference		--

Adapted from the Applicant's Clinical Overview Table 7, page 149

Table 5 Summary of Safety Findings Through One Year in Study CNTO1959PSO3011 (PROTOSTAR)

	Guselkumab		
	Ped PsO with JPsA	Ped PsO without JPsA	Ped PsO
# of Treated Subjects	3	89	92
Avg duration of follow up	46.5	46.2	46.2
Ave g# of guselkumab injections	6.0	8.7	8.6
Subjects who discontinued study due to 1 or more AEs	0	2 (2.2%)	
Subjects with 1 or more:			
Adverse Events (≥5% incidence):	2(66.7%)	70 (78.7%)	72 (78.3%)
Nasopharyngitis	1 (33.3%)	26 (29.2%)	27 (29.3%)
Headache	0	10 (11.2%)	10 (10.9%)
Upper respiratory tract infection	1 (33.3%)	9 (10.1%)	10 (10.9%)
Acne	0	6 (6.7%)	6 (6.5%)
Pharyngitis	0	5 (5.6%)	5 (5.4%)
Bronchitis	1 (33.3%)	1 (1.1%)	2 (2.2%)
Serious Adverse Events	1 (33.3%)	2 (2.2%)	3 (3.3%)
Any Infections	2 (66.7%)	50 (56.2%)	52 (56.5%)
Infections requiring treatment	1 (33.3%)	8 (9.0%)	9 (9.8%)
Serious infections	0	0	0
Injection Site Reactions	0	4 (4.5%)	4 (4.3%)

Adapted from the Applicant's Clinical Overview Table 6, page 43

Deaths

No deaths were reported in the PROTOSTAR study.

Serious Adverse Events

In PROTOSTAR Part 1, two SAEs were observed, which included a subject that experienced a radius fracture assessed to be of severe intensity and not related to study intervention and a subject that experienced chronic tonsillitis of moderate intensity and not related to study intervention. In Part 2 of the study, a single SAE was reported, which was a subject experiencing multiple injuries after a fall, assessed as moderate intensity and unrelated to study intervention.

Dropouts and/or Discontinuations Due to Adverse Effects

In PROTOSTAR Part 1, through Week 16, one subject discontinued study intervention due to AE of PsO of mild severity, considered possibly related to study intervention, and no subjects in the

guselkumab and etanercept arms discontinued. In Part 1 through Week 52, one subject discontinued the study due to an AE of pregnancy. In Part 2, one subject discontinued the study due to an AE of suicidal ideation.

> *Reviewer's comment: subject narratives reviewed and details of this discontinuation due to suicidal ideation pertained to a 17-year-old female who had a treatment-emergent AE of suicidal ideation on Day 10, assessed as mild severity. There was one additional event of suicidal ideation in the study, in open-label Part 2, in a 14-year-old female with reported pre-existing suicidal ideation; this subject received behavioral health support and continued in the study, with reported resolution of suicidal ideation at Week 20.*

Overall numbers of SAEs are small and therefore limit the conclusions that can be made. No new safety signals were identified.

There were no AE's leading to discontinuation in the LTE period (after Week 52 through January 3, 2025).

Significant Adverse Events

Protocol-specified AESI's for PROTOSTAR are as described in Section 8.3.2. Categorization of Adverse Events. In the main study, there were no AESIs (active TB or malignancy), no serious infections, no anaphylactic reactions, no serum-sickness like reactions, and no events of MACE.

In the 120-Day Safety Update report, 4 guselkumab-treated subjects reported SAEs after Week 52 through January 3, 2025. These included 1 SAE of peritonsillar abscess, 1 SAE of tonsillitis, 1 SAE of syncope, and 1 SAE of influenza. All these were single events, each reported in a single subject. They were all assessed as moderate to severe in intensity and considered to be unrelated to the study interventions. Subjects recovered within 2 to 6 days without dose change in intervention. There were no AESIs in the LTE period.

Treatment Emergent Adverse Events and Adverse Reactions

<u>Part 1, Through Week 16:</u>
Through the 16-week, randomized, placebo and active comparator-controlled period, 12.2% of subjects in the guselkumab group, 26.9% of subjects in the etanercept group, and 20% of subjects in the placebo group experienced at least 1 TEAE considered related to the study intervention; see table below. The System Organ Class (SOC) with the most subjects affected by 1 or more related TEAEs was infections and infestations; the most common related AE in this SOC was nasopharyngitis.

Table 6 Subjects with Treatment-Emergent Adverse Events with Frequency of at Least 5% in Any Treatment Group Through Week 16 by System Organ Class and Preferred Term (Part 1)

	Placebo	Guselkumab	Etanercept

Analysis set (N)	25	41	26
Avg duration of follow up (weeks)	16.3	16.4	16.1
Avg exposure (# of administrations)	2.9	3	14.9
Subjects with ≥1 AEs	17 (68%)	17 (41.5%)	15 (57.7%)
System Organ Class (SOC) *Preferred Term*			
Infections and Infestations *Nasopharyngitis* *Upper respiratory Tract Infection* *Bronchitis*	10 (40%) 7 (28%) 2 (8%) 0	12 (29.3%) 5 (12.2%) 4 (9.8%) 0	10 (38.5%) 3 (11.5%) 2 (7.7%) 2 (7.7%)
Nervous System Disorders *Headache*	0 0	3 (7.3%) 3 (7.3%)	1 (3.8%) 1 (3.8%)
General Disorders/Administration Site Conditions *Fatigue*	2 (8%) 0	1 (2.4%) 0	4 (15.4%) 2 (7.7%)
Musculoskeletal and Connective Tissue Disorders *Arthralgia*	0 0	1 (2.4%) 0	3 (11.5%) 2 (7.7%)

Adapted from Applicant's Week 52 CSR for Study CNTO1959PSO3011, page 82, Table 19

Through the 16-week, randomized, placebo and active comparator-controlled period, 12.2% of subjects in the guselkumab group, 26.9% of subjects in the etanercept group, and 20% of subjects in the placebo group experienced at least 1 TEAE considered related to the study intervention.

Part 1, Through Week 52:

Through Week 52, the proportion of subjects treated with guselkumab experiencing 1 or more AEs was 72.1% in the combined guselkumab group (guselkumab group: 80.5%, etanercept → guselkumab group: 59.1%, and placebo → guselkumab group: 69.6%). The most frequently occurring AE by SOC and PT remained infections and infestations, similar to Part 1 through Week 16, and included nasopharyngitis in 27.9% of the combined guselkumab group (guselkumab group: 29.3%, etanercept → guselkumab group: 18.2%, and placebo → guselkumab group: 34.8%).

Through Week 52, the proportion of subjects experiencing 1 or more TEAEs was 22.1% in the combined guselkumab group (guselkumab group: 24.4%, etanercept → guselkumab group: 22.7%, and placebo → guselkumab group: 17.4%).

Table 7 Subjects with Treatment-Emergent Adverse Events with Frequency of at Least 5% in Any Treatment Group Through Week 52 by System Organ Class and Preferred Term (Part 1)

	Placebo→ Guselkumab	Guselkumab	Etanercept→ Guselkumab	Total
Analysis set (N)	23	41	22	86
Avg duration of follow up (weeks)	33.61	50.14	31.74	41.01
Avg exposure (# of administrations)	4.70	4.78	4.95	4.80
Subjects with ≥1 AEs	16 (69.6%)	33 (80.5%)	13 (59.1%)	62 (72.1%)
System Organ Class (SOC) *Preferred Term*				

Infections and Infestations	12 (52.2%)	25 (61.0%)	12 (54.4%)	49 (57.0%)
Nasopharyngitis	8 (34.8%)	12 (29.3%)	4 (18.2%)	24 (27.9%)
URI	0	8 (19.5%)	3 (13.6%)	11 (12.8%)
Pharyngitis	1 (4.3%)	3 (7.3%)	1 (4.5%)	5 (5.8%)
Gastroenteritis	0	1 (2.4%)	2 (9.1%)	3 (3.5%)
Nervous System Disorders	2 (8.7%)	6 (14.6%)	2 (9.1%)	10 (11.6%)
Headache	2 (8.7%)	6 (14.6%)	2 (9.1%)	10 (11.6%)
Gastrointestinal Disorders	0	6 (14.6%)	2 (9.1%)	8 (9.3%)
Abdominal pain	0	3 (7.3%)	0	3 (3.5%)
Skin and subcutaneous tissue disorders	1 (4.3%)	5 (12.2%)	1 (4.5%)	7 (8.1%)
Acne	0	3 (7.3%)	0	3 (3.5%)

Adapted from Applicant's Week 52 CSR for Study CNTO1959PSO3011, Appendix 19, page 385, Table TSFAE31

The type and frequency of AEs in subjects < 12 years old was similar to those 12 years and older, with nasopharyngitis, upper respiratory tract infection (URI), and headache being the most common AEs in both age cohorts, and in both age cohorts, the proportion of subjects experiencing an AE was similar across the etanercept → guselkumab group and the placebo → guselkumab group.

No adverse drug reactions (ADRs) (no anaphylactic and no serum-sickness-like reactions) were identified in the main study, nor in the 120-Day Safety Update report.

Laboratory Findings

In general, there were no trends of abnormal laboratory values noted and no drug-induced liver injuries in the main study, nor in the 120-Day Safety Update report.

Hematology

In Part 1, through Week 16, there were no laboratory values of CTCAE ≥2 in the guselkumab group, and there were no laboratory values with CTCAE toxicity Grade ≥3 through Week 16. In Part 1 and 2 through Week 52, analysis of absolute values and changes from baseline by visit through Week 52 did not reveal a pattern suggesting a meaningful effect of guselkumab on any of the hematological parameters evaluated. Abnormal hematological laboratory abnormalities were rare, transient, and rates of abnormal laboratory values were low.

Chemistry

In Part 1, through Week 16, analysis showed minimal mean changes from baseline for all parameters in all treatment groups at all timepoints. Abnormal chemistry laboratory assessments with CTCAE toxicity grade ≥2 did occur, but rates were low through Week 16; 3 (7.3%) subjects in the guselkumab group had CTCAE Grade ≥2 values of increased bilirubin. One (2.4%) of 24 subjects in the etanercept group has an ALT ≥2 to <3 x ULN but did not meet criteria for a potential Hy's Law case. No cases of potential Hy's law of potential cholestatic liver injury were observed in any treatment group.

In Part 1 and 2, through Week 52, analyses did not reveal a pattern suggesting a meaningful effect of guselkumab on any of the laboratory parameters evaluated. Occurrence of markedly abnormal laboratory values remained low; there were a total of 6 cases with CTCAE Grade 2 neutropenia, 7 cases of CTCAE Grade 2 elevated bilirubin, 1 case of CTCAE Grade 3 elevated AST, and no instances of CTCAE Grade 2 ALT. The subject with Grade 3 AST also had an AE for increased ALT, which was nonserious, moderated, and resolved. There was 1 non serious AE of anemia, which was moderate, resolved, and considered unrelated to study intervention.

Vital Signs

Vital signs were assessed at all visits. There were no trends of abnormal vital signs noted in the main study, nor in the 120-Day Safety Update report.

Electrocardiograms (ECGs)

Not assessed

QT

Not assessed

8.2.3. Analysis of Submission-Specific Safety Issues

Refer to Section 8.2.2. Safety Results/Significant Adverse Events.

8.2.4. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No events of malignancy were observed in PROTOSTAR.

Human Reproduction and Pregnancy

No subjects discontinued from the study through Part 1 (through Week 16) due to pregnancy. Through Week 52, there was 1 maternal pregnancy in the guselkumab group. This subject was withdrawn from treatment and discontinued the study because of the pregnancy. Pregnancy was carried to full term without concerns and delivery resulted in a healthy newborn.

Pediatrics and Assessment of Effects on Growth

No abnormalities in growth, development, and sexual maturation were observed throughout the study period.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No new information regarding overdose, drug abuse potential, and withdrawal and rebound was submitted in this supplement.

8.2.5. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A 120-Day Safety Update report (DSUR) was submitted to the Agency on March 26, 2025. Data from this DSUR does not change the previous assessment of the safety of guselkumab of the safety of guselkumab in pediatric subjects with moderate to severe plaque PsO. Since the sBLA submission, additional data provided an additional total of 194 subject-years of follow up. During the reporting period of this DSUR, there was a low proportion of subjects reporting SAEs (all 4 reported SAEs were considered unrelated to study intervention and self-resolved within several days), there were no cases of active TB, opportunistic infections, or malignancies, there were no deaths, no pregnancies, no drug reactions, no LFT elevations, no thrombotic events, no severe depressive or suicidal ideation events, and no AEs leading to discontinuation.

Expectations on Safety in the Postmarket Setting

Postmarketing information has been accruing since the first approval of guselkumab for the treatment of adults with moderate to severe plaque psoriasis by the FDA on July 13, 2017. The estimated cumulative global exposure to guselkumab from launch through June 2024 was (b) (4) person-years. No new ADR's have been recently identified based on postmarketing data.

8.3. Integrated Assessment of Safety

The safety profile of guselkumab has largely been informed by large clinical trials in adult PsO and adult PsA; to date, an estimated 12, 890 subjects have been exposed to guselkumab in the clinical development program. Important identified risks of guselkumab are hypersensitivity reactions, infections, tuberculosis, and hepatotoxicity.

The pediatric safety profile of SC guselkumab is informed by subjects aged 6 to 17 years in the PROTOSTAR study through Week 52 and overall, SC guselkumab in this pediatric population demonstrated an acceptable safety profile consistent with the known safety profile of guselkumab in adult PsA and PsO. No new safety issues were identified relative to the safety profile in adults with PsO though the comparable placebo-controlled period (16 weeks) and over 1 year, compared to adult studies CNTO1959PSO3001 and CNTO1959PSO3002. Post-marketing data does not reveal any new safety signals; however, post-marketing data for pediatric patients is limited.

Although the Applicant's position is that it is reasonable to consider the use of SC guselkumab in JPsA patients 5 years and above as no difference has been found in immune system development between age 5 and 6 years old, and guselkumab exposures are predicted to be

similar in these age groups, guselkumab will not be approved for age 5 years old given that there is no safety data in this age group in any available study in a relevant patient population.

In conclusion, based on the data provided, it is reasonable to leverage the safety data from PROTOSTAR in the treatment of pediatric patients with PsO is relevant for JPsA as they are closely related diseases, and no new or unexpected safety signals were identified on review of the cumulative safety data from PROTOSTAR or from the DSUR sent subsequently. The safety data for the 3 subjects in PROTOSTAR with a diagnosis of JPsA was consistent with the overall safety profile of pediatric PsO subjects. Updates to the existing Warnings and Precautions include language to monitor liver enzymes for all patients on guselkumab, rather than only inflammatory bowel disease patients on guselkumab. No other updates of the existing Warning and Precautions in the current guselkumab USPI are warranted, and no additional post-marketing safety studies are necessary in pediatric patients ≥40 kg with JPsA based on this submission.

8.4. Conclusions and Recommendations

The recommended regulatory action is approval for SC guselkumab via the previously approved prefilled syringe dosage form, the OnePress, and the TREMFYA Pen for the treatment of children ages 6 years and older and also weighing ≥40kg with juvenile psoriatic arthritis.

The effectiveness of SC guselkumab is based on PK matching in pediatric and adult subjects with active PsA, which permitted extrapolation of efficacy of guselkumab from adults with active PsA. The guselkumab studies in adult PsO and PsA are adequate and well-controlled clinical trials that have been previously reviewed and supported the approval of SC guselkumab for these indications. As discussed above in Section 5, the clinical pharmacology review team agreed with the established PK-bridge between adult PsA and JPsA patients. Given that the etiology, pathophysiology, and disease manifestations are highly similar in children and adults with PsA, it is scientifically justified to extrapolate the efficacy established in adult PsA for the SC guselkumab formulation to pediatric patients with JPsA.

The safety of SC guselkumab in JPsA patients was leveraged from safety in pediatric PsO, a population relevant to JPsA since disease manifestations are highly similar. In addition, the safety of SC guselkumab has been established in adult PsO and PsA trials and has demonstrated an acceptable safety profile. Data from the pediatric PROTOSTAR study has been reviewed in this submission and does not demonstrate any new or unexpected safety signals. Additional supportive data from post-marketing data in adult studies and from PROTOSTAR's long-term extension has not revealed any new safety signals.

The Applicant has provided adequate data and information to inform the benefit-risk assessment of SC guselkumab administered at a dose of 100 mg/dose via prefilled syringe, OnePress, or Tremfya Pen every 8 weeks for the treatment of JPsA in patients 6 years of age and older and weighing ≥40 kg and to therefore approve supplement 029.

The data submitted to this sBLA 761061/S-029 are inadequate to fully fulfill PREA PMR 3899-1; this submission partially fulfills PMR 3899-1, as the required study has been conducted and submitted, but the Applicant has not developed a suitable dose strength and dosing regimen for delivery of guselkumab to pediatric patients weighing <40 kg. A deferral extension to the existing PMR is granted to allow further development of a suitable dose strength and dosing regimen for pediatric patients weighing less than 40 kg; refer to Section 10 below for details of PMR.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened for BLA 761061/S-028; no issues were identified warranting advisory committee input.

10 Pediatrics

In the approval letter for adult patients with PsA (dated July 13, 2020), the Agency required the Applicant to provide assessment of SC guselkumab for patients 5 to 17 years of age with JPsA based on extrapolation, due by April 2024.

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

- Study/Trial Completion: 10/2023
- Final Report: April 2024

In November 2022, following approval of guselkumab for the treatment of adult psoriatic arthritis in 2020, the Applicant submitted an initial Pediatric Study Plan (iPsP) under IND 124177. On review of this iPsP, which requested a waiver for the study of guselkumab in pediatric patients <6 years of age with JPsA and a deferral of the required pediatric assessment until the time of the submission of the adult sBLA, the Agency commented that there was insufficient information about efficacy or safety of (b) (4) dosing in adults with PsA to determine appropriate pediatric assessment. If the benefit-risk assessment in adults was found to be favorable, a PK-based approach to support extrapolation of efficacy would be reasonable. Additionally, the Applicant would need to provide support for safety of guselkumab dose (b) (4) in the pediatric population, which could be demonstrated by a PK and safety study in JPsA patients or safety data of similar dose/exposure in another pediatric population of the same age range with adequate justification of the relevance of the patient population to JPsA. The Agency also recommended revising the initial plan to request a waiver for patient 0 to 5 years, rather than 0 to 6 years, to align with age ranges previously waived for this product and population. This led to an agreed iPsP for SC guselkumab (March 20, 3023), comprising of a deferral of the pediatric assessment and justifications for a potential reliance on a PK-based extrapolation approach after completion of the adult studies in PsA, as well as a waiver request for ages 0 to 5 years.

On June 29, 2023, the Applicant requested a deferral extension to the pediatric final report submission date for PMR 3899-1 (initial Study completion date was October 2023). Rationale for the deferral extension request was that as agreed in the Agency's July 2, 2020 communication, the required PK and safety information could be supported based on information of disease similarity between adult and juvenile psoriatic arthritis, justification that PK would be similar in pediatric psoriasis and JPsA, rationale for PK bridging between adult PsA and JPsA, and justification of relevance of PK and safety data from pediatric PsO to JPsA. The extrapolation-based approach described above would be supported by completed and ongoing adult PsA studies, as well as data from a completed pediatric study of guselkumab in pediatric psoriasis (CNTO1959PSO3011). PMR timelines were aligned with the timeline of the PREA PMR for pediatric plaque psoriasis PMR 3225-1; study CNTO1959PSO3011 under IND 105004).

Despite efforts to increase enrollment into this study, actual enrolment averaged below initial projections. The last safety follow-up visit for the last participant was anticipated to occur in June 2024, and therefore the Applicant requested extension of both the pediatric PsO and JPsA PMR's. The new proposed final report submission date, December 2024, was accepted by the Agency.

With this current submission, the required study has been completed and submitted prior to the deadline. However, the PMR is only partially fulfilled since the Applicant has not developed a suitable presentation for delivery of guselkumab to patients weighing <40 kg. On August 8, 2025, the Sponsor submitted a proposal (b) (4)

On September 18, 2025, the Agency communicated to the Applicant that the PMR for psoriatic arthritis was partially fulfilled because the trial was conducted; however, the assessment was not completed. To complete the assessment, an age-appropriate formulation/presentation for use in the pediatric population ages 6 to 17 years old who weigh less than 40 kg. A deferral extension was granted to July 2027 in order to fulfill the PMR.

On September 23, 2026, the Applicant responded and accepted the Agency's proposed deferral extension date of July 27, contingent on the Agency's concurrence with the proposal submitted on August 8, 2025. The Agency does not provide concurrence with the proposed (b) (4)

In summary, a deferral extension is granted to the existing PMR to allow time for development of an age-appropriate formulation/presentation for use in the pediatric population ages 6 to 17 years who weigh less than 40 kg. The deferral extension is granted to July 2027.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The following is a high-level summary for the product label changes based on review of the data submitted in support of this applications, as well as major editorial changes to update the content and format of the guselkumab label.

1. Throughout USPI
    a. Because guselkumab is now indicated for pediatric and adult indications, the Agency recommended clarifying in section headings and table titles whether the information pertains to adult or pediatric studies.
    b. The terms "trial" and "study" are used in labeling. Recommended utilizing "trial" throughout the label for consistency.
    c. Minor revisions to tables for clarity
2. Indications and Usage in Highlights and Section 1
    a. Revised language to include new indications for pediatric psoriasis patients and juvenile psoriatic arthritis patients 6 years of age and older and also weighing ≥40kg:
    TREMFYA is an interleukin-23 antagonist indicated for the treatment of:
        - *Adults and pediatric patients (6 years and older who also weigh at least 40kg) with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy*
        - *Adults and pediatric patients (6 years and older who also weigh at least 40kg) with active psoriatic arthritis*
3. Section 2 Dosage and Administration
    a. Under Section 2.1, Recommended Evaluations and Immunizations Prior to Treatment Initiation, language added that states, "*For the treatment of plaque psoriasis or psoriatic arthritis, if clinically indicated, evaluate liver enzymes and bilirubin prior to initiating treatment with TREMFYA*."
    b. Language added to specify that administration in pediatric PsO and JPsA patients 6 years of age and older and weighing at least 40kg is to be done using the 1mL prefilled syringe, One-Press injector, or prefilled TREMFYA pen.
    c. Language added to clarify that TREMFYA is not intended for pediatric self-administration using any of the presentations and that pediatric patients can inject into the front of the thighs or the lower abdomen except for the 2 inches around the navel. For the PFS only, injection can be given in the back of the upper arms.
    d. Multiple revisions throughout to improve readability and organization
        i. Passive voice changed to active voice
        ii. Revisions of subheadings to separate adult and pediatric information
4. Section 5 Warnings and Precautions

   a. In subsection 5.4 Hepatotoxicity, (b) (4) . Language added to instruct providers to assess liver enzymes and bilirubin in patients with plaque psoriasis and psoriatic arthritis at baseline and periodically thereafter according to routine patient management. Language also added to instruct providers to interrupt TRMFYA if treatment-related increases in liver enzymes occur or drug-induced liver injury is suspected.

5. Section 5 Adverse Reactions
   a. Under Section 5.4, language added stating that in patients with plaque psoriasis or psoriatic arthritis, if clinically indicated, evaluate liver enzymes and bilirubin at baseline and periodically thereafter according to routine patient management
   b. Editorial changes made to clarify adult versus pediatric data and clarify titles of tables
   c. Under subsection 6.1 Clinical Trial Experience, heading 'Adverse Reactions in Pediatric Subjects with Plaque Psoriasis' added and safety information pertaining to study CNTO1959PSO3011 (referred to as PsO5 in labeling) detailed.
6. Section 8 Use in Specific Populations
   a. Under subsection 8.4 Pediatric Use, new headings 'Plaque Psoriasis' and 'Psoriatic Arthritis' added to reflect that the safety and effectiveness of TREMFYA in the treatment of moderate to severe plaque psoriasis has been established in patients 6 years and older and also weighing least 40kg and to reflect that efficacy of TRAMFYA in JPsA patients has been extrapolated from adult psoriasis, adult psoriatic arthritis, and pediatric psoriasis.
   b. Additionally, language added to reflect that safety in the JPsA population is leveraged from pediatric psoriasis patients and the systemic exposure of TRMFYA is expected to be comparable between adult and pediatric patients with psoriatic arthritis.
7. Section 12 Clinical Pharmacology
   a. Under subsection 'Specific Populations', added further subsection of 'Pediatric Subjects' and added to language to observed guselkumab trough concentrations in pediatric subjects 6 years of age and older and weighing at least 40 kg.
8. Section 14 Clinical Studies
   a. Subheading 'Pediatric Subjects with Moderate to Severe Plaque Psoriasis' added
      i. Results of Trial PsO5 detailed under this subheading

<u>Medication Guide:</u>

1. <u>Under the section "What is the most important information I should know about TREMFYA?", the Applicant has added language that states, under subsection "liver problems", that with the treatment of plaque psoriasis or psoriatic arthritis, the healthcare provider may do blood tests to check the liver before and during treatment with TREMFYA.</u>
2. The Applicant proposed to revise the statements in the "What is TREMFYA?" section by adding new indications (adults and children 6 years of age and older who also weigh at least 40 kg with moderate to severe plaque psoriasis who may benefit from taking

injections or pills (systemic therapy) or phototherapy and adults and children 6 years of age and older who also weigh at least 40kg with active psoriatic arthritis). Modifications also made to the statement 'it is not known if TREMFYA is safe and effective in children under 18 years of age' to the following:

- *It is not known if TREMFYA is safe and effective in children under 18 years of age with ulcerative colitis or Crohn's disease or in children under 6 years of age with plaque psoriasis or in children under 6 years of age with psoriatic arthritis.*

The Agency agreed with this revision.

3. Under the section "Before using TREMFYA, tell your healthcare provider about all your medical conditions, including if you:", language added to clarify that children should be brought up to date with all vaccines before starting TREMFYA.
4. Under section 'How should I use TREMFYA?", language added to clarify that adults or children with plaque psoriasis or psoriatic arthritis 6 years of age and older who also weigh at least 88 pounds (40kg) will receive TREMFYA as an injection under the skin (subcutaneous injection).
5. New heading created: "How will my child receive TREMFYA?"
    a. Under this new heading, language added to clarify that TREMFYA will be administered as a subcutaneous injection using the TREMFYA prefilled syringe, One-Press injector, or Prefilled pen.
    b. Language added to clarify that the child's first dose will be given by a healthcare provider and if the provider decides the parent or adult caregiver can administer TREMFYA injection at home, the parent or adult caregiver should be shown the right way to administer injections.

Other Prescription Drug Labeling
[Insert text here]

12 Risk Evaluation and Mitigation Strategies (REMS)

No new safety signals were identified as part of this review. Therefore, a REMS is not necessary to expand the current indication for SC guselkumab to include pediatric patients 6 years and older and also weighing ≥40kg with juvenile psoriatic arthritis.

13 Postmarketing Requirements and Commitment

Submission of this application was initially intended to support fulfillment PMR 3899-1; however, since (b) (4) approval for this indication supports only administration of guselkumab using the previously approved 100 mg/dose prefilled syringe, One-Press injector, and TREMFYA prefilled pen in patients with JPsA weighing ≥40 kg. Additional presentations will be needed to support younger age groups and to fulfill PMR 3899-1. A deferral extension to the currently existing PMR is granted to allow the Applicant to develop a suitable presentation for administration of guselkumab in patients weighing <40 kg; the deferral extension is granted to July 2027

14 Division Director (Clinical) Comments

I agree with the review team's assessment of the data submitted, the benefit-risk assessment, and the conclusions regarding the data supporting the recommended regulatory actions.

15 Appendices

15.1. References

Brunello F, Tirelli F, Pegoraro L, Dell'Apa F, et al., 2022, New insights on juvenile psoriatic arthritis. Front Pediatr, 10:884727.

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Zisman D, Gladman D, Stoll M, et al., 2017, The juvenile psoriatic arthritis cohort in the CARRA Registry: Clinical characteristics, classification, and outcomes, J Rheum, 44(3)342-351.

15.2. 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)."

Covered Clinical Study (Name and/or Number): CNTO1959PSO3011

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from Applicant)
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Pharmacometrics Review

Executive Summary

The Applicant submitted a supplemental BLA for guselkumab, a fully human IgG1λ mAb that inhibits IL-23-specific intracellular signaling and subsequent activation and cytokine production, for the treatment of pediatric patients with active psoriatic arthritis (PsA). Due to the rarity of PsA in pediatrics, the Applicant relied on an extrapolation approach, supported by evidence demonstrating:

1. Disease similarities between PsO and PsA, between adults with PsO and pediatric patients with PsO, and between adults with PsA and pediatric patients with jPsA;
2. Comparable systemic exposure of guselkumab in adults with PsO and adults with PsA;
3. Similar systemic exposure and exposure–response (E-R) relationships in adults with PsO and pediatric patients with PsO; and
4. Comparable systemic exposure in adults with PsA and pediatric patients with PsO, including those with jPsA.

Collectively, findings from the guselkumab pediatric programs (pediatric PsO and jPsA) suggest that the efficacy and safety of guselkumab in jPsA patients are expected to be consistent with those observed in adults with PsA.

Key pharmacometrics findings from this supplemental BLA:

Population PK (PopPK) analysis

The updated PopPK model, supported by diagnostic plots and pcVPC results, is robust and reliably predicts guselkumab exposures across the full body weight range in both pediatric and adult populations.

Exposure-Response Analysis

Overall, similar relationships between systemic guselkumab exposure and clinical efficacy were observed across Phase 3 studies in pediatric and adult participants with PsO. The comparability of exposure and efficacy responses between the pediatric dose and the fixed 100 mg adult dose confirms the similarity of the guselkumab E-R relationship between adult and pediatric populations.

15.3.2. **Population PK (PopPK) analysis**

Dataset and Demographics

The PopPK analysis of guselkumab in participants with plaque PsO used data from pediatric study CNTO1959PSO3011 and adult studies CNTO1959PSO2001, CNTO1959PSO3001, and CNTO1959PSO3002. The final PK dataset included 13,529 measurable serum guselkumab concentrations following SC administration, from 91 pediatric participants (up to Week 44; excluding those who received etanercept) and 1,454 adult participants (up to Week 52).

PopPK Model Development

The serum concentration–time profiles of guselkumab in pediatric and adult PsO participants were well described using a re-estimated previously established adult population model: a one-compartment linear PK model with first-order absorption and elimination, with allometric components for CL/F and V/F fixed to 0.75 and 1.0, respectively.

The covariate effects of race (Caucasian versus non-Caucasian) and diabetes comorbidity on guselkumab CL/F were also retained from the previous adult model but were considered not clinically meaningful (<20% difference between the test and reference groups).

Model diagnostic plots for pediatric participants and pcVPC plots for both pediatric and adult participants show that the final PopPK model adequately describes the central tendency and variability of the pediatric and adult guselkumab PK data.

PopPK Model-Based Simulation

Simulations using the final PopPK model were conducted to evaluate the pediatric dose regimen and to assess the appropriateness of lowering the pediatric body weight cutoff for the 100 mg fixed guselkumab dose from 70 kg to 40 kg, thereby aligning more closely with the adult dosing regimen.

The simulations were performed to compare guselkumab PK concentration versus time profiles over 52 weeks and the steady-state exposure metrics (Ctrough, AUC, and Cmax) of the treatment regimens between pediatrics and adults.

Figure 7 presents boxplots of exposure metrics across pediatric body weight groups using the studied (70 kg) and proposed (40 kg) cutoffs for the 100 mg guselkumab dose. These are compared with the 90% prediction intervals of overall adult exposures (gray dashed lines) and adult participants <70 kg (blue dashed lines). Median and interquartile ranges (IQRs) of steady-state Ctrough, AUC, and Cmax for participants for both cutoff groups generally fell within the 90% prediction intervals of overall adult exposures, except for the 40–50 kg group under the 40 kg cutoff. However, the IQR of AUC and Cmax for this group remained within the 90% prediction intervals of adult participants <70 kg, which were previously shown to be safe in Studies CNTO1959PSO3001 and CNTO1959PSO3002.

The model-predicted steady-state exposures indicate that the proposed 100 mg fixed dose in pediatric participants weighing 40–70 kg results in higher exposures compared with the studied 1.3 mg/kg pediatric dose. Therefore, additional safety evidence was evaluated to support the appropriateness of switching from weight-based dosing (1.3 mg/kg) to a fixed 100 mg dose in this subgroup (see Table 8 and Table 9). When comparing observed key safety events (AEs, SAEs, infections, and AEs leading to discontinuation) between adults and pediatric participants in the 40–70 kg subgroup, the proportions were similar across both groups and comparable to placebo through Week 16. This pattern persisted through 1 year, with no notable differences in the incidence of key safety events between adults and pediatric participants in this weight range.

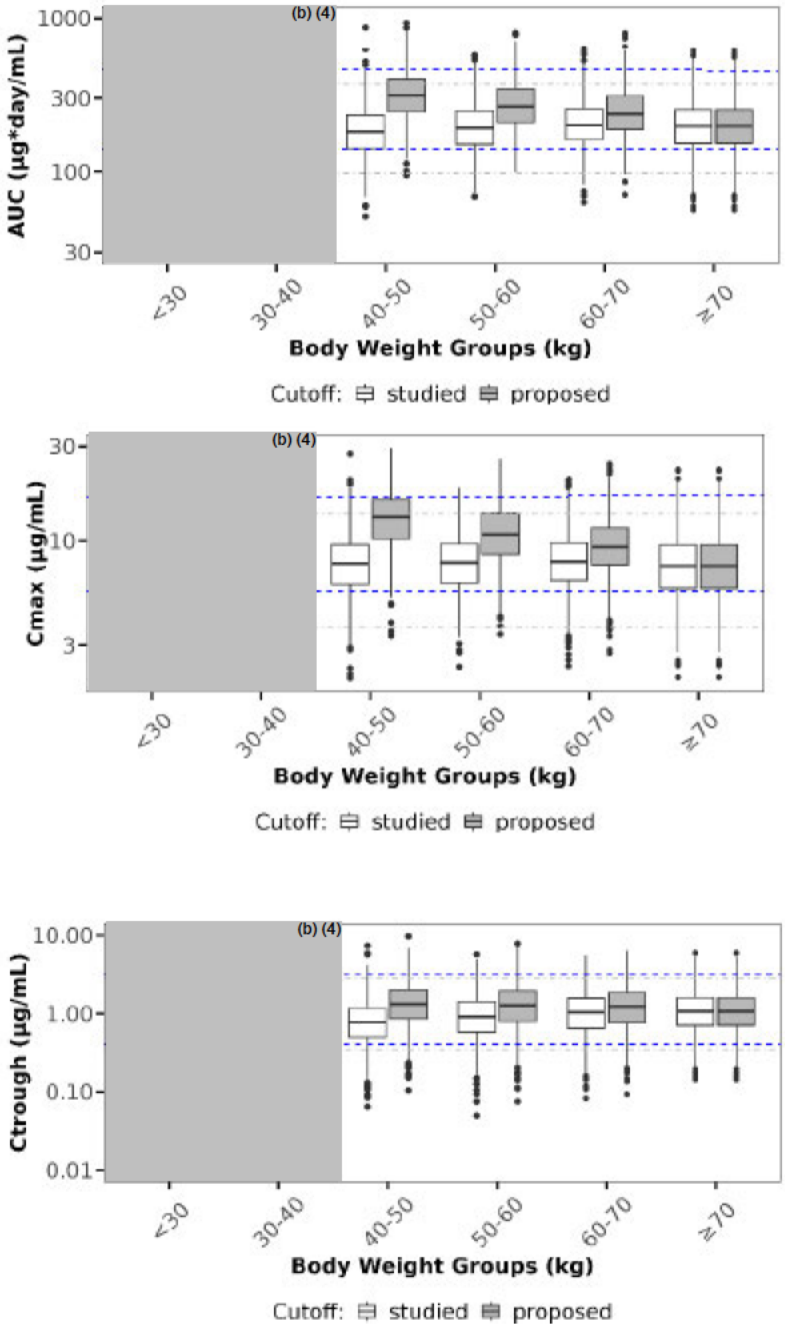
Flat versus Body-Weight Based Dosing

To address additional concerns regarding the proposed flat 100 mg dose, further simulations were conducted to evaluate the relationship between dose and systemic exposure (Figure 8). Although a 40 kg child receiving a 100 mg flat dose would nominally correspond to ~2.5 mg/kg (versus 1.3 mg/kg in the studied regimen), dose justification must be based on predicted systemic exposure rather than the arithmetic mg/kg ratio.

A population PK simulation, using a pediatric population structure consistent with CNTO1959PSO3011 and the protocol dosing schedule, compared steady-state trough concentrations (Ctrough,ss) for two regimens in 40–70 kg subjects: 1.3 mg/kg Q8W and 100 mg Q8W. The modeling incorporated allometric scaling of clearance (exponent 0.75) and volume of distribution (exponent 1.0), along with parameter estimates from the final pediatric PopPK model.

Under these conditions, the worst-case scenario for a pediatric at 40 kg demonstrated that the predicted steady-state exposure with the flat 100 mg dose does not approach a twofold increase relative to the 1.3 mg/kg regimen, but rather remains within approximately 1.5-fold of adult exposures observed at the approved dose. This outcome is consistent with pharmacologic principles, as systemic exposure is determined by both dose and clearance and clearance does not scale linearly with body weight.

Figure 7. Comparison of Model-predicted Steady-state PK Exposure Metrics for Pediatrics Using Either a 70kg or 40kg Cutoff for the 100 mg Guselkumab Dose, by Body Weight Groups, Semi-log Plot



Source: Adapted from Figure E5. Population Pharmacokinetics and Exposure-Response Report

Table 8. Safety Events Summary Through Week 16 Among Subjects with Baseline Weight Between 40 - <70 Kg in Studies: CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002

	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%)

Source: Table 3. IR Response Dated 02 June 2025

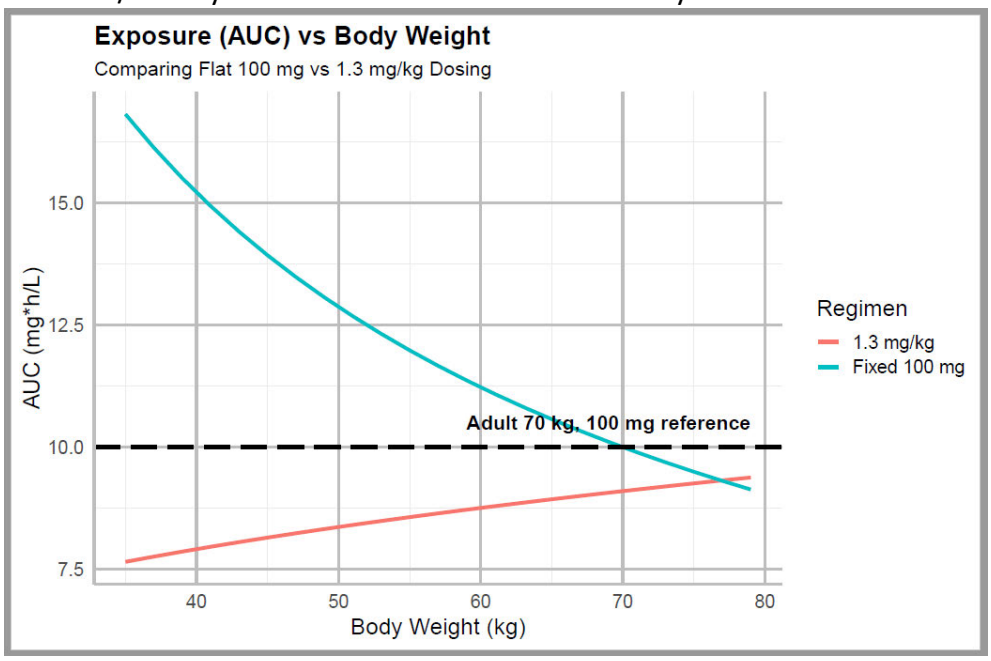
Table 9. Safety Events Summary Through 1 Year Among Subjects with Baseline Weight Between 40 - <70 Kg in Studies: CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002

	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.

Source: Table 4. IR Response Dated 02 June 2025

Figure 8. Simulated Steady-State AUC vs Body Weight for Fixed 100 mg and 1.3 mg/kg Dosing Regimens.



Source: Reviewer's analysis

15.3.3. Exposure-Response evaluation

Dataset

A total of 1,266 participants with Week 16 PASI and IGA scores were included in the final graphical E-R analysis dataset, including 25 pediatric participants treated with placebo and 41 pediatric participants (≥6 to <18 years of age) treated with guselkumab from Study CNTO1959PSO3011 Part 1, and 397 adult participants treated with placebo and 803 adult participants treated with guselkumab from the adult Phase 3 studies.

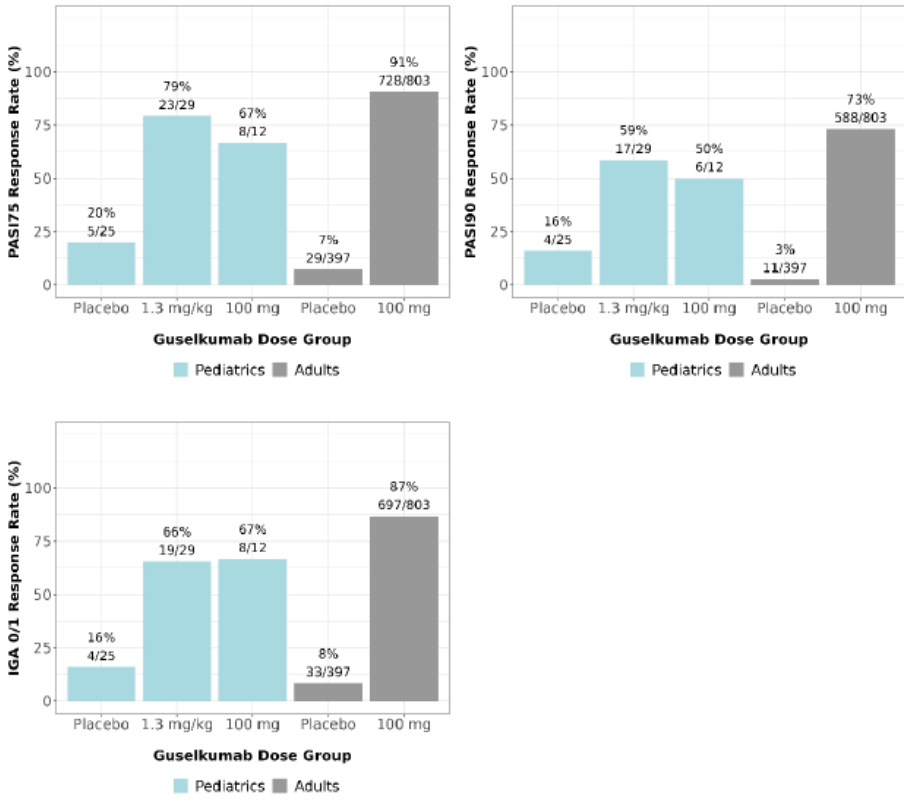
Exposure-Response comparison

Graphical evaluation of the response rate across pediatric body weight dose groups (based on the body weight cutoff of 70 kg) was performed with data from Part 1 of Study CNTO1959PSO3011 for key efficacy endpoints at Week 16 and compared with the adult data from the 2 Phase 3 studies (Figure 9).

Conclusion

Overall, the Phase 3 studies demonstrated generally similar relationships between systemic exposure to guselkumab and clinical efficacy in both pediatric and adult participants with PsO. The comparable exposure and efficacy responses observed with the pediatric dose and the adult fixed 100 mg dose further support the similarity of the guselkumab exposure–response relationship across adult and pediatric populations.

Figure 9. Proportion of Participant Responders Across Dose Regimens Between Pediatric (CNTO1959PSO3011) and Adult Participants at Week 16



Source: Figure E7. Population Pharmacokinetics and Exposure-Response Report

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