16 October 2025
EMADOC-1700519818-2583818
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tremfya

International non-proprietary name: guselkumab

Procedure No. EMA/X/0000248626

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti drug antibodies
ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANOVA	analysis of variance
AUC	area under the serum concentration versus time curve
AUCweek0-16	area under the serum concentration versus time curve from Week 0 to 16
BMI	body mass index
BSA	% body surface area involvement
CCI	Container closure integrity
CD	Crohn's disease
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CL/F	apparent clearance
Cmax	maximum serum concentration
COVID-19	SARS-CoV-2, coronavirus disease-19
CPP	Critical process parameter
CRT	Controlled room temperature
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	trough serum concentration
CV	cardiovascular
DBL	database lock
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DS	Drug substance
DP	Drug product
DT-EIA	terminology used in the CNTO1959PSO3011 CSR for revised drug-tolerant ADA ECLIA method
ECLIA	electrochemiluminescent immunoassay
eCRF	electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EIA	terminology used in the CNTO1959PSO3011 CSR for initial ADA ECLIA method
E-R	exposure-response
FDLQI	Family Dermatology Life Quality Index
FOIA	Freedom of Information Act
FVP	Final vialled product
HF	Human Factors
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ICE	intercurrent event
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IGA	Investigator's Global Assessment
IgG1λ	immunoglobulin G1 lambda
IL	interleukin
IPC	In-process control
IQ	interquartile
ISR	injection site reaction
IV	intravenous
jPsA	juvenile psoriatic arthritis

KPR	Key product requirement
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MSD	Meso Scale Discovery
NAb	neutralizing antibody
NHANES	National Health and Nutrition Examination Survey
NMSC	non-melanoma skin cancer
NONMEM	nonlinear mixed-effects modeling
NR	not reported
PASI	Psoriasis Area and Severity Index
pcVPC	prediction-corrected visual predictive checks
PD	pharmacodynamic(s)
PFS	prefilled syringe
PFS-U	prefilled syringe fitted with the UltraSafe Plus™ Passive Needle Guard device or prefilled syringe with an UltraSafe Passive® Needle Guard
PFS-V	Prefilled syringe assembled with the VarioJect device
PK	pharmacokinetic(s)
PopPK	population pharmacokinetic(s)
PRO	patient-reported outcome
PsA	psoriatic arthritis
PsO	psoriasis
PSSD	Psoriasis Symptom and Sign Diary
PT	preferred term
PUVA	psoralen plus ultraviolet light A
PY	Patient-year
QA	Quality attribute
q12w	every 12 weeks
q2w	every 2 weeks
q8w	every 8 weeks
q2w	every 2 weeks
QoL	quality of life
q.s.	Quantum satis (as much as may suffice)
RSE	relative standard error
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SBAAM	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SC	subcutaneous(ly)
SD	standard deviation
SIB	Suicidal Ideation and Behavior
SOC	System Organ Class
ss-IGA	scalp specific Investigator's Global Assessment
TB	tuberculosis
TEAE	treatment-emergent adverse events
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
URTI	upper respiratory tract infection
USA	United States of America
UVB	ultraviolet light B
Varioject pen	prefilled syringe with a Varioject Variable Dose Injector (also: adjustable dose Varioject pen)
V/F	apparent volume of distribution
VTE	venous thromboembolism

1. Background information on the procedure

1.1. Submission of the dossier

Janssen Cilag International submitted on 3 February 2025 an application for a group of variations and extension application for the following variation(s):

Variation(s) requested	Type
C.I.6.a - Change to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 45 mg /0.45 mL grouped with an extension of indication (C.I.6.a) to include treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy based on results from study CNTO1959PSO3011. This is a Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Paediatric Participants (≥6 To <18 Years of Age). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 10.3 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0346/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0346/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0346/2023.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, Janssen Cilag International did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Scientific advice

Janssen Cilag International did not seek scientific advice at the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Beata Maria Jakline Ullrich

The application was received by the EMA on	3 February 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 May 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 May 2025
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	28 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to Janssen Cilag International during the meeting on	19 June 2025
Janssen Cilag International submitted the responses to the CHMP consolidated List of Questions on	15 August 2025
The CHMP Rapporteur circulated the CHMP Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 September 2025
The PRAC Rapporteur circulated the PRAC assessment report on the responses to the List of Questions to all CHMP and PRAC members on	19 September 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 October 2025
The CHMP Rapporteur circulated the updated CHMP Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	10 October 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tremfya on	16 October 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Psoriasis (PsO) is a chronic, non-communicable, painful, immunologically mediated, disfiguring and disabling inflammatory skin disease for which there is no cure and with a negative impact on patients' quality of life (QoL).

Studies addressing the age of onset of PsO have suggested that 2 subgroups exist: early onset disease (before 30 years of age, including paediatric onset) and late onset disease (after age 30) (Christophers

1992[1]). Generally, the clinical manifestations of plaque PsO in patients with paediatric onset and those with adult or late onset disease are similar (most frequently involved areas of the body include scalp, elbows, knees, and genitalia), and not clinically distinguishable (Lewkowicz 2004[2]; Silverberg 2009[3]). Adult and paediatric plaque PsO also share similar histological features, genetic factors, and treatment options (Bronckers 2015[4]).

2.1.2. Epidemiology

Plaque PsO affects 2 to 4% of the general population. PsO is uncommon before the age of 9 years, with a first peak of PsO generally occurring after the age of 20 with an increasing trend with age until around 60 years, after which the incidence is lower. Approximately 90% of those affected with PsO have plaque PsO, with 20% having moderate to severe plaque PsO with a body surface area (BSA) involvement of >5%.

2.1.3. Aetiology and pathogenesis

The pathogenesis of PsO involves environmental factors and immune dysregulation in genetically predisposed individuals. Substantial evidence indicates that IL-23 plays an important role in innate and adaptive immune responses and may play a pivotal role in the pathogenesis of psoriasis vulgaris.

2.1.4. Clinical presentation, diagnosis

Clinically, plaque PsO is characterised by symmetrically distributed, well-defined, sharply demarcated, indurated, erythematous plaques that are covered by friable, dry, white-silvery scale. The extent of skin involved varies among affected individuals and is a primary determinant of severity. Psoriasis typically follows a chronic relapsing and remitting course around an individual's underlying baseline severity, with flare-ups occurring spontaneously or during times of illness, or psychological stress.

Although psoriasis is rarely life-threatening, the psoriatic lesions are often on visible skin and unsightly. Patients experience shedding of scale and bleeding from their plaques as well as pain and itching. Patients with moderate to severe psoriasis often experience feelings of self-consciousness and embarrassment, and as a result, may suffer depression, social isolation, and unemployment; which contribute to a significant reduction in overall patient QoL. Hence, the disease often requires chronic treatment, particularly for patients with moderate to severe disease.

In addition to the physical and psychological impact of disease, psoriasis is associated with specific co-morbidities, including psoriatic arthritis (PsA), obesity, diabetes, cardiovascular disease, metabolic syndrome, and inflammatory bowel disease (IBD). It is estimated that between 6 and 42% of psoriasis patients develop PsA. Psoriasis has also been shown to be associated with a significantly increased risk of Crohn's disease (relative risk, 3.86, 95% confidence interval [CI] 2.23 to 6.67), which is especially pronounced among psoriatic patients with concomitant PsA (relative risk, 6.43, 95% CI 2.04 to 20.32). Psoriasis is also associated with an increased risk of occlusive vascular disease, including myocardial infarction (MI) and stroke. Multiple cardiovascular risk factors are associated with psoriasis (e.g., diabetes and obesity) and are more prevalent in severe disease, though psoriasis may also be an independent risk factor for MI. Several large epidemiologic studies have further demonstrated an association between the magnitude of cardiovascular risk and severity of psoriasis.

[1] Christophers E, Henseler T. Semin Dermatol. 1992;11(4):261-266.
[2] Lewkowicz D, Gottlieb AB. Dermatol Ther. 2004;17(15):364-375.
[3] Silverberg NB. Ther Clin Risk Manag. 2009;5:849-856
[4] Bronckers IMGJ, Paller AS, van Geel MJ, van de Kerkhof PCM, Seyger MMB. Paediatr Drugs. 2015;17:373-384

2.1.5. Management

The traditional paradigms for the treatment of PsO recommend a stepwise approach to treatment starting with topical agents, followed by phototherapy, then systemic agents.

Most commonly, a 2-tiered system is recommended, divided by patients who are candidates for localised therapy and should receive topical agents versus those who are candidates for systemic and/or photo-therapy. Patients who are candidates for systemic and/or phototherapy include those who have moderate to severe disease based on the percentage of BSA involvement and/or plaque location with associated QoL issues.

Conventional systemic therapies include methrotexate (MTX), acitretin, and cyclosporine. Although effective, each is associated with significant toxicities, particularly organ damage with long-term administration, and each agent has recommended limitations for long-term administration.

Several biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumor necrosis factor alpha (TNFα) agents, IL-12/23 antagonist, and IL-17A inhibitors. These agents are generally well-tolerated, and unlike conventional systemic agents, are not associated with cumulative toxicities that limit longer-term safety. However, as immunomodulatory agents, they have the potential to increase risk for infection and malignancy. Concerns for anti-IL-17 class agents also include Crohn's disease, neutropenia, and mucosal candida infections.

MTX is currently the most commonly used systemic treatment for paediatric PsO, but carries side effects including nausea and headache, and requires monitoring of the risk for blood, liver and renal toxicity.

Several biological agents have been approved in the EU for the treatment of PsO in the paediatric population. These approved biologic agents have been shown to be substantially better than placebo in treating children with moderate to severe PsO and are associated with a significantly greater reduction in PsO severity than non-biological system therapies (Nogueira 2021[5]). With accumulating efficacy and safety data of various classes of biologic agents in paediatric PsO patients, their use is becoming more common as first-line systemic treatment.[6] The primary risk of currently available biological treatments in children is injection site reaction and infection. Patients treated with IL-17 inhibitors may have an increased risk for IBD and candida infections (Hebert 2022[7]).

2.2. About the product

Guselkumab is a human mAb directed against the p19 subunit of IL-23 and thus, specifically targets IL-23. Literature suggests that the IL 23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune mediated diseases, including plaque PsO.

The proposed indication for guselkumab in the treatment of moderate to severe plaque PsO in paediatric patients was as follows:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

[5] Nogueira M (2021), Paller AS, Torres T. Targeted Therapy for Pediatric Psoriasis. Paediatr Drugs. 2021;23(3):203 212.
[6] https://www.guidelines.edf.one/guidelines/psoriasis-guideline
[7] Hebert AA (2022), Browning J, Kwong PC, Duarte AM, Price HN, Siegfried E. Managing pediatric psoriasis: update on treatments and challenges-a review. J Dermatolog Treat. 2022;33(5):2433-2442.

2.3. Type of Application and aspects on development

The approval of guselkumab for treatment of adults with moderate to severe plaque PsO was based on 6 clinical studies:

- 2 Phase 1 studies: CNTO1959PSO1001 and CNTO1959PSO1002
- 1 Phase 2 study: CNTO1959PSO2001 (X-PLORE)
- 3 Phase 3 studies: CNTO1959PSO3001 (VOYAGE 1), CNTO1959PSO3002 (VOYAGE 2), and CNTO1959PSO3003 (NAVIGATE)

Data from Phase 3 studies in 2,700 participants exposed to guselkumab showed a favourable safety profile as well as clinically significant improvements in participants with PsO. Efficacy and safety remained consistent through the 5-year LTEs of CNTO1959PSO3001 and CNTO1959PSO3002.

The 2 pivotal Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002 in adults with moderate to severe plaque PsO served as the primary dataset for the short and long-term efficacy and safety (through 5 years) of guselkumab in plaque PsO. Both adult studies were double-blind, placebo-controlled through Week 16, had co-primary endpoints of IGA 0/1 and PASI 90 at Week 16 (in paediatric study CNTO1959PSO3011 IGA 0/1 and PASI 75 at Week 16 were used as co-primary endpoints), and administered guselkumab SC at Week 0, Week 4, and every 8 weeks thereafter, similarly to the paediatric study CNTO1959PSO3011. This adult pivotal dataset was therefore used to compare the observed efficacy and safety results from the paediatric study CNTO1959PSO3011. In addition, withdrawal and retreatment data from the CNTO1959PSO3002 adult study provided additional supportive data for the withdrawal and retreatment data from the paediatric CNTO1959PSO3011 study.

The clinical development programme for guselkumab in paediatric PsO included 1 Phase 3 paediatric clinical study (CNTO1959PSO3011) evaluating the efficacy, safety, PK, and immunogenicity of guselkumab in the treatment of paediatric participants with moderate to severe plaque PsO.

The extrapolation of clinical efficacy and safety of guselkumab in PsO from adults to paediatric population was based on literature data which suggested that paediatric and adult plaque PsO are the same disease with a common pathobiology and underlying immunological mechanism, and that paediatric PsO represents early onset of lifelong disease.

2.4. Quality aspects

2.4.1. Introduction

In the present application a new strength (45 mg/0.45 mL) of the authorised pharmaceutical form (solution for injection) in a prefilled pen is introduced to meet the treatment requirements of the new indication: the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

The finished product is presented as a solution for injection containing 45 mg / 0.45 mL guselkumab as active substance.

Other ingredients are: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80 (PS 80), and water for injections.

The product is available in a pre-filled glass syringe assembled in a single use pre-filled pen (VarioJect) with an automatic needle guard and an adjustable dose selection plunger.

2.4.2. Active Substance

The active substance, guselkumab, is a fully human IgG1λ monoclonal antibody against IL-23. The dossier does not contain CTD module 3.2.S, as there is no change and therefore no new documentation regarding the active substance.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Guselkumab finished product for paediatric use is a sterile solution in a single-use sterile pre-filled syringe (PFS) which is assembled with a device (VarioJect) into a delivery system for subcutaneous administration. The finished product is presented as a solution for injection containing 45 mg / 0.45 mL guselkumab as active substance. Other ingredients are: Sucrose, Histidine, Histidine Monohydrochloride Monohydrate, PS 80, and water for injections. The formulation and active substance concentration is the same as previously approved 100 mg presentations. Supportive data relating to a 50 ml fill volume PFS (corresponding to the current 45 mg/0.45 ml presentation) has been provided at the time of the initial marketing authorisation application, although authorisation for such a presentation was not applied for at that time.

The composition of the 45 mg/0.45 ml presentation is shown in **Table 1**.

Table 1: The composition of the 45 mg/0.45 ml PFS

Ingredient	Reference	Function
Guselkumab	Company stand-ard	Active
Sucrose	Ph. Eur.	Stabilizer/Tonicifier
L-Histidine	Ph. Eur.	Buffer
L-Histidine Monohy-drochloride Monohy-drate	Ph. Eur.	Buffer
Polysorbate 80	Ph. Eur.	Surfactant
Water for Injections	Ph. Eur.	Solvent

The primary packaging is composed of a 1 mL syringe of Type I glass, with a staked 27G half-inch stainless steel needle, covered with a needle shield, stoppered with an elastomer plunger stopper. The PFS is assembled with a VarioJect variable dose manual injector device. VarioJect is a device designed to administer a single selected dose ranging from 10 mg to 45 mg in 5 mg increments. The primary container closure system (PFS) is the same as for already approved presentations and appropriately described in the approved CTD document. New sections are included within the present application, detailing the VarioJect device.

A major objection was raised in relation to the absence of a Notified Body opinion for the VarioJect device in the initial application. In the responses a valid Notified Body opinion was presented and the major objection was therefore considered adequately resolved.

Pharmaceutical development

There are only minor revisions in the pharmaceutical development section of the PFS.

Pharmaceutical development VarioJect: Guselkumab 45 mg/0.45 mL PFS assembled with the VarioJect device (PFS-V) is a single entity combination product that allows for administration of 1 of 8 different user-selected doses ranging from 10 mg to 45 mg in 5 mg increments. Several built-in features assist the correct use of the device: an orange priming band and the arrow as a reminder of the necessity of priming, dose selection can only happen after priming, after dose administration, the plunger locks in its down position, and the administered dose locks into the dosing notch. Furthermore, the lock safeguards against the potential for reuse/misuse of the PFS-V. After being lifted from the injection site, the needle guard passively extends and locks out, reducing the potential for accidental needle stick injury. The development of the assembly process and the process control steps are well described.

Key product requirements have been identified and the relevant control points were determined.

Product design was verified, dose accuracy was established. Test methods are described with sufficient detail.

Human Factors (HF) studies: The Applicant describes simulated studies that were conducted to assess safety and effectiveness of the combination product user interface (e.g., device, product labels, secondary packaging, instructions for use (IFU)). HF studies have been conducted, and brief summaries are provided.

During VarioJect manufacture, materials used are in compliance with or exceeding the recommendation in "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" EMEA/410/01 Rev. 3 (2011/C 73/01) and ISO 22442-1:2020. No other substances of animal origin were used in any of the materials used for the manufacture.

Prior to the assembly with the VarioJect device the finished product is sterile within the primary packaging, PFS. Container closure integrity (CCI) validation studies confirmed that the device assembly process does not compromise container closure integrity.

2.4.3.2. Manufacture of the product and process controls

PFS: There is no change in the manufacturers, batch formula, description of manufacturing process and process controls, control of critical steps and intermediates, and process validation and evaluation chapters for the PFS.

VarioJect: The manufacturing process is well described, a flow-chart of the assembly process of PFS with the VarioJect is provided. The process is fully automatised, controls are well described. Labelling and loading are automated, the secondary packaging includes a tray along with a leaflet. Storage after packaging is at 2-8 ℃.

Facilities and Equipment reports are presented.

Manufacturing process validation (PV) was performed with commercial-scale assembly runs. Conformance to acceptance criteria and critical process parameters (CPPs) were monitored, impact assessment and root cause identification were presented.

Cumulative process time at controlled room temperature (including process times for assembly, labelling and packaging) was previously validated for the PFS. No new hold time validation was necessary for the VarioJect combination product. Shipping lanes are described, validated, thermal qualification of the active shipping systems is presented with a minimum and maximum load in both winter and summer conditions. Thermal and distribution qualification is presented for the passive shipping systems with minimum and maximum configurations under summer or winter conditions. Defects are listed and risk analysis was performed. All acceptance criteria were met.

The section is sufficiently detailed and thorough. Description of manufacture, and validation of manufacture and shipping systems and transportation is accepted.

2.4.3.3. Product specification, analytical procedures, batch analysis

PFS

Release and shelf-life specifications for the 50 mg PFS have been provided**Error! Reference source not found.**. The analytical methods used for testing 50 mg PFS are the same as those approved for the 100 mg PFS. Product consistency of the 50 mg PFS was supported by a new batch analysis. The batches represented the commercial manufacturing process. All results conformed to the specifications. Justification of specifications remains unchanged.

VarioJect (PFS-V)

Release and stability specifications for the prefilled syringe (PFS) assembled with VarioJect (PFS-V) were presented. Release testing includes visual inspection, functionality testing before actuation and during/after actuation, injection force, delivered volume, needle protrusion length, cover sleeve defeat force.

Analytical procedures for the PSF-V are overall well described. Validation studies were performed. Presentation of validation studies is accepted.

Batch analysis was performed with clinical and process validation batches of the VarioJect combination product for the specifications in place at the time of analysis. PFS-V manufacturing process and controls for the batches used in validation studies are representative of the proposed commercial assembly process. All acceptance criteria were met. Therefore, it is considered proven that the manufacturing process is under control.

Justification of the functional specifications of VarioJect is provided. Specifications are consistent with current regulatory requirements.

Container closure system

The primary container closure system (PFS) is the same as for already approved presentations. The primary container closure system is assembled with the VarioJect device to form a combination product. VarioJect is a manually operated, variable dose, single use and disposable device. The combination product delivers a single selected dose as a single subcutaneous injection. Doses range from 10 mg to 45 mg in 5 mg increments. The device manufacturer provides the two VarioJect device subassemblies according to the manufacturer's component release documentation. The applicant manufactures the combination product (PFS-V) by assembling the VarioJect subassemblies with the PFS. Critical dimensions for the PFS are described in 3.2.P.7 Container Closure System, Prefilled Syringe.

The description of the combination product is sufficient. Technical drawings are provided. Components and materials of the device are provided in tabular form. Sterility is not a requirement, as the device does not come in contact with the finished product solution. Skin contact materials have been tested and no evidence of adverse effect was found. The proof of biological safety of VarioJect is accepted.

2.4.3.4. Stability of the product

At the time of the initial MAA, 24 months shelf life (at 2-8°C, protected from light) has been accepted for the PFS. This was based on the stability studies presented with the MAA application and which included data on the 50 mg PFS.

The applicant proposes 24 months shelf life for the PFS-V (at 2-8°C, protected from light) based on the established shelf life of the 50 mg PFS, and on functional and biochemical data from ongoing and completed stability studies of the PFS-V.

Stability studies have been conducted in accordance with the current ICH guidelines ICH Q1A (R2).

Stability batches and process validation PFS-V batches (all representative of the commercial combination product) were placed in the functional stability program, PV PFS-V batch was placed in the biochemical stability program.

Functional testing was performed with PFSs (0.5ml), using the validated analytical procedures and acceptance criteria at the time of testing. The functional stability testing for the stability batches is completed with 36 months of data available. All functional stability results met the stability specifications. Functional stability testing for the PV batches is completed (data available for 12 months at accelerated conditions and 24 months at the recommended storage conditions for process validation batches and post PV batch).

A biochemical stability study was conducted to demonstrate that the assembly process does not adversely impact product quality over the shelf life of the combination product. The study is completed. All results at each time point tested met the stability specifications.

The proposed shelf life of 24 months at 2-8 °C, protected from light is supported by the stability studies, and therefore considered acceptable.

2.4.3.5. Adventitious agents

Non-viral (TSE, mycoplasma, bacteria, yeast and mould) and viral adventitious agents are controlled at the active substance level. The MAH refers to the already approved documentation in relation to adventitious agents, which remains unchanged. This is acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Guselkumab finished product for paediatric use is a sterile solution with the composition of 100 mg/mL guselkumab as active substrate, Sucrose, Histidine, Histidine Monohydrochloride Monohydrate, PS80 and water for injections in a single-use sterile PFS which is assembled with a device into a delivery system. The PFS is composed of a 1-mL long Type I glass syringe with a fixed 27G half inch stainless steel needle with needle shield and an elastomer plunger stopper. The 45 mg/0.45 mL PFS is assembled with a new device, the VarioJect variable dose manual injector for subcutaneous administration.

The quality dossier is overall adequate, clear and well structured. As the formulation and the primary container closure system is identical of that of the already approved presentation, changes as compared to the previously reviewed documents are minor. An Extractable and Leachable Risk Analysis report, and a new batch analysis section has been added. The stability summary and conclusion section has also been updated. All newly presented data are accepted, there is no concern regarding the quality of the finished product.

The PSF-V combination product allows for administration of 1 of 8 different user-selected doses ranging from 10 mg to 45 mg in 5 mg increments. A major objection was raised in relation to the absence of a Notified Body opinion for the VarioJect device in the initial application. In the responses a valid Notified Body opinion was presented and the major objection was therefore considered adequately resolved. The description of the design, the built-in features that assist correct use and the safety features, such as the needle guard lock out, are sufficiently detailed. Product design was verified, and the dose accuracy was established. The biocompatibility testing identified no adverse effects.

Human Factors studies were performed to assess the safety and effectiveness of the combination product user interface to minimise user errors and ensure a safe administration of the medication.

Tremfya VarioJect combination product is manufactured and tested at a GMP certified site. Facilities and Equipment reports are presented. The manufacturing process is well described, a flow-chart of the assembly process of PFS with the VarioJect is shown. The process is fully automatised, controls and in-line tests are well described. CCI validation studies confirmed that the device assembly process does not compromise container closure integrity. No substances of animal origin were used in any of the materials used for the manufacture. During VarioJect manufacture, some of the materials used were subject to treatment for the inactivation of agents responsible for transmitting animal spongiform encephalopathy. This is acceptable. Manufacturing process validation was successfully performed with commercial scale assembly runs. Shipping lanes are described, validated, thermal qualification of the active shipping systems is presented. Batch analysis was performed for the VarioJect combination product. All acceptance criteria were met for the specifications in place at the time of analysis. Justification of the functional specifications of VarioJect is adequate, and the proposed specifications are consistent with current regulatory requirements. Skin contact materials have been tested and no evidence of adverse effect was found. The proof of biological safety of VarioJect is accepted.

The proposed shelf life for the PFS-V combination product is 24 months at 2-8 °C, protected from light. This claim is based on the established shelf life of the PFS, and on functional and biochemical data from completed stability studies of the PFS-V.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data have been submitted in this application, this was accepted by the CHMP.

2.5.2. Ecotoxicity/environmental risk assessment

Guselkumab is a monoclonal antibody and is consequently classified as a protein. Guselkumab protein does not incorporate any non-natural amino acids, and hence it is considered a natural protein expected to be readily degraded, and therefore not expected to pose a risk to the environment. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 rev.1), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment.

Consequently, no Environmental Risk Assessment studies for guselkumab are required.

2.5.3. Discussion on non-clinical aspects

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, guselkumab is not expected to pose a risk to the environment.

2.5.4. Conclusion on the non-clinical aspects

No new non-clinical were provided, which was accepted by the CHMP. Guselkumab is not expected to pose a risk to the environment. No issues were raised from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH provided a statement to the effect that clinical trials conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2: Guselkumab Plaque PsO Study in Paediatric Participants: CNTO1959PSO3011 Part 1

Study Number	Disease Population	Treatments	Randomly Assigned Treatment Group	Through Week 16				Week 16 to Week 52
				Number of Participants Evaluated for PK[a]	Age (years)[b]	Body Weight (kg)[b]	Efficacy Data Included in E-R Analysis[c]	Number of Participants Treated With Guselkumab and Evaluated for PK[a]
CNTO1959PSO3011 (PROTOSTAR) Part 1	Paediatric participants with chronic moderate to severe plaque PsO (≥6 to <18 years of age)	16-week randomly assigned, placebo- and active comparator (etanercept)-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. Treatments through Week 16: • Guselkumab (1.3 mg/kg or 100 mg) at Weeks 0, 4, and 12 (n=41) • Placebo at Weeks 0, 4, and 12 (n=25) • Etanercept (weight-based dose up to 50 mg SC) weekly through Week 15 (n=26) Treatments after Week 16: • Participants maintaining guselkumab[c]: 1.3 mg/kg or 100 mg q8w through Week 52 • Participants switching from placebo to guselkumab: 1.3 mg/kg or 100 mg at Weeks 16 and 20 followed by q8w through Week 52.	**Part 1 Overall (≥6 to <18 years of age)**					
			Guselkumab	41	14.0 (6; 17)	56.7 (26; 119)	IGA/PASI	18[d]
			Placebo	0	13.0 (7; 17)	51.1 (18; 128)	-	20
			Etanercept	0	12.5 (6; 17)	51.8 (25; 99)	-	22[e]
			Part 1a (≥12 to <18 years of age)					
			Guselkumab	31	15.0 (12; 17)	59.4 (38; 119)	IGA/PASI	13[d]
			Placebo	0	15.0 (12; 17)	59.6 (41; 128)	-	13
			Etanercept	0	14.0 (12; 17)	67.3 (45; 99)	-	13[e]
			Part 1b (≥6 to <12 years of age)					
			Guselkumab	10	9.5 (6; 11)	39.1 (26; 81)	IGA/PASI	5[d]
			Placebo	0	8.5 (7; 11)	36.8 (18; 53)	-	7
			Etanercept	0	9.5 (6; 11)	38.8 (25; 69)	-	9[e]

		• Participants switching from etanercept to guselkumab: 1.3 mg/kg or 100 mg at Weeks 20 and 24 followed by q8w through Week 48.						

E-R=exposure-response; IGA=Investigator's Global Assessment; max=maximum; min=minimum; n=number of participants; PASI=Psoriasis Area and Severity Index; PK=pharmacokinetic(s); PsO=psoriasis; q8w=every 8 weeks; SC=subcutaneous(ly).

[a] Participants were defined as evaluable if they received at least 1 dose of guselkumab and had at least 1 valid guselkumab concentration with associated sampling time and dosage information.

[b] Median (range: min; max).

[c] For Part 1 of the study, the co-primary efficacy endpoints were determined at Week 16 and are included in the E-R analysis.

[d] Participants who were PASI 90 responders withdrew from guselkumab at Week 16, per protocol.

[e] Participants who received etanercept in Part 1 through Week 16 were included in descriptive PK analysis but were not included in the PopPK analyses.

Table 3: Guselkumab Plaque PsO Study in Paediatric Participants: CNTO1959PSO3011 Part 2

Study Number	Disease Population	Treatments	Number of Participants Evaluated for PK[a]	Age (years)[b]	Body Weight (kg)[b]	Efficacy Data Included in E-R Analysis
CNTO1959PSO3011 (PROTOSTAR) Part 2	Paediatric participants with chronic moderate to severe plaque PsO (≥12 to <18 years of age)[c]	Open-label, single-arm with a continuous weight-based dose regimen of guselkumab at Weeks 0, 4, and q8w thereafter through Week 52 (N=28).	28	15.5 (12; 17)	67.6 (36.2; 122)	NA[d]

E-R=exposure-response; max=maximum; min=minimum; N=number of participants; NA=not applicable; PK=pharmacokinetic(s); PsO=psoriasis.

[a] Participants were defined as evaluable if they received at least 1 dose of guselkumab and had at least 1 valid guselkumab concentration with associated sampling time and dosage information.

[b] Median (range: min; max).

[c] Part 2 of the study only enrolled adolescent participants (≥12 to <18 years).

[d] For Part 2 of the study, efficacy evaluation responses were evaluated over time through Week 52 but are not included in the E-R analysis.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Methods

Bioanalytical methods

Serum guselkumab concentrations were determined by a validated ECLIA method on the MSD platform in studies CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002. This assay was the same as that used for the initial marketing application for PsO and the method description and validation parameters of this MSD ECLIA method were described in the initial submission. The lowest quantifiable serum concentration of the PK was 0.01 µg/mL.

PD biomarkers

No biomarkers were measured in study CNTO1959PSO3011.

Immunogenicity

MSD ECLIA Method for Detection of Antibodies to Guselkumab in Human Serum

In study CNTO1959PSO3011, 2 ECLIA methods were used to detect ADA to guselkumab. The initial and revised ECLIA methods are referred to as 'EIA method' and 'DT-EIA method', respectively.

An initial ECLIA method was validated and used in the clinical studies in support of the registration of guselkumab for the treatment of PsO and PsA in adults (including in CNTO1959PSO3001 and CNTO1959PSO3002). The observed sensitivity of this method was 3.1 ng/mL of antibodies to guselkumab in human serum that did not contain guselkumab. As validated, 15 ng/mL of antibodies to guselkumab could be detected in the presence of up to 3.13 µg/mL of guselkumab in human serum samples.

The initial method was later revised to improve drug tolerance; both the initial and revised methods were used in the paediatric PsO study (CNTO1959PSO3011). The observed sensitivity of this drug-tolerant method was 0.77 ng/mL of antibodies to guselkumab in human serum that did not contain

guselkumab. As validated, 100 ng/mL of antibodies to guselkumab could be detected in the presence of up to 1000 µg/mL of guselkumab in human serum samples.

MSD Assay for Detection of NAbs to Guselkumab in Human Serum

NAb method CP2020V-071 was used in study CNTO1959PSO3011. This method was validated to detect neutralising anti-guselkumab antibodies in human serum samples from ADA-positive participants. The drug tolerance in CP2020V-071 was 63.07 µg/mL or 125.21 µg/mL of exogenous guselkumab when 0.5 µg/mL or 1 µg/mL of the positive NAb control, CNTO4610, was present in undiluted pooled human serum. The assay could tolerate a maximum of 4.14 µg/mL of exogenous guselkumab when 1 µg/mL of the positive NAb control CNTO8820 was present in undiluted pooled human serum.

Pharmacokinetic data analysis

Noncompartmental analysis

In study CNTO1959PSO3011, serum samples were collected for guselkumab determination at weeks 0, 4, 12, 16, 20, 28, 36, 44.

PopPK Model Development

The observed serum concentration-time data of guselkumab in paediatric and adult participants with PsO were described by the re-estimated (from the adult model) 1-compartment linear PK model with first-order absorption and first-order elimination and allometric components for CL/F and V/F fixed to 0.75 and 1.0, respectively. The re-estimation was carried out using only adult data, and subsequent external validation was performed using paediatric data. To perform external validation using paediatric data alone, individual parameter estimates were obtained using NONMEM with the MAXEVAL=0 option, which allowed for Bayesian estimation without re-estimating the population parameters. Analysis models were deemed appropriate if convergence had been achieved and the standard error of parameter estimates had been obtained. Standard diagnostic plots were generated to evaluate the adequacy of the PopPK models. Plots of observed guselkumab concentrations versus population predicted and individual predicted concentrations (DV versus PRED and DV versus IPRED, respectively) were used to evaluate the appropriateness of the structural model to produce reasonable predictions. The residual error components of models were evaluated via scatter plots of weighted residuals and conditional weighted residuals versus predicted data (i.e., CWRES versus PRED). The performance of the final PopPK model was evaluated for robustness and appropriateness using conventional model convergence criteria, shrinkage, VPC, and pcVPC.

Simulation

Simulations were performed using the final PopPK model to evaluate the current study (CNTO1959PSO3011) dose regimen to assess the appropriateness of decreasing the paediatric body weight cutoff for use of the 100 mg fixed dose of guselkumab from 70 kg to 40 kg (to better align with the adult dose regimen).

Virtual paediatric patients (n=1,000/group) were created from the NHANES III database (and adjusted by 15% body weight increase, to account for higher observed body weights in paediatric PsO patients compared with children in the database). The NHANES III growth database included data from 27,489 children aged ≥6 to <18 years with body weight ranging from 6.9 to 169 kg. To create the adult virtual patients used in the simulations for comparison, body weights were sampled from the original adult PK dataset, comprising of 1,459 individuals. 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 paediatrics and adults.

Pharmacokinetics

Phase 3 Study in Paediatric Participants (⩾6 to <18 Years) (CNTO1959PSO3011)

The dose of guselkumab that participants received was based on body weight. At each dose visit, participant weight was measured and the dose of guselkumab was adjusted accordingly. Participants received 1 of the following dose levels depending on their body weight:

- Weight <70 kg: 1.3 mg/kg administered using the Variojet pen (1 or 2 Variojet Variable Dose Injector pens)
- Weight ≥70 kg: 100 mg administered using the PFS-U (fixed dose injector)

The main study was conducted in 2 parts:

- In Part 1, the efficacy, safety, and PK of guselkumab was evaluated in paediatric participants (⩾12 to <18 years of age in Part 1a, ⩾6 to <12 years of age in Part 1b) during a 16-week randomised, placebo- and active comparator-controlled period followed by an uncontrolled period of continuation of treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. The active comparator used in the study was etanercept, which was administered SC weekly based on body weight (<63 kg: 0.8 mg/kg; ⩾63 kg: 50 mg).
- Part 2 was an open-label, single-arm study to collect additional efficacy, safety, and PK data for paediatric participants with a continuous weight-based dose regimen of guselkumab at Weeks 0, 4, and q8w thereafter through Week 52. Part 2 enrolled only participants aged ⩾12 to <18 years.

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

Results

Part 1 - Through Week 16

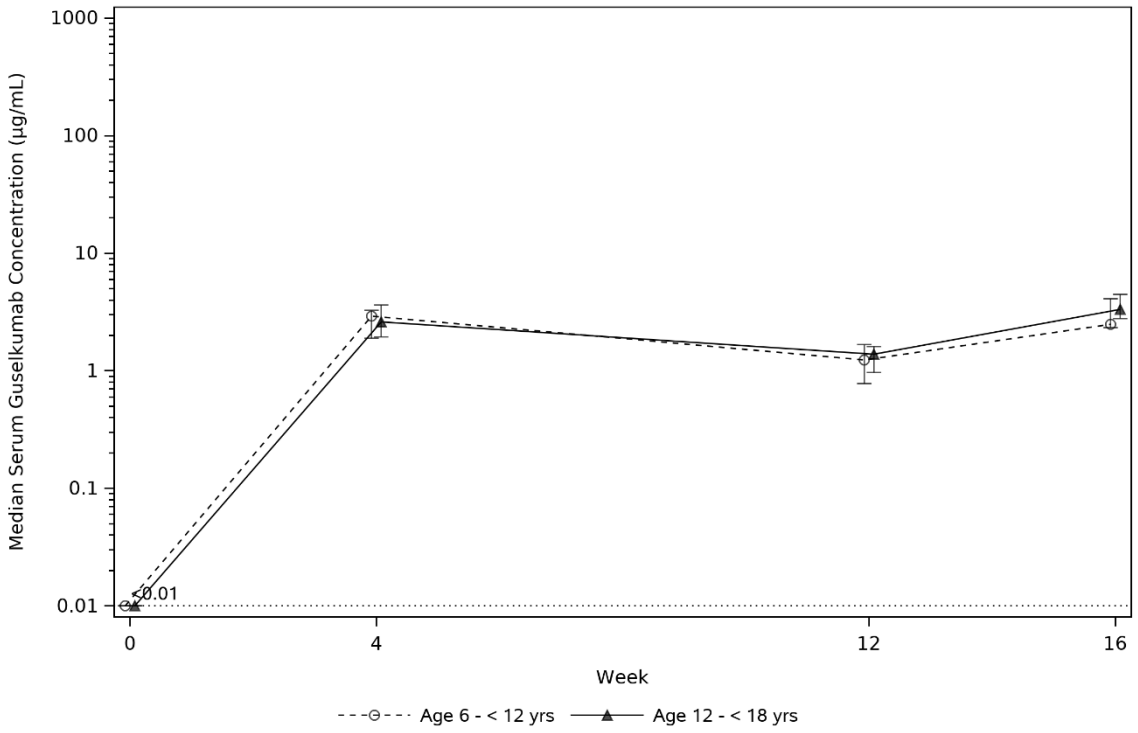
In Part 1, a total of 92 participants (55.4% male, 84.8% white) with a median body weight of 55.5 kg (range: 18 to 128 kg) and a median age of 13.0 years (range: 6 to 17 years) were enrolled and received any study intervention (placebo, guselkumab, or etanercept). Of these 92 participants, 68 (73.9%) participants had a baseline body weight <70 kg and 24 (26.1%) participants had a baseline body weight ≥70 kg.

A total of 41 participants were randomly assigned to guselkumab at Week 0 and received treatment with guselkumab through Week 16; these participants were included in the PK analysis set for the Part 1 Week 16 analysis. These participants were 58.5% male, 87.8% white, had a median body weight of 56.7 kg (range: 26 to 119 kg) and a median age of 14.0 years (range: 6 to 17 years). Of these 41 participants, 29 (70.7%) participants had a baseline body weight <70 kg and 12 (29.3%) participants had a baseline body weight ≥70 kg.

The mean and median serum guselkumab concentrations at Week 16 were 3.43 µg/mL and 3.17 µg/mL, respectively.

The mean and median serum guselkumab concentrations at Week 16 were slightly lower in the ≥6 to <12 years group compared with the ≥12 to <18 years group (**Figure 1**).

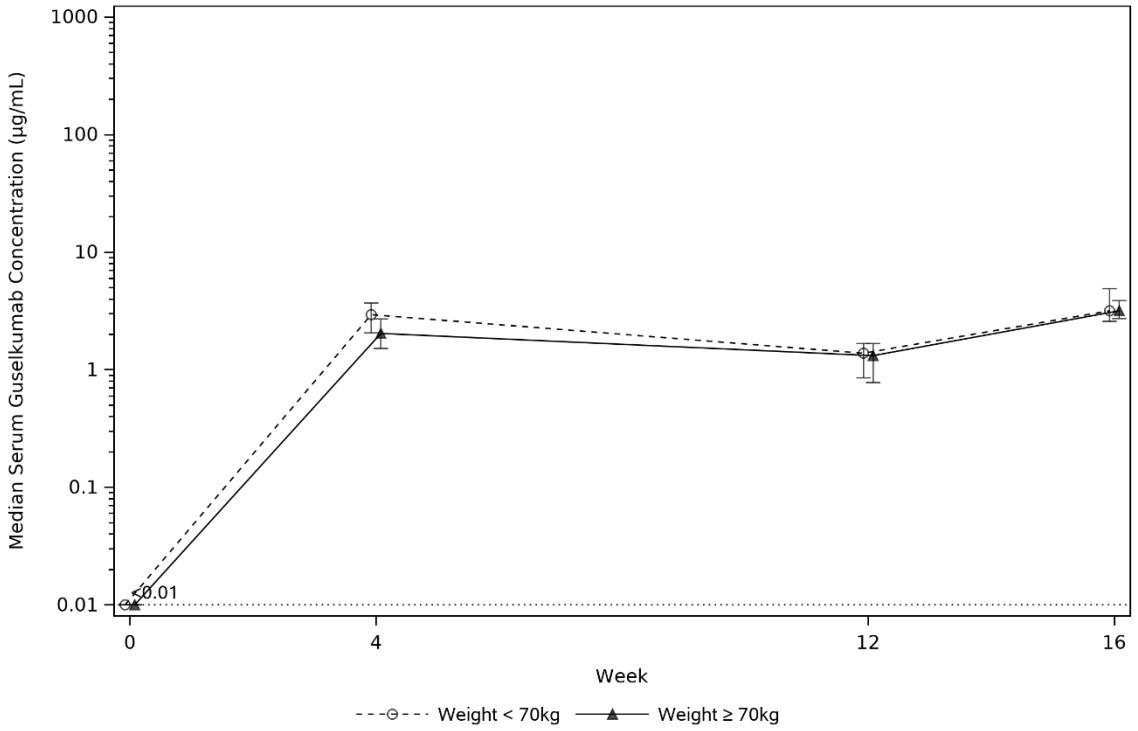
Figure 1: Median and IQ Range of Serum Guselkumab Concentrations (µg/mL) by Age (≥6 to <12, ≥12 to <18 Years) Through Week 16 (Semi-log Scale); Participants Randomly Assigned to and Treated With Guselkumab (Study CNTO1959PSO3011 Part 1)



IQ=interquartile.

At Weeks 0, 4, 12, and 16, serum guselkumab concentrations were similar in participants <70 kg and ≥ 70 kg (Figure 2).

Figure 2: Median and IQ Range of Serum Guselkumab Concentrations (µg/mL) by Baseline Body Weight (<70 kg, ≥70 kg) Through Week 16 (Semi-log Scale); Participants Randomly Assigned to and Treated With Guselkumab (Study CNTO1959PSO3011 Part 1)



IQ=interquartile.

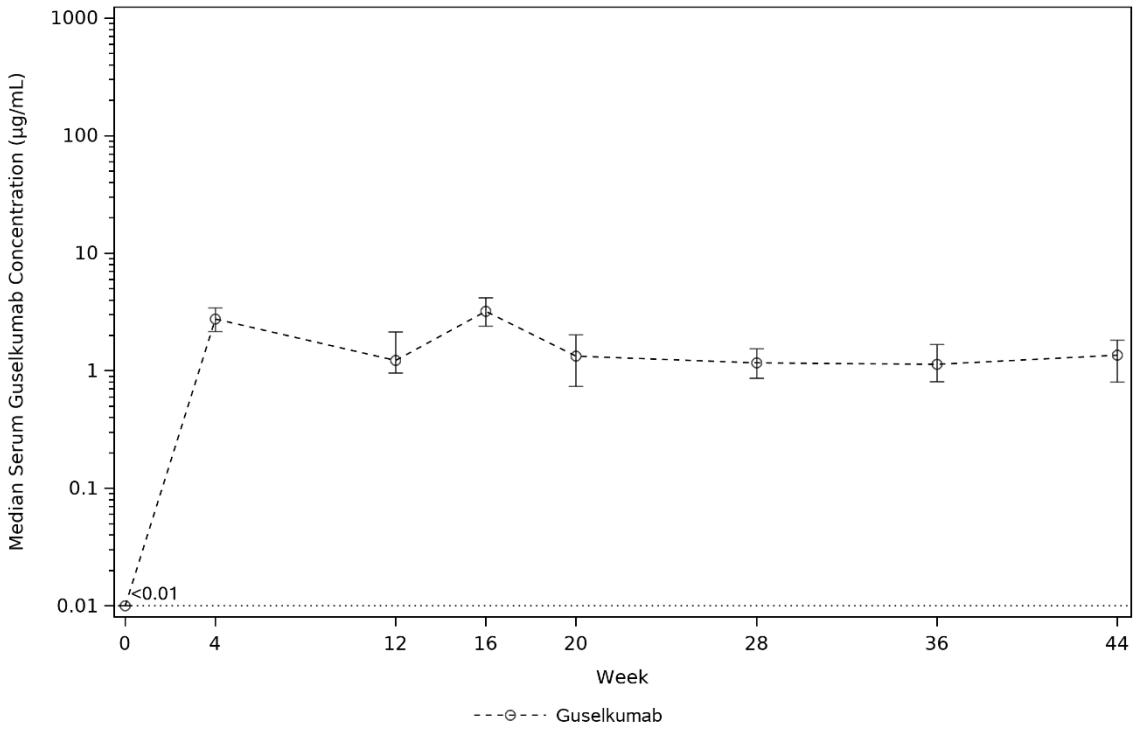
Part 2 - Through Week 44

In Part 2, a total of 28 participants (60.7% male, 100% white) with a median body weight of 67.6 kg (range: 36.2 to 122 kg) and a median age of 15.5 years (range: 12 to 17 years) were enrolled and treated with guselkumab through Week 44. Of these participants, 16 (57.1%) had a baseline body weight <70 kg and 12 (42.9%) had a baseline body weight ≥70 kg.

The median and IQ ranges of serum guselkumab concentrations by visit through Week 44 for Part 2 are shown graphically in **Figure 3**. After SC guselkumab administration at Weeks 0, 4, 12, and q8w thereafter, mean and median trough serum guselkumab concentrations were similar at Week 20 (1.52 µg/mL and 1.33 µg/mL, respectively) and Week 28 (1.27 µg/mL and 1.17 µg/mL, respectively) suggesting that serum guselkumab concentrations achieved steady-state by Week 20. The mean and median trough serum guselkumab concentrations were maintained at steady-state through Week 44 (1.38 µg/mL and 1.36 µg/mL, respectively). There was no evidence of accumulation in serum guselkumab concentrations over time beyond Week 20.

In Part 2, the PK of guselkumab was also examined by comparing serum guselkumab concentrations by body weight at baseline: participants with body weight <70 kg treated with the 1.3 mg/kg dose and participants with body weight ≥70 kg treated with the 100 mg dose. The mean and median steady-state trough serum guselkumab concentrations at Week 20 were similar for the <70 kg and ≥70 kg participants. For the <70 kg group, mean and median steady-state trough serum guselkumab concentrations at Week 20 were 1.50 µg/mL and 1.29 µg/mL, respectively. For the ≥70 kg group, the mean and median steady-state trough serum guselkumab concentrations at Week 20 were 1.54 µg/mL and 1.47 µg/mL, respectively.

Figure 3: Median and IQ Range of Serum Guselkumab Concentrations (µg/mL) Through Week 44 (Semi-log Scale); PK Analysis Set (Study CNTO1959PSO3011 Part 2)



IQ=interquartile; PK=pharmacokinetic(s).

Effect of Body Weight

Table 4 presents baseline body weights and body weight groups of paediatric participants treated with guselkumab 1.3 mg/kg (<70 kg) or 100 mg (≥70 kg) at Weeks 0, 4, 12 then q8w in study CNTO1959PSO3011 and of adults treated with guselkumab 100 mg (irrespective of body weight) at Weeks 0, 4, 12 then q8w in Phase 3 adult studies.

Table 4: Summary of Participant Baseline Body Weight in Paediatric and Adult Studies; Participants Treated With Guselkumab 1.3 mg/kg or 100 mg at Weeks 0, 4, and 12 Then Q8W

	Paediatric Study (CNTO1959PSO3011)		Adult Studies (CNTO1959-)		
	Part 1	Part 2	-PSO3001	-PSO3002	-PS03001 and -PSO3002 Combined
Analysis set: Participants treated with guselkumab	41	28	329	494[a]	823
Baseline body weight (kg)					
Median	56.7	67.6	87.1	87.7	-
Range	(26.0; 119.0)	(36.2; 122.2)	(48.0; 161.0)	(45.0; 198.0)	-
Baseline body weight group (n [%])					
<70 kg[b]	29 (70.7)	16 (57.1)	45 (13.7)	80 (16.2)	125 (15.2)
≥70 kg	12 (29.3)	12 (42.9)	284 (86.3)	414 (83.8)	698 (84.8)

n=number of participants; q8w=every 8 weeks.
[a] In Study CNTO1959PSO3002, 496 participants were randomly assigned to guselkumab, 494 participants were treated with guselkumab.

Median and IQ ranges of serum guselkumab concentrations at Weeks 16, 28, and 44 in paediatric participants in CNTO1959PSO3011 and adult participants treated with the approved 100 mg dosage in CNTO1959PSO3001 and CNTO1959PSO3002 are presented in **Table 5**.

Figure 4 presents median serum guselkumab concentrations through Week 52 in adult participants from CNTO1959PSO3001 and CNTO1959PSO3002, and through Week 44 in paediatric participants from CNTO1959PSO3011.

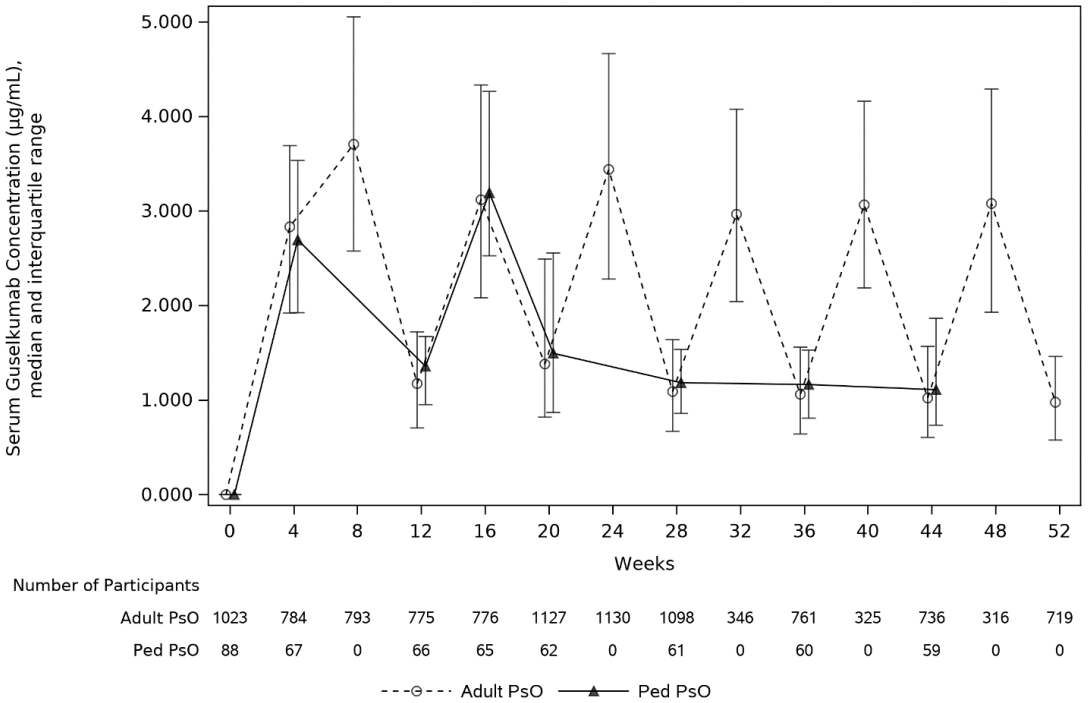
Table 5: Summary of Serum Guselkumab Concentrations (µg/mL) at Weeks 16, 28, and 44 in Participants From Paediatric and Adult Studies Treated With Guselkumab 100 mg at Weeks 0, 4, 12 Then Q8W

	Serum Guselkumab Concentrations (µg/mL)				
	Paediatric Study (CNTO1959PSO3011)			Adult Studies	
	Part 1	Parts 1 and 2	Part 2	CNTO1959PSO3001	CNTO1959PSO3002
Analysis set: participants randomly assigned to and treated with guselkumab	41	69	28	329	494
Week 16					
N	39	64	25	313	463
Mean (SD)	3.43 (1.46)	3.47 (1.51)	3.54 (1.61)	3.45 (1.80)	3.25 (1.58)
Median	3.17	3.20	3.21	3.21	3.08
Range	(0.0; 6.4)	(0.016; 7.70)	(1.30; 7.70)	(0.00; 10.5)	(0.00; 8.28)
CV (%)	42.6	43.5	45.6	-	-
IQ Range	(2.64; 4.46)	(2.51; 4.33)	(2.39; 4.18)	(2.08; 4.53)	(2.09; 4.23)
Week 28					
N	17[a]	-	25	285	438
Mean (SD)	0.950 (0.577)	-	1.28 (0.67)	1.16 (0.792)	1.16 (0.748)
Median	0.981	-	1.17	1.03	1.05
Range	(0.000, 1.85)	-	(0.00, 2.89)	(0.00; 4.51)	(0.00, 4.99)
CV (%)	60.8	-	52.575	-	-
IQ Range	(0.585, 1.31)	-	(0.867, 1.54)	(0.602; 1.54)-	(0.617, 1.54)
Week 44					
N	15[a]	-	24	277	-
Mean (SD)	1.22 (0.735)	-	1.38 (0.791)	1.15 (0.785)	-
Median	1.11	-	1.36	0.988	-
Range	(0.107, 2.66)	-	(0.104, 3.11)	(0.00, 5.71)	-
CV (%)	60.2	-	57.3	-	-
IQ Range	(0.602, 1.87)	-	(0.802, 1.81)	(0.626, 1.56)	-

CV=coefficient of variation; IQ=interquartile; N=number of participants; PASI 90=90% improvement in PASI score; q8w=every 8 weeks; SD=standard deviation.

[a] For paediatric study CNTO1959PSO3011 Part 1, data at Weeks 28 and 44 includes only participants who were randomly assigned to guselkumab and continued to receive guselkumab q8w after Week 16 (excludes PASI 90 responders at Week 16).

Figure 4: Line Plot of Median (IQ range) Serum Guselkumab Concentrations (µg/mL) Over Time in Adult PsO Participants (CNTO1959PSO3001 and CNTO1959PSO3002) and Paediatric PsO Participants (CNTO1959PSO3011); PK Analysis Set



IQ=interquartile; N=number of participants; PASI=Psoriasis Area and Severity Index; Ped=paediatric; PK=pharmacokinetic(s); PsO=psoriasis.

Note: Adult PsO includes studies CNTO1959PSO3001 and CNTO1959PSO3002, and Ped PsO includes study CNTO1959PSO3011.

Note: CNTO1959PSO3001 and CNTO1959PSO3002: Participants randomly assigned to adalimumab at Week 0 are not considered. For CNTO1959PSO3002 only, participants who were randomly assigned to guselkumab but withdrew, due to being a PASI 90 responder at Week 28 and re-randomization to placebo, are excluded after guselkumab discontinuation (N=182).

Note: CNTO1959PSO3011: Participants randomly assigned to etanercept at Week 0 are not considered. Participants who were randomly assigned to guselkumab but withdrew treatment due to being a PASI 90 responder at Week 16, are excluded after guselkumab discontinuation (N=23).

Note: For all studies, participants randomly assigned to placebo at Week 0 who later received guselkumab are only included at visits where concentrations were collected after those participants received their first dose of guselkumab (N=20).

Biopharmaceutics

The VarioJect variable-dose manual injector employed in the paediatric clinical study CNTO1959PSO3011 was considered a novel device configuration in the context of guselkumab administration. The VarioJect is a manually operated, single-use, disposable injector designed to deliver a user-selected dose via a prefilled syringe (PFS) as a single subcutaneous (SC) injection. Assembly of the PFS into the VarioJect device results in the combination product, hereafter referred to as PFS-V. The PFS-V enables administration of one of eight discrete doses, ranging from 10 mg to 45 mg in 5 mg increments. These doses correspond to volume increments of 0.05 mL, resulting in dose volumes ranging from 0.10 mL to 0.45 mL. While the VarioJect device is already authorised and in use within the European Union for the administration of another medicinal product, its application in the context of guselkumab represents a new use case.

A total of 11 participants reported issues associated with the use of the VarioJect device (**Table 6**). Of these, 10 occurred in Part 1 of the study, indicating that 24.3% of participants in that phase experienced administration-related challenges.

Table 6: List of VarioJect device related product quality complaints (PQCs) through Week 52: subjects received VarioJect injection (Study CNTO1959PSO3011 Part 1 and Part 2)

Part	Treatment Group			Scheduled Administration Visit	Medication kit	Reason for Complaint
Part1a	Etanercept->Guselkumab			Week 20	168314	Excess Fluid Expelled DuringPriming
				Week 32	108514	Device Could not Set Dose
	Guselkumab->Guselkumab			Week 4	110697	Device Damaged During Use
						Device Plunger Could not be Pushed
						Wet Injection
					124327	Device Could not Get the Bubbles
						Device Did not Prime Correctly
						Wet Injection
				Week 36	108107	Device Plunger Could not be Pushed
	Guselkumab->Withdraw to Guselkumab			Week 0	111492	Device Damaged During Use
						Device Did not Prime Correctly
				Week 0	178320	Device Did not Prime Correctly
				Week 12	119480	Wet Injection
					133732	Wet Injection
Part1b	Guselkumab->Guselkumab			Week 0	107166	Device Damaged when Opened
						Device Could not Set Dose
						Device Plunger Could not be Pushed
	Placebo->Guselkumab			Week 16	147923	Device Plunger Could not be Pushed
				Week 44	126110	Device Plunger Could not be Pushed
						Wet Injection
						Excess Fluid Expelled DuringPriming
						Plunger Expel Entire Dose
Part2	Guselkumab			Week 20	135185	Device Plunger Could not be Pushed
					163576	Excess Fluid Expelled DuringPriming

Note: The listing including subjects who reported a device complaint.

PopPK Modeling Using Combined Data From Paediatric and Adult Participants With PsO

Dataset and Demographics

The PopPK analysis of guselkumab in participants with plaque PsO was performed using data from paediatric study CNTO1959PSO3011 and adult studies CNTO1959PSO2001, CNTO1959PSO3001, and CNTO1959PSO3002. The final PK dataset comprised a total of 13,529 measurable serum guselkumab concentrations after SC administration of guselkumab from 91 paediatric participants (data up to Week 44; excluding participants who received etanercept) and 1,454 adult participants (data up to Week 52).

Paediatric participants treated with guselkumab with available data for PopPK comprised 91/1545 (5.9%) of the total number of participants included in the final PK dataset, of which 19 were children (≥6 to <12 years) and 72 were adolescents (≥12 to <18 years). The median ages of children and adolescents were 9 years (range: 6 to 11 years) and 15 years (range: 12 to 17 years), respectively. The body weight at baseline ranged from 18.0 to 80.6 kg for children and 36.2 to 128 kg for adolescents, with an overall median of 58.5 kg. The distribution of children and adolescent participants between the body weight groups was as follows:

Children:

1/19 (5.3%) participants had baseline body weight ≥70 kg

6/19 (31.6%) participants had baseline body weight ≥40 to <70 kg

12/19 (63.2%) participants had baseline body weight <40 kg

Adolescents:

26/72 (36.1%) participants had baseline body weight ≥70 kg

44/72 (61.1%) participants had baseline body weight ≥40 to <70 kg

2/72 (2.8%) participants had baseline body weight <40 kg

The majority of the children were Caucasian (16/19 [83.2%]) and female (12/19 [63.2%]), while the majority of the adolescents were Caucasian (63/72 [87.5%]) and male (43/72 [59.7%]). In adults, PsO has been associated with an increased prevalence of metabolic disorders such as obesity, hyper-lipidemia, and diabetes comorbidities. In the current pool of paediatric participants with PsO, comorbidity of diabetes or history of hyperlipidemia were reported only in adolescent participants at proportions of 1/91 (1.1%) and 2/91 (2.2%), respectively.

Adult participants comprised 1454/1545 (94%) of the total number of participants included in the final PK dataset, with a median age of 44.0 years (range: 18 to 82 years) and median body weight of 87.1 kg (range: 44.9 to 198 kg) and were primarily Caucasian (1218/1454 [83.8%]) and male (1030/1454 [70.8%]). Compared with the paediatric participants, more adult participants had a comorbidity of diabetes (129/1454 [8.9%]), and 224/1454 (15.4%) had a past or current history of hyperlipidemia. **Table 7** summarises the demographic data of the patients included in the POP-PK database.

Table 7: Demographic and Baseline Characteristics of Pooled Study Data

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

N=number of participants; PASI= Psoriasis Area Severity Index; PopPK=population pharmacokinetics; SD=standard deviation; y=years.

PopPK Model Results

The observed serum concentration-time data of guselkumab in paediatric and adult participants with PsO were described by the re-estimated (from the adult model) 1-compartment linear PK model with first-order absorption and first-order elimination and allometric components for CL/F and V/F fixed to 0.75 and 1.0, respectively. The re-estimation was carried out using only adult data, and subsequent external validation was performed using paediatric data. To perform external validation using paediatric data alone, individual parameter estimates were obtained using NONMEM with the MAXEVAL=0 option, which allows for Bayesian estimation without re-estimating the population parameters. The parameter estimates of the final adult PopPK model used for external validation are summarised in **Table 8**. All parameters were estimated with good precision, with RSEs less than 20%.

In the final PopPK model, baseline body weight was an important covariate on guselkumab CL/F and V/F. The allometric exponent of the body weight effect was fixed to the standard exponents of 0.75 for

CL/F and 1.0 for V/F, respectively. The final estimates for guselkumab CL/F and V/F were 0.517 L/day and 13.5 L, respectively. The model-derived elimination half-life in a typical adult individual was estimated as 18.1 days. 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 paediatric participants and pcVPC plots for both paediatric and adult participants show that the final PopPK model adequately describes the central tendency and variability of the paediatric and adult guselkumab PK data.

Table 8: Parameter Estimates From the Final PopPK Model

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

- BWT=baseline body weight; CI=confidence interval; CL/F=apparent clearance; CV=coefficient of variation; DIAB=diabetes comorbidity; IIV=inter-individual variability, calculated as (variance)$^{1/2}$*100%; k_a=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling; PK=pharmacokinetic(s); PopPK=population pharmacokinetics; RSE=relative standard error; V/F=apparent volume of distribution.
- [a] Mean (RSE%) [Shrinkage%] estimates by NONMEM from the final PK dataset.
- [b] The magnitude of change in the parameter estimate caused by a continuous covariate was expressed as a range, ie, % change from the median value when the covariate factor varied from the 25th to the 75th percentile of the population.
- [c] $CL/F = 0.517 \times (\frac{BWT}{87.1})^{0.75} \times 1.18^{DIAB} \times 1.07^{RACE}$
- [d] $V/F = 13.5 \times (\frac{BWT}{87.1})^{1.0}$

Simulation of Serum Guselkumab Concentration-time Profiles in Paediatric and Adult Participants

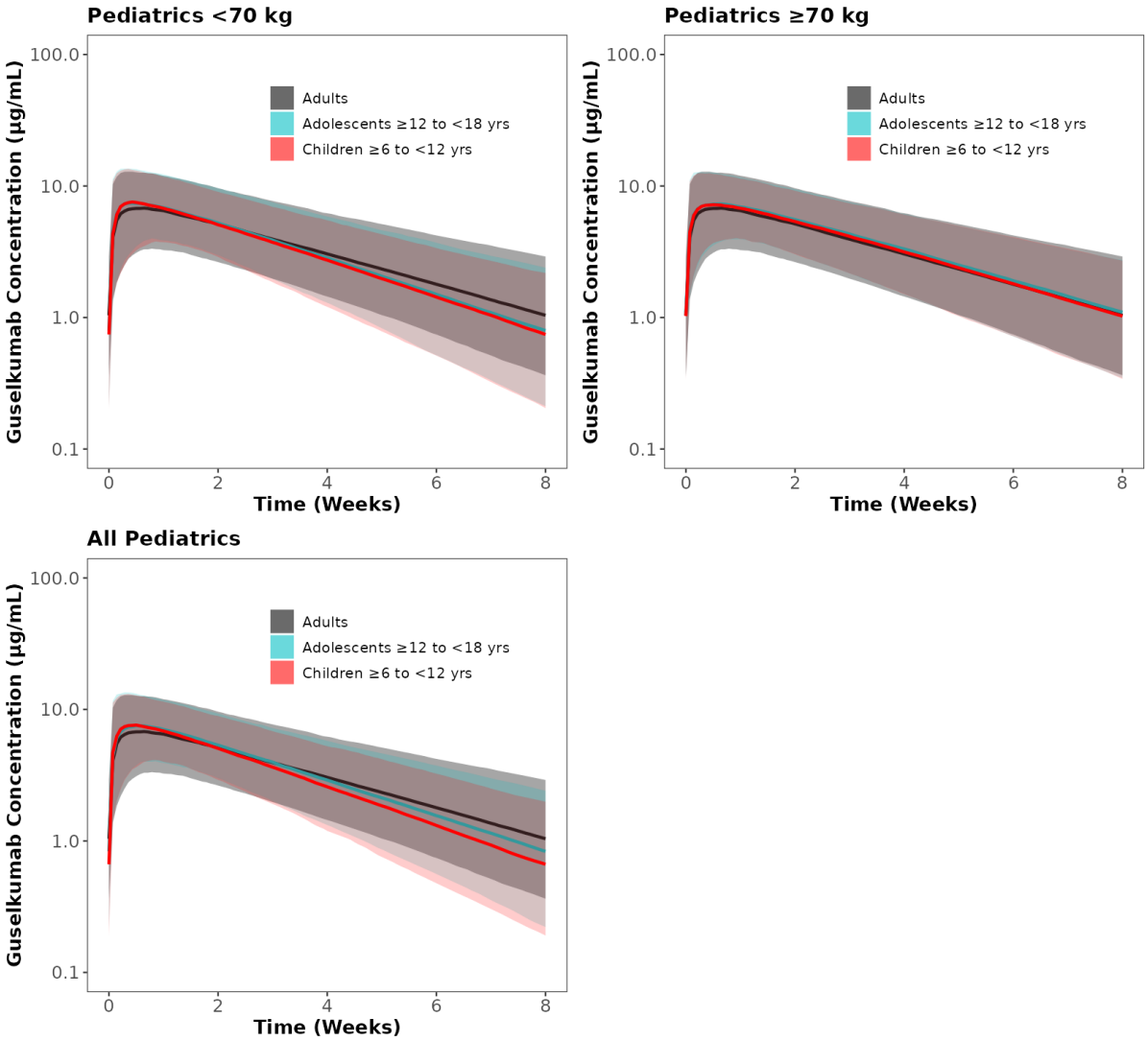
Simulations were performed using the final PopPK model to evaluate the current study (CNTO1959PSO3011) dose regimen, to assess the appropriateness of decreasing the paediatric body weight cutoff for use of the 100 mg fixed dose of guselkumab from 70 kg to 40 kg (to better align with the adult dose regimen).

Virtual paediatric patients (n=1,000/group) were created from the NHANES III database (and adjusted by 15% body weight increase, to account for higher observed body weights in paediatric PsO patients compared with children in the database). The NHANES III growth database included data from 27,489 children aged ≥6 to <18 years with body weight ranging from 6.9 to 169 kg. To create the adult virtual patients used in the simulations for comparison, body weights were sampled from the original adult PK dataset, comprising of 1,459 individuals. The simulations were performed to compare guselkumab PK concentration versus time profiles over 52 weeks and the steady-state exposure metrics (C_{trough}, AUC, and C_{max}) of the treatment regimens between paediatrics and adults.

Comparison of Model-predicted Steady-state Guselkumab Exposure Between Paediatric and Adult Participants

The concentration versus time profiles showing the model-predicted exposures for adolescents (≥12 to <18 years), children (≥6 to <12 years), and adult virtual participants who received a fixed 100 mg doses, or paediatric participants weighing <70 kg who received a 1.3 mg/kg dose, are presented in **Figure 5** in a semi-logarithmic scale.

Figure 5: Comparison of Model-predicted Steady-state Concentration Versus Time Profiles Between Paediatric and Adult Participants, Overall and Based on the Paediatric Body Weight Cutoff of 70 kg, Using a Guselkumab 100 mg Dose Regimen for all Adults and for Paediatrics ⩾70kg



♦

NHANES=National Health and Nutrition Examination Survey; PopPK=population pharmacokinetics; q8w=every 8 weeks.
Note: Paediatrics below 70 kg received a 1.3 mg/kg dose, and at or above 70 kg received a 100 mg fixed dose. All adults received 100 mg fixed dose. Doses were given at Week 0, 4 and q8w thereafter. The plot shows data from the last dose interval from Week 44 to Week 52.
Note: Simulations consist of virtual participants (n=1,000/group) sampled from the NHANES III database for paediatrics and sampled from the final PopPK dataset for adults. The covariate included was body weight. The lines (shaded area) in each figure represent the median (90% prediction intervals) of the overall adult steady-state metric.

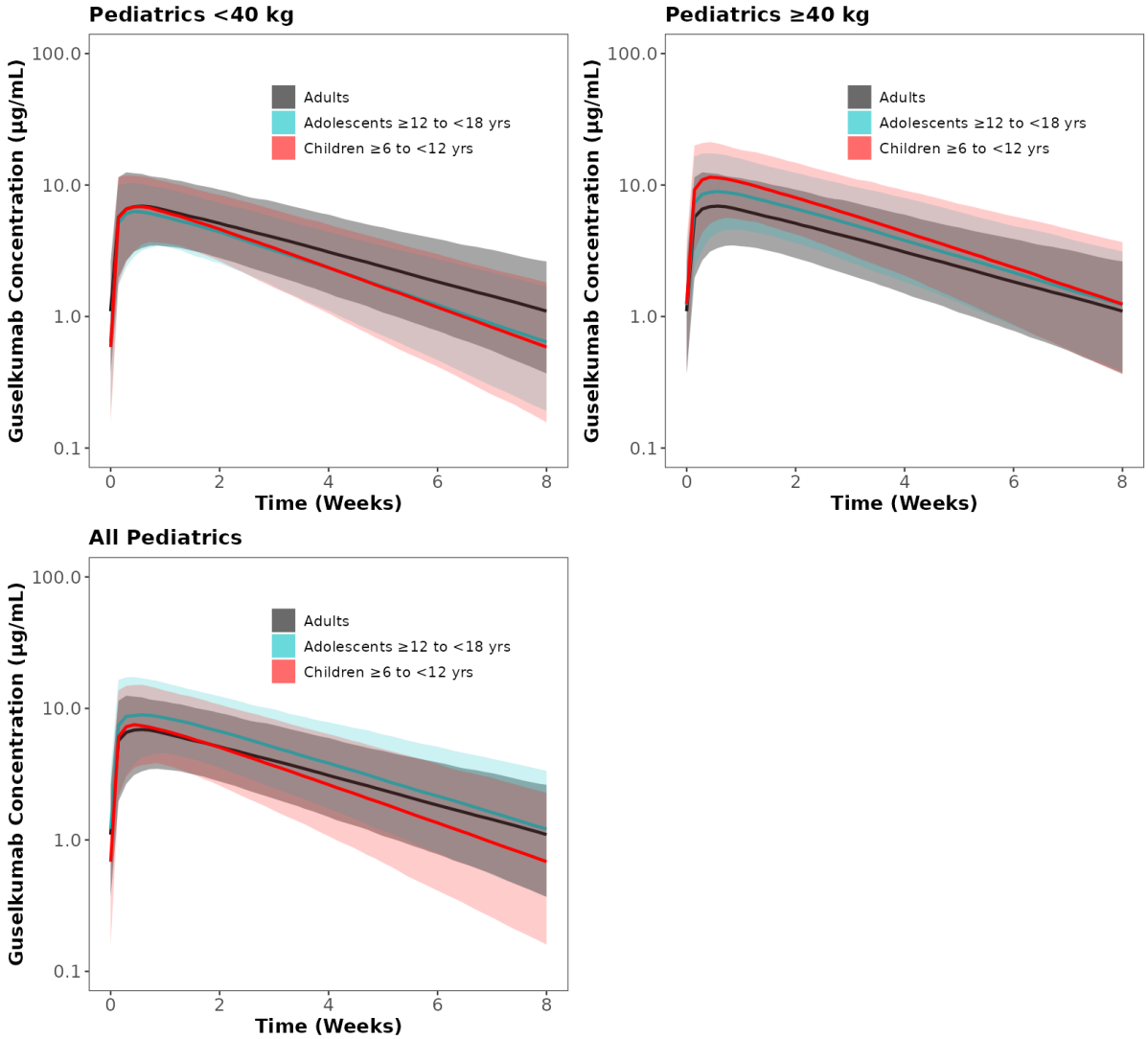
Evaluation of Appropriate Body Weight Cutoff for Use of the 100 mg Fixed Dose of Guselkumab in Paediatric Participants

In CNTO1959PSO3011, children and adolescents with body weight ≥70 kg received a 100 mg dose of guselkumab, and children and adolescents with body weight <70 kg received a 1.3 mg/kg dose of guselkumab. For adults, the recommended guselkumab dose is 100 mg, regardless of body weight, and adults with body weight as low as approximately 40 kg have received the 100 mg dose in CNTO1959PSO3001/CNTO1959PSO3002. Simulations were carried out to assess the appropriateness of lowering the paediatric body weight cutoff from 70 kg (which was studied in

Study CNTO1959PSO3011) to 40 kg for use of the adult 100 mg fixed guselkumab dose. Simulated steady-state concentration-time profiles are shown in **Figure 6** for children, adolescents, and adults based on the proposed 40 kg body weight cutoff for a guselkumab 100 mg dose regimen.

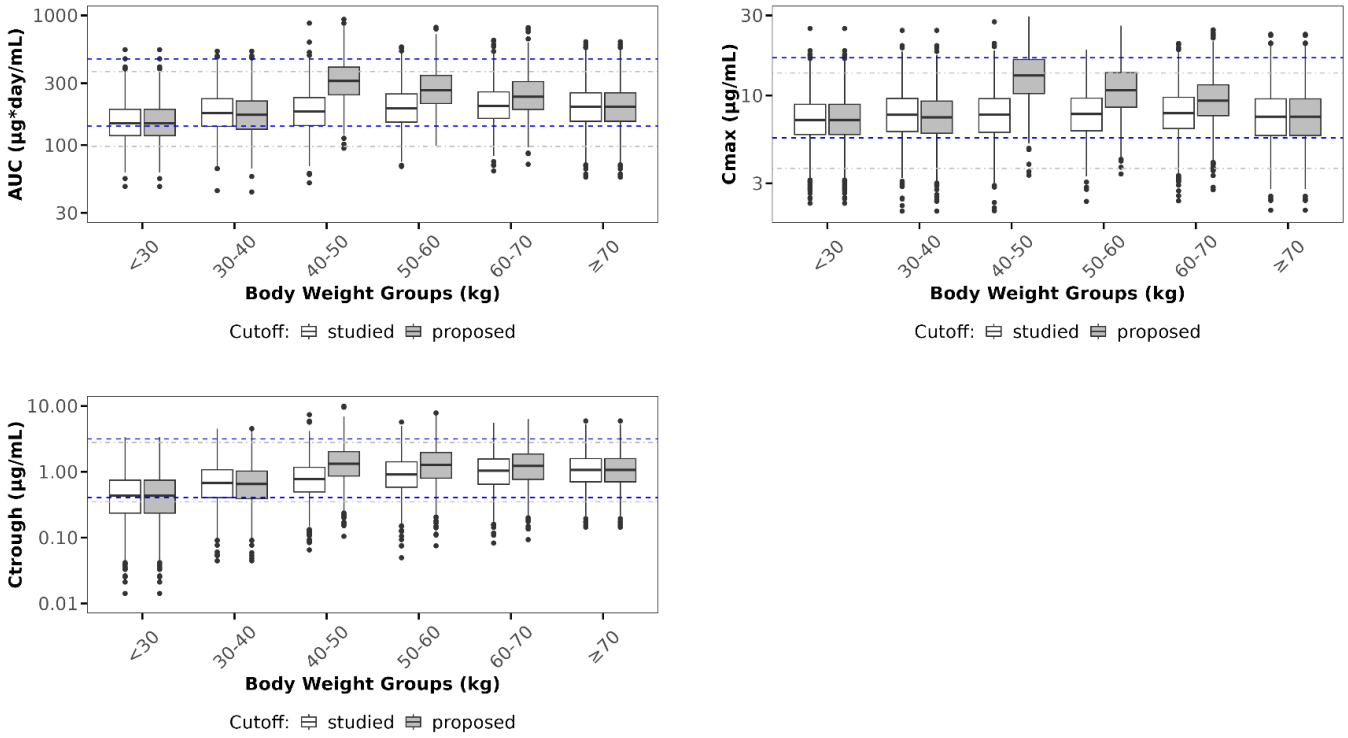
A boxplot detailing PK exposure metrics across various paediatric body weight groups using the studied and proposed paediatric body weight cutoff of 70 kg and 40 kg, respectively, for the 100 mg guselkumab dose is presented in **Figure 7**, for comparison with the target 90% prediction interval of the overall adult participant exposures or the <70 kg adult participant exposures.

Figure 6: Comparison of Model-predicted Steady-state Concentration Versus Time Profiles Between Paediatric and Adult Participants, Overall and Based on the Paediatric Body Weight Cutoff of 40 kg, Using a Guselkumab 100 mg Dose Regimen for all Adults and for Paediatrics ⩾40kg



NHANES=National Health and Nutrition Examination Survey; PopPK=population pharmacokinetics.
Note: Paediatrics weighing 35 to 40 kg received 45 mg fixed dose of guselkumab. Paediatrics below 35 kg received a 1.3 mg/kg dose, and above 40 kg received a 100 mg fixed dose. All adults received a 100 mg fixed dose. Doses were given at Week 0 and 4, and q8w thereafter. The plot shows data from the last dose interval from Week 44 to Week 52.
Note: Simulations consist of virtual participants (n=1,000/group) sampled from the NHANES III database for paediatrics and sampled from the final PopPK dataset for adults. The covariate included was body weight. The lines (shaded area) in each figure represent the median (90% prediction intervals) of the overall adult steady-state metric.

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



AUC=area under the serum concentration versus time curve; C_{max}=maximum serum concentration; C_{trough}=trough serum concentration; IQ=interquartile; PK=pharmacokinetic(s).

Note: "Studied" represents paediatric regimen based on 70 kg body weight cutoff for 100 mg guselkumab dose; "Proposed" represents paediatric regimen based on 40 kg body weight cutoff for 100 mg guselkumab dose. For the proposed regimen, paediatrics below 35 kg received a 1.3 mg/kg dose of guselkumab, paediatrics weighing 35 to 40 kg received a 45 mg fixed dose of guselkumab (note that the maximum dose that can be administered with a single Varioject pen is 45 mg), and those above 40 kg received a 100 mg fixed dose of guselkumab.

Note: Simulations consist of virtual paediatric participants (n=1,000/group).

The gray dashed lines in each figure represent the 90% prediction intervals of the overall adult (CNTO1959PSO3001/CNTO1959PSO3002) steady-state PK metric; the blue dashed lines in each figure represent the 90% prediction interval of the steady-state PK metric in adult participants with body weight <70 kg. Each boxplot represents the median and IQ range for each simulated group. The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQ range from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQ range of the hinge. Data beyond the end of the whiskers are plotted individually.

Exposure relevant for safety evaluation

In adults, relationship between drug exposure and adverse events has not been established. Supplemental PK/PD safety analyses on pooled data from adult Phase 3 PsO and PsA studies showed that safety was not associated with exposure metrics, as shown by the similar incidence of treatment-emergent adverse events by C_{trough} or AUC quartiles.

To further support the proposed dose recommendations and given the difference in body weight between paediatric and adult participants, additional safety analyses were done for adults weighing <70 kg compared with adults weighing ≥70 kg. In the adult Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002, participants with body weight as low as approximately 40 kg were included and received the guselkumab 100 mg dose. The mean and median systemic guselkumab exposure (cumulative AUC over 28 weeks) was approximately 40% higher in adults weighing <70 kg compared with adults weighing ≥70 kg. Nevertheless, there was no evident relationship between body weight at baseline and the occurrence of AEs, serious AEs, infections, or AEs leading to study intervention discontinuation. Of participants who received treatment with guselkumab, the proportions who experienced ≥1 AE through Week 16 and Week 48 were similar between participants with baseline body weight of <70 kg (55.2% and 72.8%, respectively) and participants with baseline body weight of ≥70 kg (48.1% and 70.2%, respectively). These findings were consistent in participants who received placebo or adalimumab in these studies.

In addition to the above findings in adult participants with PsO, an exposure-safety analysis was also performed for a related adult population, participants with PsA, who received the same 100 mg dose regimen as adults with PsO, which provides additional support for the overall safety profile of guselkumab in relation to exposure (Chen 2022). The relationship between systemic guselkumab exposure and the occurrence of selected safety events (AEs, serious AEs, AEs leading to discontinuation, infections, and serious infections) was also analysed during Phase 3 studies of SC guselkumab in adults with active PsA (CNTO1959PSA3001 [DISCOVER-1] and CNTO1959PSA3002 [DISCOVER-2]) (Chen 2022). These analyses showed that the occurrence of the selected safety events was not associated with observed or model-predicted exposure metrics. The incidence of the selected safety events was similar across the range of observed trough serum guselkumab concentration quartiles at steady-state (20 weeks) for the 100 mg q8w dose regimen (lowest quartile <0.53 µg/mL; highest quartile >1.6 µg/mL).

Incidence of Antibodies to Guselkumab in Paediatric Plaque PsO Study

In the CNTO1959PSO3011 study, the presence of antibodies to guselkumab in serum was determined using 2 methods: the initial and revised ECLIA methods. Through Week 16 in Part 1 of the study, 41 participants treated with guselkumab had post-treatment serum samples that were evaluable for antibodies to guselkumab. Using the initial ECLIA method, none of these participants were postbaseline positive for antibodies to guselkumab through Week 16. Using the revised ECLIA method, 4 participants (9.8%) were postbaseline positive for antibodies to guselkumab through Week 16 (11). In addition, the incidence of antibodies to guselkumab through Week 16 determined by the revised ECLIA method was comparable between the 2 baseline body weight groups (<70 kg: 10.3% [3 of 29 participants]; ≥70 kg: 8.3% [1 of 12 participants]) and between the 2 age groups (≥6 to <12 years: 10.0% [1 of 10 participants]; ≥12 to <18 years: 9.7% [3 of 31 participants]).

Overall (Part 1 and 2 combined), 114 participants treated with guselkumab had post-treatment serum samples that were evaluable for antibodies to guselkumab through Week 44 (**Table 10**). The overall incidence of antibodies to guselkumab through Week 44 was 13.2% for the initial ECLIA method, 18.4% for the revised ECLIA method, and 21.1% (24 of 114 participants) based on either the initial or

revised ECLIA method. Titers of antibodies to guselkumab were generally low (80% had titer levels ≤1:160 using the initial ECLIA method, 90% had titer levels ≤1:320 using the revised ECLIA method).

Table 9: Summary of Antibodies to Guselkumab Status Through Week 16 by Subgroup With the Revised ECLIA Method; Participants Randomly Assigned to and Treated With Guselkumab (Study CNTO1959PSO3011 Part 1)

	Guselkumab				
	Age		Baseline Body Weight		Combined
	≥6 to <12 yrs	≥12 to <18 yrs	<70 kg	≥70 kg	
Analysis set: Participants treated with guselkumab	10	31	29	12	41
Participants with appropriate samples[b]	10	31	29	12	41
Participants with baseline positive samples[c,d]	1 (10.0%)	2 (6.5%)	3 (10.3%)	0	3 (7.3%)
Participants postbaseline positive for antibodies to guselkumab[c,e]	1 (10.0%)	3 (9.7%)	3 (10.3%)	1 (8.3%)	4 (9.8%)
Peak titers					
1:11	0	3	2	1	3
1:45	1	0	1	0	1
Participants postbaseline negative for antibodies to guselkumab[c,f]	9 (90.0%)	28 (90.3%)	26 (89.7%)	11 (91.7%)	37 (90.2%)

ECLIA=electrochemiluminescent immunoassay.
[a] Revised ECLIA method was termed DT-EIA method in the source data outputs.
[b] Participants with appropriate samples had 1 or more evaluable samples obtained after their first guselkumab administration.
[c] Denominator is participants with appropriate samples.
[d] Participants with baseline samples positive had samples positive for antibodies to guselkumab at baseline, regardless of status after first guselkumab administration.
[e] Participants positive for antibodies to guselkumab includes all participants who had positive sample (treatment-boosted or treatment-induced) at any time after their first guselkumab administration through Week 16. In the instance that a participant had a positive sample at baseline (pre-dose), the participant was considered as positive only if the peak titer of the post-treatment samples was at least 4-fold higher (ie, ≥4-fold) than the titer of the baseline sample.
[f] Excludes participants who were positive at any time through Week 16.

Table 10: Summary of Antibodies to Guselkumab Status Through Week 44; Participants Treated With Guselkumab (Study CNTO1959PSO3011 Part 1 and Part 2)

	Guselkumab	
	Initial ECLIA Method[a]	**Revised ECLIA Method[b]**
Analysis set: Participants treated with guselkumab	114	114
Participants with appropriate samples[e]	114	114
Participants with baseline positive samples[d,e]	7 (6.1%)	6 (5.3%)
Participants postbaseline positive for antibodies to guselkumab[d,f]	15 (13.2%)	21 (18.4%)
Peak titers		
1:10	7	-
1:11.25	-	14
1:22.5	-	2
1:40	2	-
1:45	-	4
1:80	3	-
1:160	2	-
1:320	1	-
1:360	-	1
Participants postbaseline negative for antibodies to guselkumab[d,g]	99 (86.8%)	93 (81.6%)

ECLIA=electrochemiluminescent immunoassay.
[a] Initial ECLIA method was termed EIA method in the source data outputs.
[b] Revised ECLIA method was termed DT-EIA method in the source data outputs.
[c] Participants with appropriate samples had 1 or more evaluable samples obtained after their first guselkumab administration.
[d] Denominator is participants with appropriate samples.
[e] Participants with baseline samples positive had samples positive for antibodies to guselkumab at baseline, regardless of status after first guselkumab administration.
[f] Participants positive for antibodies to guselkumab includes all participants who had positive sample (treatment-boosted or treatment-induced) at any time after their first guselkumab administration through Week 44. In the instance that a participant had a positive sample at baseline (predose), the participant was considered as positive only if the peak titer of the post-treatment samples was at least 4-fold higher (ie, ≥4-fold) than the titer of the baseline sample.
[g] Excludes participants who were positive at any time through Week 44.

Comparison of Incidence of Antibodies to Guselkumab Between Paediatric and Adult PsO Studies

In the Phase 3 studies in adult participants, the incidence of antibodies to guselkumab through Weeks 44 to 52 ranged from 5.3% (n=26 of 492 participants through Week 52 in study CNTO1959PSO3001) to 6.6% (n=57 of 869 participants through Week 52 in study CNTO1959PSO3002).

Therefore, the incidence of antibodies to guselkumab was consistently low in paediatric participants with PsO (13.2% at Week 44 [initial ECLIA method]) and in adult participants with PsO (5.3% to 6.6% at Week 44).

Table 11: Summary of Incidence of Antibodies to Guselkumab Across Phase 3 Studies in Adult Participants With PsO (Initial ECLIA Method[a])

Dosage Groups	Analysis Timepoint	Participants With Appropriate Samples[b]	Positive Status for Antibodies to Guselkumab[c]	Positive Status for NAbs[d]
CNTO1959PSO3001				
Guselkumab 100 mg	Week 44[e]	492	26 (5.3%)	5 (19.2%)
	Week 156[e]	770	73 (9.5%)	5 (6.8%)
	Week 264[e]	770	111 (14.4%)	5 (4.5%)
CNTO1959PSO3002				
Guselkumab 100 mg	Week 48[f]	869	57 (6.6%)	2 (3.5%)
	Week 156[f]	943	86 (9.1%)	4 (4.7%)
	Week 264[f]	943	146 (15.5%)	8 (5.5%)

ECLIA=electrochemiluminescent immunoassay; NAb=neutralizing antibody; PsO=psoriasis.
[a] Initial ECLIA method was termed EIA method in the source data outputs.
[b] Participants who had 1 or more evaluable samples obtained after their first guselkumab administration.
[c] Includes all participants who had at least 1 positive sample at any time after their first guselkumab administrations. Denominator is the number of participants with appropriate samples.
[d] Denominator is participants positive for antibodies to guselkumab (all participants positive for antibodies to guselkumab were evaluable for NAbs).
[e] These data include participants who switched from placebo→guselkumab at Week 16, and adalimumab→guselkumab at Week 52. Note that the number of participants with samples positive to guselkumab at reference baseline visit (ie, Week 0 for the guselkumab group, Week 16 for the placebo→guselkumab group, and Week 52 for the adalimumab→guselkumab group) was 40 (5.2%) at Week 156 and 74 (9.6%) at Week 264.
[f] These data include participants who switched from placebo→guselkumab at Week 16, and adalimumab→guselkumab at Week 28. Note that the number of participants with samples positive to guselkumab at reference baseline visit was 45 (4.8%) at Week 156 and 80 (8.5%) at Week 264.

NAbs to guselkumab

In CNTO1959PSO3011, none of the 24 participants who were positive for antibodies to guselkumab at any time were positive for NAbs to guselkumab through Week 44.

In the Phase 3 studies in adult participants, the incidence of NAbs to guselkumab through Weeks 44 to 52 was low, varying from 0 to 19.2% of the participants who were positive for antibodies to guselkumab.

Antibodies to guselkumab and PK

In CNTO1959PSO3011, the incidence of antibodies to guselkumab was low in each treatment group, and the presence of antibodies to guselkumab did not alter the PK of guselkumab based on comparisons of serum guselkumab concentrations between participants who were positive for antibodies to guselkumab and participants who were negative for antibodies to guselkumab. In addition, no apparent impact of the peak titer levels of antibodies to guselkumab on the PK of guselkumab was observed in participants positive for antibodies to guselkumab.

In the Phase 3 studies in adult participants, the presence of detectable antibodies to guselkumab did not alter guselkumab PK, based on comparison of guselkumab serum concentration between participants who were positive for antibodies to guselkumab and participants who were negative for antibodies to guselkumab (ie, between-participant comparison) and PK comparisons in antibody-positive participants before and after the timepoint of detection of antibodies to guselkumab (ie, within-participant comparison).

Antibodies to guselkumab and efficacy

In CNTO1959PSO3011 Part 1, 3 of the 4 participants (75.0%) who were positive for antibodies to guselkumab (using the revised ECLIA method) achieved IGA scores of cleared (0) or minimal (1) at Week 16. A similar proportion of participants who were negative for antibodies to guselkumab achieved IGA scores of cleared (0) or minimal (1) at Week 16 (24 of 37 participants [64.9%]).

Of the 4 participants who were positive for antibodies to guselkumab (using the revised ECLIA method) 3 (75%) were PASI 75 responders and 2 (50.0%) were PASI 90 responders. A similar proportion of the participants who were negative for antibodies to guselkumab were PASI 75 (28 of 37 participants [75.7%]) and PASI 90 (21 of 37 participants [56.8%]) responders.

In the Phase 3 studies in adult participants (CNTO1959PSO3001 and CNTO1959PSO3002), the development of antibodies to guselkumab was not associated with a reduction in the clinical efficacy of guselkumab through Weeks 44 to 52, although the incidence of antibodies to guselkumab in these studies was also low.

Antibodies to guselkumab and safety

In CNTO1959PSO3011, none of the participants who were positive for antibodies to guselkumab had an injection-site reaction during the study period (through Week 52).

In the Phase 3 studies in adult participants with PsO, CNTO1959PSO3001 and CNTO1959PSO3002, antibodies to guselkumab had no discernible impact on development of injection-site reactions through Weeks 44 to 52, although the incidence of antibodies to guselkumab and the incidence of injection-site reactions in these studies was low.

2.6.2.2. Pharmacodynamics

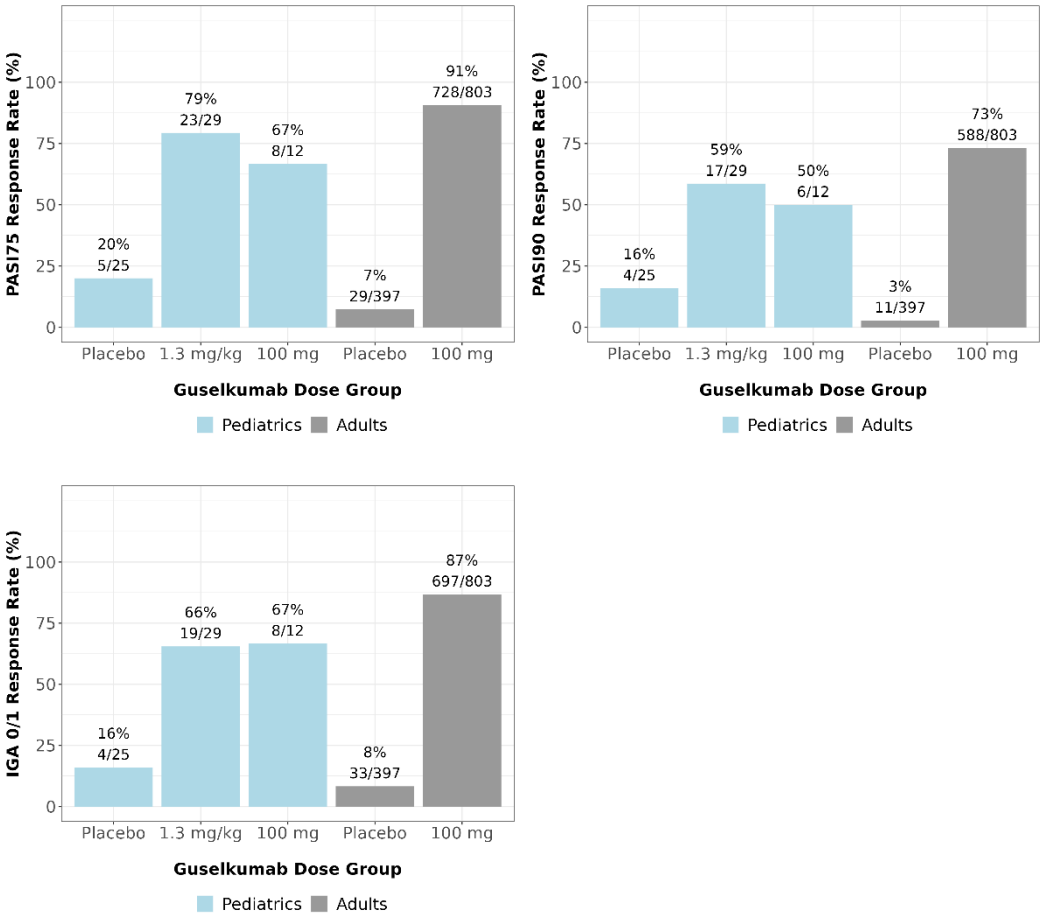
Relationship between plasma concentration and effect

Graphical evaluation of the response rate across paediatric body weight dose cohorts (based on the body weight cutoff of 70 kg) was performed with data from Part 1 of Study CNTO1959PSO3011 for key efficacy endpoints (IGA 0/1, PASI 75, and PASI 90) at Week 16 and compared with the adult data from the 2 Phase 3 studies CNTO1959PSO3001 and CNTO1959PSO3002.

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 paediatric participants treated with placebo and 41 paediatric 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.

The dose regimens of guselkumab 1.3 mg/kg and 100 mg in the paediatric participants achieved generally similar IGA 0/1, PASI 75, and PASI 90 scores (**Figure 8**).

Figure 8: Proportion of Participant Responders Across Dose Regimens Between Paediatric (CNTO1959PSO3011) and Adult Participants CNTO1959PSO3001/ CNTO1959PSO3002) at Week 16

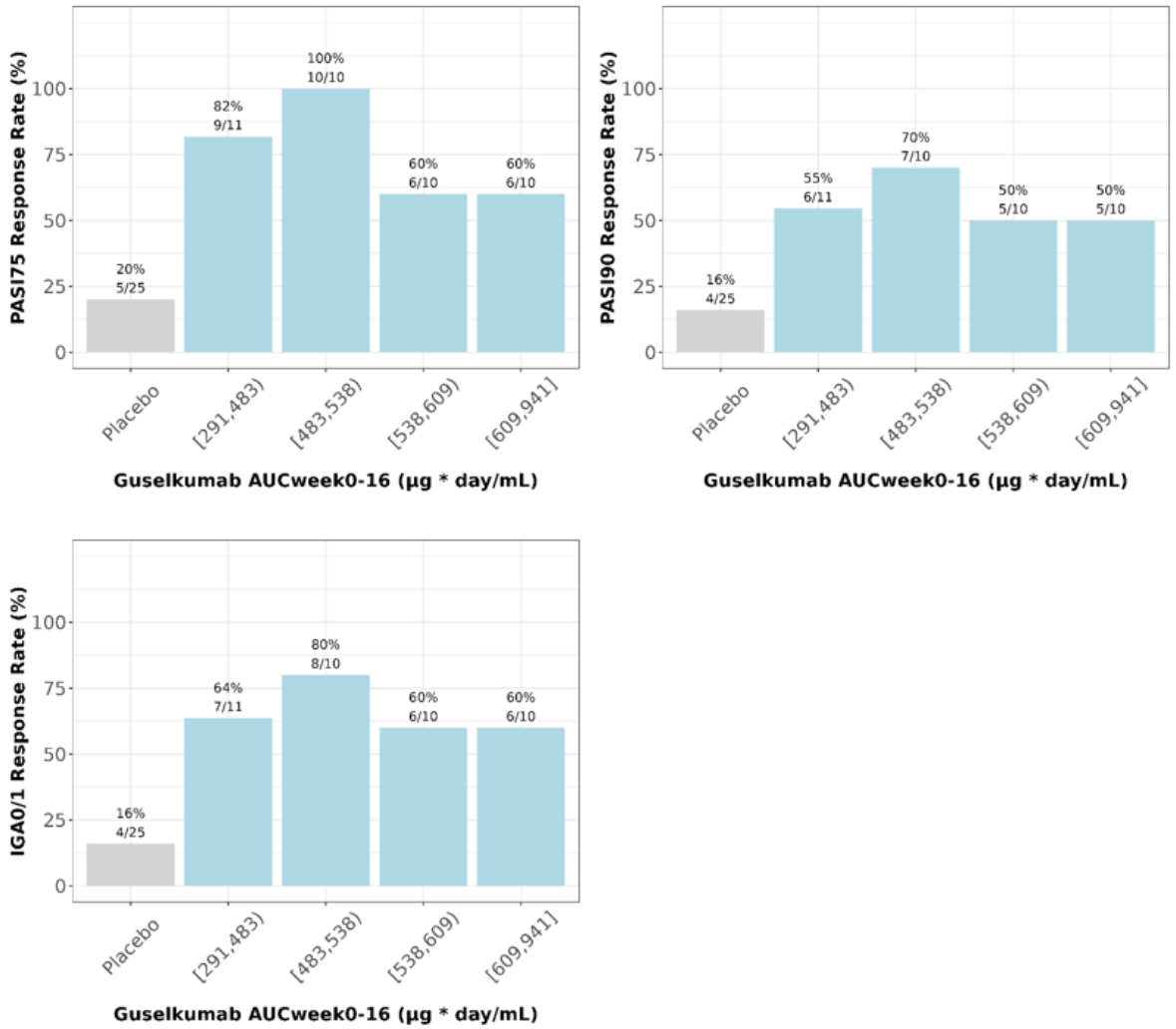


IGA=Investigator's Global Assessment; IGA0/1=IGA score of minimal (1) or cleared (0); PASI=Psoriasis Area Severity Index; PASI75=75% improvement in PASI score; PASI90=90% improvement in PASI score.

Note: Paediatrics below 70 kg received a 1.3 mg/kg dose, and 70 kg or above received a 100 mg fixed dose. All adults received the 100 mg fixed dose.

For the paediatric study, the graphical E-R relationships for the guselkumab exposure metric AUCweek0-16 and all 3 selected key efficacy endpoints at Week 16 are shown in **Figure 9**.

Figure 9: Proportion of Paediatric Participant Responders Across Efficacy Endpoints at Week 16 by Serum Guselkumab AUC, Week 0-16 Quartiles

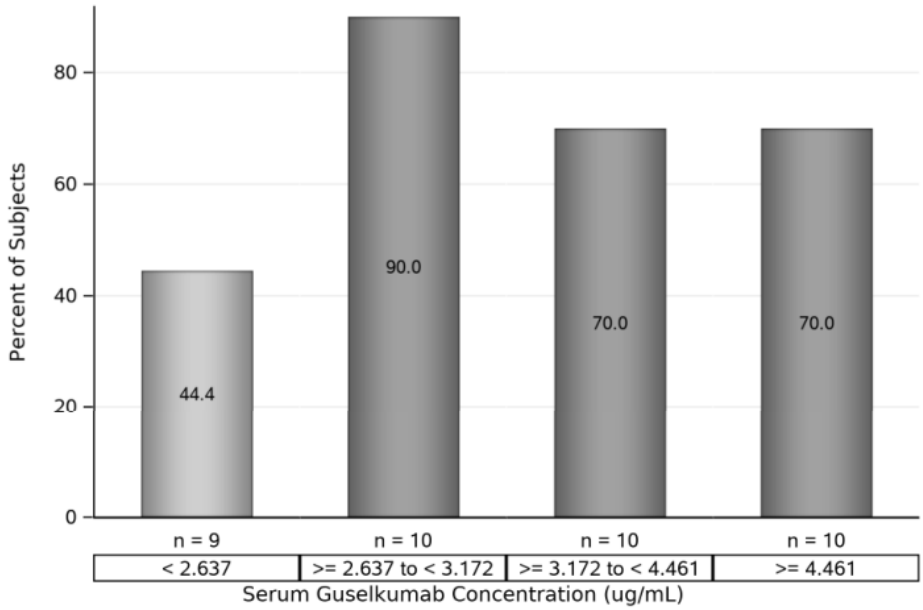


$AUC_{week0-16}$=area under the serum concentration versus time curve from Week 0 to 16; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; IGA0/1=IGA score of minimal or cleared; PASI75=75% improvement in PASI score; PASI90=90% improvement in PASI score.
Note: Paediatrics below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

IGA Responses and Serum Guselkumab Concentrations

Percent of Subjects Achieving an IGA Score of 0 or 1 at Week 16 by Serum Guselkumab Concentrations at Week 16 Among Subjects Randomized to Guselkumab at Week 0 are presented in **Figure 10**.

Figure 10: Percent of Subjects Achieving an IGA Score of 0 or 1 at Week 16 by Serum Guselkumab Concentrations at Week 16 Among Subjects Randomized to Guselkumab at Week 0



Dose justification

The proposed dose recommendation for paediatric patients ≥6 years of age with moderate to severe plaque PsO was based on the analyses of data from the paediatric PsO study CNTO1959PSO3011, analyses comparing the paediatric data with the adult PsO data from CNTO1959PSO3001 and CNTO1959PSO3002, and additional PK and safety analyses to support the proposed body weight cutoff for paediatric patients to use the adult dose.

In CNTO1959PSO3011, guselkumab at the doses studied (1.3 mg/kg for participants <70 kg [administered by 1 or 2 Varioject pens] and 100 mg for participants ≥70 kg [administered by 1 PFS-U]) was considered effective and safe in paediatric participants with moderate to severe PsO, with results generally comparable to those in adults:

- Significantly higher proportions of paediatric participants with plaque PsO on guselkumab achieved responses in both co-primary and key secondary clinical efficacy outcomes, compared with placebo. Efficacy outcomes in the paediatric study were generally similar to adult efficacy outcomes (CNTO1959PSO3001 and CNTO1959PSO3002), although paediatric participants achieved slightly lower numerical clinical response rates at comparable systemic drug exposure levels.
- Systemic exposure to guselkumab in the paediatric participants in CNTO1959PSO3011 was comparable to that observed in adults in the Phase 3 studies.
- Safety profile of guselkumab was comparable to placebo over 16 weeks, and comparable with that of adults, with no demonstrable differences in safety or tolerability between the paediatric and adult population.

The chosen cut-off of ≥70 kg for the 100 mg guselkumab dose for study CNTO1959PSO3011 was based on a comparison of predicted exposures with the overall adult data, regardless of body weight, and was therefore considered conservative by the MAH. For adults with moderate to severe plaque PsO, the fixed 100 mg dose is recommended regardless of body weight. In the Phase 3 studies, adults

<70 kg (going as low as approximately 40 kg) had a 40% higher average systemic exposure when compared with adults weighing ≥70 kg, however, there were no discernible differences in safety profile between these weight subgroups. Also, supplemental PK/PD safety analyses on pooled data from adult Phase 3 PsO and PsA studies showed that safety was not associated with exposure metrics, as shown by the similar incidence of treatment-emergent adverse events by Ctrough or AUC quartiles (Chen 2022).

To better align paediatric and adult dose regimens, PK modeling and simulation was used to assess the impact of lowering the paediatric body weight cutoff for the 100 mg guselkumab dose from 70 kg to 40 kg. For the simulation, the assumed dose regimen was 1.3 mg/kg up to a maximum of 45 mg (maximum deliverable dose with the adjustable dose Varioject pen) for patients weighing <40 kg, and 100 mg for patients weighing ≥40 kg, given at Week 0, Week 4, and q8w thereafter (simulated to steady-state). The simulations have shown that even though the predicted systemic exposure for paediatric patients weighing 40 kg to 70 kg and receiving the 100 mg fixed guselkumab dose would be higher than what was studied in the paediatric Phase 3 study, they would not exceed the systemic exposure observed in adults weighing <70 kg, which is considered safe as described above. For efficacy, there should be no negative impact as there was no apparent E-R relationship in paediatric participants, and a tendency for slightly lower clinical responses in adult participants in the lower Ctrough quartiles. Even though with the proposed dose regimen, paediatric patients weighing ≥35 to <40 kg received a lower dose than that in study CNTO1959PSO3011, their predicted Ctrough was not below that observed in adults. There is a tendency to use a lower paediatric body weight cutoff for the adult dose for biologics, particularly if that is supported by a wide therapeutic window as is the case for guselkumab (Yang 2019). Also, with the proposed weight-based dosage, the MAH highlighted that paediatric patients would be dosed more conveniently with either 1 Varioject pen or 1 PFS-U, ie, a single injection to administer the dose.

Taken together, based on the totality of supporting PK, safety, and efficacy data for guselkumab in paediatric and adult participants, as well as practical considerations, the MAH proposed the following paediatric dose for guselkumab, to be given at Week 0, Week 4, and q8w thereafter:

- Body weight <40 kg (at time of dose): body weight-based dose, between 10 and 45 mg, administered with the adjustable dose pen (Varioject pen)

Table 12: Recommended Dose of Guselkumab for Subcutaneous Injection in Paediatric Patients With Plaque PsO

Body Weight	Dose (mg)[a]
12 to 15 kg	20
16 to 19 kg	25
20 to 23 kg	30
24 to 26 kg	35
27 to 30 kg	40
31 to 39 kg	45
≥40 kg	100

PsO=psoriasis.

[a] Doses up to and including 45 mg are administered using the Varioject pen (variable dose injector); the 100 mg dose is administered using the PFS-U (100 mg prefilled syringe fitted with the UltraSafe Plus™ Passive Needle Guard device).

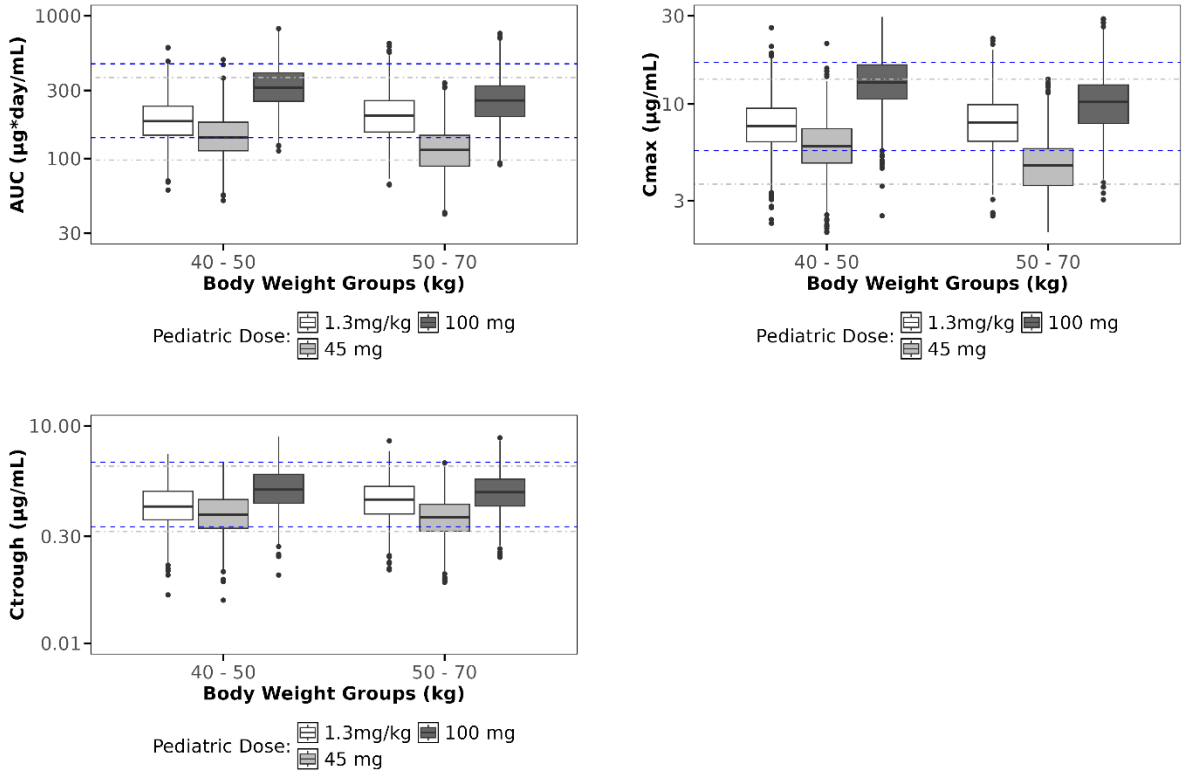
- Body weight ≥40 kg (at time of dose): 100 mg administered with the prefilled syringe (PFS-U)

Upon the CHMP's request, the MAH provided additional simulations evaluating a 45 mg fixed dose for children between 40 and 70 kg as compared with the proposed 100 mg fixed dose and the studied 1.3 mg/kg dose.

Figure 11 represents results from the model-predicted exposure metrics for paediatric participants weighing 40-50 kg and 50-70 kg. Model-predicted exposure metrics in paediatric patients (40-50 kg and 50-60 kg) receiving a fixed 45 mg or a fixed 100 mg dose, and adult patients (70-90 kg, 90-120 kg, 120-198 kg) receiving the (approved) 100 mg dose are provided in Figure 12.

Table 13 shows the percentages of adult and paediatric participants by body weight group predicted to have steady-state trough guselkumab concentration <0.67 µg/mL.

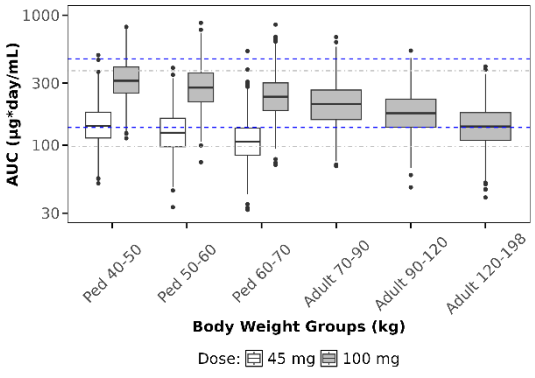
Figure 11: Comparison of Model-predicted Steady-State PK Exposure Metrics in Pediatric Participants Weighing 40–50 kg and 50–70 kg Administered 1.3 mg/kg, 45 mg, or 100 mg Doses

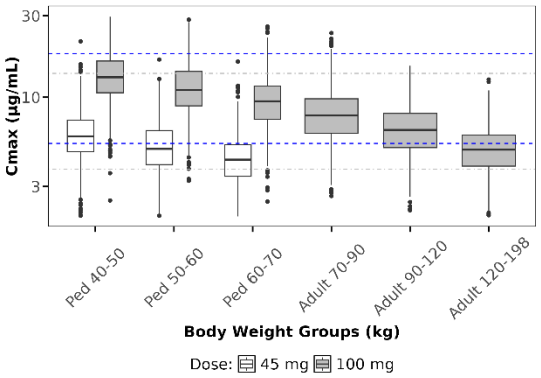


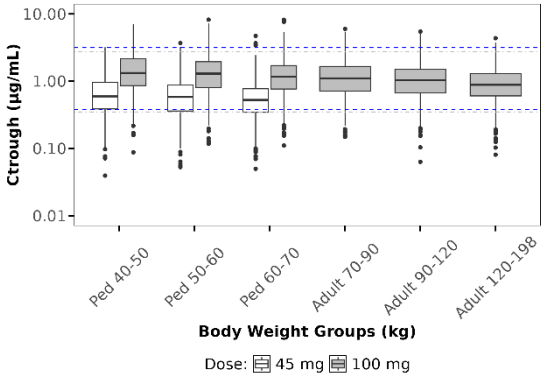
Note: Data represent simulations for virtual participants (1,000/group). The grey dashed lines in each figure represent the 90% prediction intervals of the overall adult steady-state PK metric. The blue dashed lines in each figure represent the 90% prediction interval of the steady-state PK metric in adult participants with body weight <70 kg. Each boxplot represents the median and IQR for each simulated group. The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

Weight groups are lower bound inclusive and upper bound exclusive.

Figure 12: Model-predicted Exposure Metrics for a Fixed 45 mg or 100 mg Guselkumab SC Dose, by Body Weight Category in Paediatrics, as Compared to Adults (100 mg Dose)







Note: Simulations consist of virtual participants (1,000/group). The grey dashed lines in each figure represent the 90% prediction intervals of the overall adult steady-state PK metric. The blue dashed lines in each figure represent the 90% prediction interval of the steady-state PK metric in adult participants with body weight <70 kg. Each boxplot represents the median and IQR for each simulated group. The lower and upper hinges of the boxplot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5*IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5*IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

Weight groups are lower bound inclusive and upper bound exclusive.

Table 13: Percentage of Participants With Predicted Steady-state Trough Guselkumab Concentration <0.67 µg/mL

	q8w guselkumab dose		
Body weight group	1.3 mg/kg	45 mg	100 mg
Peds 40-50 kg	41.2%	56.5%	16.4%
Peds 50-60 kg	31.6%	58.3%	17.8%
Peds 60-70 kg	27.2%	66.2%	19.6%
Adults (40-198 kg)			24.0%
Adults 70-90 kg			21.5%
Adults 90-120 kg			25.8%
Adults 120-198 kg			31.6%

Note: Simulations were performed for 1,000 virtual participants in each body weight group. Simulations consist of virtual participants sampled from the NHANES III database for pediatrics and sampled from the final PopPK dataset for adult studies. Body weight groups are lower bound inclusive and upper bound exclusive.

2.6.3. Discussion on clinical pharmacology

To support the claimed indication in paediatric patients with plaque PsO, the MAH submitted study CNTO1959PSO3011 (PROTOSTAR), which evaluated guselkumab for the treatment of chronic plaque PsO in paediatric participants (ages 6 to <18 years). In this study, guselkumab was administered at 1.3 mg/kg to participants weighing <70 kg (using one or two VarioJect pen injections) and at a fixed dose of 100 mg to those weighing ≥70 kg (using the PFS-U device). An industry-standard method was used to measure guselkumab concentrations and anti-drug antibodies. The validity of the analytical data is not questioned, and the individual concentration–time profiles were subsequently submitted at additional request.

The observed serum concentration-time data in paediatric patients were pooled with data from adult PsO patients for a PoP-PK analysis. The final model used was a one-compartment linear PK model with first-order absorption and elimination, including allometric scaling of clearance (CL/F) and volume of distribution (V/F), fixed to 0.75 and 1.0, respectively. The model assumed equal SC bioavailability in adults and children. Although this assumption was necessary for technical reasons, it may not hold true, especially for children aged 6–12 years, due to factors such as thinner subcutaneous fat layers, differences in lymphatic flow, and immature dermal systems. However, the clinical relevance of these factors is uncertain and the MAH pointed out in its response that these concerns lack solid experimental or clinical evidence. Sporadic observations may be explained by other factors, such as smaller injected volume. Furthermore, guselkumab's bioavailability is comparable to other monoclonal antibodies; therefore, no concern was raised.

Another issue potentially impacting comparability with adult data was the use of the VarioJect device. The VarioJect (PFS-V) is a manually operated, variable-dose, single-use injector used in the paediatric

trial. This device allows selection of one of eight doses, ranging from 10 mg to 45 mg in 5 mg increments (0.10 to 0.45 mL volume in 0.05 mL increments). In study CNTO1959PSO3011, 11 participants reported complaints related to VarioJect usage, for 5 of these, this occurred in Part 1 through Week 16 and for 6 of these, this occurred from Week 16 through Week 52. Since administration in Part 1 was performed by study staff, the CHMP raised a concern as these complaints may point to product-related issues rather than user error. Upon the CHMP's request, the MAH presented a summary of thorough investigations to identify the root cause of these administration errors. No manufacturing defect was identified; user error was considered the most likely cause. Further, the MAH assured that adequate training will be provided on the use of the device. Considering also the warnings included in the SmPC and PIL requiring administration by appropriately trained personnel, the CHMP considered that these measures were sufficient to minimise the risk of users errors.

The PoP-PK model confirmed that guselkumab exposure in the paediatric population is weight-dependent. Although serum concentrations differed slightly between paediatric and adult groups, the overlap in concentration ranges indicated that these differences would not be clinically relevant. Thus, the MAH's weight-based dosing approach in CNTO1959PSO3011 was found acceptable. Though, the CHMP noted some limitations.

For patients under 40 kg, the weight-based dose recommendation applied in the SmPC Section 4.2 differed from the dosing applied in Study CNTO1959PSO3011 (i.e. the 1.3 mg/kg dose). However, for the weight categories between 12 kg up to 30 kg, the proposed dose recommendations are within the upper limits of the respective weight category used in study CNTO1959PSO3011. Further, for the weight category of 31-39 kg, the recommended dose of 45 mg is close to the median of the lower and upper dose limits of the bodyweight-based category used in study CNTO1959PSO3011 (40.3-50.7 mg). Hence, the weight-based posology in patients under 40 kg was acceptable to the CHMP.

A fixed dosing of 100 mg, which corresponds to the adult dose, was proposed in SmPC Section 4.2 in children weighing 40 kg and above. The proposed dosing was mainly supported by simulations of the PoP-PK model since only 29 participants in Part 1 and 16 in Part 2 in study CNTO1959PSO3011 were under 18 years old and weighed <70 kg. The MAH further justified the fixed dose of 100 mg in patients ≥40 kg since the weight-based dosing in study CNTO1959PSO3011 required two VarioJect injections for participants ≥40 kg, which is inconvenient and may prompt deviation from the study regimen. However, the CHMP noted that the simulated exposure in children weighing 40–50 kg could indicate overexposure compared to other groups, including adults. In the absence of exposure–response relationship shown in the paediatric population, further justification to the proposed dosing was requested including exploring alternatives such as a 45 mg fixed dose (requiring only one VarioJect injection). In response to the CHMP's request, the MAH provided additional simulations. These simulations were considered in light of adult E–R data, where maintaining steady-state concentration (Css) ≥0.67 µg/mL was the therapeutic goal. The 45 mg fixed dose regimen was not considered appropriate in view of the large proportion of patients underexposed (Css <0.67 µg/mL) that would be up to 66.2% of paediatric patients. From an efficacy perspective, the 100 mg dose was found acceptable as the proportion of paediatric patients underexposed (16.4–19.6%) was closely aligned with the adult population (24%). Further, regarding safety, no exposure–safety relationship was observed in Phase 3 adult studies across the range of exposures expected with the 100 mg dose. AE incidence in guselkumab exposure quartiles was similar to placebo. The 100 mg fixed dose was considered adequate also for the subgroup of patients 40-50kg. Therefore, the 100 mg q8w fixed dose for the patients weighing 40 kg and above paediatric group was agreed by the CHMP.

In terms of efficacy, the CHMP noted that response rates (PASI75 and IGA 0/1) were lower in paediatric participants compared with adults. However, the differences in PASI75 response were not

considered clinically relevant, given the consistency of efficacy in adults, the absence of safety concerns at higher exposure, and supportive long-term extension data from Study CNTO1959PSO3011 showing sustained efficacy in paediatric patients.

There was no apparent association between the development of antibodies and the development of injection site reactions. There was no apparent effect of antibodies on PK or clinical efficacy. However, the small numbers of participants positive to antibodies precluded to draw firm conclusions. The SmPC Section 4.8 was updated to include immunogenicity results in paediatric patients with PsO.

2.6.4. Conclusions on clinical pharmacology

The totality of evidence, including PK modelling, PD analyses, clinical efficacy, and safety, supported the proposed paediatric dosing regimen. The fixed 100 mg q8w dose for patients ⩾40 kg was acceptable to the CHMP, despite exceeding the maximum studied dose, as it ensures adequate exposure and aligns with adult therapeutic targets. For patients <40 kg, weight-based dosing with the VarioJect is appropriate.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The paediatric PsO programme of guselkumab did not include dedicated dose-response study.

2.6.5.2. Main study(ies)

CNTO1959PSO3011 - A Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Paediatric Participants (⩾6 To <18 Years of Age)

Methods

Study CNTO1959PSO3011 was an ongoing at time of submission, Phase 3, multicenter, randomised, placebo- and active comparator controlled study evaluating the efficacy, safety, and PK of subcutaneously administered guselkumab for the treatment of chronic plaque PsO in paediatric participants ⩾6 to <18 years of age whose disease cannot be adequately controlled with phototherapy and/or topical therapies.

The main study (through Week 52) is complete and was conducted in 2 parts. In Part 1, the efficacy, safety, and PK of a weight-based dose regimen of guselkumab was evaluated in paediatric participants during a 16-week randomised, placebo- and active comparator-controlled period, followed by an uncontrolled period of continued treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. In the reference arm, the active comparator (etanercept) was administered in an open-label fashion during the controlled period of the study, and efficacy was assessed by a blinded efficacy evaluator to reduce potential bias during data collection and evaluation of clinical endpoints. The open-label reference treatment arm through Week 16 was included to support comparison of the efficacy of etanercept with placebo and was intended to help internally validate the overall results of the paediatric PsO study. This study was not powered for an efficacy comparison between etanercept and guselkumab treatment groups. Placebo and guselkumab treatments were administered in a blinded fashion.

Part 1 of the study was divided into Part 1a (⩾12 to <18 years of age, adolescents) and Part 1b (⩾ 6 to <12 years of age, young children).

Part 2 of the main study was open-label and single arm, with the aim of collecting additional efficacy, safety, and PK data for paediatric participants with a continuous weight-based dose regimen of guselkumab at Week 0, Week 4, and q8w thereafter through Week 52. A total of 92 participants were randomised in Part 1 and a total of 28 participants were enrolled in Part 2 of the study.

Participants who completed Week 52 of the main study and who have had a beneficial response from guselkumab treatment as determined by the investigator, had the option of continuing with a weight-based guselkumab q8w regimen of at least 1 year in the LTE of study CNTO1959PSO3011 until they reached 18 years, from when, they become eligible for guselkumab therapy according to the adult PSO indication.

- **Study Participants**

Main inclusion criteria were as follows:

- The participant population was comprised of boys and girls who have had a diagnosis of moderate to severe plaque PsO, defined as having an IGA ≥3, and a PASI ≥12, and a BSA ≥10, and at least one of the following:
    - very thick lesions,
    - clinically relevant facial, genital, or hand/foot involvement,
    - PASI ≥20, BSA >20, or
    - IGA=4.
- Participants were also required to be a candidate for systemic treatment or phototherapy of plaque PsO and have plaque PsO considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy. Participants with nonplaque forms of PsO (eg, erythrodermic, guttate, or pustular) were excluded from the study.
- Be considered, in the opinion of the investigator, a suitable candidate for etanercept therapy according to their country's approved etanercept product labeling.
- Tuberculosis (TB)-screening criteria:
    - Had no history of latent or active TB before screening.
    - Had no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - Had had no recent close contact with a person with active TB.

  Within 10 weeks before the first administration of study intervention, had a negative QuantiFERON-R-TB test result. If the QuantiFERON-TB test was not approved/registered in that country or the tuberculin skin test was mandated by local health authorities, within 10 weeks before the first administration of study intervention, a negative tuberculin skin test was additionally required.
- Acceptable evidence of immunity to measles, mumps, rubella, and varicella.
- Must have agreed not to receive a bacille Calmette-Guerin (BCG) vaccination within 12 months of screening, during the study, or within 12 months after the last administration of study intervention.
- Must avoid prolonged sun exposure and use of tanning booths or other ultraviolet light sources during study.

- screening laboratory test results within prespecified values

Main exclusion criteria were as follows:

Medical history-related exclusion criteria

- Nonplaque forms of psoriasis (eg, erythrodermic, guttate, or pustular), drug-induced psoriasis
- Is pregnant, nursing, or planning a pregnancy or fathering a child while enrolled in the study or within 12 weeks after receiving the last administration of study intervention.
- History of or current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease
- Major surgery (general anesthaesia + hospitalization) within 8 weeks before screening, surgery planned during the time the participant is expected to participate in the study, with the exclusion of planned surgical procedures under local anestheasia, prior organ transplantation
- Unstable suicidal ideation or suicidal behaviour.
- Substance abuse problem within the previous 12 months.

Medical therapies-related exclusion criteria

- Had previously received guselkumab or etanercept.
- Contraindications to the use of etanercept per local prescribing information.
- Anti-TNFα biologic therapy (with the exception of etanercept, see exclusion 9) within the previous 3 months before the first administration of study intervention.
- Contraindication for anti-TNFα therapy (history of known demyelinating diseases, known or suspected intolerance or hypersensitivity to anti-TNFα medications, history of/concurrent congestive heart failure (CHF), including medically controlled CHF.
- Use of any therapeutic agent directly targeted to IL-12/23, IL-17, or IL-23 within 6 months of the first administration of study intervention
- Had received natalizumab, efalizumab, or agents that deplete B or T cells within 12 months of screening, or, if after receiving these agents, evidence is available at screening of persistent depletion of the targeted lymphocyte population.
- Had received any systemic immunosuppressants within 4 weeks of the first administration of study intervention.
- Had received phototherapy or any systemic medications/treatments that could affect psoriasis or IGA evaluations within 4 weeks of the first administration of study intervention.
- Had used topical medications/treatments that could have affected psoriasis or IGA evaluations within 2 weeks of the first administration of study intervention.
- Was currently receiving lithium, antimalarials, or intramuscular (IM) gold, or had received lithium, antimalarials, or IM gold within 4 weeks of the first administration of study intervention.
- Had received an experimental antibody or biologic therapy within the previous 6 months or received any other experimental therapy or new investigational agent (topical or systemic) within 30 days or 5 half-lives (whichever is longer) of any study intervention administration or is currently enrolled in another study using an investigational agent or procedure.

- Had received / expected to receive, any live virus or bacterial vaccination (with the exception of varicella or MMR vaccines; see inclusion criterion 12) within 3 months (or longer as indicated in the package insert of the relevant vaccine) prior to the first administration of study intervention, during the study, or within 12 weeks after the last administration of study intervention.
- BCG vaccination within 12 months of screening.
- Previous immediate hypersensitivity response, including anaphylaxis, to an immunoglobulin product (eg, plasma derived or recombinant mAb).
- Known allergies, hypersensitivity, or intolerance to guselkumab or its excipients (refer to Investigator's Brochure) or etanercept or its excipients.

Infections or predisposition to infections

- History of chronic or recurrent infectious disease, open, draining, or infected skin wounds or ulcers, latent or active granulomatous infection, including TB, histoplasmosis, or coccidioidomycosis, nontuberculous mycobacterial infection opportunistic infection prior to screening.
- Had or had had a serious infection (eg, sepsis, pneumonia or pyelonephritis), or herpes zoster, or had been hospitalized or received IV antibiotics for an infection during the 2 months before screening.
- Persistently indeterminate (indeterminate on repeat sampling) QuantiFERON-TB test results.
- HIV infection (positive serology for HIV antibody), test positive for antibodies to hepatitis C virus (HCV) Tests positive for hepatitis B virus (HBV) infection at screening.
- Documented history of immune deficiency syndrome (eg, severe combined immunodeficiency syndrome, T cell deficiency syndromes, B cell deficiency syndromes and chronic granulomatous disease).
- COVID-19 infection:
    - During the 6 weeks prior to baseline, had had any of the following (regardless of vaccination status):
        a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (test positive) OR
        b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results) OR
        c) close contact with a person with known or suspected SARS-CoV-2 infection
    - Exception: may have been included with a documented negative result for a validated SARS-CoV-2 test:
        - obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, [eg, fever, cough, dyspnea]) AND
        - with absence of all conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

Malignancy or increased potential for malignancy

- Known history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance (MGUS); signs and symptoms suggestive of possible lymphoproliferative disease, known malignancy or a history of malignancy.

- **Treatments**

Part 1 through Week 16

- Guselkumab: one of the following dose levels depending on their weight:
    - Weight <70 kg: 1.3 mg/kg sc., administered using 1 or 2 VarioJect pens at Week 0, Week 4, and Week 12.
    - Weight ≥70 kg: 100 mg sc., administered using the PFS-U, at Week 0, Week 4, and Week 12.
- Placebo: received sc. injections with a volume determined using the same weight-based dose calculation as for guselkumab at Week 0, Week 4, and Week 12.
- Etanercept: Commercially available etanercept was administered in a weight-based dose:
    - Weight <63 kg: 0.8 mg/kg once weekly using 25 mg powder and solvent for solution for SC injection.
    - Weight ≥63 kg: 50 mg once weekly administered using a 50 mg prefilled syringe for SC injection.

Part 1 from Week 16 to Week 52

Participants in Part 1 received treatment from Week 16 through Week 52 as outlined in **Table 14**.

Participants enrolled in Part 2 of the study received the same weight-based sc. doses of guselkumab as patients in Part 1, but in open-label setting at Week 0, Week 4, and q8w thereafter through Week 52.

Table 14*:* Part 1: Dosing Week 16 to Week 52

Group	Randomized to	Who	Treatment
Group 1a	Guselkumab	PASI 90 responders at Week 16	Withdrawn from study intervention Retreatment upon loss of ≥50% of their Week 16 PASI improvement: weight-based guselkumab SC dose at time of retreatment, 4 weeks later, and thereafter q8w through Week 52
Group 1b	Guselkumab	PASI 90 nonresponders at Week 16	Placebo at Week 16 and guselkumab q8w from Week 20 through Week 52
Group 2a	Placebo	PASI 90 responders at Week 16	Withdrawn from study intervention Initiation of guselkumab treatment upon loss of ≥50% of their Week 16 PASI improvement: weight-based guselkumab SC dose at time of initiation, 4 weeks later, and thereafter q8w through Week 52
Group 2b	Placebo	PASI 90 nonresponders at Week 16	Guselkumab dose at Week 16 and q8w from Week 20 through Week 52
Group 3	Etanercept	Those who elected to continue in the study	Guselkumab dose at Week 20 and Week 24, followed by q8w dosing thereafter through Week 48

- **Objectives**

The primary objective of Study CNTO1959PSO3011 was to evaluate the efficacy and safety of guselkumab in paediatric participants aged ≥6 through <18 years with chronic plaque PsO.

The primary hypotheses were that guselkumab treatment is superior to placebo as assessed by the proportion of participants achieving an IGA score of cleared (0) or minimal (1) and the proportion of participants achieving a PASI 75 response at Week 16.

- **Outcomes/endpoints**

Co-primary endpoints were as follows: proportion of participants achieving an IGA score of cleared (0) or minimal (1) and the proportion of participants achieving a PASI 75 response at Week 16.

There were 4 major secondary endpoints in this study to be compared between the guselkumab group and the placebo group:

- The proportion of participants achieving a PASI 90 response at Week 16.
- The proportion of participants achieving an IGA score of cleared (0) at Week 16.
- The proportion of participants achieving a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16.

- **Sample size**

Approximately 40 participants were randomised to guselkumab, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) were randomised to placebo. With the assumptions of response rates of 65% in the guselkumab treatment group and 13% in the placebo group, the proposed 40 participants in the guselkumab group and 25 in the placebo group provided at least 99% power to detect a significant difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between the guselkumab and placebo treatment groups at a 2-sided significance level of 0.05. These sample sizes were also chosen to ensure sufficient power for major secondary endpoints. With approximately 25 participants (15 in Part 1a and 10 in Part 1b) randomised to receive etanercept, and approximately 25 participants (15 in Part 1a and 10 in Part 1b) in the placebo group, there was at

least 81% power to detect a 40% difference in the proportion of IGA responders (0 or 1) and PASI 75 responders at Week 16 separately between etanercept (assumed response rate 53%) and placebo (assumed response rate 13%) treatment groups at a 2-sided significance level of 0.05.

- **Randomisation and Blinding (masking)**

All participants were centrally randomized (Part 1) and centrally assigned (Part 2) to study intervention using an IWRS.

Participants in Part 1a (≥12 to <18years of age) were randomized in a 2:1:1 ratio to guselkumab, placebo, or etanercept and participants in Part 1b (≥6 to <12 years of age) were randomized separately in a 1:1:1 ratio to 1 of same 3 treatment groups using computer-generated randomization schedules.

This study design included investigator, efficacy evaluator, caregiver(s) and participant blinding/masking for Part 1. Treatment in Part 1 was blinded for guselkumab and placebo through Week 16, etanercept was open-label. Part 2 of the study was open-label and did not employ blinding, with the exception of using a blinded efficacy evaluator. All participants in Part 2 received open-label guselkumab treatment.

- **Statistical methods**

Full Analysis Set

Part 1

Full Analysis Set (FAS) included all randomised subjects in Part 1a and Part 1b, this was the efficacy analysis set for Part 1. During the efficacy analysis, subjects in the FAS were analysed according to their assigned treatment group regardless of their actual treatment received.

Depending on the endpoints, selected secondary efficacy analyses were performed on subsets of all randomized subjects:

- PASI 90 responders withdrawn from study agent at Week 16
- PASI 90 responders withdrawn from study agent at Week 16 and later retreated with guselkumab
- PASI 90 non-responders at Week 16 who continued guselkumab treatment
- Etanercept subjects who crossed over to receive treatment of guselkumab

Part 2

The efficacy analyses for Part 2 of the study were based upon the FAS which included all subjects enrolled in Part 2.

LTE

The efficacy analyses for Long Term Extension were based upon the FAS which included all subjects who entered into the LTE period.

Per Protocol Analysis Set

The efficacy analysis for the co-primary endpoints were also performed based on the per protocol analysis set. The per protocol population included subjects in full analysis set except those who did not meet some prespecified inclusion/exclusion criterion

There were 2 co-primary endpoints in this study: the proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) at Week 16 and the proportion of subjects who achieved a PASI 75 response at Week 16.

To address the primary objective, a 2-sided (α=0.05) Fisher's exact test, stratified by age group (≥6 to <12 years, ≥12 to <18 years) and pooled region (NA, EU), was used for the co-primary endpoints. Both co-primary endpoints were tested at a 2-sided α-level of 0.05. The study was planned to be considered positive if the guselkumab group was significantly different from the placebo group for both co-primary endpoints. In addition, the comparison between etanercept and placebo for the co-primary endpoints was also performed using Fisher's exact test, stratified by age and region, and nominal p-values were reported.

One interim analysis was planned for this study after all participants ≥12 to <18 years of age in Part 1a had completed Week 16. All available guselkumab PK data for participants ≥12 to <18 years of age through Week 16 was evaluated via modeling and simulation, to determine if the body weight-based dose used in Part 1a provided exposure comparable to adults, or whether a revised body weight-based dose should be instituted in Part 1b. Efficacy data was not analyzed in the interim analyses and no adjustment was made for the significance level.

Multiplicity Adjustment for Testing Procedures

Both of the co-primary endpoint analyses were compared between the guselkumab treatment group and the placebo group and tested at a 2-sided α-level of 0.05. If one of the comparisons was not significant at the 2-sided α-level of 0.05, the co-primary endpoints were planned to be considered not significant.

In order to control the overall Type 1 error rate, the co-primary analyses and major secondary analyses were tested in a fixed sequence. The analyses of the major secondary endpoints were performed only if both primary analyses are significant, and were performed in the fixed sequence testing approach, using the following order of key secondary endpoints:

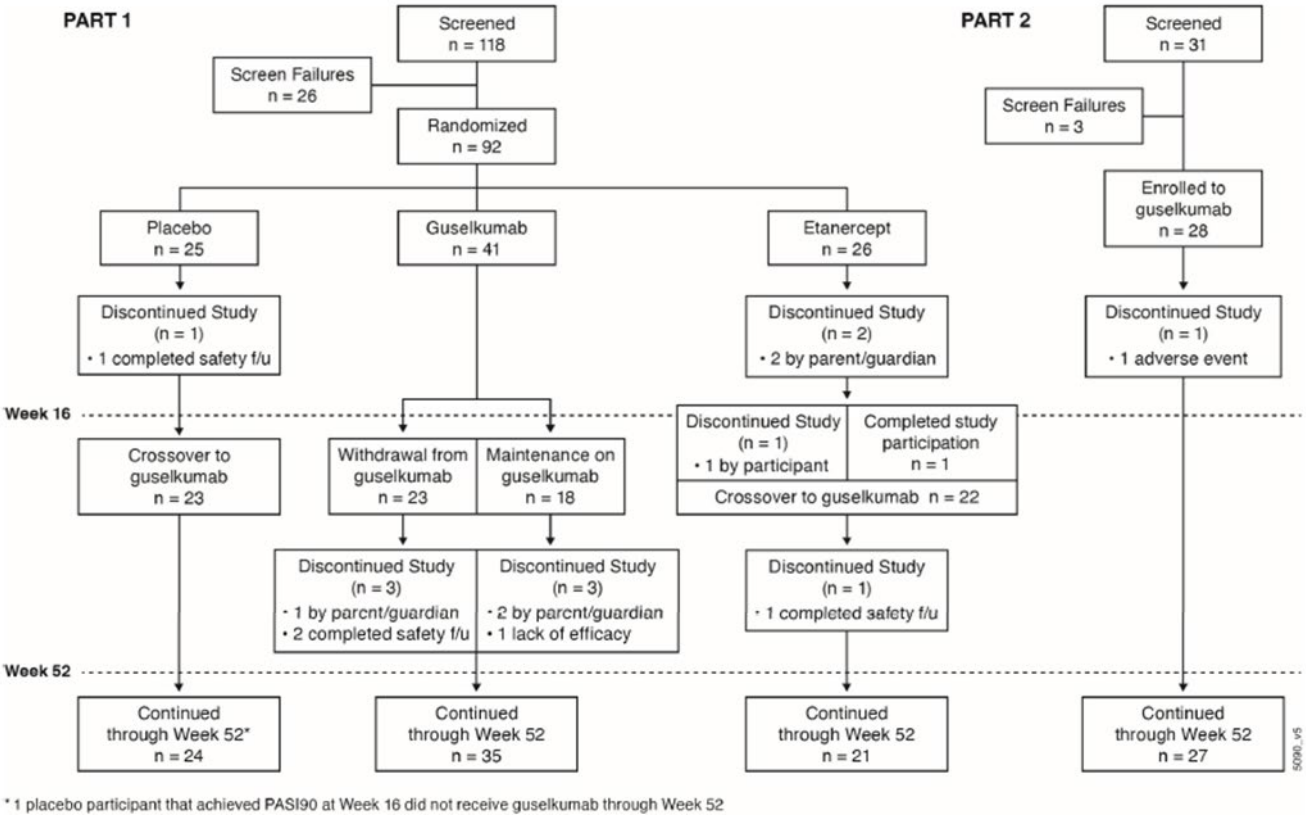
- The proportion of subjects who achieved a PASI 90 response at Week 16.
- The proportion of subjects who achieved an IGA score of cleared (0) at Week 16.
- The proportion of subjects who achieved a PASI 100 response at Week 16.
- The change from baseline in CDLQI at Week 16

If a given comparison between the guselkumab treatment group and the placebo group was not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in this sequence would be considered not significant and will be considered as supportive analyses.

Results

- **Participant flow**

Figure 13: Participant flow



- **Recruitment**

Screening of 1st patient: 12 July 2018

Last observation from last participant: 29 March 2024

- **Conduct of the study**

Original protocol was dated on 21 December 2017 and has undergone 4 amendments:

- Amendment 1 (9 May 2018) concerned to address health authority advice, and included insertion or removal of some assessment (Physical examination, Haematology/Chemistry, VarioJect Injection Assessment Questionnaire) to or from specified visits;
- Amendment 2 (8 May 2019) clarified that assessment of serum guselkumab concentrations and antibodies to guselkumab were not required at Weeks 0, 4, and 12 for participants who were randomized to etanercept;
- Amendment 3 (19 February 2020) clarified information related to the management of liver function test abnormalities;
- Amendment 4 (24 February 2022) included clarifications and additions to align with the latest protocol template for COVID-19 situations, tuberculosis language, handling potential Hy's law situations, and a clarification on a post-trial access and the long-term extension.

Protocol deviations

Part 1: Through Week 16

Major protocol deviations through Week 16 are provided in **Table 15**.

Two participants in the guselkumab group had a major protocol deviation due to not satisfying the entry criteria; 1 participant in Part 1a received phototherapy within 4 weeks of first drug administration, and 1 participant in Part 1b previously received a dose of etanercept.

One participant on placebo had a major protocol deviation due to administration of an incorrect dose based on their weight. A further 6 participants (2 in each treatment group) had 7 major protocol deviations for other reasons, including 2 deviations related to informed consent, 4 related to assessments not being done by a trained efficacy evaluator, and 1 participant that received an MMR vaccination after being randomized in the study.

Table 15: Summary of Subjects With Major Protocol Deviations Through Week 16; Full Analysis Set (Study CNTO1959PSO3011 Part 1)

	Placebo	Guselkumab	Etanercept	Total
Analysis set: Full analysis set	25	41	26	92
Subjects with major protocol deviations	3 (12.0%)	4 (9.8%)	2 (7.7%)	9 (9.8%)
Developed withdrawal criteria but not withdrawn	0	0	0	0
Entered but did not satisfy criteria	0	2 (4.9%)	0	2 (2.2%)
Received a disallowed concomitant treatment	0	0	0	0
Received wrong treatment or incorrect dose	1 (4.0%)	0	0	1 (1.1%)
Other	2 (8.0%)	2 (4.9%)	2 (7.7%)	6 (6.5%)

Part 1 and Part 2: Through Week 52

No additional major protocol deviations were observed from Week 16 through Week 52 in Part 1 of the study.

Major protocol deviations through Week 52 in Part 2 of the study are provided in **Table 16**.

Two participants received wrong treatment or an incorrect dose. Both participants received a lower than planned dose due to inaccurate weight recording in IWRS. An additional 3 participants had major protocol deviations for other reasons, including 2 related to critical assessments not being done, and 1 related to assessments not being done by a trained efficacy evaluator.

Table 16: Summary of Subjects With Major Protocol Deviations Through Week 52; Full Analysis Set (Study CNTO1959PSO3011 Part 2)

	Guselkumab
Analysis set: Full analysis set	28
Subjects with major protocol deviations	5 (17.9%)
Developed withdrawal criteria but not withdrawn	0
Entered but did not satisfy criteria	0
Received a disallowed concomitant treatment	0
Received wrong treatment or incorrect dose	2 (7.1%)
Other	3 (10.7%)

A sensitivity analysis was conducted on the per protocol population, pre-specified in the SAP.

- **Baseline data**

Table 17: Summary of Demographics, Clinical Disease Characteristics, and PsO Medication History at Baseline in CNTO1959PSO3011 Study; FAS

	Part 1				Part 2
	Placebo	Guselkumab	Etanercept	Total	
Analysis set: FAS	25	41	26	92	28
Demographics					
Mean (SD) age (years)	12.4 (3.63)	13.4 (2.86)	12.5 (3.29)	12.9 (3.20)	15.1 (1.59)
Males	12 (48.0%)	24 (58.5%)	15 (57.7%)	51 (55.4%)	17 (60.7%)
Mean (SD) height (kg)	152.2 (18.75)	162.4 (16.07)	156.2 (17.19)	157.9 (17.51)	171.58 (11.203)
Mean (SD) weight (kg)	54.6 (24.82)	59.4 (20.33)	56.4 (19.15)	57.3 (21.19)	68.42 (17.288)
Median BMI (kg/m^2)	21.3	20.6	21.2	20.7	22.20
Race					
White	20 (80.0%)	36 (87.8%)	22 (84.6%)	78 (84.8%)	28 (100%)
Asian	1 (4.0%)	1 (2.4%)	2 (7.7%)	4 (4.3%)	0
Black or African American	2 (8.0%)	1 (2.4%)	1 (3.8%)	4 (4.3%)	0
Ethnicity					
Hispanic or Latino	2 (8.0%)	2 (4.9%)	1 (3.8%)	5 (5.4%)	0
Not Hispanic or Latino	23 (92.0%)	39 (95.1%)	25 (96.2%)	87 (94.6%)	27 (96.4%)
Clinical disease characteristics					
Median PsO disease duration (years)	4.6	4.1	3.6	4.4	6.2
PsO disease duration ≥3 years	16 (64.0%)	33 (80.5%)	16 (61.5%)	65 (70.7%)	23 (82.1%)
Median age at diagnosis (years)	7.0	8.0	6.5	7.0	9.0
Median BSA	20.0	20.0	20.0	20.0	24.0
BSA ≥20	15 (60.0%)	22 (53.7%)	15 (57.7%)	52 (56.5%)	19 (67.9%)
Median PASI score (0-72)	17.2	17.5	16.6	17.4	19.6
PASI score ≥20	6 (24.0%)	17 (41.5%)	6 (23.1%)	29 (31.5%)	13 (46.4%)
IGA score of 3 (0-4)	20 (80.0%)	31 (75.6%)	21 (80.8%)	72 (78.3%)	15 (53.6%)
IGA score of 4 (0-4)	5 (20.0%)	10 (24.4%)	5 (19.2%)	20 (21.7%)	13 (46.4%)
Median CDLQI (0-30)	7.0	8.0	7.0	7.0	5.5
CDLQI score <10	14 (56.0%)	26 (63.4%)	14 (53.8%)	54 (58.7%)	19 (67.9%)
Median FDLQI (0-30)	9.0	10.0	10.0	10.0	11.0
PsO medication history					
Ever used topical therapies	25 (100.0%)	41 (100.0%)	26 (100.0%)	92 (100.0%)	28 (100%)
Ever used phototherapy (UVB or PUVA)	4 (16.0%)	15 (36.6%)	10 (38.5%)	29 (31.5%)	7 (25.0%)
Ever used non-biologic systemic therapies (PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib) (≥ 1 therapy)	7 (28.0%)	14 (34.1%)	8 (30.8%)	29 (31.5%)	13 (46.4%)
Ever used biologic therapies (infliximab, alefacept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab)	1 (4.0%)	4 (9.8%)	4 (15.4%)	9 (9.8%)	4 (14.3%)
Ever used non-biologic systemic or biologic therapies	8 (32.0%)	16 (39.0%)	12 (46.2%)	36 (39.1%)	14 (50.0%)

	Part 1				Part 2
	Placebo	Guselkumab	Etanercept	Total	
Ever used IL-12/23 inhibitors (ustekinumab, briakinumab)	0	4 (9.8%)	2 (7.7%)	6 (6.5%)	1 (3.6%)
Ever used anti-TNF-α therapies (adalimumab, infliximab)	0	0	1 (3.8%)	1 (1.1%)	0

Note: For demographics, n's for each parameter reflect non-missing values.

There were 3 participants (3.3%) with a history of PsA.

- **Numbers analysed**

Table 18: Number of Subjects in Each Analysis Set; All randomized Subjects (Study CNTO1959PSO3011 Part 1)

	Placebo	Guselkumab	Etanercept
Analysis set: All randomized subjects	25	41	26
Full analysis set	25 (100.0%)	41 (100.0%)	26 (100.0%)
Number of subjects at Week 16	25 (100.0%)	41 (100.0%)	NA
PASI 90 Responders	4 (16.0%)	23 (56.1%)	NA
PASI 90 Non-Responders	21 (84.0%)	18 (43.9%)	NA
Per protocol analysis set	25 (100.0%)	39 (95.1%)	23 (88.5%)
Safety analysis set	25 (100.0%)	41 (100.0%)	26 (100.0%)

- **Outcomes and estimation**

PART 1 results through Week 16

Co-primary endpoints

Table 19: Number of Subjects With an IGA Score of Cleared (0) or Minimal (1) and a PASI 75 Response

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

Note 1: CIs are based on exact method
Note 2: P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled). The primary comparison is between guselkumab and placebo.

Key secondary endpoints

Table 20: Number of Subjects with a PASI 90, PASI 100 and IGA 0/1 Response at Week 16 (Main Analysis); Full Analysis Set

	Placebo	Guselkumab	Etanercept
Analysis set: Full analysis set	25	41	26
PASI 90 responders	4 (16.0%)	23 (56.1%)	14 (53.8%)
Treatment difference (95% CI)		40.1 (15.6, 61.3)	37.8 (11.8, 61.8)
p-value		0.003	0.009
Subjects with IGA scores of cleared (0)	1 (4.0%)	16 (39.0%)	7 (26.9%)
Treatment difference (95% CI)		35.0 (10.5, 56.8)	22.9 (-3.9, 48.4)
p-value		0.004	0.061
PASI 100 responders	0	14 (34.1%)	7 (26.9%)
Treatment difference (95% CI)		34.1 (9.7, 56.1)	26.9 (0.1, 51.8)
p-value		0.002	0.013

Note 1: CIs are based on exact method
Note 2: P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region(pooled).

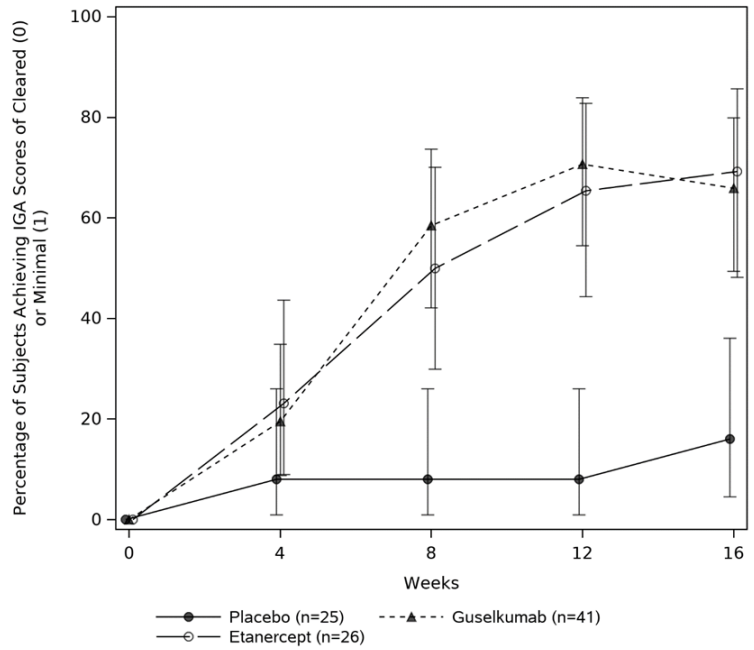
Table 21: Summary of Change From Baseline in CDLQI Score at Week 16 (Main Analysis); Full Analysis

	Placebo	Guselkumab	Etanercept
Analysis set: Full analysis set	25	41	26
Week 16			
N	25	41	26
Mean (SD)	-1.68 (6.323)	-7.12 (7.633)	-6.08 (5.692)
Median	-1.00	-4.00	-4.00
Range	(-18.0; 10.0)	(-27.0; 6.0)	(-19.0; 4.0)
IQ range	(-5.00; 1.00)	(-14.00; -2.00)	(-9.00; -2.00)
LSMean (95% CI)	-1.88 (-3.81, 0.05)	-7.28 (-8.87, -5.68)	-6.06 (-7.96, -4.15)
LSMean difference (95% CI)		-5.40 (-7.73, -3.06)	-4.18 (-6.74, -1.62)
p-value		<0.001	0.002

Key: IQ = interquartile
Note 1: The missing data was imputed as zero change from baseline after applying treatment failure rules and rescue treatment rules
Note 2: Test for no difference between treatments from MMRM model with factors of treatment group, region, age group, baseline CDLQI score, visit, baseline CDLQI score by visit and treatment by visit.

Figure 14: Percentages of Participants Achieving an IGA Score of Cleared (0) or Minimal (1) and an IGA Score of Cleared (0) Through Week 16 by Visit in CNTO1959PSO3011 Study; FAS, Part 1

IGA score of 0/1



IGA score of 0

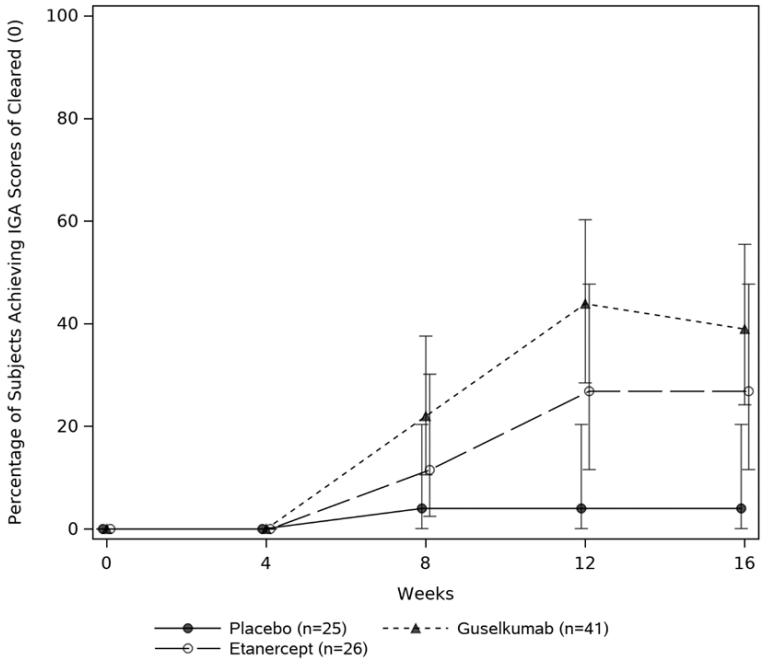
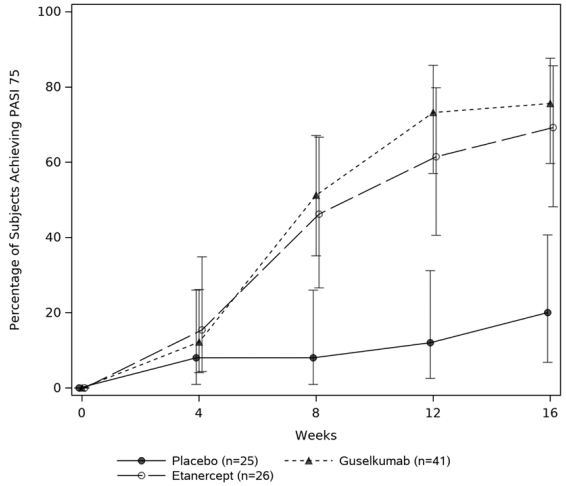
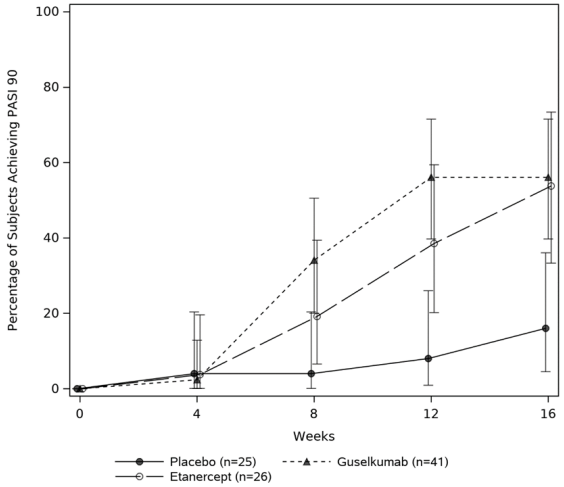


Figure 15: Percentages of Participants Achieving a PASI 90, PASI 75, and PASI 100 Response Through Week 16 by Visit in CNTO1959PSO3011 Study; FAS, Part 1

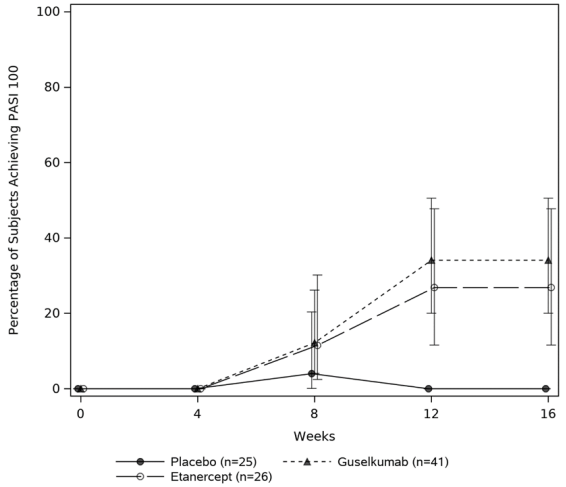
PASI 75



PASI 90



PASI 100



Efficacy Analyses From Week 16 Through Week 52 (Part 1; Withdrawal and Retreatment or Initiation of Treatment With Guselkumab)

Guselkumab PASI 90 Responders

For the 23 (56.1%) of 41 guselkumab-treated participants that achieved PASI 90 response at Week 16, after withdrawal of guselkumab, the loss of response was gradual:

- Loss of PASI 90 response was noted as early as 12 weeks after withdrawal of guselkumab treatment with a life-table estimated median time to loss of PASI 90 response of approximately 24 weeks from Week 16.
- IGA and PASI responses decreased through Week 52 after withdrawal of guselkumab treatment.
- Median BSA stayed 0 through 16 weeks after treatment withdrawal (Week 32) for the 23 guselkumab treated participants that achieved PASI 90 response at Week 16, and slowly increased after Week 32 through Week 52.
- Improvements in HRQoL were sustained through Week 28 (12 weeks post-treatment withdrawal) for the guselkumab PASI 90 responders that had treatment withdrawn at Week 16.
- Four (17.4%) of 23 participants required retreatment with guselkumab due to loss of ≥50% of Week 16 PASI improvements, with 2 participants retreated at Week 44 and 2 participants re-treated at Week 48.

Guselkumab PASI 90 Non-responders

Continued guselkumab treatment for an additional 32 weeks for the 18 (43.9%) of 41 PASI 90 non-responders at Week 16 resulted in response rates for an IGA score of 0/1 (13 [72.2%] participants), PASI 75 response (13 [72.2%] participants), PASI 90 response (11 [61.1%] participants), and an IGA score of 0 (8 [44.4%] participants) at Week 52.

Etanercept Crossover to Guselkumab

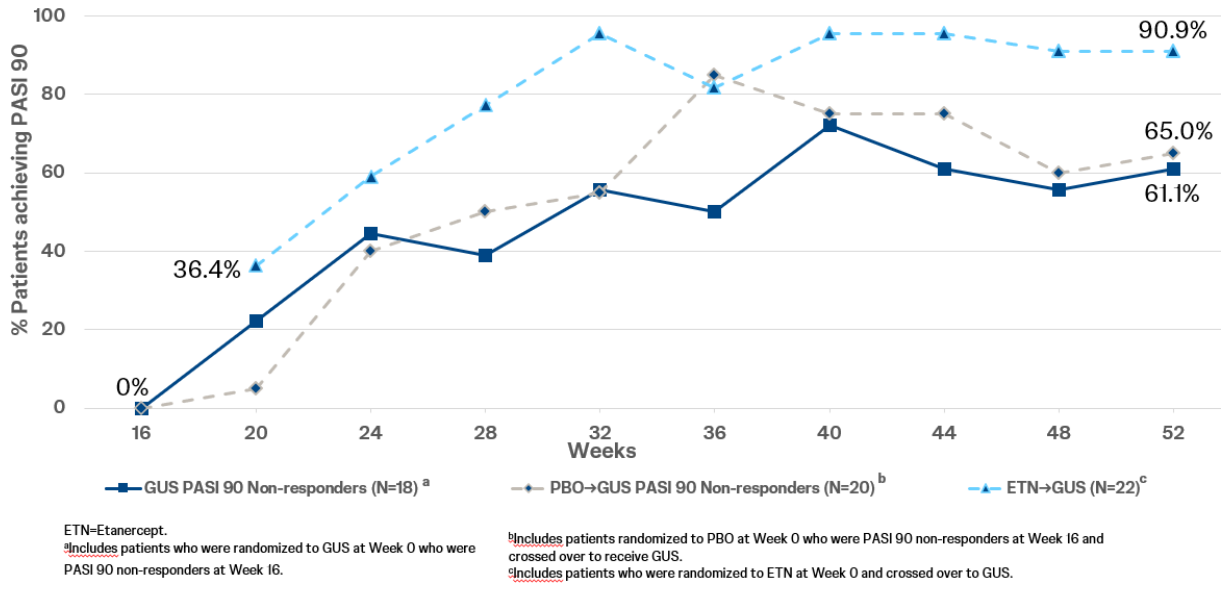
Initiation of guselkumab treatment for the 22 (84.6%) of 26 etanercept crossover participants at Week 20 resulted in 20 [90.9%] participants achieving an IGA score of 0/1, 21 [95.5%] participants achieving a PASI 75 response, 20 [90.9%] participants achieving a PASI 90 response, and 17 [77.3%] participants achieving an IGA score of 0 at Week 52.

Placebo Crossover to Guselkumab

Initiation of guselkumab treatment for the 20 (80.0%) of 25 placebo crossover PASI 90 non-responders at Week 16 resulted in 16 [80.0%] participants achieving an IGA score of 0/1, 19 [95.0%] participants achieving a PASI 75 response, 13 [65.0%] participants achieving a PASI 90 response, and 10 [50.0%] participants achieving an IGA score of 0 at Week 52.

Time course of PASI 90 response rate in the Week 16 non-responder group is presented in **Figure 16**.

Figure 16: Proportion of Participants in Part 1 Achieving PASI 90 Response from Week 16 Through Week 52 by Visit



ETN=Etanercept.
[a]Includes patients who were randomized to GUS at Week 0 who were PASI 90 non-responders at Week 16.
[b]Includes patients randomized to PBO at Week 0 who were PASI 90 non-responders at Week 16 and crossed over to receive GUS.
[c]Includes patients who were randomized to ETN at Week 0 and crossed over to GUS.

Guselkumab PASI 50 non-responders at Week 16

In the paediatric study CNTO1959PSO3011 Part 1, 5 out of 41 guselkumab treated participants (~12%) did not reach PASI 50 at Week 16. However, upon continued guselkumab treatment, 4 of these patients achieved a PASI 50 response: 3 at Week 24 and 1 at Week 28. Over the course of the study, these 4 patients all reached a minimum score of PASI 75 and 3 of those reached PASI 90. There was only 1 guselkumab non-responder that did not reach PASI 50 at Week 16 that did not respond after continued treatment through week 32, after which the patient discontinued the study.

Part 2 results

Table 22: Summary of Efficacy at Week 16 and Week 52; FAS (Study CNTO1959PSO3011 Open-label Part 2)

	Guselkumab	
	Week 16	**Week 52**
Analysis set: FAS	28	28
IGA scores of cleared (0) or minimal (1)	25 (89.3%)	24 (85.7%)
PASI 75 responders	23 (82.1%)	26 (92.9%)
PASI 90 responders	18 (64.3%)	23 (82.1%)
IGA scores of cleared (0)	13 (46.4%)	21 (75.0%)
PASI 100 responders	10 (35.7%)	15 (53.6%)
BSA change from baseline		
N	26	27
Mean (SD)	-22.7 (13.57)	-26.4 (14.52)
Median	-21.0	-24.0
Range	(-56, 0)	(-57, -2)
IQ range	(-34.0, -12.0)	(-35.0, -15.0)
Participants with CDLQI of 0 or 1 (n=24)	14 (58.3%)	16 (66.7%)
CDLQI change from baseline		
N	26	26
Mean (SD)	-6.8 (6.32)	-7.3 (6.83)
Median	-5.0	-5.0
Range	(-24, 0)	(-23, 1)
IQ range	(-9.0, -2.0)	(-10.0, -3.0)
Participants with FDLQI of 0 or 1 (n=22)	7 (31.8%)	11 (50.0%)
FDLQI change from baseline		
N	25	26
Mean (SD)	-5.5 (5.90)	-7.8 (5.68)
Median	-7.0	-8.5
Range	(-14, 7)	(-19, 0)
IQ range	(-10.0, -2.0)	(-11.0, -3.0)

Quality of life measures – Part 1 and Part 2

Table 23: Summary of Participants With a CDLQI/FDLQI Score of 0 or 1 in Participants with a Baseline CDLQI/FDLQI Score Greater Than 1; FAS (Study CNTO1959PSO3011 Part 1 and Part 2)

Part 1		
Guselkumab PASI 90 nonresponders	**Week 16**	**Week 52**
Participants with CDLQI of 0 or 1	6 (37.5%)	8 (50.0%)
Participants with FDLQI of 0 or 1	4 (25.0%)	6 (37.5%)
Placebo PASI 90 nonresponders	**Week 16**	**Week 52**
Participants with CDLQI of 0 or 1	2 (11.1%)	12 (66.7%)
Participants with FDLQI of 0 or 1	2 (11.1%)	6 (33.3%)
Etanercept crossovers	**Week 28**	**Week 52**
Participants with CDLQI of 0 or 1	13 (59.1%)	19 (86.4%)
Participants with FDLQI of 0 or 1	9 (42.9%)	13 (61.9%)
Part 2		
Open-label cohort	**Week 16**	**Week 52**
Participants with CDLQI of 0 or 1	14 (58.3%)	16 (66.7%)
Participants with FDLQI of 0 or 1	7 (31.8%)	11 (50.0%)

- **Ancillary analyses**

Table 24: Summary of Primary and Major Secondary Endpoints at Week 16 by Age Group: Full Analysis Set (in CNTO1959PSO3011 Part 1 Study)

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

During the procedure, upon the CHMP's request, the MAH provided the following *post hoc* sensitivity analysis excluding subjects with major protocol deviations due to PsO assessment not performed by a sponsor trained efficacy assessor:

Table 25: Number of Subjects With an IGA Score of Cleared (0) or Minimal (1), a PASI 75 Response and a PASI 90 Response at Week 16 (Sensitivity Analysis, excluding subjects with major protocol deviations due to PSO assessment not performed by a sponsor trained efficacy assessor); Full Analysis Set (Study CNTO1959PSO3011 Part 1)

	Placebo	Guselkumab
Analysis set: Full analysis set	24	39
Subjects with IGA scores of cleared (0) or minimal (1)	4 (16.7%)	25 (64.1%)
Treatment difference (95% CI)		47.4 (22.9, 67.9)
p-value		<0.001
PASI 75 responders	5 (20.8%)	29 (74.4%)
Treatment difference (95% CI)		53.5 (29.3, 72.7)
p-value		<0.001
PASI 90 responders	4 (16.7%)	21 (53.8%)
Treatment difference (95% CI)		37.2 (12.0, 59.1)
p-value		0.003

Note 1: CIs are based on exact method.
Note 2: P-values represent the comparisons with placebo and are based on the Fisher's exact test stratified by age group and region (pooled).
Note 3: Excluding subjects with major protocol deviations due to PSO assessment not performed by a sponsor trained efficacy assessor.

During the procedure, upon the CHMP's request, the MAH provided longer term extension data of Study CNTO1959PSO3011 for the withdrawn and retreatment patients:

A total of 94 participants entered the LTE (70 from Part 1, 24 from Part 2). Through the LTE data cutoff of 03 January 2025, of the 94 participants that entered the LTE, 39 (41%) were still ongoing in the LTE. For the 55 (59%) participants that ended treatment and participation in the LTE, the most common reason was the participant reaching 18 years of age (45 [82%]). One LTE participant discontinued treatment and study participation due to withdrawal by parent/caregiver attributed to

insufficient efficacy. Of the 9 LTE participants that discontinued the LTE due to other reasons, 7 were due to withdrawal by parent/guardian or subject, 1 was lost to follow up, and 1 for other reasons.

- *Guselkumab PASI 90 responders at Week 16 had guselkumab treatment withdrawn during the main study and all participants re-initiated guselkumab by Week 52:*
    - The IGA 0/1 response rate at Week 52 was 56.5%. At the first LTE visit at Week 60, the IGA 0/1 response was 88.9% and was maintained with response rates ranging between 80-100% through Week 228.
    - The PASI 75 and PASI 90 response rates at Week 52 were 56.5% and 30.4%, respectively. At LTE Week 60, the PASI 75 and PASI 90 response rates were 88.9% and 83.3%, respectively, and were both maintained with response rates ranging between 80-100% through Week 228.
- *Guselkumab PASI 90 non-responders at Week 16 continued to receive guselkumab treatment through main study and LTE:*
    - The IGA 0/1 response rate was 92.3% at Week 60 and was maintained with response rates ranging between 80-100% through Week 228.
    - The PASI 75 and PASI 90 responses were 100% and 92.3%, respectively, at Week 60 and were generally maintained with response rates ranging between 80-100% through Week 228.
- *Placebo participants (crossed over to receive guselkumab or withdrawn/retreated) in the main study continued to receive guselkumab in the LTE:*
    - Clinical response for IGA 0/1 was 81% at Week 60 and was maintained with response rates ranging between 75-100% through Week 228.
    - PASI 75 and PASI 90 responses were 95.2% and 61.9%, respectively, at Week 60 and were both maintained with response rates ranging between 80-100% through Week 228.
- *Etanercept participants crossed over to guselkumab at Week 20 in the main study and continued to receive guselkumab in the LTE:*
    - Clinical response for IGA 0/1 was 77.8% at Week 60 and response rate was maintained at 100% from Week 84 through Week 228.
    - PASI 75 and PASI 90 responses were 100% and 88.9%, respectively, at Week 60 and response rates were maintained at 100% from Week 84 through Week 228.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for trial CNTO1959PSO3011

Title: A Phase 3, Multicenter, Randomized, Placebo- and Active Comparator-Controlled Study Evaluating the Efficacy, Safety, and Pharmacokinetics of Subcutaneously Administered Guselkumab for the Treatment of Chronic Plaque Psoriasis in Pediatric Participants (≥6 To <18 Years of Age)			
Study identifier	CNTO1959PSO3011 EudraCT Number: 2017-003053-42 EU Trial Number: 2023-503378-19 Paediatric Investigational Plan: PIP: EMEA-001523-PIP02-14-M03		
Design	Multi-center, Randomized, Placebo- and Active Comparator-Controlled Study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks (placebo-controlled until Week 16) not applicable 12 weeks (safety follow-up)
Hypothesis	Superiority (guselkumab compared to placebo). Comparisons between open-label etanercept and placebo were performed to test for assay sensitivity; associated p-values were considered nominal. No statistical comparisons were made between guselkumab and etanercept.		
Treatments groups	Part 1a (≥12 to <18 years of age [ie, adolescents]) 2:1:1 ratio - guselkumab, placebo, and etanercept		92 participants (118 screened) were randomized: guselkumab=41, etanercept=26, and placebo=25 Guselkumab or placebo for guselkumab: - 100 mg 1.0 mL single-use prefilled syringe (PFS-U) for SC injection - 50 mg 0.5 mL single-use adjustable dose VarioJect pen (PFS-V; 10 mg to 45 mg) for SC injection Etanercept: - 25 mg powder and solvent for solution for SC injection - 50 mg PFS for SC injection
	Part 1b (≥6 to <12 years of age [ie, young children]) 1:1:1 ratio - guselkumab, placebo, and etanercept		
Endpoints and definitions	Co-Primary endpoints	To evaluate the efficacy of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque PsO	IGA score of cleared (0) or minimal (1) at Week 16
			PASI 75 response at Week 16
	Major Secondary Efficacy Endpoints	To evaluate the efficacy of guselkumab in pediatric participants aged ≥6 through <18 years with chronic plaque PsO	PASI 90 response at Week 16
			IGA score of cleared (0) at Week 16
			PASI 100 response at Week 16

			Change from baseline in CDLQI at Week 16	
Database lock	29 March 2024 (date of last observation from last participant as part of the DBL for this 52-Week CSR)			
Results and Analysis				
Analysis description	**Primary Endpoints**			
Analysis population and time point description	Full Analysis Set.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26
	Number (%) of participants achieving an IGA score of cleared (0) or minimal (1) at Week 16	4 (16.0%)	27 (65.9%)	18 (69.2%)
Effect estimate per comparison	Primary endpoint: IGA scores of cleared (0) or minimal (1)	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		Treatment difference (95% CI)	49.9 (25.9, 69.4)	53.2 (27.1, 74.3)
		p-value	<0.001	<0.001 (nominal)
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26

	Number (%) of participants achieving a PASI 75 response at Week 16	5 (20.0%)	31 (75.6%)	18 (69.2%)
Effect estimate per comparison	Primary endpoint: PASI 75 responders	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		Treatment difference (95% CI)	55.6 (32.1, 74.0)	49.2 (22.4, 71.1)
		p-value	<0.001	<0.001 (nominal)
Notes	Not applicable			
Analysis description	**Major Secondary Endpoints**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26
	Number (%) of participants achieving a PASI 90 response at Week 16	4 (16.0%)	23 (56.1%)	14 (53.8%)
Effect estimate per comparison	Major secondary endpoint: PASI 90 response at Week 16	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		Treatment difference (95% CI)	40.1 (15.6, 61.3)	37.8 (11.8, 61.8)
		p-value	0.003	0.009 (nominal)
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26
	Number (%) of participants achieving an IGA score of 0 at Week 16	1 (4.0%)	16 (39.0%)	7 (26.9%)
Effect estimate per comparison	Major secondary endpoint: IGA score of 0 at Week 16	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		Treatment difference (95% CI)	35.0 (10.5, 56.8)	22.9 (-3.9, 48.4)

		p-value	0.004	0.061 (nominal)
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26
	Number (%) of participants achieving a PASI 100 response at Week 16	0	14 (34.1%)	7 (26.9%)
Effect estimate per comparison	Major Secondary endpoint: PASI 100 response at Week 16	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		Treatment difference (95% CI)	34.1 (9.7, 56.1)	26.9 (0.1, 51.8)
		p-value	0.002	0.013 (nominal)
Descriptive statistics and estimate variability	Treatment group	Placebo	Guselkumab	Etanercept
	Number of participants	25	41	26
	LSMean (95% CI) change from baseline in CDLQI at Week 16	-1.88 (-3.81, 0.05)	-7.28 (-8.87, -5.68)	-6.06 (-7.96, -4.15)
Effect estimate per comparison	Major Secondary endpoint: Change from baseline in CDLQI at Week 16	Comparison groups	Guselkumab vs placebo	Etanercept vs placebo
		LSMean difference (95% CI)	-5.40 (-7.73, -3.06)	-4.18 (-6.74, -1.62)
		p-value	<0.001	0.002 (nominal)
Notes	Not applicable			

2.6.5.3. Supportive study(ies)

Comparison of study populations

Table 27: Summary of Demographics, Clinical Disease Characteristics, and PsO Medication History at Baseline in CNTO1959PSO3011, CNTO1959PSO3001, and CNTO1959PSO3002 Studies; FAS

	CNTO1959PSO3011 (Part 1)	CNTO1959PSO3001	CNTO1959PSO3002
Analysis set: FAS	92	837	992
Demographics			
Mean (SD) age (years)	12.9 (3.20)	43.7 (12.72)	43.5 (12.18)
Males	51 (55.4%)	608 (72.6%)	692 (69.8%)
Mean (SD) weight (kg)	57.3 (21.19)	89.6 (21.75)	88.7 (20.68)

	CNTO1959PSO3011 (Part 1)	CNTO1959PSO3001	CNTO1959PSO3002
Median BMI (kg/m^2)	20.7	28.4	28.4
Clinical disease characteristics			
Median age at diagnosis (years)	7.0	24.0	24.0
Median PsO disease duration (years)	4.4	15.0	16.0
Median BSA	20.0	22.0	24.0
BSA ≥20	52 (56.5%)	488 (58.3%)	622 (62.7%)
Median PASI score (0-72)	17.4	19.00	19.00
IGA score of 3 (0-4)	72 (78.3%)	624 (74.6%)	766 (77.2%)
IGA score of 4 (0-4)	20 (21.7%)	210 (25.1%)	225 (22.7%)
Median CDLQI/DLQI (0-30)	7.0 (CDLQI)	14.0 (DLQI)	14.5 (DLQI)
PsO medication history			
Ever used topical therapies	92 (100.0%)	762 (91.1%)	947 (95.6%)
Ever used phototherapy (UVB or PUVA)	29 (31.5%)	454 (54.3%)	565 (57.0%)
Ever used non-biologic systemic therapies (PUVA, methotrexate, cyclosporine, acitretin, apremilast, or tofacitinib)	29 (31.5%)	517 (61.8%)	639 (64.4%)
Ever used biologic therapies (infliximab, alefacept, efalizumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, or adalimumab[a]/etanercept[a])	9 (9.8%)	175 (20.9%)	204 (20.6%)
Ever used non-biologic systemic or biologic therapies	36 (39.1%)	568 (67.9%)	709 (71.5%)
Ever used IL-12/23 inhibitors (ustekinumab, briakinumab)	6 (6.5%)	95 (11.4%)	97 (9.8%)
Ever used anti-TNF-α therapies (adalimumab[a]/etanercept[a], infliximab)	1 (1.1%)	88 (10.5%)	105 (10.6%)

[a] Prior use of etanercept was exclusionary in the paediatric study, and prior use of adalimumab was exclusionary in the adult studies.

	CNTO1959PSO3011 (Part 1)	CNTO1959PSO3001	CNTO1959PSO3002
Analysis set: FAS	92	836	990
IGA=4 and PASI score ≥20	8 (8.7%)	136 (16.3%)	143 (14.4%)
IGA=4 and 12 ≤ PASI score <20	12 (13.0%)	74 (8.9%)	82 (8.3%)
IGA=3 and PASI score ≥20	21 (22.8%)	237 (28.3%)	295 (29.8%)
IGA=3 and 12 ≤ PASI score <20	51 (55.4%)	387 (46.3%)	468 (47.3%)

Comparison of Efficacy Results of CNTO1959PSO3011 With CNTO1959PSO3001 and CNTO1959PSO3002

Table 28: Summary of Select Efficacy Endpoints at Week 16 in CNTO1959PSO3011 (Part 1), CNTO1959PSO3001, and CNTO1959PSO3002 Studies; FAS

	CNTO1959PSO3011 (Part 1)		CNTO1959PSO3001		CNTO1959PSO3002	
	Placebo	**Guselkumab**	**Placebo**	**Guselkumab**	**Placebo**	**Guselkumab**
Analysis set: FAS	25	41	174	329	248	496
IGA scores of cleared (0) or minimal (1)	4 (16.0%)	27 (65.9%)	12 (6.9%)	280 (85.1%)	21 (8.5%)	417 (84.1%)
p-value[a]		<0.001		<0.001		<0.001
PASI 75 responders	5 (20.0%)	31 (75.6%)	10 (5.7%)	300 (91.2%)	20 (8.1%)	428 (86.3%)
p-value[a]		<0.001		<0.001		<0.001
PASI 90 responders	4 (16.0%)	23 (56.1%)	5 (2.9%)	241 (73.3%)	6 (2.4%)	347 (70.0%)
p-value[a]		0.003		<0.001		<0.001
IGA scores of cleared (0)	1 (4.0%)	16 (39.0%)	2 (1.1%)	157 (47.7%)	2 (0.8%)	215 (43.3%)
p-value[a]		0.004		<0.001		<0.001
PASI 100 responders	0	14 (34.1%)	1 (0.6%)	123 (37.4%)	2 (0.8%)	169 (34.1%)
p-value[a]		0.002		<0.001		<0.001

[a] The p-values were based on the Fisher's exact test stratified by age group and region (pooled) for the CNTO1959PSO3011 study. The p-values were based on Cochran-Mantel-Haenszel chi-square test stratified by investigator site (pooled) for the CNTO1959PSO3001 and CNTO1959PSO3002 studies. In the adult CNTO1959PSO3001 and CNTO1959PSO3002 studies, nominal p-values are presented for the IGA scores of cleared (0), PASI 75, and PASI 100 efficacy endpoints.

Note: For CNTO1959PSO3011, the co-primary endpoints were the proportion of participants who achieved an IGA score of cleared (0) or minimal (1) and the proportion of participants who achieved a PASI 75 response (PASI 90 for US-FDA) at Week 16. The major secondary endpoints were PASI 90 (PASI 75 for US-FDA), IGA 0, and PASI 100 at Week 16.

Note: For CNTO1959PSO3001 and CNTO1959PSO3002, the co-primary endpoints were the proportion of participants who achieved an IGA score of cleared (0) or minimal (1) and the proportion of participants who achieved a PASI 90 response at Week 16. PASI 75, IGA 0, and PASI 100 at Week 16 were other secondary endpoints.

Table 29: Change From Baseline in CDLQI/DLQI Scores at Week 16 in CNTO1959PSO3011, CNTO1959PSO3001, and CNTO1959PSO3002 Studies; FAS

	CNTO1959PSO3011 (Part 1)		CNTO1959PSO3001		CNTO1959PSO3002	
	Placebo	Guselkumab	Placebo	Guselkumab	Placebo	Guselkumab
Analysis set: FAS	25	41	174	329	248	496
CDLQI/DLQI score at baseline						
N	25	41	170	322	248	495
Mean (SD)	9.3 (6.57)	9.4 (6.99)	13.3 (7.12)	14.0 (7.48)	15.1 (7.21)	14.7 (6.93)
Median	7.0	8.0	13.0	14.0	15.0	14.0
Change from baseline in CDLQI/DLQI score at Week 16						
N	25	41	170	322	248	495
Mean (SD)	-1.68 (6.323)	-7.12 (7.633)	-0.6 (6.36)	-11.2 (7.24)	-2.6 (6.85)	-11.3 (6.82)
Median	-1.00	-4.00	0.0	-11.0	-2.0	-11.0
p-value[a]		<0.001		<0.001		<0.001
Participants with baseline CDLQI/DLQI score >1	23	39	168	320	246	491
CDLQI/DLQI scores of 0 or 1 at Week 16	4 (17.4%)	25 (64.1%)	7 (4.2%)	180 (56.3%)	8 (3.3%)	254 (51.7%)
p-value[b]		0.002		<0.001		<0.001

[a] The p-values were based on the MMRM model with factors of treatment group, age group, region (pooled), baseline score, visit, baseline score by visit, and treatment by visit, for the CNTO1959PSO3011 study. The p-values were based on ANOVA model adjusting for investigator site (pooled) for the CNTO1959PSO3001 and CNTO1959PSO3002 studies.
[b] The p-values were based on the Fisher's exact test stratified by age group and region (pooled) for the CNTO1959PSO3011 study. The p-values were based on Cochran-Mantel-Haenszel chi-square test stratified by investigator site (pooled) for the CNTO1959PSO3001 and CNTO1959PSO3002 studies. In both the paediatric and adult studies, nominal p-values are presented.
Note: CDLQI assessments performed in paediatric participants and DLQI assessments performed in adult participants.

2.6.6. Discussion on clinical efficacy

The clinical development programme for guselkumab in paediatric PsO included one Phase 3 paediatric clinical study evaluating the efficacy, safety, PK, and immunogenicity of guselkumab in the treatment of paediatric participants with moderate to severe plaque PsO.

Design and conduct of clinical studies

Study CNTO1959PSO3011 was a Phase 3, multicenter, randomised, placebo- and active comparator-controlled study, that evaluated the efficacy, safety, and PK of SC administered guselkumab for the treatment of moderate to severe plaque PsO in paediatric participants ≥6 to <18 years of age. Participants had to have a diagnosis of chronic plaque-type PsO, defined as having an IGA ≥3, a PASI ≥12, a BSA ≥10, and at least 1 of the following: very thick lesions, clinically relevant facial, genital, or hand and foot involvement, PASI ≥20, BSA >20 or IGA=4. Participants were also required to be candidates for phototherapy or systemic treatment of plaque PsO and had plaque PsO considered by the investigator as inadequately controlled with phototherapy and/or topical therapy after an adequate dose and duration of therapy. Participants with non-plaque forms of PsO (eg. erythrodermic, guttate, or pustular) were excluded from the study. The studied population was in line with the applied indication of children and adolescents from the age of 6 years with moderate to severe plaque psoriasis who are candidates for systemic therapy.

Besides the paediatric study CNTO1959PSO3011, the two pivotal Phase 3 adult PSO studies CNTO1959PSO3001 and CNTO1959PSO3002 served as supportive data for the assessment of clinical efficacy of guselkumab in paediatric patients with moderate to severe plaque psoriasis.

Study CNTO1959PSO3011 through Week 52 was complete and conducted in 2 parts. In Part 1, the efficacy, safety, and PK of guselkumab was evaluated in two age subsets of paediatric participants (Part 1a ≥12 to <18 years of age [i.e. adolescents] and Part 1b ≥6 to <12 years of age) during a 16-week randomised, placebo- and active comparator-controlled period followed by an uncontrolled period of continued treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. In the single arm, open-label Part 2 of the study, additional efficacy, safety, and PK data for guselkumab in paediatric participants were collected through Week 52.

Study CNTO1959PSO3011 was not powered for the assessment of efficacy difference between etanercept and guselkumab treatment arms. Comparison of etanercept active control group with guselkumab group was limited by the low number of patients (overall and per treatment groups). Further, treatment to etanercept was not blinded due to the different dosing schedule of etanercept. Hence, results from the etanercept group were considered supportive only.

Timing of the assessment of primary and key secondary endpoint (Week 16) was the same as it was in the adult PsO studies and was considered adequate by the CHMP.

As for open label Part 2 of Study CNTO1959PSO3011, only adolescent patients were included.

In study CNTO1959PSO3011, the co-primary endpoints were the proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 16 and the proportion of subjects who achieve a PASI 75 response at Week 16. These co-primary endpoints are similar to those of the adult PSO studies CNTO1959PSO3001 and CNTO1959PSO3002 (PASI 90 response rate and IGA 0/1 response rate). Albeit PASI 90 response rate was a more stringent clinical efficacy endpoint, the co-primary endpoints of PASI75 response rate and IGA 0/1 response rate were considered adequate.

Secondary efficacy endpoints included PASI 90, PASI 100 and IGA 0 responses, as well as change from baseline in Children's dermatology life quality index and/or Family Dermatology Life Quality index at Week 16.

Statistical analyses

To address the primary objective, a 2-sided (α=0.05) Fisher's exact test, stratified by age group and pooled region, was used for the co-primary endpoints. The study was considered positive if the guselkumab group was significantly different from the placebo group for both co-primary endpoints. In addition, the comparison between etanercept and placebo for the co-primary endpoints was also performed using Fisher's exact test, stratified by age and region, and nominal p-values were reported.

In order to control the overall Type 1 error rate, the co-primary analyses and major secondary analyses were tested in a fixed sequence. If a given comparison between the guselkumab treatment group and the placebo group was not significant at the 2-sided α-level of 0.05, the remaining treatment group comparisons in the sequence was planned to be considered not significant and considered as supportive analyses. The statistical analyses were considered adequate by the CHMP.

Efficacy data and additional analyses

The original protocol was dated on 21 December 2017 and was amended 4 times between 2018 and 2022. No concerns were raised regarding the amendments made.

Ten protocol deviations were reported in 9 subjects in Part 1 and 6 in 5 subjects in Part 2 both through Week 52.

The following MPDs were considered to potentially affect clinical efficacy and/or clinical safety:

- In Part 1, 4 MPDs were related to assessments not being done by a trained efficacy evaluator, and 1 participant received an MMR vaccination after being randomized in the study.
- In Part 2, 2 MPDs were related to critical assessments not being done, and 1 MPD was related to assessments not being done by a trained efficacy evaluator and two participants received a lower than planned dose due to inaccurate weight recording in IWRS.

The MAH provided a sensitivity analysis on the per-protocol population, however, and according to the SAP, patients underwent PsO assessment by a non-trained study staff, were not included in the per-protocol analysis set. Since PsO assessment by a non-trained study staff might affect the clinical efficacy data, upon the CHMP's request, the MAH provided sensitivity analyses for IGA 0/1, PASI 75 and PASI 90 response rate endpoints where all patients with MPDs were excluded. Results of these sensitivity analyses were similar to the results for the Full (efficacy) Analysis set including patients with MPD of "Investigator reported outcome assessments on one or more timepoints not being performed by a sponsor-trained blinded efficacy evaluator". It was overall concluded that the MPD did not affect significantly the study results.

According to the study design and participant flow, the exposures to guselkumab were, as follows:

- From Week 0 to Week 16, 41 patients were exposed to guselkumab.
- From Week 16 to Week 52, 23 placebo patients were switched to guselkumab. From the guselkumab group, 15 patients remained on guselkumab after Week 16. Between Week 16 and Week 52, three patients discontinued from the guselkumab group, therefore 12 guselkumab patients remained on guselkumab between Week 16 and Week 52.
- From the etanercept group, 21 patients remained on guselkumab from Week 20 to Week 52.

Overall, 41 paediatric PsO patients were exposed to guselkumab from Week 0 to Week 16, and 12 patients were exposed to guselkumab from Week 0 to Week 52. The exposure to guselkumab in Study CNTO1959PSO3011 was considered limited. However, the studies in adult patients with PSO were supportive of the clinical efficacy in paediatric patients with PsO. In Part1 of Study CNTO1959PSO3011, the baseline characteristics reflected adequately the indication of moderate to severe plaque psoriasis. Some imbalances were noted, remarkably, there was a lower proportion of subjects with PASI ≥ 20 in the placebo (24%) and etanercept (23.1%) groups compared to guselkumab group (41.5%). The CHMP considered that this difference might have resulted in overestimating the PASI response rates in the guselkumab group and the effect size, as well. Differences in prior medication would also be towards the estimation of a more severe population randomised to guselkumab than those in the placebo and etanercept groups. The CHMP noted also that the median PsO disease duration was the highest in the placebo group. Overall, the CHMP considered that these imbalances were not expected to affect significantly the study results.

At Week 16 of Part 1 of the study, significantly higher proportion of patients achieved the co-primary endpoints: IGA scores of cleared (0) or minimal (1) and PASI 75 response with guselkumab than placebo (65.9% vs. 16 % and 75.6% vs 20%, respectively). All secondary endpoints (i.e. treatment difference for PASI 90 responders, IGA scores of cleared (0), PASI 100 responders, change from baseline in CDLQI score) supported the co-primary ones.

As for time course of PASI and IGA responses, separation between placebo and active groups was observed from Week 8 for PASI 75, PASI 90 and IGA 0/1 responses. Separation of response rates was less clear for PASI 100 and IGA 0 responses, however, this was expected for these more stringent endpoints. Response rates in guselkumab group were numerically higher compared to those in etanercept group during the first 16 weeks of Study CNTO1959PSO3011, however, at Week 16,

etanercept response rates seemed to reach those in guselkumab group. However, as explained under *Design and conduct of clinical studies* these results were supportive only and no conclusion was made on the effectiveness of guselkumab compared to etanercept.

After the last dose of guselkumab at week 12, loss of PASI 90 response in patients who achieved PASI 90 at Week 16 was noted as early as 12 weeks after withdrawal of guselkumab treatment. IGA and PASI responses decreased through Week 52 after withdrawal of guselkumab treatment. Improvements in HRQoL were sustained through Week 28 (12 weeks post-treatment withdrawal) for the guselkumab PASI 90 responders that had treatment withdrawn at Week 16.

Four of 23 participants required retreatment with guselkumab due to loss of ⩾50% of Week 16 PASI improvements, with 2 participants retreated at Week 44 and 2 participants retreated at Week 48. The CHMP noted the limitations of the data available on retreatment, hence no conclusion could be drawn on the effectiveness of a retreatment after withdrawal of guselkumab.

Guselkumab patients who were PASI 90 non-responders at Week 16 and switched to guselkumab at Week 20, achieved a clear improvement in PASI 90 response through Week 52.

Treatment discontinuation is recommended in adult patients with PsO who have shown no response after 16 weeks of treatment, the discontinuation statement was based on the evaluation of the PASI 50 response rate in the adult psoriasis studies. In study CNTO1959PSO3011 in paediatric patients, there were ~12% (5/41) PASI 50 non-responders at Week 16. Upon continued guselkumab treatment, 4 of these patients achieved a PASI 50 response including 3 at Week 24. Over the course of the study, these 4 patients all reached a minimum score of PASI 75 and 3 of those reached PASI 90. Based on these results, there is a subset of paediatric patients who require longer than 16 weeks to show a clinical response. Hence, the SmPC Section 4.2 recommends to consider discontinuing treatment in paediatric patients who have shown no response after 24 weeks of treatment. This was agreed by the CHMP.

Placebo patients switched to guselkumab at Week 20 showed slightly higher PASI 90 response rates compared to guselkumab patients. This slight effect might be a chance finding or might be explained by the fact that PASI 90 non-responders at Week 16 might be a more refractory subpopulation compared to those in the placebo group. However, no conclusion could be drawn due to the low patient numbers. Patients on etanercept and switched to guselkumab at Week 20 showed higher PASI 90 response after the switch, higher response was also observed compared to the PASI 90 non-responders at Week 16. However, no firm conclusion was drawn considering the low number of patients.

Upon the CHMP's request, the MAH provided clinical efficacy data from the long-term extension of Study CNTO1959PSO3011. Mean response rates for PASI 75, PASI 90 and IGA 0/1 were very close or over 80% for guselkumab and placebo patients who were PASI 90 non-responders at Week 16 and for patients switched from etanercept to guselkumab at Week 20. A lower response was observed for PASI 90 in the Placebo → Guselkumab group (61.9%) at Week 60. However, the response rate improved to 80% through Week 228. While acknowledging the limited number of patients beyond 3 years, the longer-term efficacy data from Study CNTO1959PSO3011 were overall reassuring.

Guselkumab demonstrated superior efficacy to placebo in the whole studied population i.e. children and adolescents, however, especially in the younger (age ≥ 6 to < 12) population the number of participants was low (n=10 in each arm).

Subgroup analysis of primary and key secondary efficacy endpoints by age (⩾6-<12 Years and ⩾12-<18 Years) showed superiority of guselkumab over placebo in the subgroups. In the subgroup ⩾6-<12 years, the CHMP noted a higher placebo effect and lower PASI and IGA response rates in the guselkumab treatment group. This could be explained by the fact that the baseline PASI scores were

lower in this age group. As for the adolescent group, the effect size and the response rate in the guselkumab group were higher than in the whole study population. However, no conclusions could be drawn from these observations in the subgroups due to the small number of participants.

Comparison of baseline PSO characteristics of patients in adult (CNTO1959PSO3001, CNTO1959PSO3002, CNTO1959PSO3003) and paediatric (CNTO1959PSO3011) studies showed median baseline PASI values higher in the adolescent population than in adults and lower baseline PASI in younger children. However, these differences did not hamper comparison between the adult and the paediatric population. Comparison of results in the adult and paediatric PSO studies could be performed at Week 16 only due to the differences in design of the mentioned studies. In Study CNTO1959PSO3011, remarkably higher placebo effect was observed, led by the younger patient subpopulation aged 6-12 years. Higher placebo response was observed in paediatric psoriasis studies of other medicinal products approved. For all response rate efficacy endpoints, higher Week 16 response rates were observed in the adult PSO studies than in the paediatric CNTO1959PSO3011 study. The MAH attributed the lower clinical response rates in the paediatric study to the smaller sample size. The CHMP still concluded that the effect of guselkumab was statistically significant versus placebo and clinically relevant. Further, clinical efficacy data from the LTE part of Study CNTO1959PSO3011, showed that IGA 0/1, PASI 75 and PASI 90 response rates seem to reach those observed in adult PSO studies. This is reassuring, even though LTE results beyond 3 years should be handled with caution due to the low number of patients reaching this period of LTE.

2.6.7. Conclusions on the clinical efficacy

Clinical efficacy of guselkumab in Study CNTO1959PSO3011 showed statistical significance over placebo in paediatric plaque psoriasis patients, and the effect was considered clinically relevant. The agreed therapeutic indication is for the *treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.*

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Table 30: Summary of Extent of Exposure Through 1 Year in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Safety Analysis Set

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

Note: Extent of exposure through Week 52 in CNTO1959PSO3011 study, and through Week 48 in CNTO1959PSO3001 and CNTO1959PSO3002 study.

2.6.8.2. Adverse events

Overall safety summary

Part 1 through Week 16

Table 31: Overall Summary of Treatment-Emergent Adverse Events Through Week 16; Safety Analysis Set (Study CNTO1959PSO3011 Part 1)

	Placebo	Guselkumab	Etanercept
Analysis set: Safety	25	41	26
Avg duration of follow-up (weeks)	16.3	16.4	16.1
Avg exposure (number of administrations)	2.9	3.0	14.9
Subjects with 1 or more adverse events	17 (68.0%)	17 (41.5%)	15 (57.7%)
Subjects with 1 or more serious adverse events	0	1 (2.4%)	0
Subjects with 1 or more adverse events leading to discontinuation	1 (4.0%)	0	0
Subjects who died while on study	0	0	0
Subjects with 1 or more severe adverse events	0	1 (2.4%)	0
Subjects with 1 or more reasonably related adverse events	5 (20.0%)	5 (12.2%)	7 (26.9%)
Subjects with 1 or more reasonably related serious adverse events	0	0	0
Subjects with 1 or more infections	10 (40.0%)	12 (29.3%)	10 (38.5%)
Subjects with 1 or more serious infections	0	0	0
Subjects with 1 or more opportunistic infections	0	0	0
Subjects with active TB	0	0	0
Subjects with 1 or more malignancies	0	0	0

Part 1 through week 52

Through Week 52, the proportion of participants treated with guselkumab experiencing 1 or more AE was 72.1% in the combined guselkumab group (guselkumab group: 80.5%, etanercept → guselkumab group: 59.1%), and placebo → guselkumab group: 69.6%.

Table 32: Summary of Key Safety Findings Through the Placebo-controlled Periods (Week 16) in CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 Studies; Safety Analysis Set

	Pediatric Psoriasis CNTO1959PSO3011		Adult Psoriasis CNTO1959PSO3001/3002	
	Placebo	Guselkumab	Placebo	Guselkumab
Analysis set: Safety analysis set	25	41	422	823
Avg duration of follow-up (weeks)	16.3	16.4	15.9	16.2
Subjects who discontinued study agent due to AEs	1 (4.0%)	0	4 (0.9%)	11 (1.3%)
Treatment difference (95% CI)		-4.0 (-28.1, 20.7)		0.4 (-0.8, 1.6)
Subjects with 1 or more:				
Adverse events	17 (68.0%)	17 (41.5%)	197 (46.7%)	405 (49.2%)
Treatment difference (95% CI)		-26.5 (-49.0, -1.4)		2.6 (-3.3, 8.4)
Common adverse event*	8 (32.0%)	11 (26.8%)	62 (14.7%)	133 (16.2%)
Nasopharyngitis	7 (28.0%)	5 (12.2%)	33 (7.8%)	65 (7.9%)
Upper respiratory tract infection	2 (8.0%)	4 (9.8%)	19 (4.5%)	41 (5.0%)
Headache	0	3 (7.3%)	14 (3.3%)	37 (4.5%)
Serious adverse events	0	1 (2.4%)	6 (1.4%)	16 (1.9%)
Treatment difference (95% CI)		2.4 (-22.0, 26.6)		0.5 (-0.9, 2.0)
Any infections	10 (40.0%)	12 (29.3%)	90 (21.3%)	191 (23.2%)
Serious infections	0	0	1 (0.2%)	1 (0.1%)
Treatment difference (95% CI)		NE (NE, NE)		-0.1 (-0.6, 0.4)
Infections requiring treatment	3 (12.0%)	1 (2.4%)	30 (7.1%)	55 (6.7%)
Malignancy	0	0	0	1 (0.1%)
Treatment difference (95% CI)		NE (NE, NE)		0.1 (-5.8, 6.0)

Key: NE = Not Evaluable
*≥5% in guselkumab dose group in CNTO1959PSO3011
For CNTO1959PSO3011 study, the CIs are based on exact method.
For combined studies, the treatment difference and 95% CIs are adjusted for study using Mantel-Haenszel (MH) weights.

Common AEs

Part 1 through Week 16

Table 33: Number of 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; Safety Analysis Set (Study CNTO1959PSO3011 Part 1, Table 19 of CSR)

	Placebo	Guselkumab	Etanercept
Analysis set: Safety	25	41	26
Avg duration of follow-up (weeks)	16.3	16.4	16.1
Avg exposure (number of administrations)	2.9	3.0	14.9
Subjects with 1 or more AEs	17 (68.0%)	17 (41.5%)	15 (57.7%)
System organ class Preferred term			
Infections and infestations	10 (40.0%)	12 (29.3%)	10 (38.5%)
Nasopharyngitis	7 (28.0%)	5 (12.2%)	3 (11.5%)
Upper respiratory tract infection	2 (8.0%)	4 (9.8%)	2 (7.7%)
Bronchitis	0	0	2 (7.7%)
Nervous system disorders	0	3 (7.3%)	1 (3.8%)
Headache	0	3 (7.3%)	1 (3.8%)
General disorders and administration site conditions	2 (8.0%)	1 (2.4%)	4 (15.4%)
Fatigue	0	0	2 (7.7%)
Musculoskeletal and connective tissue disorders	0	1 (2.4%)	3 (11.5%)
Arthralgia	0	0	2 (7.7%)

Part 1 through Week 52

The most frequently occurring AEs by PT and treatment group 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%), and URTI in 12.8% of the combined guselkumab group (guselkumab group:19.5%, etanercept → guselkumab group:13.6%, and placebo → guselkumab group: 0%).

The type and frequency of AEs in participants younger than 12 years old was similar to those 12 years and older, with nasopharyngitis, URTI, and headache being the most frequently reported AEs in both age groups.

Related AEs

Part 1 through Week 16

Through the 16-week, randomized, placebo- and active comparator-controlled period, 12.2% of participants in the guselkumab group, 26.9% of those in the etanercept group, and 20.0% of those in the placebo group experienced at least 1 TEAE considered related to the study intervention by the investigator.

The SOC with the most participants with 1 or more related TEAEs was infections and infestations (7.3%, 19.2%, and 8.0% in the guselkumab, etanercept, and placebo groups, respectively). The most common related AE in this SOC was nasopharyngitis (reported in 7.3%, 7.7%, and 8.0% of participants that received guselkumab, etanercept, and placebo, respectively).

Part 1 through Week 52

Through Week 52, the proportion of participants experiencing 1 or more related TEAEs (considered as related to study intervention as assessed by the investigator) was 22.1% in the combined guselkumab group (guselkumab group: 24.4%, etanercept → guselkumab group: 22.7%, and placebo → guselkumab group: 17.4%).

Through Week 52 the SOC with the most participants with 1 or more related TEAEs was Infections and infestations with 17.4% of participants in the combined guselkumab group (guselkumab group: 17.1%, etanercept → guselkumab group: 22.7%, and placebo → guselkumab group: 13.0%). The most common related TEAE in this SOC was nasopharyngitis reported in 12.8% of the combined guselkumab group (guselkumab group: 17.1%, etanercept→ guselkumab group: 9.1%, and placebo → guselkumab group: 8.7%).

2.6.8.3. Serious adverse event/deaths/other significant events

Death

No deaths were reported in study CNTO1959PSO3011 through Week 52 (Part 1 and Part 2).

Serious adverse events

Part 1 Through Week 16

Through Week 16, 1 participant in the guselkumab group reported a SAE, no participants in the placebo or etanercept group reported SAEs. The SAE reported was radius fracture due to a fall (severe intensity) and was assessed as not related to study intervention by the investigator.

Part 1 Through Week 52

In addition to the SAE reported in Part 1 through Week 16, 2 SAEs were reported in 2 participants through Week 52. These included:

- Chronic tonsillitis: 1 of 23 participants in the placebo → guselkumab group. This SAE was reported in Part 1 from Week 16 through Week 52 and was an SAE of chronic tonsillitis of moderate severity. This event was not considered a serious infection, nor was it considered related to study intervention
- Multiple injuries: 1 of 41 participants in the guselkumab groups. This SAE was reported in Part 2 through Week 52 and was an SAE of 'multiple injuries' due to accidental fall, severe in severity, and was considered as not related to study intervention.

Adverse events of special interest

TB and malignancy

In study CNTO1959PSO3011 AESIs included TB and malignancy. Apart from them, occurrence of AEs of Infections, Serious infections, Anaphylactic or Serum Sickness-like Reactions, MACEs, Suicidal Ideation, Suicidal Behaviour, or Self-injurious Behaviour, Psoriasis and Injection site reactions were also followed.

There were no AESIs of TB and Malignancies through Week 52 (Part 1 or Part 2).

Anaphylactic or Serum Sickness-like Reactions

No participants treated with study intervention reported anaphylactic or serum sickness-like reactions through Week 52 (Part 1 or Part 2).

Major Adverse Cardiovascular Events

There were no reports of MACE (eg, myocardial infarctions, strokes, VTE) through Week 52 (Part 1 or Part 2).

Suicidal Ideation, Suicidal Behaviour, or Self-injurious Behaviour

There were no reported events of suicidal ideation, suicidal behaviour, or self-injurious behaviour reported through Week 52 (Part 1).

In the open-label Part 2, 2 participants reported suicidal ideation or suicidal behavior through Week 52. A 17-year-old female participant had a TEAE of suicidal ideation on Day 10 that was assessed as mild in severity and 'doubtful' in its relatedness to study intervention. The principal investigator determined that the participant should discontinue, and the study intervention was withdrawn. A 14-year-old female participant had an AE of suicidal ideation. It was uncovered by the investigator that the participant's suicidal thoughts actually preceded study enrollment by 9 days. The AE was moderate and not related to study intervention. The participant received behavioural health intervention and completed the study.

AE of PsO

In Part 1, 2 participants experienced an AE of PsO: 1 participant in the placebo group (through Week 16), and 1 participant in the guselkumab group (through Week 52). In Part 2 through Week 52, no cases of an AE of PsO were reported.

Infections

Any Infections

Part 1 Through Week 16

Through the placebo-controlled portion of the study, the proportions of participants experiencing at least 1 AE categorized as infection by the investigator were 29.3% in the guselkumab group, 38.5% in the etanercept group and 40% in the placebo group. The most common infections were nasopharyngitis (12.2% in the guselkumab group, 11.5% in etanercept group and 24% in the placebo group) and URTI (9.8% in the guselkumab group, 7.7% in the etanercept group and 8.0% in the placebo group). All infections were of mild or moderate intensity, no severe infections were reported through Week 16. Through Week 16, no serious infections, opportunistic infections, or active TB were reported.

Through Week 52

Part 1 through Week 52, the most common infections in the guselkumab group remained nasopharyngitis and URTI. All infections were of mild or moderate intensity, there were no severe infections. The type and frequency of AEs in the ≥6 to <12-year-old group and in the ≥12 to 18-year-old age group were similar through Week 52.

Part 2 through Week 52, the most common infections in the guselkumab group were nasopharyngitis and COVID-19.

Infections Requiring Antimicrobial Treatment

Part 1 Through Week 16 (the Placebo-controlled Period)

Through Week 16, the proportions of participants with 1 or more infections requiring oral or parenteral antimicrobial treatment were 2.4% in the guselkumab group, 19.2% in the etanercept group, and 12.0% in the placebo group.

Through Week 52

Through Week 52 (Part 1), the types of infections requiring oral or parenteral antimicrobial treatment were consistent with Part 1 through Week 16 with the most frequently occurring infections requiring antimicrobial treatment: being bronchitis and nasopharyngitis.

Through Week 52 (Part 2), there was 1 of 28 participants who required oral or parenteral antimicrobial treatment given for an AE of arthropod bite.

Injection-site Reactions

Part 1 Through Week 16 (the Placebo-controlled Period)

The number of participants with ISRs through Week 16 was 1 participant in each of the placebo, guselkumab, and etanercept treatment groups, all were mild in intensity.

Through Week 52

In Part 1 through Week 52, there were 6 (0.9%) of 667 guselkumab injections that resulted in an ISR. All 6 cases were reported in 2 participants, and all were mild in intensity. In Part 2 through Week 52 there were 2 participants with a total of 9 ISRs, all mild in intensity.

No ISRs were reported in participants retreated with guselkumab.

Data from CNTO1959PSO3011 did not show an association between the development of antibodies to guselkumab and the development of injection-site reactions. None of the 24 participants who were positive for antibodies to guselkumab reported any injection-site reactions after the development of antibodies to guselkumab through Week 52.

2.6.8.4. Laboratory findings

Haematology

No clinically significant changes in haematology tests were observed through Week 52 for study CNTO1959PSO3011. Through Week 16 there were no laboratory values of CTCAE ⩾2 in the guselkumab group. One participant (4%) in the placebo group had a CTCAE toxicity Grade 2 decreased platelet count and 1 participant (4%) in the etanercept group had a CTCAE toxicity Grade 2 decreased neutrophil count. There were no laboratory values with CTCAE toxicity Grade ⩾3 through Week 16.

Clinical Chemistry Assessments

Through Week 16, 3 (7.3%) participants in the guselkumab group had laboratory values of CTCAE toxicity Grade 2 of increased total bilirubin. One (2.4%) of 24 participants in the etanercept group, who at baseline had a normal ALT, had an ALT ≥2 to <3×ULN but did not meet criteria for a potential Hy's Law case.

No events of DILI were observed in the study.

Comparison Between CNTO1959PSO3011 and the Pivotal Adult Studies

In adult studies, no consistent trends were observed over 5 years to suggest that an association exists between guselkumab and clinically relevant changes in routine laboratory parameters. In the pooled CNTO1959PSO3001 and CNTO1959PSO3002 dataset, no Grade 4 haematology events were reported in guselkumab-treated participants through Week 264 for either study, and for the proportion of participants with Grade 4 chemistry events in the guselkumab group were low for both studies.

The frequency of CTCAE toxicity Grade ≥2 abnormal clinical chemistry and haematology values in the guselkumab group was comparable to the placebo through Week 16 for the pooled safety data for the CNTO1959PSO3001 and CNTO1959PSO3002 studies.

Vital signs, physical findings, and other observations related to safety

In study CNTO1959PSO3011, vital signs remained stable over time across treatment groups from baseline through Week 52. Through Week 52, physical findings related to growth (weight, height, and BMI, measurements) were consistent with expected growth over time for paediatric participants ≥6 to <18 years of age.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Demographic Characteristics

Subgroup analyses were performed for key safety findings through Week 16 and through Week 52 for baseline demographic characteristics of *age* (<12 years or ≥12 years), *sex* (male or female), *weight* (<70 kg or ≥70 kg), and *race* (white or other).

Analysis of safety data revealed no age, weight- or sex-related trends in AEs, AEs leading to discontinuation of study intervention, SAEs, or infections. Key safety findings were also evaluated by race, but the population of the study was predominately white and precluded conclusion by race. Given that the overwhelming majority of participants in both Part 1 (95%) and Part 2 (96%) were not Hispanic or Latino, a safety analysis stratified by ethnicity would yield insufficient numbers in the Hispanic or Latino subgroup for meaningful comparison.

Baseline Disease Severity

Subgroup analyses were performed for key safety findings through Week 16 and through Week 52 for baseline disease severity: BSA (<20% or ≥20%), PGA score (<4 or =4), and PASI score (≥20 or <20).

Overall, no trends were observed in the occurrence of AEs, SAEs, or any infection for subgroups examined by baseline BSA, PGA, or PASI.

Use in Pregnancy and Lactaction

One maternal pregnancy was reported in study CNTO1959PSO3011 through Week 52. The participant was withdrawn from treatment and discontinued the study as a result of the pregnancy but signed consent to being followed-up during the pregnancy. Pregnancy was carried to full term without concerns and delivery resulted in a healthy newborn.

As of the most recent assessment cumulatively through on 12 July 2024, a total of 139 reports of pregnancy were identified in ongoing and completed interventional clinical studies of guselkumab which have been unblinded. These clinical studies included participants with PsA, PsO, Crohn's disease, UC, palmoplantar pustulosis, hidradenitis suppurativa, and healthy participants. There were 73 pregnancies in female participants exposed to guselkumab participating in these clinical studies (ie, maternal pregnancies) and 66 partner pregnancies (ie, paternal pregnancies). No foetal abnormalities or congenital malformations were reported.

2.6.8.7. Immunological events

Please refer to Section 2.6.2. Clinical pharmacology.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Drug-drug interaction studies were not performed with guselkumab in the paediatric age group.

2.6.8.9. Discontinuation due to adverse events

Part 1 through Week 16, 1 participant in the placebo group discontinued study intervention due to an AE of PsO (of mild severity and considered possibly related to study intervention) and no participants in the guselkumab or etanercept groups discontinued.

Part 1 through Week 52, 1 participant in the guselkumab group discontinued study intervention due to pregnancy.

Part 2 through Week 52, 1 participant in the guselkumab group discontinued study intervention due to suicidal ideation. The principal investigator determined that the participant should discontinue study participation. This TEAE was assessed to be mild in severity and the relationship to study intervention was doubtful.

Upon the CHMP's request, the MAH provided during the procedure updated clinical safety data from the long-term extension of Study CNTO1959PSO3011, as summarised hereafter.

Since the initial submission, an additional 194 patient-years of LTE safety data became available beyond Week 52 through 03 January 2025 for Study CNTO1959PSO3011.

Four (4) guselkumab-treated participants reported SAEs (peritonsillar abscess, tonsillitis, syncope and influenza) after Week 52 through 03 January 2025: all of them were single events, moderate to severe in intensity, each reported in a single participant. All SAEs were considered as not related to study intervention. Participants recovered within 2 to 6 days without dose change of study intervention.

There were no deaths, AESIs of active TB or malignancy, other AEs of interest (potential opportunistic infections, anaphylactic reactions, serum-sickness or serum-sickness like reactions, prespecified liver enzyme elevations, pregnancies with a negative outcome, MACE, VTE and suicidal ideation and behavior) reported.

No new ADRs have been identified in study CNTO1959PSO3011.

2.6.8.10. Post marketing experience

The estimated cumulative global exposure to guselkumab from launch through 30 June 2024 was 588,988 person-years. The cutoff date for postmarketing data was 12 July 2024, which coincided with the most recent Periodic Safety Update Report (PSUR) cutoff date. As of the end of the reporting interval no new important identified or important potential risks have been identified from clinical studies or postmarketing experience in the most recent PSUR.

Psoriasis

PSOLAR 2

The PSOLAR registry (Protocol C0168Z03) is an international, multicenter, prospective, observational registry for monitoring the long-term safety experience and clinical status of patients with moderate to severe PsO who are ≥18 years of age and eligible to receive or are actively receiving any systemic therapies for PsO. The design of PSOLAR allows the capture of real-world exposure to the Applicant's

product(s) and allows the evaluation of safety and disease outcomes in the clinical context of patients exposed to other biologic and systemic treatments for PsO.

PSOLAR was initiated in 2007 to collect safety information pertaining to infliximab in typical dermatologic practice as part of a postmarketing commitment to health authorities. In 2009, the protocol was amended to include ustekinumab cohort to fulfil another postmarketing commitment to health authorities (PSOLAR Protocol Amendment 3, dated 19 March 2009), a component of the ustekinumab European Union Risk Management Program to monitor long-term outcomes in patients with PsO (with and without PsA). In March 2018, the PSOLAR protocol was amended (PSOLAR 2) to allow enrollment of patients receiving treatment with guselkumab or an IL-17 inhibitor (eg, secukinumab, ixekizumab, brodalumab) as part of a postmarketing commitment to health authorities for guselkumab. The first patient enrolled into PSOLAR 2 on 14 January 2019; the last patient enrolled on 31 March 2023.

This PSOLAR interim safety report gave information on the cumulative enrollment and follow up time for each cohort, descriptive analyses of baseline demographics of guselkumab-exposed patients, and AEs, including SAEs, reported through 12 July 2024. Recruitment into PSOLAR 2 was closed, as the last patient enrolled on 31 March 2023. Among all patients: a total of 3,513 patients were enrolled in PSOLAR 2 cumulatively through 12 July 2024. In the guselkumab cohort: a total of 2,198 patients with PsO receiving or starting guselkumab had been enrolled in PSOLAR 2 cumulatively through 12 July 2024. As of 12 July 2024, the on-registry exposure for patients ever-exposed to guselkumab was 6,646 PY with a median duration of follow-up of 2.98 years.

Of the 2198 guselkumab patients, 65 had completed an enrollment visit only; 68 patients had completed a 6 month follow-up visit, 91 patients had completed a 1-year follow-up visit, 259 patients had completed a 1.5-year follow-up visit, 391 patients had completed a 2-year follow-up visit, and 1,324 patients had completed a 2.5- to 5.5-year follow-up visit.

All AEs

Rates of AEs and SAEs were calculated based on 2 definitions of exposure:

- Exposure at any time prior to the event (ever-exposed definition), and
- Exposure within a risk window of 91 days prior to the event for biologic agents (91 day exposed definition). To address treatment changes by registry patients within the 91 day safety analyses, events and exposure occurring greater than 91 days from the last dose of biologic were counted in the nonbiologic cohort.

The cumulative unadjusted incidence rates for AEs and SAEs using the ever-exposed definition of exposure were 26.09/100 PY and 4.81/100 PY, respectively for the guselkumab cohort. The cumulative unadjusted incidence rates for AEs and SAEs using the 91-day exposure definition were 30.43/100 PY and 5.73/100 PY, respectively for the overall population of registry patients. The cumulative unadjusted incidence rates in the guselkumab cohorts were numerically similar to or lower than the cumulative unadjusted incidence rates in the IL 17 cohorts.

Using the ever-exposed definition of exposure, the cumulative unadjusted incidence rates for reported cardiac disorders was similar for guselkumab cohort versus IL 17 cohort. The overall cumulative unadjusted incidence rate for AEs contained within the neoplasms SOC was numerically lower in the guselkumab cohort versus IL 17 cohort; incidence rates for individual PTs contained within the SOC were numerically similar between the guselkumab and IL 17 cohorts. Using the 91-day exposure definition, the cumulative unadjusted incidence rates for infections/infestations were numerically lower in the guselkumab versus IL-17 cohorts. Given short duration of follow-up for the PSOLAR 2 registry (and the protocol-specified attribution rules for the ever-exposed analyses), these unadjusted incidence

rates should be interpreted with caution. Additionally, a majority of these AESIs in guselkumab-treated patients were also reviewed during the analysis of the cases retrieved from the Company global safety database.

PsoBest

The German registry on Treatment of PsoBest (Protocol [CNTO1959PSO4001]) is a prospective observational study designed to examine the long-term safety and effectiveness of systemic therapies, including biologics, available to treat adults with moderate to severe plaque PsO or PsA in Germany.

Based on the PsoBest twelfth interim report covering the period 01 July 2023 to 31 December 2023 and providing information on the cumulative follow-up time accrued for each cohort, a total of 18,552 patients were registered cumulatively (13 December 2017 to 31 December 2023) in the registry. The cumulative number of patients included in the guselkumab cohort is 1,435 (62% males); median age and duration of illness were 48 years and 14 years, respectively. The number of exposure years for total patients ever exposed on guselkumab was 1,816.80.

Overall, the cumulative and interval incidence rates for AEs, SAEs, and all-cause death and malignancies for the guselkumab cohort were generally low.

There were 924 SAEs and 812 AEs in the PsoBest period from 13 December 2007 to 31 December 2023 in the guselkumab cohort. Among the 924 SAEs reported, the most frequently reported MedDRA PTs were in the following SOCs: Surgical and medical procedures (n=239) and Injury, poisoning and procedural complications (n=81). During this period, 29 patients exposed to guselkumab reported 39 malignancy SAEs (SOC Neoplasm benign, malignant and unspecified [incl cysts and polyps]). A total of 11 all-cause deaths were reported in the guselkumab cohort during the period from 13 December 2007 to 31 December 2023.

Pregnancy

OTIS

The Tremfya (guselkumab) Pregnancy Exposure Registry is a North American based, observational pregnancy registry designed to monitor planned or unplanned pregnancies exposed to guselkumab to treat an approved indication (PsO or PsA), and to collect follow-up information on the health status of the infants through approximately 1 year of age. The registry is conducted by the OTIS Research Group as an integrated project within the existing OTIS Autoimmune Diseases in Pregnancy Project.

Initiating in August 2018, the registry aims to recruit 100 patients exposed to guselkumab from the United States and Canada. Through 31 May 2024, 13 patients were enrolled. Outcomes were collected on 10 pregnancies including 6 live born infants, 3 spontaneous abortions and 1 lost to follow-up. No major malformations were reported. Three pregnancy outcomes were still pending.

2.6.9. Discussion on clinical safety

Results from Study CNTO1959PSO3011 in paediatric patients with plaque psoriasis (n=120 patients) were submitted in support of this application. The CHMP noted the limited longer term exposure to guselkumab in this study and the low number of paediatric patients. However, supportive information were available from the studies in adult patients with PSO.

By Week 16, lower incidences of TEAEs and related TEAEs were reported in guselkumab group than in the comparator group and placebo group. One serious adverse event (SAE, radius fracture) was reported in one patient in the guselkumab group. No participants in the placebo or comparator group reported SAEs. No SAE was considered to treatment-related. The lowest AE-frequency for infections was reported in guselkumab group, infections occured with similar frequency in comparator and

placebo groups. No severe infections, opportunistic infections, or active tuberculosis occured in any of the groups. No malignancies were observed in any of the subjects. The most common TEAEs (>5%) in the treatment groups per SOC and PT were Infections and infestations (29.3%, 38.5% in guselkumab and active comparator groups, respectively) followed by Nervous system disorders (7.3% and 3.8% in guselkumab and active comparator groups, respectively), General disorders and administraton site conditions (2.4%, 15.4% in guselkumab and active comparator groups, respectively) and Muskuloskeletal and connective tissue disorders (2.4% and 11.5% in guselkumab and active comparator groups, respectively). The most common (>5%) TEAEs in the treatment groups were nasopharyngitis, upper respiratory tract infection, headache, fatigue and arthralgia.

In Part 1 through Week 52, the most frequently occurring AEs by PT and treatment group included nasopharyngitis in 27.9% of the combined guselkumab group and URTI in 12.8% of the combined guselkumab group.

The type and frequency of AEs in participants younger than 12 years old was similar to those 12 years and older, with nasopharyngitis, URTI, and headache being the most frequently reported AEs in both age groups.

No death was reported in study CNTO1959PSO3011 through Week 52.

AESI

There were no AESIs of TB and Malignancies through Week 52 (Part 1 or Part 2)

There were no reports of serum sickness-like reaction and MACEs, through Week 52 of Part 1 and Part 2 of Study CNTO1959PSO3011.

There were no reports of suicidal ideation, behaviour or self-injurious behaviour through Week 52 in Part 1 of the study. In Part 2, 2 participants reported suicidal ideation or suicidal behaviour through Week 52: one patient, 17 years, had a TEAE of suicidal ideation of mild severity and doubtful relatedness. This patient discontinued the treatment. A 14-year-old female participant had an AE of suicidal ideation; the participant's suicidal thoughts preceded study enrolment. The AE was moderate and not related to study intervention. The participant received behavioural health intervention and completed the study.

As for infections, by Week 16 (Part 1), the AE frequency in the respective SOC was the lowest for the guselkumab groups and the highest in the placebo group. Most common infections were nasopharyngiitis and URTI. Through Week 52 of Part 1, the most common infections in the guselkumab group remained nasopharyngitis and URTI. However, these conditions are known ADRs of guselkumab under the High Level Group Term of Respiratory tract infections.

In Part 1 through Week 52, 6 cases of ISR were reported in 2 participants, all were mild in intensity. No ISRs were reported in participants retreated with guselkumab. Data from Study CNTO1959PSO3011 did not show an association between the development of antibodies to guselkumab and the development of injection site reaction.

Haematology and clinical chemistry alterations were generally rare, mild and transient in nature.

Three patients discontinued from Study CNTO1959PSO3011, one from the placebo arm during the 16-week period of Part 1 due to mild psoriasis, one participant from guselkumab group in Part 1 through week 52 due to pregnancy and a third one from Part 2 due to suicidal ideation. All these discontinuations were in accordance with the study protocol. No concern was raised.

One pregnancy was reported during Study CNTO1959PSO3011. The patient discontinued from the study as previously mentioned. Exposure during pregnancy is already listed as missing information in the RMP and is expected to be further characterised post-approval.

Summary of key safety findings per hundred subject-years of follow-up through the placebo-controlled periods (Week 16) from studies CNTO1959PSO3011, CNTO1959PSO3001 and CNTO1959PSO3002 indicated overall a safety profile somewhat less favourable in the paediatric population compared to the adult PSO populations. The higher event rates for infections and respiratory tract infections could be explained by the characteristics of the general paediatric population who is more prone to URTI rather than a specific unfavourable effect of guselkumab in children. However, the CHMP noted the higher event rates of headache ADR and SAEs which might be of concern. Nevertheless, the CHMP considered that these observations should be handled with caution due to the low overall patient number in Study CNTO1959PSO3011. Headache is already listed as an adverse reaction (frequency common), hence, no update of the product information was deemed necessary.

Upon the CHMP's request, the MAH provided longer term safety data from the Study CNTO1959PSO3011 during the procedure. No new safety concerns were identified compared to adult PsO/PsA studies as well as other adult guselkumab studies. Long term safety of guselkumab was already listed as missing in the RMP. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP to further characterise the long-term safety of guselkumab post-approval but also the safety concerns of serious infection, malignancy, serum sickness and MACE.

No new safety concerns for guselkumab were identified based on post-marketing safety data sources presented by the MAH.

2.6.10. Conclusions on the clinical safety

The safety profile of guselkumab in paediatric patients with PsO was consistent with the known safety profile of the product. While acknowledging the limited long-term data available in paediatric patients with PsO, no new safety concerns were identified compared to adult PsO/PsA studies as well as other adult guselkumab studies. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP to further characterise this missing information on long term safety of guselkumab.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	None
Important potential risks	Serious infection
	Malignancy
	Serum sickness
	Major adverse cardiovascular events (MACE)
Missing information	Exposure during pregnancy
	Use in patients ≥65 years of age
	Long-term safety of guselkumab

2.7.2. Pharmacovigilance plan

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances Not applicable				
Category 3 – Required additional pharmacovigilance activities				
C0168Z03 (PSOLAR) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	20 June 2007: The registry was expanded to include TREMFYA patients on 26 March 2018 and the first TREMFYA patient was enrolled in PSOLAR on 25 February 2019.
			Interim report	4Q 2025
			End of data collection for TREMFYA	4Q 2029
			Final report	4Q 2030
CNTO1959PSO4001 (PsoBest) Ongoing	To study the long-term safety of guselkumab	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Exposure during pregnancy • Use in patients ≥65 years of age • Long-term safety of guselkumab	Protocol submission	March 2018
			Registry start	January 2008: The registry was expanded to include TREMFYA patients and the first TREMFYA patient was enrolled in PsoBest in January 2018.
			Interim report	After enrollment of the first 500 patients treated with guselkumab (of which 250 have been treated for at least 1 year)
			End of data collection for TREMFYA	To be determined
			Final report	4Q 2030
PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Ongoing	To monitor pregnancy outcomes in women exposed to guselkumab during pregnancy and linked infant outcomes in	• Exposure during pregnancy	Protocol submission	August 2018
			Start of data collection	31 December 2022
			Interim report	4Q 2025
			End of data collection	30 June 2030

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	infants up to 1 year of age		Final report	2Q 2031
Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 44 assessments as part of the Maintenance Study. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection	31 July 2020
			End of data collection	3Q 2027
			Final report	3Q 2028
Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Ongoing	To study the long-term safety of guselkumab for up to approximately 4 additional years of treatment following the Week 48 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	April 2024
			Start of data collection: GALAXI 1: 10 May 2018 GALAXI 2: 08 January 2020 GALAXI 3: 22 January 2020	
			End of data collection	3Q 2027
			Final reports	3Q 2028
Long-term extension of Study CNTO1959UCO3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment following the Week 24 assessments. Total duration of follow-up will be 5 years.	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	2Q 2025
			Start of data collection	13 September 2022
			End of data collection	4Q 2028
			Final report	4Q 2029
Long-term extension of Study CNTO1959CRD3004 Ongoing	To study the long-term safety of guselkumab for up to approximately 4.5 additional years of treatment	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular	Protocol submission	January 2025
			Start of data collection	19 January 2022
			End of data collection	2Q 2028

Study and Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	following the Week 24 assessments. Total duration of follow-up will be 5 years.	events (MACE) • Long-term safety of guselkumab	Final report	2Q 2029
Long-term extension of the Phase 3 Study CNTO1959PSO3011 Ongoing	To study the long-term safety of guselkumab in pediatric psoriasis patients until study completion or termination	• Serious infection • Malignancy • Serum sickness • Major adverse cardiovascular events (MACE) • Long-term safety of guselkumab	Protocol submission	February 2025
			Start of data collection	20 September 2018
			End of data collection	Q4 2026
			Final report	Q2 2027

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Serious infection	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029 Long-term extension of the Phase 3 Study CNTO1959PSO3011 Final report: Q2 2027
Malignancy	**Routine risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	Additional risk minimization measures: None	C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029 Long-term extension of the Phase 3 Study CNTO1959PSO3011 Final report: Q2 2027
Serum sickness	**Routine risk minimization measures:** SmPC Section 4.3 (Contraindications) SmPC Section 4.4 (Special Warnings and Precautions for Use) Package Leaflet Section 2 (What you need to know before you use Tremfya) PL Section 4 (Possible side effects) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOIQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029 Long-term extension of the Phase 3 Study CNTO1959PSO3011 Final report: Q2 2027
Major adverse cardiovascular events (MACE)	**Routine risk minimization measures:** None **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TOI TFUQ **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	None	Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029 Long-term extension of the Phase 3 Study CNTO1959PSO3011 Final report: Q2 2027
Exposure during pregnancy	**Routine risk minimization measures:** SmPC Section 4.6 (Fertility, Pregnancy and Lactation) Package Leaflet Section 2 (What you need to know before you use Tremfya) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up of reported pregnancies **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030 PCSIMM001324 (TREMFYA [guselkumab] pregnancy healthcare database study) Final report: 2Q 2031
Use in patients ≥65 years of age	**Routine risk minimization measures:** SmPC Section 4.2 (Posology and Method of Administration) **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030
Long-term safety of guselkumab	**Routine risk minimization measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** C0168Z03 (PSOLAR) Final report: 4Q 2030 CNTO1959PSO4001 (PsoBest) Final report: 4Q 2030

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
		Long-term extension of the Phase 3 Maintenance Study CNTO1959UCO3001 Final report: 3Q 2028 Long-term extensions of the Phase 2 and Phase 3 trials of Study CNTO1959CRD3001 Final reports: 3Q 2028 Long-term extension of Study CNTO1959UCO3004 Final report: 4Q 2029 Long-term extension of Study CNTO1959CRD3004 Final report: 2Q 2029 Long-term extension of the Phase 3 Study CNTO1959PSO3011 Final report: Q2 2027

2.7.4. Conclusion

The CHMP considered that the risk management plan version 14.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by Janssen Cilag International fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by Janssen Cilag International show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Psoriasis is a chronic, non-communicable, painful, immunologically mediated, disfiguring and disabling inflammatory skin disease for which there is no cure and with great negative impact on patients' QoL.

Studies addressing the age of onset of PsO have suggested that 2 subgroups exist: early onset disease (before 30 years of age, including paediatric onset) and late onset disease (after age 30) (Christophers 1992[8]). Generally, the clinical manifestations of plaque PsO in patients with paediatric onset and those with adult or late onset disease are similar (most frequently involved areas of the body include scalp, elbows, knees, and genitalia), and not clinically distinguishable (Lewkowicz 2004[9]; Silverberg 2009[10]). Adult and paediatric plaque PsO also share similar histological features, genetic factors, and treatment options (Bronckers 2015[11]). Therefore, the consensus of the literature is essentially that plaque PsO is a lifelong chronic disease with a variable age of onset, and that paediatric plaque PsO is probably most accurately characterised as early onset disease rather than as an entity distinct from adult plaque PsO.

3.1.2. Available therapies and unmet medical need

Conventional systemic therapies include MTX, acitretin, and cyclosporine. Although effective, they are associated with significant toxicities, particularly organ damage with long-term administration, and have recommended limitations for long-term administration.

Five biological agents have been approved in the EU for the treatment of PsO in the paediatric population. These approved biologic agents have been shown to be substantially better than placebo in treating children with moderate to severe PsO and are associated with a significantly greater reduction in PsO severity than non-biological system therapies (Nogueira 2021[5]).

Although stepwise therapy is mentioned frequently in the literature, the optimal treatment approach for paediatric patients with moderate to severe plaque PsO is less clear than for adults due to the practical scheduling issues of phototherapy in school aged children, the known, often cumulative, toxicities of traditional non-biological systemic therapies and the limited approved therapeutic options for this age group. For these reasons, a proportion of paediatric patients with plaque PsO are currently undertreated (Hebert 2022[7]; Seyger 2022[12]). Hence, there is an unmet medical need for additional safe, effective, and convenient therapies in paediatric patients with moderate to severe plaque PsO.

3.1.3. Main clinical studies

Study CNTO1959PSO3011 was an ongoing, Phase 3, multicenter, randomized, placebo- and active comparator controlled study evaluating the efficacy, safety, and PK of subcutaneously administered guselkumab for the treatment of chronic plaque PsO in paediatric participants ≥6 to <18 years of age whose disease cannot be adequately controlled with phototherapy and/or topical therapies.

The main study (through Week 52) was complete and conducted in 2 parts. In Part 1, the efficacy, safety, and PK of a weight-based dose regimen of guselkumab was evaluated in paediatric participants during a 16-week randomized, placebo- and active comparator-controlled period, followed by an uncontrolled period of continued treatment, withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. In the reference arm, the active comparator (etanercept]) was administered in an open-label fashion during the controlled period of the study, and efficacy was assessed by a

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[12] Seyger MMB (2022), Augustin M, Sticherling M, et al. Physician-reported clinical unmet needs, burden and treatment patterns of paediatric psoriasis patients: a US and EU real-world evidence study. Acta Derm Venereol. 2022;102:adv00660.

blinded efficacy evaluator to reduce potential bias during data collection and evaluation of clinical end-points.

The open-label reference treatment arm through Week 16 was included to support comparison of the efficacy of etanercept with placebo and was intended to help internally validate the overall results of the paediatric PsO study. This study was not powered for an efficacy comparison between etanercept and guselkumab treatment groups, hence, the results are not presented in the benefit risk-balance section of the assessment report. Placebo and guselkumab treatments were administered in a blinded fashion.

In the single arm, open-label Part 2 of the study, additional efficacy, safety, and PK data for guselkumab in paediatric participants were collected through Week 52.

The two pivotal Phase 3 adult PSO studies CNTO1959PSO3001 and CNTO1959PSO3002 served as supportive data for the assessment of clinical efficacy of guselkumab in paediatric patients with moderate to severe plaque psoriasis.

3.2. Favourable effects

At Week 16 of Study CNTO1959PSO3011, IGA 0/1, IGA 0, PASI 75, 90 and 100, and responses were significantly higher in the guselkumab group compared to placebo. Changes from baseline in Children's Dermatology Life quality index were also significantly higher in the guselkumab group. The differences in response rates were considered clinically relevant.

Through Week 52, the PASI 90 response rate further increased in the Week 16 PASI 90 non-responder group.

Among the 5 PASI 50 non-responders at Week 16, 4 of these patients achieved a PASI 50 response including 3 at Week 24 after continued treatment. This supported the recommendation to consider discontinuing treatment in paediatric patients who have shown no response after 24 weeks of treatment in SmPC section 4.2.

The posology used in Study CNTO1959PSO3011 differed from the recommended posology in SmPC section 4.2. However, simulations showed that the recommended posology resulted in similar predicted serum guselkumab exposure in paediatric patients with plaque psoriasis compared to adults across the body weight ranges including in patients of the 40-70 kg bodyweight subgroup where a fixed 100 mg dose is recommended compared to the body weight-based posology used in Study CNTO1959PSO3011.

3.3. Uncertainties and limitations about favourable effects

A main limitation of the clinical efficacy data from Study CNTO1959PSO3011 was the low patient number. However, the studies in adult patients with PSO were supportive of the clinical efficacy in paediatric patients with PsO. Higher Week 16 response rates were observed in the adult PSO studies than in the paediatric CNTO1959PSO3011 study which may be explained by a higher placebo response in children.

At Week 16, the guselkumab treatment was withdrawn from PASI 90 responder participants. Therefore, long-term (through Week 52) clinical efficacy data in paediatric patients were considered limited.

3.4. Unfavourable effects

Nasopharyngitis and URTI were the most commonly reported adverse events in Study CNTO1959PSO3011, which are known ADR for guselkumab. No cases of TB were reported in Study CNTO1959PSO3011. Serious infection was already an important potential risk for guselkumab. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP and is expected to further characterise the important potential risk of serious infection.

The other adverse events observed with highest frequency in Study CNTO1959PSO3011 were head-ache, fatigue and arthralgia, which are known ADRs of Tremfya.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainty of unfavourable effects arose from the limited number of patients on guselkumab and the withdrawal retreatment design, which resulted in an even more limited longer term (through Week 52) clinical safety exposure for guselkumab. However, supportive information was available from the studies in adult patients with PSO. Further, long-term safety of guselkumab was already listed as missing information in the RMP. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP to further characterise this missing information on long term safety of guselkumab.

Concerning malignancy, serum sickness and MACE which are already important potential risks for guselkumab, no cases were reported in paediatric PSO patients through Week 52 of Study CNTO1959PSO3011. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP and is expected to further characterise malignancy, serum sickness and MACE.

3.6. Effects Table

Table 34: Effects Table for guselkumab, paediatric PsO.

Effect	Short Description	Unit	GUS	PBO	ETA	Uncertainties/ Strength of evidence	References
Favourable Effects							
PASI 75 response at Week 16, co-primary	percent of patients reaching 75% improvement in PASI	%	75.6	20.0	69.2	low patient number, unblinded ETA patients, VarioJect device errors in GUS arm	Study CNTO1959 PSO3011
IGA 0/1 response at Week 16, co-primary	percent of patients reaching IGA 0 or 1	%	65.9	16.0	69.2	low patient number, unblinded ETA patients, VarioJect device errors VarioJect device errors	Study CNTO1959 PSO3011
PASI 90 response at Week 16, key secondary	percent of patients reaching 90% improvement in PASI	%	56.1	16.0	53.8	low patient number, unblinded ETA patients, VarioJect device errors	Study CNTO1959 PSO3011

Effect	Short Description	Unit	GUS	PBO	ETA	Uncertainties/ Strength of evidence	References
IGA 0 response at Week 16, key secondary	percent of patients reaching IGA 0	%	39.0	4.0	26.4	low patient number, unblinded ETA patients, VarioJect device errors	Study CNTO1959 PSO3011
PASI 100 response at Week 16, key secondary	percent of patients reaching 100% improvement in PASI	%	34.1	0	26.9	low patient number, unblinded ETA patients, VarioJect device errors	Study CNTO1959 PSO3011
change from baseline in CDLQI at Week 16, key secondary			-7.28 (-8.87, -5.68)	-1.88 (-3.81, 0.05)	-6.06 (-7.96, -4.15)	low patient number, unblinded ETA patients, VarioJect device errors	Study CNTO1959 PSO3011
Unfavourable Effects – at Week 16							
Nasopharyngitis		%	12.2	28	11.5		Study CNTO1959 PSO3011
URTI		%	9.8	8	7.7		Study CNTO1959 PSO3011
Headache		%	7.3	0	3.8		Study CNTO1959 PSO3011
Fatigue		%	2.4	8	7.7		Study CNTO1959 PSO3011
Arthralgia		%	0	0	7.7		Study CNTO1959 PSO3011

Abbreviations: GUS: guselkumab, PBO: placebo, ETA: etanercept

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Clinical efficacy of guselkumab showed statistical significance over placebo in paediatric plaque psoriasis patients in Study CNTO1959PSO3011 (PASI 75, 90, 100, IGA 0 and IGA 0/1 responses), and the effect was considered clinically relevant.

The effect of guselkumab on clinical efficacy outcomes in the paediatric study with PsO was less pronounced compared to adult PSO studies. Stronger placebo effect was observed compared to adults, especially in the younger age group. No firm conclusion was drawn because of the small sample size in the paediatric study. However, clinical efficacy data from the LTE part of study CNTO1959PSO3011 showed that mean IGA 0/1 and PASI responses reached those observed earlier in adult CNTO1959PSO3001 study.

A subset of patients treated with guselkumab who were PASI 50 non-responders at Week 16 benefited from a continued treatment. These findings support the recommendation included in SmPC Section 4.2

to consider discontinuing treatment in paediatric patients who have shown no response after 24 weeks of treatment.

The safety profile of guselkumab in paediatric patients with PsO was consistent with the known safety profile of guselkumab in adult PSO. Headache, URTI, fatigue and arthralgia were the most commonly reported events which are known ADRs for guselkumab.

The CHMP acknowledged the limited long-term safety in paediatric patients. Long-term safety of guselkumab is listed as missing information in the RMP. The long-term extension of Study CNTO1959PSO3011 was added as Category 3 study in the agreed RMP to further characterise this missing information.

3.7.2. Balance of benefits and risks

Clinical efficacy of guselkumab was shown over placebo in paediatric plaque psoriasis patients in Study CNTO1959PSO3011. The therapeutic responses of guselkumab in paediatric PsO patients was lower than in adults, but the effect was still considered clinically relevant. Safety findings in Study CNTO1959PSO3011 were generally similar compared to adult PsO studies. During LTE, therapeutic response seemed to reach those observed in adult PSO studies. The long-term safety information is limited but will be further characterised from the ongoing long-term extension of Study CNTO1959PSO3011. This study is also expected to address the safety concerns of serious infection, malignancy, serum sickness and MACE.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Tremfya is positive in the following indication:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Tremfya 45 mg/ 0.45 mL strength is favourable in the following indication:

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Tremfya subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

Janssen Cilag International shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0346/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension application to add a new strength of 45 mg/0.45 mL grouped with an extension of indication for Tremfya 100 mg for injection in pre-filled syringe to include the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy based on results from study CNTO1959PSO3011. This is a Phase 3, multicenter, randomized, placebo- and active comparator-controlled study evaluating the efficacy, safety, and pharmacokinetics of subcutaneously administered guselkumab for the treatment of plaque psoriasis in paediatric participants (≥6 to <18 years of age). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for Tremfya 100 mg for injection in pre-filled syringe are updated.

Update of the sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for Tremfya 100 mg OnePress solution for injection in pre-filled pen and Tremfya 100 mg PushPen solution for injection in pre-filled pen to reflect the paediatric data available for the treatment of plaque psoriasis in children.

Editorial changes were also implemented.

The Package Leaflet and Labelling are updated in accordance.

Version 14.1 of the RMP is agreed.