Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Guselkumab

Proprietary Product Name: Tremfya / Janssen Guselkumab

Sponsor: Janssen-Cilag Pty Ltd

Date of first round report: 30 June 2017

Date of second round report: 22 December 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement criteria
ADA	Anti-Drug Antibody
AE	Adverse Events
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BLQ	Below Level of Quantification
BMI	Body Mass Index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCL4/MIP-1β	Chemokine (C-C motif) ligand 4 also known as Macrophage Inhibitory Protein 1 Beta
CCL22/MDC	C-C motif chemokine ligand 22/Macrophage Derived Chemokine
CI	Confidence interval
CL	Systemic clearance
CL/F	Apparent Clearance
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CRP	C-Reactive Protein
CS	Corticosteroids
CTCAE	Common terminology Criteria for Adverse Events
CV	Coefficient of Variation/Cardiovascular
CXCL8/IL-8	C-X-C Motif chemokine Ligand 8/IL-8 protein
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-Rheumatic Drug

Abbreviation	Meaning
DP	Drug Product
ECLIA	Electrochemiluminescent Immunoassay
ECG	Electrocardiogram
EMA	European Medicines Agency
EP	Erythrodermic psoriasis
ESR	Erythrocyte Sedimentation Ratio
FDA	Food and Drug Administration
f-PGA	Fingernail Physician's global Assessment
GCP	Good Clinical Practice
GPP	Generalized pustular psoriasis
HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire – Disability Index
hf-PGA	Physician's Global Assessment of Hands and /or Feet
IBD	Inflammatory bowel disease
ICH	International Council on Harmonization
IGA	Investigator's Global Assessment
IgG1lambda	Immunoglobulin G1 Lambda
IL	Interleukin
ISR	Injection site reaction
IV	Intravenous
mAb	Monoclonal Antibody
MTX	Methotrexate
NAPSI	Nail Psoriasis Area and Severity Index
NMSC	Nonmelanoma skin cancer
NSAID	Non-Steroidal Anti-Inflammatory Drug

Abbreviation	Meaning
NK	Natural killer
PASI	Psoriasis Area and Severity index
PASI 75	Subjects achieving ³ 75% improvement in the PASI from baseline
PASI 90	Subjects achieving ³ 90% improvement in the PASI from baseline
PASI 100	Subjects achieving ³ 100% improvement in the PASI from baseline
PD	Pharmacodynamic
PFS	Pre-filled syringe
PGA	Physician' Global Assessment
PK	Pharmacokinetic
PPP	Palmoplantar pustulosis
PPSI	Palmoplantar Psoriasis Area and Severity Index
PPPASI	Palmoplantar Pustular Psoriasis Area Severity Index
PPPASI-50	Proportion of patients achieving an improvement from baseline of ≥50%
PsA	Psoriatic Arthritis
PSSD	Psoriasis Symptom and Sign Diary
PSSI	Psoriasis Scalp Severity index
PUVA	Psoralen plus ultraviolet therapy
q2w	Every other week
q8w	Every 8 weeks
q12w	Every 12 weeks
QOL	Quality of Life
QTPP	quality target product profile
RA	Rheumatoid Arthritis
S100A2	S100 calcium-binding protein A2
SAE	Serious Adverse Event

Abbreviation	Meaning
SC	Subcutaneous
SF-36	Medical Outcomes Study 36-Item Short Form
ss-IGA	Scalp-specific IGA
$T_{1/2}$	Terminal half life
TB	Tuberculosis
Th1	T-helper 1
Th17	T-helper 17
T_{max}	Time to reach maximum serum concentration
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
URTI	Upper respiratory tract infection
VAS	Visual Analogue Scale
VD	Volume of Distribution
Vdz	Volume of distribution during the terminal phase
V/F	Apparent volume of distribution based on the terminal phase after extravascular administration
WLQ	Work Limitations Questionnaire

1. Submission details

1.1. Identifying information

Submission number	PM-2017-00552-1-1
Sponsor	Janssen-Cilag Pty Ltd
Trade name	Tremfya
Active substance	Guselkumab

1.2. Submission type

This is a submission by Janssen-Cilag Pty Ltd of an application to register a new biological entity, Tremfya/Janssen Guselkumab (guselkumab) solution for injection, for the treatment of moderate to severe plaque, scalp, nail, and hand and foot psoriasis.

1.3. Drug class and therapeutic indication

Guselkumab is a human immunoglobulin G1 lambda (IgG1lambda) monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL-23) protein with high specificity and affinity, resulting in the inhibition of the biological effects of IL-23.The proposed indication for Tremfya is for the treatment of moderate to severe plaque psoriasis, scalp, nail, and hand and foot psoriasis, and improvement of health-related quality of life in adult patients who are candidates for systemic therapy or phototherapy.

1.4. Dosage forms and strengths

The product will be supplied in a single-use 1 mL pre-filled syringe (PFS) containing 100 mg guselkumab. The PFS is assembled into an UltraSafe Plus™ passive needle guard and will be supplied in packs of 1.

1.5. Dosage and administration

The recommended dose is 100 mg by SC injection at Weeks 0 and 4, followed by 100 mg every 8 weeks (q8w) thereafter.

1.6. Proposed changes to the product documentation

Not applicable.

2. Background

2.1. Information on the condition being treated

Skin psoriasis is a chronic, immunologically-mediated, inflammatory condition that affects 2-3% of the population. Approximately 30% of patients with skin psoriasis develop psoriatic arthritis,

and 85-90% of patients have chronic plaque psoriasis. Some 10% of these have severe disease. Its onset is typically between the ages of 30 and 55 years and it affects men and women equally. Psoriasis is thought to arise from a combination of pathogenic factors including genetic susceptibility and environmental exacerbation, which results in activation of dendritic cells in the skin and differentiation of T cells. In turn, these T cells produce cytokines that induce keratinocyte hyperproliferation and result in characteristic raised, well-demarcated erythematous lesions of psoriasis. Clinically, it is characterised by symmetrically distributed, well-defined, sharply demarcated, indurated, erythematous plaques that are covered by friable, dry, white-silvery scale. Areas of the body that are frequently involved include the scalp, elbows, knees, buttocks, and genitalia. The extent of skin involved varies among affected individuals, and is a primary determinant of severity. The psoriatic lesions may be triggered by injury to the skin are often on visible skin and unsightly. Patients experience shedding of scales and bleeding from their plaques, as well as pain and itching. This disease has a significant impact on functional capacity, quality of life, mental health and work productivity, and it is linked to other comorbid conditions such as cardiovascular disease, metabolic syndrome, and arthritis.

A variety of biologic systemic therapies have been developed and approved for the treatment of psoriasis, including anti-tumour necrosis factor alpha (TNFα) agents, IL-12/23 antagonists, and IL-17A inhibitors. The pro-inflammatory cytokine interleukin (IL)-23 and its resulting T helper 17 (Th17) pathway play perhaps a more important role in mediating psoriasis than IL-12.IL-23 induces differentiation and maintenance of Th17 cells, which produce the effector cytokines IL-17, IL-22, and tumour necrosis factor-alpha (TNFα).IL-23 is a heterodimer composed of two subunits, p40 and p19.While p40 is also present in IL-12, p19 is specific for IL-23.Levels of IL-23p19 and IL-12/23p40 messenger RNA (mRNA) are upregulated in psoriatic plaques and decrease with effective treatment.

IL-17A is the principal effector of TH17 cells and plays an important role in host defence against extracellular bacteria and fungi at mucosal surfaces.IL-17A also promotes inflammatory pathology in autoimmune disease.IL-17A activates a highly pro inflammatory program of gene expression.

Despite the availability of multiple therapeutic modalities, the treatment of chronic moderate to severe psoriasis remains challenging. While the response rates of available treatments have increased over time, there is still substantial room for improving the proportion of patients that achieve clear skin. In addition, the currently available treatments have practical limitations due to tolerability, toxicity, safety risks, and/or issues with ease of use or convenience.

2.2. Current treatment options

The traditional paradigm for the treatment of psoriasis was a stepwise approach to treatment starting with topical agents, followed by phototherapy, then systemic agents. More recently, this approach has been replaced by treatment selection based on patient presentation, disease severity and patient-specific characteristics. Patients are now typically divided into those who are candidates for localised therapy and should receive topical agents versus those who are candidates for systemic and/or phototherapy.

Protection from trauma and frequent emollient application is generally advocated.

Topical treatment is generally preferred as the first-line therapy, but more than two-thirds of the patients require systemic therapy.

Keratolytic agents such as salicylic acid are safe and may be tried alone or in combination with other topical products such as potent topical corticosteroids to reduce scaling. If potent topical corticosteroids are insufficient, calcipotriol + betamethasone dipropionate is indicated for chronic stable plaque type psoriasis vulgaris. Coal tar is another inexpensive agent and known

to have some efficacy. Increased strength increases efficacy at the cost being increasingly cosmetically unacceptable.

Different types of phototherapy such as PUVA therapy are widely used for treatment of psoriasis.PUVA has a definite potential to cause skin cancer, including melanomas and the risk of developing skin cancer is directly related to the amount of energy administered. PUVA will cause photo-aging that is unavoidable. If not appropriately monitored, PUVA can produce severe ultraviolet light burns. Narrow band UVB is also used and has similar efficacy.

2.2.1. Systemic agents

Approved drugs for PsO include non-biological disease-modifying antirheumatic drugs (DMARDs; methotrexate (MTX), sulfasalazine and leflunomide) and several biologics.

Several low molecular weight drugs (including cyclosporine, methotrexate), and biologics, including TNF-α antagonists (adalimumab, etanercept, infliximab), anti IL17A (secukinumab) and anti IL12/IL23 (ustekinumab) have been approved for the treatment of psoriasis. Many of these treatments are associated with certain safety concerns (including, organ toxicity, infections including tuberculosis, malignancies including lymphoma, immunogenicity and demyelinating neurologic events), which limits their value in the long-term management of psoriasis. Few achieve the goal of clear/almost clear skin for a majority of patients.

Acitretin is a systemic agent used for severe intractable psoriasis. Precautions include hepatotoxicity, hyperostosis and lipid effects.

High-dose methotrexate is a folate antagonist and is used for psoriasis. It may be superior to acitretin but it requires careful monitoring can cause myelosuppression, hepatotoxicity, pneumonitis, opportunistic infections and renal toxicity.

Cyclosporine is a potent immunosuppressive agent that has specific and reversible inhibition of immunocompetent lymphocytes in the G0- and G1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2.In dermatological practice, the daily dose of cyclosporine is usually in a therapeutic range of 2.5–5 mg/kg. The use of such doses for a short-term course (12–16 weeks) has been shown to cause a rapid and significant improvement or complete remission in 80–90% of psoriasis patients. The efficacy of cyclosporine in plaque psoriasis has been evidenced by several randomised studies, which also showed the dosage-dependent therapeutic effects, using the drug at dosages ranging from 1.25 to 5 mg/kg/day for 10–16 weeks on average for the induction of psoriasis remission. Cyclosporine is limited by its nephrotoxic effects, effect on immune system and tendency to increase the risk of neoplasia.

Leflunomide is a disease-modifying antirheumatic medication that inhibits de novo pyrimidine synthesis. It has moderate efficacy for treatment of psoriasis and psoriatic arthritis but potential toxicities caused by leflunomide are predominantly gastrointestinal irritation (diarrhea, nausea and dyspepsia), elevated liver enzymes, leukopenia, drug eruption, headaches, and increased risk of infections, neuropathy and teratogenicity.

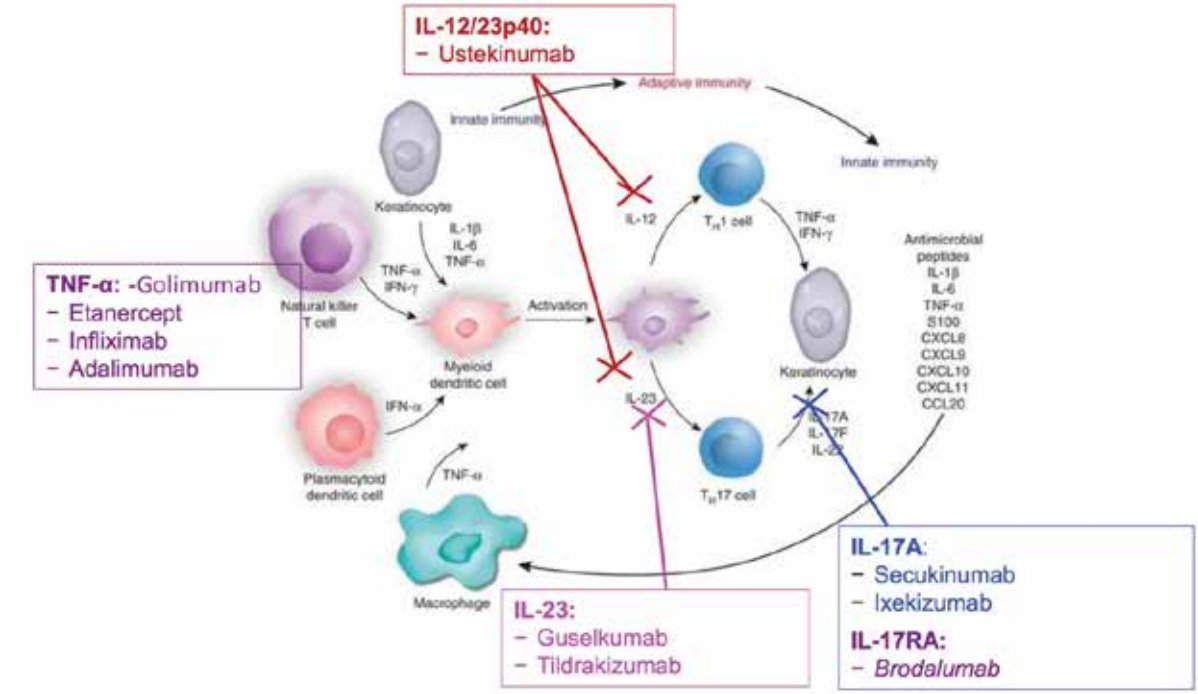
Ustekinumab, another fully human immunoglobulin G1kappa monoclonal antibody that blocks interleukin IL-12 and IL-23 by binding to the p-40 subunit of both IL-12 and IL-23 so that they subsequently cannot bind to their receptors. By binding to the shared p40 subunit of IL-12 and IL-23, USK may exert its clinical effects in both psoriasis and psoriatic arthritis through interruption of the T helper cell (Th1 and Th17) cytokine pathways which are central to the pathology of these diseases. It is thought that IL-12 induces proliferation of naïve T-cell populations and that IL-23 is stimulatory to memory T-cell populations. Precautions include the possibility of serious infections, malignancy and reversible posterior leukoencephalopathy syndrome.

Secukinumab and ixekizumab are monoclonal antibody selectively neutralising interleukin-17A and have demonstrated good efficacy and safety in the treatment of moderate-to-severe psoriasis and psoriatic arthritis with a rapid onset of action and sustained response.IL- 17 receptors are expressed on various cell types including keratinocytes. As a result, these monoclonals inhibit the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces IL- 17A mediated contributions to autoimmune and inflammatory diseases. Clinically relevant effects include reduction in erythema, induration and desquamation present in plaque psoriasis lesions. There may be an increase in mild or nonserious infections including mucosal candidiasis with these agents seen in the pivotal studies compared to placebo. Other concerns or precautions include the possibility of serious infections, TB exacerbations, Crohn's disease, neutropenia, the potential for increased risk of malignancy with long term use and hypersensitivity.

Apremilast is an oral medication for the treatment of certain types of psoriasis and psoriatic arthritis. It may also be useful for other immune system related inflammatory diseases. The drug acts as a selective inhibitor of the enzyme phosphodiesterase 4 (PDE4) and inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells. Adverse effects are usually mild to moderate and include headache, back pain, nausea, diarrhoea, fatigue, nasopharyngitis and upper respiratory tract infections. Worsening depression, suicidal thoughts, other mood changes, drug-drug interactions and weight loss may occur with Apremilast.

Adalimumab, infliximab, golimumab and etanercept are TNF-inhibiting, anti-inflammatory, biologic medications. These agents have efficacy in plaque psoriasis and/or psoriatic arthritis. Because TNFα is also part of the immune system, which protects the body from infection, treatment with these may increase the risk of haematological reactions, serious infections or reactivations of infections (including hepatitis B and TB), and malignancy. Other concerns include central demyelinating disorders.

Figure 1: Cytokine targeting of biologics for plaque psoriasis



Modified from www.accessdata.fda.gov

Historically, approved SC biologic agents have shown maximum response rates of 70% to 80% of subjects achieving ≥ 75% improvement in the Psoriasis Area and Severity Index (PASI) from

baseline (PASI 75), which was considered a benchmark of efficacy. The most recently approved anti-IL-17A therapeutic agents (secukinumab and ixekizumab) have demonstrated consistently higher PASI 75 responses than previous agents and as a class have reported PASI 90 response rates after 12 weeks of treatment of up to 71% and PASI 100 response rates up to 41%.

The use of most systemic products can result in substantial improvement in psoriatic signs and symptoms, but the use of these products have significant limitations. Many patients with psoriasis on the more severe end of the spectrum tend to have unremitting disease requiring continuous treatment and many of those using systemic agents will experience an eventual waning of treatment effect over time. Few patients can remain on one therapy over the course of their disease. Additionally, as outlined above, all systemic products currently available are associated with potentially serious risks.

2.3. Clinical rationale

While the response rates of available treatments, including those for more stringent measures of efficacy, have increased over time, there is still substantial room for improving the proportion of patients that achieve clear skin. In addition, the currently available treatments have practical limitations due to tolerability, toxicity, safety risks, and/or issues with ease of use or convenience.

Guselkumab is a human mAb directed against the p19 subunit of IL-23 and thus, specifically targets IL-23.A rapidly growing body of literature suggests that the IL 23/IL-17 pathway contributes to the chronic inflammation underlying the pathophysiology of many immune-mediated diseases, including plaque psoriasis, erythrodermic psoriasis (EP), generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), IBD, ankylosing spondylitis, and PsA.

Susceptibility to psoriasis, PsA, and IBD has been shown to be associated with genetic polymorphismes in IL-23/IL-23R components.

IL-12 is a heterodimeric cytokine, comprised of p35 and p40 subunits, while IL-23 is a heterodimeric cytokine comprised of the same p40 subunit as IL-12 and a unique p19 subunit. In contrast to ustekinumab, which antagonizes the activities of both IL-12 and IL-23, guselkumab only antagonizes the activity of IL-23 via its p19 subunit. Therefore, guselkumab utilizes a mechanism of action that overlaps with that of ustekinumab, but selectively targets only IL-23.

IL-23 is a key driver of Th17 cell differentiation and survival and an upstream regulator of IL-17A, a central pro-inflammatory effector cytokine implicated in psoriasis pathogenesis. Moreover, IL-23 stimulates production of other Th17 cytokines (for example, IL-17F, IL-22) by Th17 and other cell types, including innate lymphoid cells, type 3 cells, and γδT-cells. Therefore, inhibition of IL-23 blocks downstream production of IL-17A, IL-17F and IL-22 by Th17 cells and other cell types. Since many IL-17A-producing cells are dependent upon IL-23 for survival; inhibition of IL-23 may reduce the number of these pathogenic cells.IL-23p19 and IL-12/23p40, but not IL-12p35, expression is increased in human psoriatic lesions, and there is a marked increase in the abundance of mature dendritic cells in lesions associated with increased IL-23 levels. This suggests that IL-23 may play a more dominant role in psoriasis than IL-12.The exceptional efficacy results shown in the Phase II study of guselkumab also provided further insight into the relative importance of IL-23 dependent Th17 pathways compared to the IL-12 dependent Th1 pathway in the pathogenesis of psoriasis.

2.4. Formulation

2.4.1. Formulation development

During the clinical development of guselkumab, 1 cell line (C1707B) that was developed from a genetically engineered Chinese hamster ovary cell line was used for guselkumab production. The quality target product profile (QTPP) for guselkumab drug product (DP) required the development of a sterile liquid dosage form with at least 18 months shelf life at 2-8 °C, in a PFS, for single use with no preservative, for subcutaneous (SC) administration capable of delivering 50 mg/syringe (0.5 mL at 100 mg/mL) or 100 mg/syringe (1 mL at 100 mg/mL).The QTPP also required that the DP formulation and PFS be capable of assembly with the UltraSafe Plusä Passive Needle Guard (UltraSafe Plus).

For Phase I and II clinical studies, the DP was either 100 mg of guselkumab for reconstitution with 1.0 mL of water for injection (WFI) or 83 mg of guselkumab for reconstitution with WFI to achieve a 0.83 mL volume of 100 mg/mL solution for subcutaneous (SC) administration.

Prior to the start of Phase III clinical studies, the DP presentation was changed from a lyophile in a vial to a liquid in a PFS. The formulation excipients composition of the reconstituted lyophile and the liquid in the syringe were similar with the exception of an increase in polysorbide 80 for the PFS formulation, and slight differences in histidine concentration. Overall, the assessment demonstrated that the changes would not be expected to adversely impact the safety and efficacy of guselkumab.

2.4.2. Excipients

The excipients used in the drug product are the same as those used in the drug substance (including sucrose, polysorbate 80 and histidine).No additional excipients are included.

2.5. Guidance

There is one specific regulatory guideline relevant to the requested indication. The TGA has adopted the EU Guideline on Clinical Investigation for Medicinal Products for the Treatment of Psoriasis (effective 28 July 2005) with one annotation

2.6. Evaluator's commentary on the background information

The validity of the stated rationale is acceptable and consistent with the currently accepted role of IL-23 in mediating inflammation in psoriasis. The drug development program is in line with current guidelines and no issues are identified with overseas or other regulatory bodies.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

3.1.1. Clinical data

The pharmacokinetic profiles of guselkumab were assessed in 4 studies:

CNTO1959NAP1001

Phase I, Open-label, Randomised, Parallel Study to Assess the Pharmacokinetic Comparability of 2 Formulations and to Evaluate Pharmacokinetic Comparability of Guselkumab (CNTO 1959) Delivered by 2 Different Devices in 141 Healthy Subjects

CNTO1959NAP1002

Phase I, Open-label, Single-dose Study to Characterize the Elimination of Guselkumab Glycoform Variants in 8 Healthy Subjects

CNTO1959PSO1001

A Randomised, Double-blind, Placebo-controlled, Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNTO 1959 following a Single Intravenous or a Single Subcutaneous Administration in 47 Healthy Subjects and in 24 Subjects with Moderate to Severe Psoriasis

CNTO1959PSO1002

A Randomised, Double-blind, Placebo-controlled, Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNTO 1959 following a Single Subcutaneous Administration in 24 Japanese Subjects with Moderate to Severe Plaque Psoriasis

The efficacy of guselkumab in the treatment of moderate to severe plaque psoriasis in adults is supported by analyses from 6 core psoriasis studies:

Two Phase I studies:

CNTO1959PSO1001 (referred to as PSO1001)

A Randomised, Double-blind, Placebo-controlled, Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNTO 1959 following a Single Intravenous or a Single Subcutaneous Administration in 47 Healthy Subjects and in 24 Subjects with Moderate to Severe Psoriasis

CNTO1959PSO1002 (referred to as PSO1002)

A Randomised, Double-blind, Placebo-controlled, Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNTO 1959 following a Single Subcutaneous Administration in 24 Japanese Subjects With Moderate to Severe Plaque Psoriasis

One Phase II study:

CNTO1959PSO2001 (X-PLORE, PSO2001)

A Phase II Multicenter, Randomised, Placebo- and Active comparator-controlled, Dose-ranging Trial to Evaluate CNTO 1959 for the Treatment of approximately 280 Subjects with Moderate to Severe Plaque-type Psoriasis (X-PLORE)

Three Phase III studies:

CNTO1959PSO3001 (VOYAGE 1, PSO3001)

A Phase III, Multicenter, Randomised, Double-blind, Placebo and Active Comparator controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of approximately 750 Subjects with Moderate to Severe Plaque-type Psoriasis (VOYAGE-1)

CNTO1959PSO3002 (VOYAGE 2, PSO3002)

A Phase III, Multicenter, Randomised, Double-blind, Placebo and Active Comparator- Controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of approximately 992 Subjects with Moderate to Severe Plaque-type Psoriasis with Randomised Withdrawal and Retreatment

CNTO1959PSO3003 (NAVIGATE, PSO3003)

A Phase III, Multicenter, Randomised, Double-blind Study to Evaluate the Efficacy and Safety of Guselkumab for the Treatment of approximately 871 Subjects with Moderate to Severe Plaque-type Psoriasis and an Inadequate Response to Ustekinumab

The safety of guselkumab was evaluated primarily in the psoriasis population in a total of 1,748 subjects with moderate to severe plaque psoriasis treated in Studies PSO2001, PSO3001, PSO3002, and PSO3003.In the analysis of the Phase III safety data from Studies PSO3001 and PSO3002, 1,367 subjects included in the primary analysis data set received the proposed guselkumab dose regimen of 100 mg, administered SC, at Weeks 0 and 4 and then q8w thereafter, including 592 subjects treated for 48 weeks (1 year).The size of this safety database is sufficient to provide a robust evaluation of the safety of guselkumab in the target population and conforms to International Conference on Harmonization (ICH) requirements.

In addition to the 6 core psoriasis studies, 4 completed (CNTO1959NAP1001, CNT01959NAP1002, CNTO1275ARA2001, CNTO1959PPP2001) and 5 ongoing studies (CNTO1959PSO1003, CNTO1959PSA2001, CNTO1959PPP3001, CNTO1959PSO3004, CNTO1959PSO3005) with guselkumab in other indications (PPP, PsA), as well as studies in other populations (for example, from Japan only) and investigating drug-drug interactions (Study CNTO1959PSO1003), provided supportive safety and/or pharmacokinetic (PK) and immunogenicity information in the submission.

3.2. Paediatric data

No clinical studies of guselkumab have been conducted in paediatric subjects (< 18 years).An initial paediatric study plan for use of guselkumab in the treatment of psoriasis was agreed with the United States Food and Drug Administration (FDA) on 21 November 2014.[1]

3.3. Good clinical practice

All of the studies in the guselkumab clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

3.4. Evaluator's commentary on the clinical dossier

No important shortcomings of the development program are identified.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The submitted studies providing pharmacokinetic information are described in Table 1 below.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Synopsis
PK in healthy adults	General PK Single dose	CNTO1959NAP1002	Characterisation of the elimination of guselkumab glycoform variants following a single IV administration of guselkumab at 10 mg/kg dose in healthy subjects
		CNTO1959PSO1001	To assess the safety and tolerability of CNTO 1959 following single IV and SC

[1] Sponsor clarification: There is also an approved EU PIP.

PK topic	Subtopic	Study ID	Synopsis
			doses administered to subjects (Part 1) and following single SC doses administered to subjects (Part 2)
	Bio-equivalence † Single dose	CNTO1959NAP1001	PK comparison of lyophilized and liquid formulations following a single SC administration of 100 mg guselkumab in healthy subjects
PK in special populations	Target population § Single dose	CNTO1959PSO1001	To assess the safety and tolerability of CNTO 1959 following single IV and SC doses administered to subjects (Part 1) and following single SC doses administered to subjects (Part 2)
		CNTO1959PSO1002	To assess the safety and tolerability of CNTO 1959 following a single SC dose in Japanese subjects
	Target population § Multi dose	CNTO1959PSO2001	A Phase II Multicenter, Randomised, Placebo- and Active-Comparator-Controlled, Dose-Ranging Trial to Evaluate CNTO 1959 for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis
		CNTO1959PSO3001	A Phase III, Multicenter, Randomised, Double-blind, Placebo and Active Comparator controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis
		CNTO1959PS3002	A Phase III, Multicenter, Randomised, Double-blind, Placebo and Active Comparator-Controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis with Randomised Withdrawal and Retreatment
		CNTO1959PSO3003	A Phase III, Multicentre, Randomised, Double-blind, Placebo-controlled study to compare the efficacy and safety of switching to guselkumab versus continuing on ustekinumab in subjects who have achieved an inadequate response to ustekinumab at Week 16 (IGA ≥ 2)
		CNTO1275ARA2001	Efficacy/safety C_{trough} and steady-state PK. Immunogenicity of SC: 90 mg

PK topic	Subtopic	Study ID	Synopsis
			ustekinumab, 50 mg guselkumab, 200 mg guselkumab, or placebo in 274 patients with Rheumatoid Arthritis
	Other special populations	CNTO1959PPP 2001	Efficacy/safety C_{trough} and steady-state PK Immunogenicity of SC: Placebo, 200 mg guselkumab in 49 patients with Palmoplantar pustulosis
		Summary of clinical pharmacology	Pooled PPK analysis of guselkumab in healthy subjects
Population PK analyses	Healthy subjects		PK Modelling Report: Pooled PPK analysis of guselkumab in psoriasis Intrinsic and Extrinsic factors including Concomitant medications (NSAIDs, corticosteroids, paracetamol, acetylsalicylic acid, isoniazid) included in the analysis
	Target population	Summary of clinical pharmacology and PopPK Report	
	Other (RA and PPP)		

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Comment: No results have been excluded from consideration.

4.2. Summary of pharmacokinetics

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. *Absorption*

Guselkumab was slowly absorbed into the systemic circulation. In healthy subjects (NAP1001), the median T_{max} occurred between 5.0 to 5.5 days after a single 100 mg SC administration. In healthy subjects (PSO1001 Part 1), the median T_{max} occurred 5 days after a single 3 mg/kg SC administration.Following SC administration, the primary route of absorption of guselkumab is likely the lymphatic circulation based on its molecular weight of approximately 150 kilodalton.

4.2.1.2. *Bioavailability*

Based on a comparison of the AUC_{inf} values obtained from the SC and IV cohorts in healthy subjects (NAP1001), the mean bioavailability (F%) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6% to 54.9%.This is consistent with

previous reports for other typical therapeutic IgG1 mAbs following SC administration. Based on a comparison of the AUC_{inf} values obtained from the SC and IV cohorts in healthy subjects (NAP1001), the mean bioavailability (F%) of guselkumab following a single 100 mg SC administration was estimated to be approximately 47.6% to 54.9%.This is consistent with previous reports for other typical therapeutic IgG1 mAbs following SC administration.

A summary of the absorption parameters of guselkumab after a single SC administration in subjects with psoriasis and healthy subjects is presented in Table 2.

Table 2: Summary of guselkumab absorption parameters after a single subcutaneous administration

Study Population[a]		Summary Statistics	C_{max} (µg/mL)	T_{max} (day)	AUC_{inf}[b] (µg-day/mL)
Study ID	Dose Regimen				
Subjects with Psoriasis					
PSO1001	10 mg	N	5	5	4
(Part 2)		Mean ± SD	0.54 ± 0.11	-	14.9 ± 6.6
		Median	0.50	6.03	15.1
	30 mg	N	5	5	5
		Mean ± SD	1.14 ± 0.47	-	30.3 ± 15.4
		Median	0.97	4.06	23.0
	100 mg	N	5	5	5
		Mean ± SD	4.81 ± 4.26	-	108.5 ± 79.2
		Median	3.37	3.16	84.6
	300 mg	N	5	5	5
		Mean ± SD	18.97 ± 7.71	-	510.3 ± 178.0
		Median	22.70	5.27	574.6
PSO1002	10 mg	N	5	5	3
		Mean ± SD	0.46 ± 0.19	-	14.0 ± 7.8
		Median	0.42	4.02	17.3
	30 mg	N	5	5	5
		Mean ± SD	1.52 ± 0.56	-	40.8 ± 15.8
		Median	1.34	5.93	35.6
	100 mg	N	5	5	5
		Mean ± SD	6.14 ± 2.29	-	159.9 ± 65.2
		Median	5.24	6.02	133.5
	300 mg	N	5	5	4
		Mean ± SD	15.08 ± 5.15	-	427.1 ± 156.7
		Median	16.52	6.03	470.3
Healthy Subjects					
PSO1001	3 mg/kg	N	6	6	6
(Part 1)		Mean ± SD	9.46 ± 2.50	-	257.0 ± 48.2
		Median	8.46	5.00	251.6
NAP1001	100 mg Lyo	N	40	40	39
		Mean ± SD	7.67 ± 1.98	-	183.2 ± 65.4
		Median	7.30	5.50	168.7
	100 mg PFS-U	N	40	40	35
		Mean ± SD	8.09 ± 3.68	-	187.7 ± 94.2
		Median	7.40	5.50	175.2
	100 mg PFS-FID	N	41	41	40
		Mean ± SD	9.01 ± 2.86	-	211.5 ± 72.0
		Median	8.34	5.00	211.1

[a] All values presented are rounded based upon data reported in the individual CSRs.
[b] AUC from time 0 to infinity with extrapolation of the terminal phase.
Key: AUC=area under the concentration versus time curve; C_{max}= maximum observed concentration; ID=identification; Lyo=lyophilized; N=sample size; PFS-FID=prefilled syringe with a SelfDose™ facilitated injection device; PFS-U=prefilled syringe with an UltraSafe Passive® Delivery System; SD=standard deviation; T_{max}= time to reach the maximum serum concentration.

No bioavailability of multiple dosing was evaluated in healthy subjects.

4.2.1.3. *Distribution*

A summary of the distribution parameters of guselkumab after a single IV or SC administration in subjects with psoriasis and healthy subjects is presented in Table 3.

Table 3: Summary of guselkumab distribution parameters after a single intravenous or subcutaneous administration

Study Population[a]		Summary Statistics	V_z or V_z/F (L)[b]	V_z or V_z/F (mL/kg)[b]
Study ID	Dose Regimen			
Subjects with Psoriasis				
PSO1001 (Part 2)	10 mg SC	N	4	4
		Mean ± SD	16.9 ± 2.7	180.9 ± 29.3
		Median	17.2	177.4
	30 mg SC	N	5	5
		Mean ± SD	23.6 ± 8.2	231.6 ± 65.1
		Median	22.7	217.1
	100 mg SC	N	5	5
		Mean ± SD	28.0 ± 15.9	250.8 ± 111.7
		Median	25.6	216.7
	300 mg SC	N	5	5
		Mean ± SD	16.1 ± 6.7	177.1 ± 59.0
		Median	12.7	159.8
PSO1002	10 mg SC	N	3	3
		Mean ± SD	19.6 ± 8.3	273.5 ± 87.0
		Median	17.4	294.5
	30 mg SC	N	5	5
		Mean ± SD	18.1 ± 7.0	243.1 ± 99.1
		Median	17.7	201.8
	100 mg SC	N	5	5
		Mean ± SD	17.4 ± 5.2	248.4 ± 67.8
		Median	18.4	242.2
	300 mg SC	N	4	4
		Mean ± SD	17.3 ± 5.8	237.6 ± 116.3
		Median	15.5	273.2
Healthy Subjects				
PSO1001 (Part 1)	0.03 mg/kg IV	N	3	3
		Mean ± SD	7.3 ± 2.5	105.7 ± 22.4
		Median	8.7	115.2
	0.1 mg/kg IV	N	3	3
		Mean ± SD	10.1 ± 1.5	117.3 ± 21.6
		Median	9.6	108.6
	0.3 mg/kg IV	N	6	6
		Mean ± SD	8.3 ± 2.4	115.6 ± 28.4
		Median	8.2	109.4
	1 mg/kg IV	N	6	6
		Mean ± SD	8.2 ± 1.3	99.4 ± 8.7
		Median	7.6	99.7
	3 mg/kg IV	N	6	6
		Mean ± SD	8.0 ± 0.7	100.9 ± 9.1
		Median	7.9	97.7
	10 mg/kg IV	N	6	6
		Mean ± SD	9.9 ± 1.9	123.2 ± 17.3
		Median	9.9	117.9
	3 mg/kg SC	N	6	6
		Mean ± SD	22.0 ± 4.8	288.0 ± 54.1
		Median	21.9	285.6
NAP1001	100 mg Liq IV	N	19	19
		Mean ± SD	6.7 ± 2.1	97.8 ± 25.5
		Median	6.6	93.4
	100 mg Lyo SC	N	39	39
		Mean ± SD	14.4 ± 4.7	208.7 ± 76.8
		Median	13.7	173.8
	100 mg PFS-U SC	N	35	35
		Mean ± SD	16.6 ± 8.9	241.0 ± 124.9
		Median	14.5	199.4
	100 mg PFS-FID SC	N	40	40
		Mean ± SD	12.9 ± 4.8	191.1 ± 73.6
		Median	11.9	171.7

[a] All values presented are rounded based upon data reported in the individual CSRs.
[b] For subcutaneous studies, volume of distribution is apparent volume of distribution (V_z/F).
Key: ID=identification; Liq=liquid; Lyo=lyophilized; N=sample size; PFS-FID=prefilled syringe with a SelfDose™ facilitated injection device; PFS-U=prefilled syringe with an UltraSafe Passive® Delivery System; SD=standard deviation; V_z=volume of distribution based on the terminal phase; V_z/F=apparent volume of distribution during terminal phase after extravascular administration.

4.2.1.4. *Metabolism*

The exact metabolic pathway for guselkumab has not been characterised. As a fully human IgG1lambda mAb, guselkumab is expected to be metabolised in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Renal excretion and hepatic enzyme mediated metabolism are therefore unlikely to represent major elimination routes.

4.2.1.5. *Excretion*

Variations in renal and hepatic function are not expected to affect the elimination of guselkumab.

Intra and inter individual variability of pharmacokinetics

The factors that contributed to at least 10% change in CL/F or V/F of guselkumab are outlined in Table 4.

Table 4: Parameter Estimates with Covariate Effects in the Final Reduced Population Pharmacokinetic Model

Parameter	Estimate[a]	95th Confidence Interval	Magnitude of Change[b]
CL/F (L/day)[c]	0.516 (1.19)	0.504-0.528	
Baseline body weight (BWT) on CL/F	0.998 (4.37)	0.913-1.080	-14.1% – 14.8% (28.9%)
Diabetes (DIAB) on CL/F	1.12 (2.41)	1.07-1.17	12%
Non-Caucasian (RACE) on CL/F	1.11 (1.56)	1.08-1.14	11%
V/F (L)[d]	13.5 (1.08)	13.2-13.8	
Baseline body weight (BWT) on V/F	0.829 (4.61)	0.754-0.904	-11.9% – 12.1% (24.0%)
ka (1/day)	1.11 (14.1)	0.804-1.42	
IIV of CL/F (%)	35.6 (6.54) [4.30]	33.3-37.9	--
IIV of V/F (%)	28.0 (9.85) [15.4]	25.2-30.6	--
IIV of ka (%)	129 (22.9) [74.7]	96-156	--
Correlation between IIV of CL/F and V/F	0.834		--
Proportional residual error (CV%)	20.0% (2.44)	19.0-21.0%	--
Additive residual error (µg/mL)	0.00289 (--)		--

[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 percentile to 75th percentile of the population values).

[c] $CL/F = 0.516 \times (\frac{BWT}{87.1})^{0.998} \times 1.12^{DIAB} \times 1.11^{RACE}$

[d] $V/F = 13.5 \times (\frac{BWT}{87.1})^{0.829}$

Note: Run 25

Key: BWT=baseline body weight; CL/F=apparent total systemic clearance of drug after extravascular administration; CV%=percentage coefficient of variance; DIAB=diabetes; IIV=inter-individual variability (calculated as [variance]1/2*100%); k_a=first-order absorption rate constant; NONMEM=nonlinear mixed-effect modeling; RSE%=relative standard error; V/F=apparent volume of distribution.

Pharmacokinetics in the target population

Higher C_{max} and AUC values but lower Vz/F and CL/F values were reported in healthy subjects compared with subjects with psoriasis. These observations may be attributed to a variety of factors including small sample size in Phase I studies in subjects with psoriasis (N=3 to 5 in each treatment group), inter-study and/or inter-subject variability, differences in body weight between the study populations, or potential differences in the IL-23 level between subjects with psoriasis and healthy subjects. Median T_{max} values were generally comparable between subjects with psoriasis and healthy subjects. In subjects with psoriasis (PSO1001 Part 2 and PSO1002), the median T_{max} occurred between 3.2 to 6.0 days after a single SC administration at doses ranging from 10 mg to 300 mg.

Pharmacokinetics in special populations

No formal studies were performed to evaluate pharmacokinetics in special populations. No formal study of drug-drug interaction has been performed with guselkumab and there is no data on the effect of guselkumab upon vaccine responses in the target population.

4.2.2. Population pharmacokinetics

4.2.2.1. *PopPK analysis ID*

Pharmacokinetic interactions

An in vitro study was conducted using cryopreserved human hepatocytes to assess whether IL-12 and/or IL-23 modulate the expression or activity of multiple cytochrome (CYP) P450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4).The results of this in vitro study (FK7422) suggest that therapeutic protein-drug interactions between guselkumab and CYP450 substrates are unlikely.

Clinical implications of in vitro findings

However, it is noted by the sponsor that in vitro studies are considered to have limited value in prediction of the clinical interactions between therapeutic proteins and small molecule drugs. To confirm the finding from the in vitro study, a Phase I clinical study (PSO1003) is being conducted in subjects with moderate to severe psoriasis to evaluate if blocking IL-23 with guselkumab for treatment of psoriasis will alter the metabolism of probe substrates metabolized by CYP450 isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]).The study is currently ongoing, and the results are not available for this SCP.

4.2.3. Immunogenicity

4.2.3.1. *Incidence of Antibodies to Guselkumab*

A total of 1,730 subjects in Phase II and III psoriasis studies who received guselkumab had posttreatment serum samples that were evaluable for antibodies to guselkumab. The overall incidence of antibodies to guselkumab through up to 52 weeks after exposure to guselkumab was 5.5% (n=96).Titres of antibodies to guselkumab was generally low with the majority (76 of 96; 79.2%) being ≤1:160 up to 52 weeks after exposure to guselkumab. Seven (7.3%) of the 96 antibody positive subjects were positive for neutralizing antibodies (NAbs) to guselkumab. Therefore, the overall incidence of NAbs in subjects who received guselkumab and had samples that were evaluable for antibodies to guselkumab was 0.4%.

4.2.3.2. *Effect of Antibodies to guselkumab on pharmacokinetics*

Mean and median serum guselkumab concentrations in subject's positive for antibodies to guselkumab were generally similar compared with those who were negative for antibodies to guselkumab in Studies PSO2001, PSO3001, PSO3002, and PSO3003.In addition, no apparent impact of the peak titre levels of antibodies to guselkumab on the PK of guselkumab was observed in subjects positive for antibodies to guselkumab.

4.3. Evaluator's overall conclusions on pharmacokinetics

Preclinical studies showed some staining of striated cardiac or skeletal myocytes but no cross reactivity of guselkumab with non-IL23 proteins such as human or porcine heavy chain myosin.

4.3.1. Absorption, distribution, metabolism and excretion in healthy subjects

In healthy subjects, systemic exposure (C_{max} and AUC) of guselkumab increased in an approximately dose-proportional manner after a single IV administration at doses ranging from 0.03 to 10 mg/kg (that is, approximately 2.7 mg to 900 mg for a subject weighing 90 kg.

No studies examined the effects of food, multiple dosing or administration timing, on PKs of guselkumab in healthy subjects.

In healthy subjects, higher C_{max} and AUC values but lower Vz/F and CL/F values were reported in healthy subjects compared with subjects with psoriasis. T_{max} was similar.

The lyophilised presentation and PFS forms of guselkumab were bioequivalent.

4.3.2. Absorption, distribution, metabolism and excretion in target population

In subjects with psoriasis, following a single SC dose of 100 mg guselkumab, the mean C_{max} (µg/mL) was 4.81±4.26 and 6.1±2.29 and AUC_{inf} values were 4.8 to 6.1 µg/mL and 108.5 to 159.9 µg·day/mL.

The mean $T_{1/2}$ values ranged from approximately 14.7 to 17.6 days after a single SC administration in subjects with psoriasis (PSO1001 Part 2 and PSO1002).

Following a single SC administration, the mean Vz/F values were approximately 16.1 to 28.0 L (177 to 288 mL/kg) in subjects with psoriasis (PSO1001 Part 2 and PSO1002)

The PK profiles of guselkumab from the Phase II and Phase III psoriasis studies were adequately described by a one-compartment linear model with first-order absorption and first-order elimination; the population apparent total systemic clearance of drug (CL/F) and apparent volume of distribution (V/F) values were estimated to be 0.516 L/day and 13.5 L, respectively, among subjects with median body weight of 87.1 kg in the pooled Phase II and Phase III studies.

The percent coefficient of variance (CV%) of C_{max} values ranged from approximately 26% to 46% and the CV% of AUC_{inf} values ranged from approximately 34% to 50%, indicating a large inter-subject variability in systemic exposure to guselkumab after SC administration in population pharmacokinetic analysis.

Although no studies examined the metabolic pathways involved in guselkumab metabolism, it is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

4.3.3. Effect of intrinsic and extrinsic factors on guselkumab PK

No studies examined the PKs of guselkumab in patients with either hepatic or renal impairment, in a paediatric population or in pregnant women. Based on population PK analysis, clearance in elderly patients and patients less than 65 years of age was similar. Population PK analysis indicated that bodyweight was the major influence the bioavailability in patients with moderate to severe psoriasis following multiple doses followed by intrinsic factors including as diabetes and race.

No studies examined the interaction of guselkumab with other drugs in either healthy subjects or the target population.

4.3.4. Limitations of pharmacokinetic data

- No studies compared the bioequivalence following doses of guselkumab administered via the PFS versus the lyophilised formulation in target populations.
- No studies examined the effects of food, multiple dosing or administration timing, on PKs of guselkumab in healthy subjects.
- Information regarding the intra subject variability in healthy subjects or the target population could not be identified in the evaluation materials.
- No pharmacokinetic data are available from paediatric patients, breast feeding/pregnant women or patients with hepatic/renal impairment.
- No studies examined the interaction of guselkumab with other drugs in either healthy subjects or the target population.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Table 5 below summarises the studies submitted with pharmacodynamic information.

Table 5: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*	Synopsis
Primary and Secondary Pharmacology	Effect of guselkumab on a panel of soluble proteins associated with psoriasis and the IL-23/Th17 and Th22 pathways from serum samples from all subjects randomised into the study.	CNTO1959PSO 2001	*	A Phase II Multicenter, Randomised, Placebo- and Active-Comparator-Controlled, Dose-Ranging Trial to Evaluate CNTO 1959 for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis
		CNTO1959PSO 3001	*	A Phase III, Multicenter, Randomised, Double-blind, Placebo and Active Comparator controlled Study Evaluating the Efficacy and Safety of Guselkumab for the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis
	Effect of guselkumab on histological analysis and gene expression profiles of skin	CNTO1959PSO 1001	*	Randomised, double-blind, placebo controlled, and ascending single-dose study in healthy subjects and target population

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.‡ And adolescents if applicable.

CNTO1959PSO3002 included a substudy of skin biopsy and serum biomarkers but the results were not presented and the results of this have been excluded from consideration.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Psoriasis is an autoimmune inflammatory skin disease characterised by the activation of innate and adaptive IL-23/Th17 responses. Cytokines involved in the IL-23/Th17 pathway have been identified as key modulators of immune responses associated with the initiation, progression, and maintenance phases of psoriasis. In subjects with psoriasis, IL-23, IL-17A, IL-17F, IL-22, and additional markers associated with the IL-23/Th17 pathway are elevated in psoriatic skin lesions and serum.IL-23 is a key regulatory cytokine produced by activated antigen-presenting cells that affects the differentiation, expansion, and maintenance of CD4+ IL-17 producing T helper 17 (Th17) cells.Th17 cells secrete IL-17A and IL-17F, and are a likely source of IL-17A in

psoriatic skin.IL-17A has a direct effect on the regulation of genes expressed by keratinocytes that are involved in innate immune defence, including defensins, S100 family proteins, and lipocalin, as well as a range of CXCL chemokines that regulate neutrophil trafficking.IL-23 also augments production of IL-22 from Th22 cells and from group 3 innate lymphoid cells (ILC3).Th22 cells have been identified as a source of IL-22 in psoriasis lesions.IL-22 is associated with keratinocyte hyperplasia, increased synthesis of S100 proteins, and accelerated loss of surface keratinocytes and elimination of pathogens.ILC3 cells are a group of innate hematopoietic lymphoid cells which lack rearranged antigen-specific receptors.ILC3 cells rely on the transcription factor RORgt and respond to IL-1β and IL-23; a subset of ILC3 cells is associated with the production of IL-17A and IL-22 in psoriasis lesions. Additionally, IL-23 maintains some regulatory capacity for IL-17-producing CD8+ T cells (Tc17).

By binding IL-23, guselkumab blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor (IL-23R), disrupting IL-23 mediated signalling, activation and cytokine cascades.

5.2.2. Pharmacodynamic effects

5.1.1.1 Primary pharmacodynamic effects

Histological analysis of skin biopsy

Treatment with guselkumab resulted in improvement in histological measures of psoriasis at Week 12 including reductions in epidermal thickness, T-cell density, and dendritic cells. At baseline, increases in T-cell counts (CD3), myeloid dendritic cell (DC) counts (CD11c), and epidermal hyperplasia and KRT16 were observed in lesional skin compared with values in non-lesional skin. At Week 1, modest improvement was observed from baseline in epidermal thickness and in numbers of CD3 and CD11c immune cells. At Week 12, statistically significant reductions in epidermal thickness and T-cell and inflammatory CD11c DC counts were observed for each guselkumab dose group compared with baseline ($p<0.05$ each).Langerhans cells, which are displaced in active psoriatic lesions, resumed a normal panepidermal pattern in guselkumab-treated biopsy specimens at Week 12.No reduction was observed in epidermal thickness or T-cell density in placebo-treated subjects; however, a reduction from baseline in DC counts was observed for placebo at Week 12.

Microarray analysis

Gene transcripts associated with epidermal hyperplasia, including keratin 6A (KRT6A) and Keratin 16 (KRT16) and STAT3, were decreased with guselkumab treatment to levels less than those observed in non-lesional skin, indicating a strong reduction in regenerative epidermal growth. Expression of gene transcripts associated with the IL-23/Th17 pathway was also determined: Lipocalin 2 (LCN2), CXCL1, S100A7A (S100A15), S100A7 (psoriasin), S100A8 and S100A9, which are strongly induced by IL-17 in psoriatic lesions, were significantly decreased after guselkumab treatment.

Serum-based biomarker analysis

Baseline levels of serum IL-17A, IL-17F and IL-22 were shown to be higher in the moderate to severe psoriasis study population than in an independent cohort of healthy control subjects' uselkumab consistently reduced IL-17A, IL-17F and IL-22 serum levels compared with placebo and compared with adalimumab.

In addition to expected reductions in effector cytokines associated with the IL-23/Th17 and Th22 pathways by guselkumab, other markers which are associated with psoriasis were reduced compared to placebo, including CCL22/MDC and CXCL8/IL-8, however the impact was moderate.CCL4/MIP-1β was decreased by adalimumab but not guselkumab.

This observation is aligned with the selective mechanism of action of guselkumab targeting the IL-23/Th17 axis.

5.2.3. Secondary pharmacodynamic effects

5.2.3.1. *Time course of pharmacodynamic effects*

Interpretation of a time course of pharmacodynamic effects is limited.

5.2.3.2. *Relationship between drug concentration and pharmacodynamic effects*

No specific studies examined whether there were relationships between drug concentration and PD response following treatment with guselkumab.

5.2.3.3. *Genetic, gender and age related differences in pharmacodynamic response*

No specific studies examined whether there was genetic, gender or age related differences in PD response following treatment with guselkumab.

5.2.4. Pharmacodynamic interactions

No PD interactions were evaluated.

5.3. Evaluator's overall conclusions on pharmacodynamics

- Treatment with guselkumab resulted in improvement in histological characteristics of psoriasis at Week 12, including reductions in epidermal thickness, T-cell density, and dendritic cells.
- Treatment with guselkumab resulted in reductions in the gene expression of the IL - 23/Th17 pathway and psoriasis-associated gene expression profiles.
- Treatment with guselkumab impacted disease- and mechanism-related serum-based biomarkers. Reduced serum IL-17A, IL-17F and IL-22 levels were observed compared to placebo and compared to blockade of TNF with adalimumab in guselkumab-treated psoriatic subjects in Phase II and Phase III studies.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The Phase I study PSO1001, demonstrated proof-of-concept of guselkumab efficacy in psoriasis subjects at all guselkumab dose levels examined (10 mg, 30 mg, 100 mg, and 300 mg single doses), and all doses were well tolerated.PK analysis showed that guselkumab exhibited approximately dose proportional PK across the dose range tested with a mean half-life of approximately 17 days.

6.2. Phase II dose finding studies

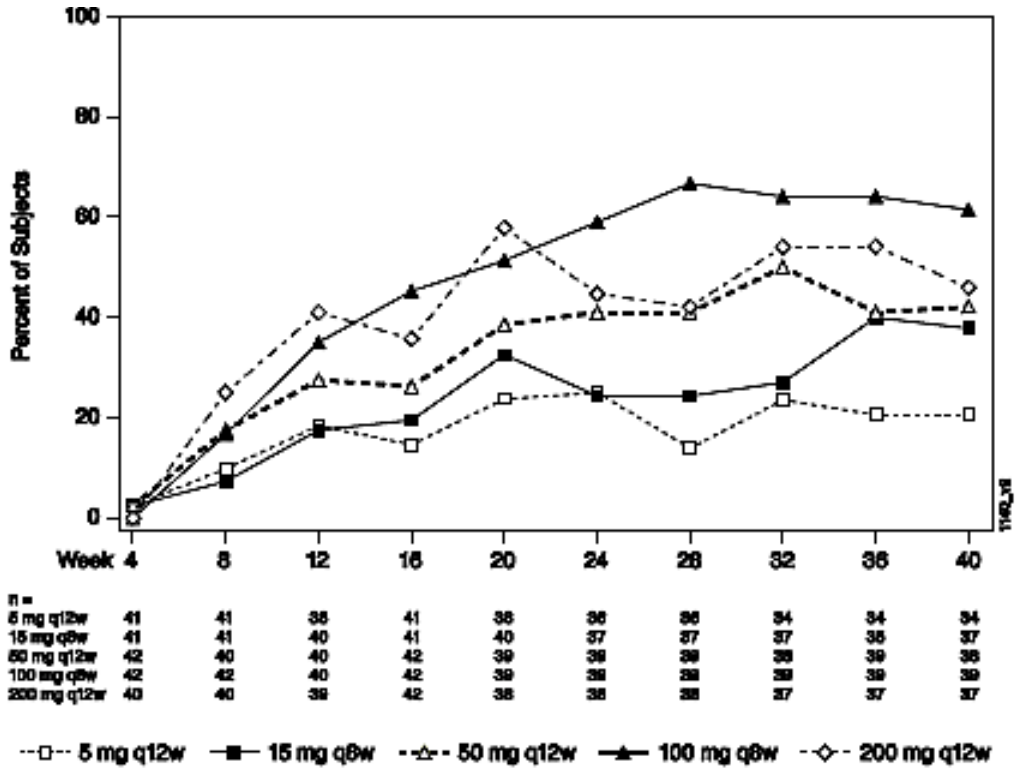
Based on preliminary exposure-response modelling and simulation, a Phase II dose ranging study (PSO2001) including five dose levels (5, 15, 50, 100, and 200 mg) and two dosing intervals (q8w and q12w) was conducted to further characterize the guselkumab dose- and exposure-response in psoriasis.

The results of Study PSO2001 showed efficacy in all guselkumab doses studied. A significantly greater proportion of subjects in each guselkumab dose group achieved a PGA of cleared (0) or minimal (1) (all $p \leq 0.002$) and PASI 75 (all $p < 0.001$) at Week 16 than in the placebo group. Also, a substantially greater proportion of subjects in the guselkumab 50 mg q12w, 100 mg q8w, and 200 mg q12w groups achieved PGA 0/1 than in the adalimumab group at Week 16.When comparing q8w versus q12w dose regimens, a loss of efficacy toward the end of each dosing

interval was evident for the q12w dosing groups and this was not apparent among subjects receiving q8w dosing.

A clear dose-response in efficacy was observed across several clinically important PASI and IGA measures of response from the 5mg dose regimen up to the 100 mg dose regimen. The dose response was most apparent at the higher PASI and PGA thresholds (for example, PASI 90 and 100 responses, and PGA 0 (Figure 2).Moreover, the proportions of subjects who achieved a PGA score of cleared (0) or minimal (1), or cleared (0), or PASI 75 responses at Weeks 16 and 40 increased with increasing trough serum guselkumab levels and subjects with trough serum guselkumab concentrations ≥ 0.67 µg/mL at Week 40 achieved the highest levels of efficacy. Among all the dose regimens studied in PSO2001, the 100 mg q8w dose regimen provided the highest serum guselkumab concentrations, and also resulted in a majority of subjects maintaining a trough serum guselkumab concentration ≥ 0.67 µg/mL at Week 40.Therefore, the 100 mg q8w dose regimen was selected for study in Phase III. To expedite the onset of response, a loading dose of 100 mg guselkumab was also given at Week 4 prior to 100 mg q8w maintenance dosing in the Phase III program.

Figure 2: Percentage of Subjects Achieving a PGA score of Cleared (0) through Week 40 by Visit; randomised subjects in Study CNTO1959PSO2001



6.3. Phase III pivotal studies investigating more than one dose regimen

Phase III studies utilised only guselkumab 100 mg SC for treatment of moderate to severe plaque psoriasis.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The dose selection strategy was based on the clinical data obtained in the Phase II program in the target indication of moderate to severe plaque psoriasis and used data from PSO2001 with modelling approaches. Overall, 100 mg was identified as the most effective dose to be tested in

Phase III studies. Furthermore, the need for an initial period of more frequent dosing (weekly during the first four weeks) was identified, and subsequent dosing at intervals of eight weeks was considered appropriate for maintenance treatment as q12w strategies was associated with loss of response rate at the end of the treatment cycle.

Hence, the two guselkumab dose groups chosen for evaluation in the pivotal Phase III studies were adequately justified.[2]

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The overview of the efficacy of guselkumab 100 mg SC in moderate to severe plaque psoriasis primarily focusses on the Phase III Studies PSO3001 and PSO3002 because they provide the key efficacy data in support of the application for an indication in psoriasis. In addition, efficacy results from Study PSO3003 are presented.

7.2. Pivotal or main efficacy studies

7.2.1. CNTO1959PSO3001

7.2.1.1. *Study design, objectives, locations and dates*

This was a Phase III, randomised, double-blind, multicenter, placebo and active-comparator-controlled study evaluating safety and efficacy in subjects with moderate to severe plaque-type psoriasis.

Objectives

Primary: To evaluate the efficacy, safety, and tolerability of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis.

Secondary: To compare the efficacy of guselkumab to adalimumab in subjects with moderate to severe plaque-type psoriasis, to evaluate the effect of treatment with guselkumab on other measures of signs and symptoms of psoriasis, and to evaluate the effect of treatment with guselkumab on health-related quality of life.

Other Secondary: To assess the pharmacokinetics (PK) and immunogenicity of guselkumab following subcutaneous (SC) administration in subjects with moderate to severe plaque-type psoriasis.

Exploratory: To explore the pharmacodynamics (PD) (biomarkers) of treatment with guselkumab or adalimumab in subjects with moderate to severe plaque-type psoriasis and to explore the association between genetic and epigenetic factors and 1) the efficacy of guselkumab or adalimumab and 2) psoriasis.

Locations: Australia, Canada, Germany, Spain, Hungary, Korea, Poland, Russia, Taiwan, USA

Dates: 3 Dec 2014 to 27 Apr 2016, Ongoing.

7.2.1.2. *Inclusion and exclusion criteria*

Important inclusion criteria:

[2] Study 3001 had 3 treatment groups. Group 1 received the proposed guselkumab dose regimen of 100 mg at Weeks 0, 4, and 12 then every 8 weeks to Week 44. Group 2 received placebo for the first 16 weeks then the same guselkumab dose regimen as in Group 1 to Week 44 and Group 3 received adalimumab at its recommended dose regimen for psoriasis of 80 mg at Week 0 then 40 mg at Week 1 and every 2 weeks through to Week 47.

- Have a diagnosis of plaque-type psoriasis (with or without PsA) for at least 6 months before the first administration of study drug.
- Have a PASI ≥12 at screening and at baseline.
- Have an IGA ≥ 3 at screening and at baseline.
- Have an involved BSA ≥ 10% at screening and at baseline.

Important exclusion criteria

- History of lymphoproliferative disease, current or recent malignancy and uncontrolled infections disease.
- Recent anti-TNF treatment or treatment with other biologics.
- Is expected to receive any live virus vaccination.

7.2.1.3. *Study treatments*

Group I received guselkumab 100 mg at Weeks 0, 4, and 12, and every 8 weeks (q8w) thereafter through Week 44.

Group II received placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20 and q8w thereafter through Week 44.Group III received adalimumab 80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks (q2w) thereafter through Week 47.

An open-label guselkumab treatment period was to begin after Week 48 and extend through Week 160.

Subjects in Groups I and II continued to receive guselkumab 100 mg at Week 52 and q8w thereafter through Week 148.Subjects in Group III initially randomised to adalimumab entered a washout period after their final dose of adalimumab at Week 47 and initiated guselkumab 100 mg at Week 52 and then q8w thereafter through Week 148.

7.2.1.4. *Efficacy variables and outcomes*

The co-primary efficacy variables were:

- The proportion of subjects achieving an IGA score of cleared (0) or minimal (1) and the proportion of subjects achieving a PASI 90 response at Week 16.

Other efficacy variables were:

- Scalp-specific IGA (ss-IGA), Nail Psoriasis Area and Severity Index (NAPSI), Fingernail Physician's Global Assessment (f-PGA), and Physician's Global Assessment of Hands and/or Feet (hf-PGA).Patient-reported outcomes: Dermatology Life Quality Index (DLQI) and Psoriasis Symptom and Sign Diary (PSSD).
- Safety: Adverse events (AEs), serious adverse events (SAEs), injection site and allergic reactions, clinical laboratory parameters (haematology and chemistry, including lipid panel; urine pregnancy test), physical examinations, vital signs, electrocardiograms (ECGs), and early detection of tuberculosis.
- Pharmacokinetics, immunogenicity, Biomarkers and Pharmacogenomics were also evaluated.

7.2.1.5. *Randomisation and blinding methods*

The double-blind treatment period extended from Week 0 through Week 44.At Week 0, subjects who satisfied all inclusion and exclusion criteria were randomised in a 2:1:2 ratio to 1 of 3 treatment groups.

7.2.1.6. *Analysis populations*

836 were treated in the study.

Among all randomised subjects at baseline, the majority were White (81.7%) and male (72.6%).The median weight was 86.5 kg, and the median age was 44.0 years.

7.2.1.7. *Sample size*

Of these 836 treated subjects, 174 were randomised to the placebo treatment group, 329 were randomised to the guselkumab treatment group, and 333 were randomised to the adalimumab treatment group at Week 0.One subject randomised in the adalimumab treatment was not treated due to a protocol violation.

Through Week 48, guselkumab and adalimumab treated subjects continued to receive their treatment. At Week 16, 165 (94.8%) of the 174 placebo treated subjects crossed over to receive guselkumab.

7.2.1.8. *Statistical methods*

In the primary efficacy analysis, data from all randomised subjects were analysed according to their assigned group. Subjects who met treatment-failure criteria before Week 16 were considered non-responders for the primary endpoints at Week 16. In addition, subjects who did not return for evaluation at Week 16 were considered non-responders. To address the primary objective, a Cochran-Mantel-Haenszel (CMH) chi-square statistical test (α=0.05) stratified by pooled site was used for the co-primary endpoints. If one of the comparisons was not significant at the 2-sided α-level of 0.05, the co-primary endpoints would be considered not significant. In addition, a comparison between adalimumab and placebo for the 2 co-primary endpoints was also performed.

For the major secondary analyses to test the non-inferiority of guselkumab to adalimumab, a 1-sided (α=0.025) MH Z-test adjusted by site was specified. The 95% confidence interval (CI) for treatment difference between the guselkumab and adalimumab treatment groups was provided. The designated non-inferiority margin was 10%, that is, the lower bound of the 2-sided 95% CI of P1 to P2 was to be greater than or equal to -10% to claim non-inferiority, where P1 and P2 were the proportions of subjects achieving the corresponding endpoints at Week 16 in the guselkumab and the adalimumab groups, respectively.

Continuous response parameters were compared using an analysis of variance model with investigator site (pooled) as a covariate. Rank-based analysis of variance was used for percent improvement from baseline in PASI and NAPSI due to the skewed nature of these data.

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses were tested in a fixed sequence.

7.2.1.9. *Participant flow*

A total of 1,036 subjects were screened, of which 837 subjects were enrolled. No data is provided on the reason for screen failure in the 199 subjects not enrolled.

7.2.1.10. *Major protocol violations/deviations*

Approximately 12.7% of subjects experienced major protocol deviations; the major sources being other (6.6%)[3] and study entry but not satisfying criteria (3.1%).Moreover, a significant

[3] Sponsor clarification: The most common deviations classified as 'Other' were clinician reported outcomes not being completed at critical visits and incorrect/old versions of initial informed consent form signed at screening instead of current approved version.

proportion received incorrect study agent[4] although the evaluator concludes, after review of the detail of these deviations, that this is not likely to affect study outcomes.

7.2.1.11. *Baseline data*

Among all randomised subjects at baseline, the majority were White (81.7%) and male (72.6%).The median weight was 86.5 kg, and the median age was 44.0 years.

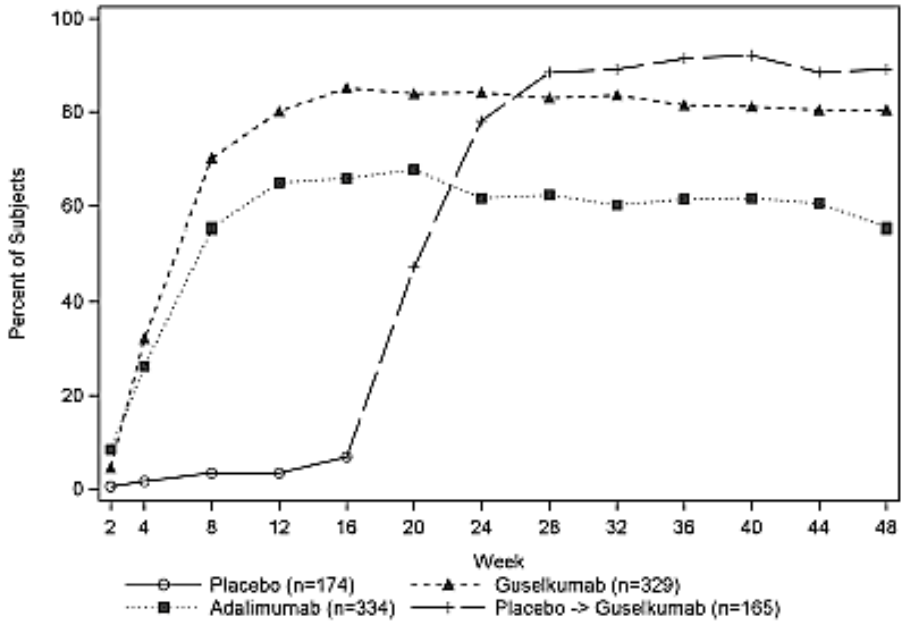
Among all randomised subjects, the median duration of psoriasis at baseline was 15.0 years, the median percent of body surface area involved was 22.0%, the median PASI score was 19.0, the proportion of subjects with an IGA=3 (moderate) was 74.6%, and the proportion of subjects with an IGA=4 (severe) was 25.1%.Baseline disease characteristics were generally comparable across the 3 treatment groups.

The proportions of subjects who previously received phototherapy (54.3%), non-biologic systemic therapies (61.8%), and biologic therapy (20.9%) were comparable across the 3 treatment groups. A total of 32.1% of subjects were naïve to all prior no-biologic systemic and biologic therapies.

7.2.1.12. *Results for the primary efficacy outcome*

Significantly (p<0.001) greater proportions of subjects in the guselkumab group achieved the study co-primary endpoints: an IGA score of cleared (0) or minimal (1) and a PASI 90 response at Week 16 (85.1% and 73.3%, respectively; p<0.001 for both endpoints) than in the placebo group (6.9% and 2.9%, respectively) (see Figure 3).

Figure 3: Percent of Subjects Achieving an IGA Score of Cleared (0) or Minimal (1) Through Week 48 by Visit; Subjects Randomised at Week 0



At Week 16 in guselkumab group versus placebo: revealed significant improvements in guselkumab versus placebo in the following variables: IGA 0, IGA 0/1, PASI 100, PASI 90, and PASI 75 (Table 6).

[4] Sponsor clarification: Of these 24 subjects, 20 deviations were due to subject error (the order of active and placebo study agent injections was potentially switched by the subject) and 4 deviations were due to site error (incorrect study kits were given to subjects). Overall only 1 subject actually injected the incorrect active study agent.

Table 6: Efficacy Endpoints for Psoriasis Improvement in Studies PSO3001 and PSO3002

	PSO3001			PSO3002		
	Placebo	Guselkumab[a]	Adalimumab[b]	Placebo	Guselkumab[a]	Adalimumab[b]
Number of subjects	174	329	334	248	496	248
Week 16						
IGA 0	2 (1.1%)	157 (47.7%)	88 (26.3%)	2 (0.8%)	215 (43.3%)	71 (28.6%)
p-value		<0.001	nc		<0.001	nc
IGA 0/1	12 (6.9%)	280 (85.1%)	220 (65.9%)	21 (8.5%)	417 (84.1%)	168 (67.7%)
p-value		<0.001[c]	<0.001[d]		<0.001[c]	<0.001[d]
PASI 100	1 (0.6%)	123 (38.1%)	57 (17.4%)	2 (0.8%)	169 (34.1%)	51 (20.6%)
p-value		<0.001	nc		<0.001	nc
PASI 90	5 (2.9%)	241 (73.3%)	166 (49.7%)	6 (2.4%)	347 (70.0%)	116 (46.8%)
p-value		< 0.001[c]	< 0.001[d]		< 0.001[c]	< 0.001[d]
PASI 75	10 (5.7%)	300 (91.2%)	244 (73.1%)	20 (8.1%)	428 (86.3%)	170 (68.5%)
p-value		< 0.001	<0.001[d]		< 0.001	<0.001[d]
Week 24						
IGA 0	na	173 (52.6%)	98 (29.3%)	na	257 (51.8%)	78 (31.5%)
p-value			<0.001[d]			<0.001[d]
IGA 0/1	na	277 (84.2%)	206 (61.7%)	na	414 (83.5%)	161 (64.9%)
p-value			<0.001[d]			<0.001[d]
PASI 100	na	146 (44.4%)	83 (24.9%)	na	219 (44.2%)	66 (26.6%)
p-value			<0.001			<0.001
PASI 90	na	264 (80.2%)	177 (53.0%)	na	373 (75.2%)	136 (54.8%)
p-value			<0.001[d]			<0.001[d]
PASI 75	na	300 (91.2%)	241 (72.2%)	na	442 (89.1%)	176 (71.0%)
p-value			<0.001			<0.001

Data are presented as number of subjects (%).

[a] p-values are for comparisons between guselkumab and placebo

[b] p-values are for comparisons between guselkumab and adalimumab

[c] p-values are for the comparisons for the co-primary endpoints

[d] p-values are for the comparisons for major secondary endpoints

IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; na=not applicable; nc=not calculated

7.2.1.13. *Results for other efficacy outcomes*

Consistent improvements were observed in scalp psoriasis, nail psoriasis, and hand or foot psoriasis in the guselkumab group compared with the placebo group at Week 16 across Studies PSO3001 and PSO3002 for subjects with an ss-IGA, f-PGA, and/or hf-PGA score ≥ 2 at baseline or with a NAPSI score >0 at baseline (Table 7).

Table 7: Efficacy Endpoints for Regional Psoriasis in Studies PSO 3001 and PSO 3002

	PSO3001			PSO3002		
	Placebo	Guselkumab[a]	Adalimumab[b]	Placebo	Guselkumab[a]	Adalimumab[b]
Week 16						
ss-IGA, n[c]	145	277	286	202	408	194
ss-IGA 0/1[d]	21 (14.5%)	231 (83.4%)	201 (70.3%)	22 (10.9%)	329 (80.6%)	130 (67.0%)
p-value		<0.001[a]	nc		<0.001[a]	nc
f-PGA, n[c]	88	174	173	123	246	124
f-PGA 0/1	14 (15.9%)	68 (39.1%)	88 (50.9%)	18 (14.6%)	128 (52.0%)	74 (59.7%)
p-value		<0.001	nc		<0.001	nc
NAPSI, n[c]	99	194	191	140	280	140
% improvement	-0.93 (37.893)	34.37 (42.448)	37.95 (53.872)	1.82 (53.825)	39.61 (45.648)	46.92 (48.091)
p-value		<0.001	nc		<0.001	nc
hf-PGA, n[c]	43	90	95	63	114	56
hf-PGA 0/1[d]	6 (14.0%)	66 (73.3%)	53 (55.8%)	9 (14.3%)	88 (77.2%)	40 (71.4%)
p-value		<0.001	nc		<0.001	nc
Week 24						
ss-IGA, n[c]		277	286		408	194
ss-IGA 0/1[d]	na	234 (84.5%)	198 (69.2%)	na	348 (85.3%)	131 (67.5%)
p-value			<0.001			<0.001
f-PGA, n[c]		174	173		246	124
f-PGA 0/1	na	98 (56.3%)	108 (62.4%)	na	154 (62.6%)	83 (66.9%)
p-value			0.176			0.376
NAPSI, n[c]		194	191		280	140
% improvement	na	49.78 (44.156)	49.42 (60.042)	na	54.98 (46.804)	53.69 (49.456)
p-value			0.739			0.667
hf-PGA, n[c]		90	95		114	56
hf-PGA 0/1[d]	na	71 (78.9%)	54 (56.8%)	na	93 (81.6%)	37 (66.1%)
p-value			0.001			0.046
Week 48						
ss-IGA, n[c]		277	286			
ss-IGA 0/1[d]	na	217 (78.3%)	173 (60.5%)	na	na	na
p-value			<0.001			
f-PGA, n[c]		174	173			
f-PGA 0/1	na	130 (74.7%)	107 (61.8%)	na	na	na
p-value			0.038			
NAPSI, n[c]		194	191			
% improvement	na	68.14 (42.998)	61.37 (49.204)	na	na	na
p-value			0.229			
hf-PGA, n[c]		90	95			
hf-PGA 0/1[d]	na	68 (75.6%)	59 (62.1%)	na	na	na
p-value			0.045			

Data are presented as number of subjects (%) or mean ± standard deviation.
[a] p-values are for comparisons between guselkumab and placebo
[b] p-values are for comparisons between guselkumab and adalimumab
[c] Includes only subjects with ss-IGA, f-PGA, hf-PGA score ≥2, and/or NAPSI score >0 at baseline.
[d] Includes only subjects also achieving ≥2-grade improvement in ss-IGA and/or hf-PGA.
[e] p-values are for the comparisons for major secondary endpoints.
f-PGA=fingernail PGA; hf-PGA=Physician's Global Assessment of Hands and/or Feet; NAPSI=Nail Psoriasis Severity Index; ss-IGA=Scalp Specific Investigator Global Assessment; na= not applicable; nc=not calculated

Across both studies (PSO3001 and PSO3002) significant improvements in DLQI scores were observed in the guselkumab group compared with the placebo group at Week 16 (all $p<0.001$) and numerically greater improvements compared with the adalimumab group at Week 24 (Table 8). The difference in proportion of patients achieving a DLQI of 0/1 was significantly higher for guselkumab than for adalimumab at Week 24 ($p<0.001$). In addition, the proportion of subjects that achieving several measures of improvement in patient symptoms and signs using the PSSD were significantly greater for guselkumab compared to placebo at Week 16 and for guselkumab compared with adalimumab at Week 24 (Table 8).

Table 8: Efficacy Endpoints for Patient Reported Outcomes in Studies PSO3001 and PSO 3002

	PSO3001			PSO3002		
	Placebo	Guselkumab[a]	Adalimumab[b]	Placebo	Guselkumab[a]	Adalimumab[b]
Week 16						
DLQI, n	170	322	328	248	495	247
Change in DLQI score	-0.6 (6.36)	-11.2 (7.24)	-9.3 (7.80)	-2.6 (6.85)	-11.3 (6.82)	-9.7 (6.84)
p-value		*<0.001[a]*	*nc*		*<0.001[a]*	*nc*
DLQI score >1 at baseline, n	168	320	319	246	491	246
DLQI 0/1	7 (4.2%)	180 (56.3%)	123 (38.6%)	8 (3.3%)	254 (51.7%)	96 (39.0%)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
PSSD Change from baseline, n	129	249	274	198	411	201
Symptom score	-3.0 (19.56)	-41.9 (24.61)	-35.4 (28.45)	-8.3 (23.67)	-40.4 (26.52)	-32.8 (24.91)
p-value		*<0.001[a]*	*nc*		*<0.001[a]*	*nc*
Sign score	-4.1 (17.87)	-44.6 (22.00)	-39.7 (26.44)	-9.8 (22.84)	-42.9 (23.71)	-34.6 (23.52)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
PSSD clinically meaningful changes from baseline (≥40)						
n	78	174	188	154	280	138
Change in symptom score ≥40	6 (7.7%)	128 (73.6%)	124 (66.0%)	19 (12.3%)	203 (72.5%)	72 (52.2%)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
n	95	197	221	166	305	153
Change in sign score ≥40	4 (4.2%)	144 (73.1%)	149 (67.4%)	24 (14.5%)	223 (73.1%)	80 (52.3%)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
PSSD symptom score >0 at baseline, n	129	248	273	198	410	200
Symptom score=0	1 (0.8%)	67 (27.0%)	45 (16.5%)	0	112 (27.3%)	30 (15.0%)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
PSSD sign score >0 at baseline, n	129	248	274	198	411	201
Sign score=0	0	50 (20.2%)	32 (11.7%)	0	86 (20.9%)	21 (10.4%)
p-value		*<0.001*	*nc*		*<0.001*	*nc*
Week 24						
DLQI		322	328		495	247
Change in DLQI score n	na	-11.6 (7.55)	-9.5 (7.89)	na	-11.9 (6.98)	-9.9 (7.40)
p-value			*nc*			*nc*
DLQI score >1 at baseline, n		320	319		491	246
DLQI 0/1	na	195 (60.9%)	126 (39.5%)	na	283 (57.6%)	101 (41.1%)
p-value			*<0.001*			*<0.001*
PSSD Change from baseline, n		249	274		411	201
Symptom score	na	-44.0 (24.57)	-36.0 (28.36)	na	-42.1 (26.80)	-31.9 (26.99)
p-value			*<0.001*			*<0.001*
Sign score	na	-47.2 (22.19)	-40.1 (26.49)	na	-44.5 (24.06)	-33.6 (25.34)
p-value			*<0.001*			*<0.001*
PSSD clinically meaningful changes from baseline (≥40)						
n		174	188		280	138
Change in symptom score ≥40	na	139 (79.9%)	120 (63.8%)	na	213 (76.1%)	73 (52.9%)
p-value			*<0.001*			*<0.001*
n		197	221		305	153
Change in sign score ≥40	na	155 (78.7%)	144 (65.2%)	na	233 (76.4%)	79 (51.6%)
p-value			*<0.001*			*<0.001*
PSSD symptom score >0 at baseline, n		248	273		410	200
Symptom score=0	na	90 (36.3%)	59 (21.6%)	na	144 (35.1%)	45 (22.5%)
p-value			*<0.001[a]*			*<0.001[a]*
PSSD sign score >0 at baseline, n		248	274		411	201
Sign score=0	na	73 (29.4%)	40 (14.6%)	na	114 (27.7%)	34 (16.9%)
p-value			*<0.001*			*0.003*

Data are presented as number of subjects (%) or mean ± standard deviation; DLQI=Dermatology Life Quality of Index; PSSD=Psoriasis Symptom and Sign Diary; na=not applicable; nc=not calculated

[a] p-values are for comparisons between guselkumab and placebo.

[b] p-values are for comparisons between guselkumab and adalimumab.

[c] p-values are for the comparisons for major secondary endpoints.

7.2.1.14. *Evaluator commentary*

The aim of this pivotal study was to evaluate the short-term efficacy of guselkumab (16 weeks) in comparison to placebo for treatment of moderate to severe psoriasis. Guselkumab showed superior efficacy to placebo on all primary, secondary and many exploratory endpoints, and in particular, high rates of PASI 90 and PASI 100 responses. A further aim was to demonstrate longer term efficacy of guselkumab (up to 48 weeks) and to demonstrate superiority to adalimumab. These endpoints were also achieved. Results of long term extension study are not available. With the availability of more effective biological agents including ixekizumab, ustekinumab and secukinumab, the relevance of these data to prescribers has been elevated.

7.2.2. CNTO1959PSO3002

7.2.2.1. *Study design, objectives, locations and dates*

This was a Phase III, randomised, double-blind, multicenter, placebo and active-comparator-controlled study evaluating safety and efficacy of guselkumab in subjects with moderate to severe plaque-type psoriasis with randomised withdrawal and retreatment.

Objectives

Primary: To evaluate the efficacy of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis and to assess the safety and tolerability of guselkumab in subjects with moderate to severe plaque-type psoriasis.

Secondary: To compare the efficacy of guselkumab to adalimumab in subjects with moderate to severe plaque-type psoriasis, to evaluate the maintenance of response to guselkumab in subjects continuing on a 100 mg every 8 weeks (q8w) regimen compared with the maintenance of response in subjects who had active treatment withdrawn, to evaluate the effect of treatment with guselkumab on other measures of signs and symptoms of psoriasis, and to evaluate the effect of treatment with guselkumab on health-related quality of life and health economic outcomes.

Other Secondary: To assess the pharmacokinetics (PK) and immunogenicity of guselkumab following subcutaneous (SC) administration in subjects with moderate to severe plaque-type psoriasis.

Exploratory: To explore the pharmacodynamics (biomarkers) of treatment with guselkumab or adalimumab in subjects with moderate to severe plaque-type psoriasis and to explore the association between genetic and epigenetic factors and 1) the efficacy of guselkumab or adalimumab and 2) psoriasis.

Locations: Australia, Canada, Germany, Spain, Czech Republic, Korea, Poland, Russia, USA

Dates: 3 Nov 2014 to 19 May 2016, Ongoing.

7.2.2.2. *Inclusion and exclusion criteria*

No significant differences from PSO3001.[5]

7.2.2.3. *Study treatments*

Week 0 through Week 24 (Active Comparator Controlled Period) Subjects were randomised, in a 2:1:1 ratio to 1 of 3 arms.

Group I: Guselkumab 100 mg at Weeks 0, 4, 12, and 20.Beginning at Week 28 the therapy for all subjects based on their level of response at that visit.

- PASI 90 non-responders continues guselkumab 100 mg.
- PASI 90 responders were re-randomised in a 1:1 ratio to receive: a) Guselkumab 100 mg, b) Placebo; upon loss of ≥50% of the improvement in PASI achieved at Week 28, subjects were then retreated with guselkumab 100 mg Group II: Placebo beginning at Week 0 followed by guselkumab 100 mg at Weeks 16 and 20 Beginning at Week 28, therapy for all subjects was based on their level of response at that visit.
- PASI 90 non-responders continued guselkumab 100 mg.
- PASI 90 responders received placebo; upon loss of ≥50% of the improvement in PASI achieved at Week 28, subjects were then retreated with guselkumab 100 mg (n=248).

[5] Sponsor clarification: Same as Study PSO3001.

Open-label period (Week 76 to Week 160): All subjects received guselkumab q8w starting at Week 76 (n=496).

Group III: Adalimumab (80 mg at Week 0 followed by adalimumab 40 mg at Week 1 and every 2 weeks [q2w] thereafter through Week 23) Beginning at Week 28, therapy for all subjects was based on their level of response at that visit.

- PASI 90 non-responders received guselkumab 100 mg.
- PASI 90 responders received placebo; upon loss of ≥50% of the improvement in PASI achieved at Week 28, subjects were treated with guselkumab 100 mg (n=248).

7.2.2.4. *Efficacy variables and outcomes*

This study shared the same co-primary outcome variables and many major secondary outcome variables as PSO3001 (Table 9).

Table 9: Efficacy Endpoints for Phase III Clinical Studies PSO3001 and PSO3002

	Guselkumab vs Placebo	Guselkumab vs Adalimumab	Maintenance vs Withdrawal
Co-primary endpoints [a]			
Proportion of subjects who achieved IGA 0/1 and Proportion of subjects who achieved PASI 90 response at Week 16	3001/3002		
Major secondary endpoints [a]			
Proportion of subjects who achieved IGA 0 at Week 24 [b]		3001/3002	
Proportion of subjects who achieved IGA 0/1 at Week 24 [b]		3001/3002	
Proportion of subjects who achieved PASI 90 response at Week 24 [b]		3001/3002	
The time to loss of PASI 90 response at Week 28 to Week 48			3002
Proportion of subjects who achieved an IGA 0 at Week 48 [b]		3001	
Proportion of subjects who achieved an IGA 0/1 at Week 48 [b]		3001	
Proportion of subjects who achieved PASI 90 response at Week 48 [b]		3001	
Change from baseline in DLQI score at Week 16	3001/3002		
Proportion of subjects who achieved an IGA 0/1 at Week 16 [c]		3001/3002	
Proportion of subjects who achieved PASI 90 response at Week 16 [c]		3001/3002	
Proportion of subjects who achieved PASI 75 response at Week 16 [c]		3001/3002	
Proportion of subjects who achieved ss-IGA 0/1 at Week 16 [d]	3001/3002		
Change from baseline in PSSD symptom score at Week 16	3001/3002		
Proportion of subjects with PSSD symptom score=0 at Week 24 [b]		3001/3002	

[a] To control the overall Type 1 error rate (p=0.05), the primary analysis and major secondary analyses were tested using a fixed sequence method. Specifically, the first major secondary endpoint was tested only if the co-primary endpoints were positive, and subsequent endpoints were tested only if the preceding endpoint in the sequence was positive.
[b] Tested for superiority of the guselkumab group compared with the adalimumab group.
[c] Tested for noninferiority of the guselkumab group compared with the adalimumab group for the three endpoints in the above order before any of the superiority tests for the same endpoints in the above order.
[d] Included only randomized subjects with baseline ss-IGA score ≥2.
DLQI=Dermatology Life Quality Index, IGA 0=IGA (Investigator's Global Assessment) response of cleared (0), IGA 0/1=IGA response of cleared (0) or minimal (1), PASI=Psoriasis Area and Severity Index , PASI 75=≥75% improvement in PASI score from baseline, PASI 90=≥90% improvement in PASI score from baseline, PSSD=Psoriasis Symptom and Sign Diary, and ss-IGA=Scalp Specific Investigator Global Assessment

Additional patient-reported outcomes were examined including SF-36, HADS and WLQ.

Safety: Adverse events (AEs), serious adverse events (SAEs), injection site and allergic reactions, clinical laboratory parameters (haematology and chemistry, including lipid panel; urine pregnancy test), physical examinations, vital signs, electrocardiograms (ECGs), and early detection of tuberculosis.

Pharmacokinetics, immunogenicity, Biomarkers and Pharmacogenomics were also evaluated.

7.2.2.5. *Randomisation and blinding methods*

The double-blind treatment period extended from Week 0 through Week 44[6]. At Week 0, subjects who satisfied all inclusion and exclusion criteria were randomised in a 2:1:1 ratio to 1 of 3 treatment groups.

7.2.2.6. *Analysis populations*

Among all randomised subjects at baseline, the majority were White (82.1%) and male (69.8%).The median weight was 86.1 kg, and the median age was 43.0 years. Baseline variables of subjects were comparable to PSO3001.

Among all randomised subjects, the median duration of psoriasis at baseline was 16 years, the median percent of BSA involved was 24.0%, the median PASI score was 19.00, the proportion of subjects with an IGA=3 (moderate) was 77.2%, and the proportion of subjects with an IGA=4 (severe) was 22.7%.

Baseline disease characteristics were generally comparable across the 3 treatment groups.

Among all randomised subjects, 57.0% previously received phototherapy, 64.4% previously received 1 or more non-biologic systemic therapies, and 20.6% previously received biologic therapy. Overall, 28.5% of subjects were naïve to all prior non-biologic systemic and biologic therapies. The proportions of subjects who previously received phototherapy, non-biologic systemic therapies, and biologic therapy were generally comparable across the 3 treatment groups.

7.2.2.7. *Sample size*

992 were randomised in the study at Week 0 as follows:

- Group I (guselkumab): 496 subjects
- Group II (placebo): 248 subjects
- Group III (adalimumab): 248 subjects

Among all randomised subjects at baseline, the majority were White (81.7%) and male (72.6%).The median weight was 86.5 kg, and the median age was 44.0 years.

At Week 28:

Group I (guselkumab):

- 95 subjects were PASI 90 non-responders and continued guselkumab 100 mg q8w
- 375 subjects were PASI 90 responders, of which
  - 193 subjects were re-randomised to guselkumab 100 mg q8w
  - 182 subjects were re-randomised to placebo until a loss of ≥50% of the PASI improvement achieved at Week 28, at which point subjects were re-treated with guselkumab 100 mg.

Group II (placebo):

- 80 subjects were PASI 90 non-responders and continued guselkumab 100 mg q8w
- 147 subjects were PASI 90 responders and received placebo until a loss of ≥ 50% of the PASI improvement achieved at Week 28, at which point subjects were re-treated with guselkumab 100 mg.

Group III (adalimumab):

[6] Sponsor clarification: Treatment through Week 72 from Week 44. However, the double blinded period was to Week 44 only, then it was an open study with no comparison between guselkumab and any other treatment.

- 112 subjects were PASI 90 non-responders and were to initiate guselkumab 100 mg, followed by a 100 mg dose 4 weeks later, and then 100 mg q8w thereafter.
- 116 subjects were PASI 90 responders and received placebo until a loss of ≥ 50% of the PASI improvement achieved at Week 28, at which point subjects initiated treatment with guselkumab 100 mg.

7.2.2.8. *Statistical methods*

The co-primary endpoints in this study were the proportion of subjects who achieved an IGA score of cleared (0) or minimal (1) and the proportion of subjects who achieved a PASI 90 response at Week 16, comparing the guselkumab group and the placebo group.

In the primary efficacy analysis, data from all randomised subjects were analysed according to their assigned group. Subjects who met treatment-failure criteria before Week 16 were considered non-responders for the primary endpoints at Week 16.In addition subjects who did not return for evaluation at Week 16 were considered non-responders. To address the primary objective, a Cochran-Mantel-Haenszel (CMH) chi-square statistical test (α=0.05) stratified by pooled site was used for the co-primary end-points. If one of the comparisons was not significant at the 2-sided α-level of 0.05, the co-primary endpoints would be considered not significant. In addition, a comparison between adalimumab and placebo for the 2 co-primary endpoints was also performed.

For the major secondary analyses to test the non-inferiority of guselkumab to adalimumab, a one-sided (α=0.025) CMH Z-test adjusted by investigator site (pooled) was used. The 95% confidence interval (CI) for treatment difference between guselkumab and adalimumab treatment groups was provided. The designated non-inferiority margin was 10%, that is, the lower bound of the 2-sided 95% CI of P1 - P2 was greater than -10%, where P1 and P2 were the proportions of subjects achieving the corresponding endpoints at Week 16 in the guselkumab and the adalimumab groups, respectively. Continuous response parameters were compared using an analysis of variance model with investigator site (pooled) as a covariate. Rank-based analysis of variance was used for percent improvement from baseline in PASI and NAPSI due to the skewed nature of these data. Time-to-event endpoint was compared using log-rank test stratified by pooled site.

In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses were tested in a fixed sequence. That is, the first major secondary endpoint was tested only if the co-primary endpoints were positive, and the subsequent endpoint(s) was (were) tested only if the preceding endpoint in the sequence was positive. In addition, superiority was tested only if non-inferiority was established.

7.2.3. Participant flow

[7]992 subjects were randomised. No data is given on screen failures.

7.2.3.1. *Major protocol violations/deviations*

Approximately 18.8% of subjects experienced major protocol deviations; the major source being 'other'[8] and study entry but not satisfying criteria (5.4%).The proportion was comparable across three treatment groups and is not likely to affect study conclusions.

[7] A total of 1279 subjects were screened

[8] Sponsor clarification: The most common deviations classified as 'Other' were missing efficacy assessments at critical visits, study procedures performed prior to consent and study agent administration with unapproved study kit or without appropriate storage temperature confirmation,.

7.2.3.2. *Baseline data*

Among all randomised subjects at baseline, the majority were White (81.7%) and male (72.6%).The median weight was 86.5 kg, and the median age was 44.0 years. Baseline characteristics were comparable to subjects participating in PSO3001.

Among all randomised subjects, the median duration of psoriasis at baseline was 15.0 years, the median percent of body surface area involved was 22.0%, the median PASI score was 19.0, the proportion of subjects with an IGA=3 (moderate) was 74.6%, and the proportion of subjects with an IGA=4 (severe) was 25.1%.Baseline disease characteristics were generally comparable across the 3 treatment groups.

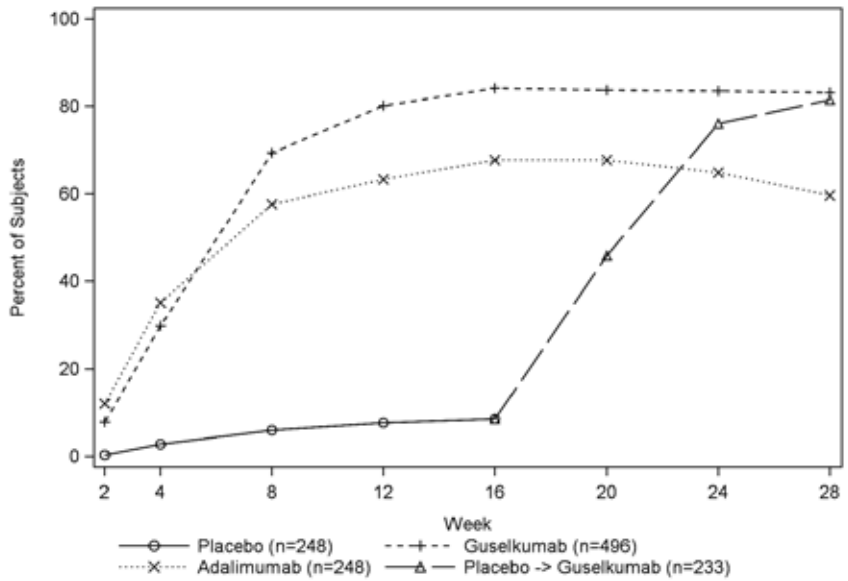
The proportions of subjects who previously received phototherapy (54.3%), non-biologic systemic therapies (61.8%), and biologic therapy (20.9%) were comparable across the 3 treatment groups. A total of 32.1% of subjects were naïve to all prior non-biologic systemic and biologic therapies.

7.2.3.3. *Results for the primary efficacy outcome*

Significantly greater proportions of subjects in the guselkumab group achieved the co-primary endpoints of:

- The proportion of subjects who achieved an IGA score of cleared (0) at Week 16 was significantly higher in the guselkumab group compared with the placebo group (84.1% versus 8.5%; p<0.001).
- The proportion of subjects who achieved a PASI 90 response at Week 16 was significantly higher in the guselkumab group compared with the placebo group (70.0% versus 2.4%; p<0.001).

Figure 4: Percent of Subjects Achieving IGA Score of Cleared (0) or Minimal (1) Through Week 28 by Visit; Subjects Randomised at Week 0



7.2.3.4. *Results for other efficacy outcomes*

At Week 16, PASI 100 responses were observed in 34.1% of the subjects in the guselkumab group compared with 0.8% in the placebo group (p<0.001).

Impact of Maintenance Therapy

Maintenance therapy with guselkumab yielded significantly better maintenance of PASI 90 responses than withdrawal of therapy through Week 48 (PSO3001 and PSO3002).

Subjects randomised to continue guselkumab maintenance therapy had a significantly greater proportion of PASI 90 responders at Week 48 compared to subjects withdrawn from guselkumab at Week 28 (88.6% and 36.8%, respectively, p<0.001).

A significantly greater proportion of subjects receiving continuous guselkumab maintenance therapy also had an IGA 0/1 at Week 48 compared to subjects in the withdrawal group (90.2% and 45.1%, respectively, p<0.001).

The estimated median time to loss of PASI 90 response was 15.9 weeks after withdrawal of therapy at Week 28 in the combined guselkumab group and 8.6 weeks for subjects in the adalimumab group.

SF-36

- Guselkumab treatment resulted in significant improvements from baseline in the SF-36 physical and mental component summary scores at Week 16 compared to placebo (p<0.001).These improvements from baseline increased from Week 16 to Week 24.
- The proportion of guselkumab-treated subjects with an improvement of 5 or more from baseline in SF-36 physical and mental component summary scores was significantly greater compared to placebo (p<0.001) at Week 16 and maintained through Week 24.

HADS

- Subjects treated with guselkumab had a significantly greater mean improvement from baseline in hospital anxiety score at Week 16 compared with the placebo group (-1.7 and -0.2, respectively, p<0.001), and significantly greater mean improvement from baseline in depression score at Week 16 compared with the placebo group (-1.6 and -0.1, respectively, p<0.001).
- Significantly greater proportions of subjects in the guselkumab had a hospital anxiety score <8 and depression score <8 at Week 16 as compared to the placebo group among subjects with a baseline score ≥ 8 (all p<0.001).
- For subjects randomised to guselkumab at Week 28, the mean reduction in HADS scores were maintained over time through Week 48.

WLQ

- Subjects treated with guselkumab had significantly greater improvement in all WLQ scores (physical demands, time management, mental, and output demands) as compared to the placebo group (p≤0.026 for all scores) at Week 16.
- Subjects re-randomised to guselkumab at Week 28 generally maintained the changes from baseline in WLQ scores through Week 48.

Efficacy and serum guselkumab concentrations

- Consistently high clinical responses (IGA score of 0/1, IGA score of 0, PASI 90, and PASI 100) were observed across all 4 trough serum guselkumab concentration quartile levels at Week 28.However; clinical responses appeared to be related to serum guselkumab concentration levels. In general, subjects in the lower quartiles of trough serum guselkumab concentrations tended to have slightly lower clinical responses when compared with subjects with higher trough serum guselkumab levels.
- Across guselkumab and placebo→ guselkumab groups, serum guselkumab concentrations over time in subjects who achieved an IGA score of clear (0) or minimal (1) or PASI 90 responders at Week 28 were generally higher than those in subjects who had an IGA score of >1 or PASI 90 non-responders at Week 28.

Efficacy and antibodies to guselkumab

- The development of antibodies to guselkumab and the titre levels of antibodies to guselkumab were not associated with a reduction in the clinical efficacy of guselkumab, although the incidence of antibodies to guselkumab was low.

Evidence for superior efficacy of guselkumab compared to adalimumab is presented in the pooled data discussion.

7.2.3.5. *Evaluator commentary*

The aim of this pivotal study was to evaluate the short-term efficacy of guselkumab (16 weeks) in comparison to placebo for treatment of moderate to severe psoriasis. Guselkumab showed superior efficacy to placebo on all primary, secondary and many exploratory endpoints. A further aim was to demonstrate longer term efficacy of guselkumab (up to 28 weeks) and to demonstrate superiority to adalimumab.9 These co-primary endpoints were also achieved. Results of open label treatment in long term extension study are not available.

7.3. Other efficacy studies

7.3.1. CNTO1959PSO3003

In this Phase III, randomised, double-blind, multicenter study, enrolled subjects received open-label ustekinumab 45 mg or 90 mg (according to the subject's baseline [Week 0] weight) at Weeks 0 and 4.At Week 16, subjects were to be assessed for efficacy according to the IGA, which determined their subsequent treatment through Week 44: subjects with IGA≥ 2 were randomised to either switch to guselkumab 100 mg at Weeks 16 and 20 and then every 8 weeks (q8w) thereafter or continue on ustekinumab every 12 weeks (q12w); subjects with an IGA=0 or 1 were to continue to receive open-label ustekinumab q12w.

A total of 872 subjects were enrolled and received open-label ustekinumab at Weeks 0 and 4.At Week 16, 585 subjects (67.2%) had an IGA=0 or 1 and continued to receive open-label ustekinumab, while 268 subjects (30.8%) had an IGA ≥2 and were randomly assigned in a 1:1 ratio to switch to guselkumab 100 mg at Weeks 16 and 20 and then q8w thereafter (n=135) or to continue on ustekinumab q12w (n=133).

A number of measures indicated superior efficacy for guselkumab (Table 10).For example, the proportion of randomised subjects who achieved an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from Week 16 at Week 28 was significantly higher (p<0.001) in the guselkumab group compared to ustekinumab (Figure 5).

Table 10: Efficacy Endpoints for the Phase III Clinical Study PSO3003

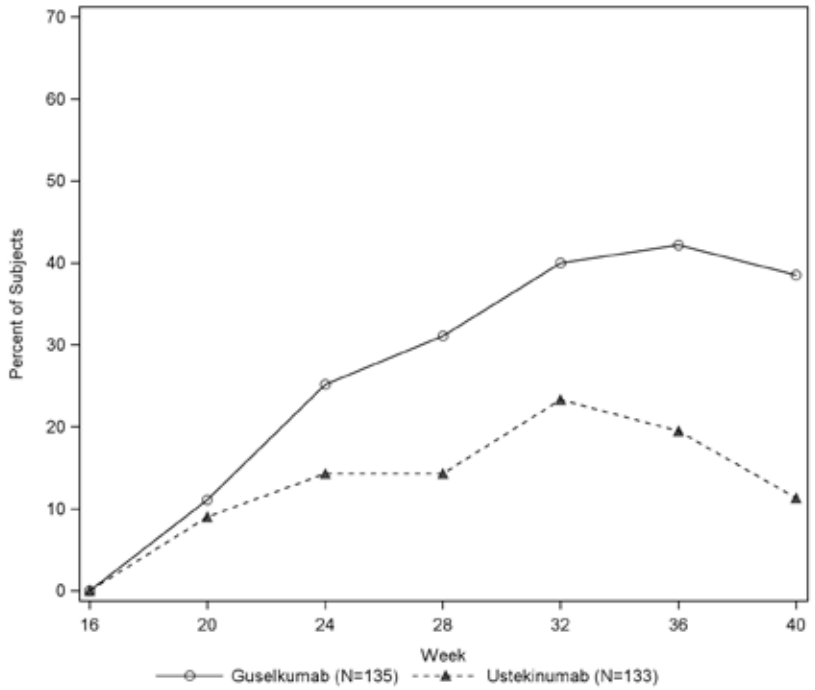
CNTO1959PSO3003

Primary endpoint[a]
Number of visits[b] at which subjects achieved IGA 0/1 and ≥2-grade improvement (relative to Week 16) from Week 28 through Week 40
Major secondary endpoints[a]
Number of visits[b] at which subjects achieved PASI 90 between Week 28 and Week 40
Number of visits[b] at which subjects achieved IGA 0 between Week 28 and Week 40
Proportion of subjects with IGA 0/1 and ≥ 2-grade improvement (relative to Week 16) at Week 28

[a] Comparisons are for guselkumab versus ustekinumab
[b] Maximum number of visits from Week 28 through Week 40 = 4.
IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index;

[9] Sponsor clarification: The study also sought to show that long term maintenance therapy with guselkumab was superior to withdrawal from therapy.

Figure 5: Percent of Subjects Who Achieved IGA Score of Cleared (0) or Minimal (1) and at least 2 Grade Improvement from Week 16 through Week 40 by visit; randomised subjects



7.3.1.1. *Evaluator commentary: other efficacy studies*

Study results demonstrate that psoriasis patients who have not achieved a 'cleared' or 'minimal' response on ustekinumab by Week 16 derive significant benefit from switching to guselkumab relative to remaining on ustekinumab; although numerically, the proportion achieving IGA 0 or 1 appear lower than in the 2 pivotal studies. Further pharmacokinetic, immunogenicity and safety data is provided.

7.4. Analyses performed across trials: pooled and Meta analyses

All Phase III clinical studies achieved primary and major secondary endpoints (see Table 5).Multiplicity was controlled using fixed sequence testing for both the primary and major secondary endpoints in all studies.PSO3001 and PSO3002 shared the same co-primary endpoints and major secondary endpoints through Week 24.

At Week 16, a significantly greater proportion of subjects in the guselkumab group achieved an IGA 0 and IGA 0/1 scores, and PASI 100, PASI 90, and PASI 75 responses compared with the placebo group and for IGA 0/1, PASI 90, and PASI 75 compared to the adalimumab group (Table 7).

Pooling of the exposure-response data from PSO2001, PSO3001 and PSO3002 confirmed that the Phase III dose regimen was near the plateau portion of the guselkumab exposure response curve. Moreover, relevant data from PSO3001 and PSO3002 indicate the development of antibodies to guselkumab and peak titres did not appear to be associated with a reduction in the efficacy of guselkumab.

7.5. Evaluator's conclusions on clinical efficacy

Main efficacy analyses are based on 2 large pivotal Phase III trials, with patients randomised to guselkumab, placebo, and adalimumab. The study design and efficacy endpoints of the Phase II and III studies complied with the CHMP guidelines for evaluation of systemic treatments for

psoriasis. The study population evaluated in the studies were representative of the target patient population for guselkumab.

A robust Phase II program allowed for appropriate dose and regimen selection for the Phase III trials. The population studied in Phase II and III was in line with precedent and health authority recommendations and reflective of the proposed target population.

The large, pivotal Phase III program [Studies PSO3001 and PSO3002] subsequently demonstrated the responder rates to PASI 75, 90, 100 and to IGA 0 or 0/1 to be statistically significantly different from placebo in all studies. Pooled analysis demonstrated efficacy was exposure-related when response was evaluated with respect to serum guselkumab concentration quartiles at Week 16 with a higher proportion of PASI 75, 90, 100 and IGA 0/1 responses seen across all 4 trough serum guselkumab quartiles.

Guselkumab demonstrated superior efficacy over placebo and adalimumab in the treatment of patients with moderate to severe plaque psoriasis on both co-primary endpoints (PASI 90 and IGA 0/1), and secondary endpoints (PASI 90, PASI 100, dermatology life quality index (DLQI).With the availability of more effective biological agents including ixekizumab, ustekinumab and secukinumab, the relevance of these measures of efficacy to prescribers has been elevated.

Superiority to placebo and adalimumab was also demonstrated for all major secondary endpoints in analyses of Phase III efficacy data.

Response rates reached a plateau around Week 16 and the high response rates were sustained up to 48 weeks of treatment in PSO3001.

Relapse was demonstrated on withdrawal of guselkumab in Study PSO3002 with an estimated median time to loss of PASI 90 response of 15.9 weeks after withdrawal of therapy at Week 28 in the guselkumab group in PSO3002.

The superior efficacy of guselkumab versus placebo in the PASI 75, IGA 0/1, and PASI 90 responses at Week 16 was consistent in all subgroups of body weight, age, race (Asian versus Non-Asian) and disease severity.

The efficacy section of the proposed PI was an accurate representation of the results of the submitted studies.

7.5.1. Limitations

The long-term open label efficacy and safety results of the Phase III studies which evaluated guselkumab should be provided on completion of these studies.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

No pivotal studies assess safety as the sole primary outcome.

8.1.2. Pivotal and/or main efficacy studies

The safety database from the core psoriasis Phase II and 3 Phase III clinical studies includes 1,748 subjects with moderate to severe plaque psoriasis who were exposed to guselkumab, including 1,393 subjects exposed for at least 6 months and 728 subjects exposed for at least 1 year (that is, treated through at least 48 weeks).

Safety and tolerability information of guselkumab was monitored by collecting information on adverse events (AEs), including injection-site reactions (ISRs) and allergic reactions, clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), concomitant medication review, and early detection of active TB (through clinical activation and if required consultation with a physician specialising in TB), as specified in the Time and Events Schedule of the protocol. Serum and/or plasma samples collected for PK or biomarker analyses could also be used to evaluate safety concerns that arose during or after the study period. Safety was monitored through Week 48 for all subjects in PSO3001[10] and PSO3002 and 52 weeks in PSO2001.

8.1.3. Other studies

8.1.3.1. *Other efficacy studies*

Other studies with evaluable safety data include CNTO1275ARA2001 (55 subjects receiving 50 mg guselkumab q8w and 54 subjects receiving guselkumab 200 mg q8w for 28 weeks), CNTO1959PPP2001 (24 subjects receiving a single 200 mg guselkumab dose), and CNTO1959PSO3005 (21 subjects receiving 50-100 mg guselkumab q8w for up to 52 weeks).

8.2. Patient exposure

Table 11 summarises patient exposure to guselkumab, placebo, and comparators adalimumab and ustekinumab in clinical studies. Table 12 provides a summary of duration of guselkumab exposure and total guselkumab dose through the end of the reporting period; subjects treated with guselkumab in psoriasis Phase II and Phase III studies.

Table 11: Exposure to guselkumab, placebo and comparators adalimumab and ustekinumab in clinical studies

Study type/ Indication	Controlled studies				Uncontrolled studies
	G	Placebo	A	U	G
Clinical pharmacology Single dose NAP1001					160 HC 100 mg
NAP1002		11 HC			8 HC 10 mg/kg
	3 HC 0.03mg/kg	4 TP			
PSO1001	3 HC 0.1mg/kg				
	6 HC 0.3mg/kg				
	6 HC 1mg/kg				
	12 HC 3mg/kg				
	6 HC 10 mg/kg				
	5 TP 10 mg				
	5 TP 30 mg				

[10] Sponsor clarification: Through Week 40 in PSO3003.

Study type/ Indication	Controlled studies				Uncontrolled studies
	G	Placebo	A	U	G
PSO1002	5 TP 100 mg 5 TP 100 mg 5 TP 300 mg 4 TP 10 mg 4 TP 30 mg 4 TP 100 mg 4 TP 300 mg	4 TP			
Dose finding: PSO2001	41 TP 5 mg 41 TP 15 mg 41 TP 50 mg 41 TP 100 mg 41 TP 200 mg	42 TP	43 TP		
Moderate to severe plaque type psoriasis One year exposure q8w					
PSO3001 PSO3002	329 TP 496 TP	174 TP 248 TP	334 TP 248 TP		
PSO3003	135 TP			133 TP	
Subtotal Single dose Subtotal Phase III Multiple dose (100 mg Weeks 0, 4, and q8w)	41 TP 44 HC 960 TP	11 HC 8 TP 422 TP	582 TP	133 TP	
Subtotal multiple dose (Phase II and III all guselkumab doses)	1168 TP	464 TP	625 TP	133 TP	

Study type/ Indication	Controlled studies				Uncontrolled studies
	G	Placebo	A	U	G
Rheumatoid Arthritis ARA2001 (28 weeks q8w)	55 TP 50 mg 55 TP 200 mg		55 TP	110 TP	
PPP PPP2001 Single dose	25 TP 200 mg	24 TP			
GPP or EP PSO3005 For 52 weeks q8w	21 50-100 mg				
Subtotal other indications	25 single dose 131 multiple dose				
HC = healthy controls, TP = target population; G= guselkumab; A= adalimumab; U= ustekinumab; *Control= Comparator					

Table 12: Summary of duration of guselkumab exposure and total guselkumab dose through the end of the reporting period; Subjects treated with guselkumab in psoriasis Phase II and Phase III Studies (Studies CNTO1959PSO2001, CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003)

	Guselkumab at Doses Lower Than 100 mg[a]	Guselkumab 100 mg[b]	Guselkumab 200 mg	All Guselkumab[c]
Analysis set: Subjects treated with guselkumab	124	1583	41	1748
Duration of guselkumab exposure				
At least 6 months[d]	117 (94.4%)	1238 (78.2%)	38 (92.7%)	1393 (79.7%)
At least 1 year[e]	78 (62.9%)	624 (39.4%)	26 (63.4%)	728 (41.6%)

[a] Includes guselkumab 5 mg (q12w), 15 mg (q8w), and 50 mg (q12w) in CNTO1959PSO2001 study.
[b] Includes all subjects treated with guselkumab 100 mg q8w in CNTO1959PSO2001 (including placebo crossover subjects), CNTO1959PSO3001 (including placebo crossover subjects), CNTO1959PSO3002 (including placebo crossover and adalimumab crossover subjects), and CNTO1959PSO3003.
[c] Includes data from Guselkumab at Doses Lower Than 100 mg column, Guselkumab 100 mg column and Guselkumab 200 mg column.
[d] The duration between the first and last guselkumab administration was at least 16 weeks.
[e] The duration between the first and last guselkumab administration was at least 40 weeks.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. *Integrated analysis of pivotal efficacy studies*

Safety data from 2 global Phase III psoriasis studies (PSO3001 and PSO3002) were pooled and served as the primary safety analysis set for the integrated analyses of safety because they had similar study designs, subject populations, dose regimens through Week 28, including a placebo control through Week 16 and an active comparator control through Week 28.

For most common AEs, the frequency of AEs was comparable in the guselkumab and placebo groups (Table 13).One notable exception was injection site erythema, which was twice as frequent in the guselkumab group as in the placebo group (Guselkumab 1.9% vs placebo 0.7%).The proportions of subjects with SAEs through Week 16 were low and comparable across the guselkumab (1.9%), placebo (1.4%), and adalimumab (2.1%) groups.

Table 13: Number of Subjects with 1 or More Treatment-emergent Adverse Events through Week 16; Treated Subjects (Studies PSO3001 and PSO3002)

	Placebo	Guselkumab 100 mg	Adalimumab
Analysis set: Subjects treated	422	823	581
Avg duration of follow-up (weeks)	15.88	16.19	16.11
Avg exposure (number of administrations)	10.63	10.77	10.71
Subjects with 1 or more:			
adverse events	197 (46.7%)	405 (49.2%)	290 (49.9%)
serious adverse events	6 (1.4%)	16 (1.9%)	12 (2.1%)
adverse events leading to study agent discontinuation	4 (0.9%)	11 (1.3%)	7 (1.2%)
infections[a]	90 (21.3%)	191 (23.2%)	143 (24.6%)
serious infections	1 (0.2%)	1 (0.1%)	4 (0.7%)
malignancies[b]	0	1 (0.1%)	0
cardiovascular events	0	3 (0.4%)	3 (0.5%)
MACE	0	1 (0.1%)	2 (0.3%)
other adjudicated CV events	0	2 (0.2%)	1 (0.2%)
adverse events of psoriasis	6 (1.5%)	2 (0.2%)	8 (1.4%)
suicidal ideation and behavior	0	0	1 (0.2%)

CV=cardiovascular; MACE=major adverse cardiovascular event (defined as MI, stroke, or CV death).
[a] AEs categorized by the investigator as an infection were used in this analysis.
[b] One subject in the guselkumab group was reported to have an nonmelanoma skin cancer

Through the end of the reporting period in PSO3001 and PSO3002 (that is, through Week 48) for the pooled safety analysis set, the average duration of follow-up was similar (~41 weeks) for subjects in the guselkumab and adalimumab treatment groups. Consideration of this pooled safety analysis set allows some evaluation of the potential for exposure-related AEs. The incidence of AEs through Week 48 in the guselkumab group was 259.42/100 subj-yrs, and was not higher than that for the adalimumab group (332.84/100 subj-yrs).In general, the rates for AEs within each SOC through Week 48 were similar for the guselkumab and adalimumab groups, with the notable exception of the SOC, General Disorders and Administration Site Conditions, which was lower in the guselkumab group (22.37/100 subj-yrs vs 65.88/100 subj-yrs in adalimumab group).This observation was primarily due to differences in the event rates for some ISRs.

In the guselkumab group, the most common AEs through Week 48 were nasopharyngitis (32.84/100 subj-yrs), URTI (17.24/100 subj-yrs), headache (7.29/100 subj-yrs), arthralgia (5.95/100 subj-yrs), and hypertension (5.13/100 subj-yrs). All other AEs in the guselkumab group were reported at rates of < 5.0/100 subj-yrs, with most individual AEs reported at rates of <1/100 subj-yrs.

A comparison of exposure-adjusted rates for AEs in the guselkumab groups across the 3 analysis periods did not show any increase in overall AE event rates over time (330.11, 295.20, and 259.42 per 100 subj-yrs through Week 16, Week 28, and Week 48, respectively.

8.3.1.2. *Other studies*

Other efficacy studies: ARA2001

ARA2001 is considered here because the comparator is different. In general, both, ustekinumab and guselkumab were overall well-tolerated in this 48 week study in subjects with moderate to severe RA, with TEAEs rates generally comparable to placebo, no dose limiting AEs, low rates of SAEs, low rates of serious infections, no opportunistic infections and no new or unexpected safety signals. However, the number of study participants in this study was small, making interpretation of the infrequent events or observations difficult.

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. *Integrated safety analyses*

No difference in treatment-related adverse events was seen in the guselkumab treated subjects compared to placebo through Week 16 with the exception of an increased report of injection site reactions.

8.3.3. Deaths and other serious adverse events

8.3.3.1. *Integrated safety analyses*

Across Studies PSO3001 and PSO3002, there were no deaths in guselkumab-treated subjects through the end of the reporting period.

One death occurred in a subject assigned to the adalimumab group in PSO3001.Of note, across the other studies in the core psoriasis clinical development program for guselkumab, a single death was reported in a guselkumab-treated subject (due to fatal MI in a subject with multiple CV risk factors in Study PSO2001).In addition, a death was reported in the nonrandomised group of Study PSO3003.This 59-year-old White male subject received 4 doses of ustekinumab 45 mg through Week 28, and died on Day 292 due to metastatic pancreatic carcinoma.

After the 30 June 2016 cut-off date for this submission, the sponsor became aware of 2 additional deaths in ongoing Phase III studies: one cancer related and the other suicide.

Key findings for other SAEs reported in the PSO3001 and PSO3002 are as follows:

- The frequency of SAEs with guselkumab was low and consistent with that observed for placebo through Week 16.
- There was no evidence for an increase in the reporting rate for SAEs over time up through Week 48 in subjects treated with guselkumab, and most SAEs reported in subjects exposed to guselkumab were single events.
- With longer treatment (through Week 28 or Week 48), the overall frequency and rates of SAEs in the guselkumab group were comparable with those for adalimumab.
- SAEs of note reported in the guselkumab or adalimumab groups included
  - TB (a small proportion of subjects in the studies received concomitant treatment for latent TB due to study requirements)[11]
  - Malignancies which were infrequent in the guselkumab group and of rates similar to what would be expected in the general population (6 NMSC and 3 other malignancies).

[11] Sponsor clarification: Active TB was diagnosed in 2 patients in the adalimumab group.

- Neuropsychiatric disorders: no reports of suicide were identified in the clinical development program through the cutoff date.
- One notable SAE of thrombocytopenia was reported in the guselkumab group; the subject's platelet count decreased to a nadir of 27 kU/L and recovered without intervention after discontinuation of guselkumab (within 8 weeks of last dose).

8.3.4. Discontinuations due to adverse events

8.3.4.1. *Integrated safety analyses*

Key findings concerning AEs leading to discontinuation of study drug in PSO3001 and PSO3002 are as follows:

- Discontinuation of treatment with guselkumab 100 mg SC for an AE(s) was infrequent in PSO3001 and PSO3002, and the frequency of discontinuation of study drug due to AEs was similar for the guselkumab and placebo groups through Week 16.
- There was no evidence for an increase in the event rate of AEs leading to discontinuation of guselkumab therapy over time. Additionally, most AEs leading to discontinuation of guselkumab treatment were single events.
- The overall frequency and rates of AEs leading to discontinuation were no higher for the guselkumab group than for the adalimumab group for the Week 28 and Week 48 analysis periods.

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Infections

8.4.1.1. *Pivotal efficacy studies*

Clinically meaningful differences in gastroenteritis events were observed between the guselkumab and adalimumab groups in Study PSO3001 through Week 48 but not Week 16.The difference in frequencies for gastroenteritis, along with the biologic plausibility of an infection as an adverse reaction of an immune-modulating drug like guselkumab, formed the basis for the sponsor's decision to make gastroenteritis an ADR.

8.4.1.2. *Integrated safety analyses*

Although infection is a theoretical risk for guselkumab based on its immune-modulating mechanism of action, guselkumab did not appear to be associated with an increased frequency of infections requiring the use of oral or parenteral antimicrobial treatment. There was no increase in infection rate with longer duration of treatment.

The only ADR that was identified as an ADR for guselkumab was gastroenteritis.

8.4.2. Cardiovascular events

8.4.2.1. *Integrated safety analyses*

For the pooled safety analysis set, there were no CV events in the placebo group. The event rate for all adjudicated CV events in the guselkumab group was comparable with that for the adalimumab group for all 3 analysis periods.

8.4.3. Serum sickness/anaphylaxis

8.4.3.1. *Integrated safety analyses*

No reports of serum sickness like events or anaphylaxis related to study drug.

8.4.4. Liver function and liver toxicity

8.4.4.1. *Integrated safety analyses*

- ALT elevations (reported in 2 subjects) were the only CTCAE Grade 3 chemistry abnormalities reported in more than 1 subject in the guselkumab group.
- In all 3 treatment groups, shifts from normal baseline to an elevated value in ALT and AST were the most common clinically relevant shifts and were reported for 7.5% and 5.1% of subjects, respectively, in the guselkumab group; 5.4% and 5.8% of subjects, respectively, in the placebo group; and in 13.1% and 8.6% of subjects, respectively, in the adalimumab group.

8.4.5. Renal function and renal toxicity

8.4.5.1. *Integrated safety analyses*

- The frequencies of chemistry laboratory values of CTCAE toxicity Grade 2 or higher in the guselkumab group through Week 16 were comparable with those for the placebo and adalimumab groups.
- No subject in any treatment group had a chemistry laboratory value of CTCAE toxicity Grade 4 through Week 16.

8.4.6. Other clinical chemistry

8.4.6.1. *Integrated safety analyses*

CTCAE toxicity Grade 3 chemistry abnormalities were infrequent through Week 16 in all treatment groups; decreased sodium was reported in 5 subjects.

8.4.7. Haematology and haematological toxicity

8.4.7.1. *Integrated safety analyses*

For each haematology laboratory parameter (haemoglobin, RBC, platelets, WBC, lymphocytes, and neutrophils), 1.5% or less of subjects in the guselkumab group had a value with CTCAE toxicity Grade ≥ 2 through Week 16.

Shift analysis through Week 16 indicated that almost all subjects (>96%) in the guselkumab group had haematology laboratory values that remained within the normal range at baseline and Week 16.

The most common Grade ≥ 2 haematology abnormality through Week 48 in the guselkumab group was low lymphocyte counts, which occurred in 2.5% of subjects (n=31; maximum grade of 2 in 29 subjects and maximum grade of 3 in 2 subjects).

8.4.7.2. *Other studies*

Other efficacy studies

In Study PPP2001 in subjects with PPP treated with guselkumab 200 mg SC, no trends or clinically meaningful changes in haematology or clinical chemistry parameters were observed. One subject discontinued guselkumab due to urticarial reaction.

In Study ARA2001 in subjects with active RA, no consistent, clinically important differences were observed in the guselkumab treatment groups (50 and 200 mg SC) in mean changes from baseline in clinical chemistry or haematology laboratory parameters through Week 48, and the majority of abnormalities in post-baseline chemistry and haematology measurements were CTCAE Grade 1-2, with the distribution of toxicity grades generally comparable between the guselkumab groups and placebo.

In Study PSO3005 in Japanese subjects with GPP/EP, no clinically meaningful mean changes from baseline to Week 28 were observed in haematology and chemistry parameters. Few

subjects with had abnormal haematology and chemistry parameters of CTCAE Grade ≥ 2 through Week 28.

8.4.8. Other laboratory tests

8.4.8.1. *Integrated safety analyses*

No other relevant laboratory tests were identified.[12]

8.4.9. Electrocardiograph findings and cardiovascular safety

8.4.9.1. *Integrated safety analyses*

For the pooled safety analysis set, the frequency of new postbaseline ECG abnormalities was low and occurred at comparable rates for the guselkumab and adalimumab groups, and the types of recorded abnormalities appeared similar for the two groups.

There was no evidence for any clinically meaningful changes from baseline in ECG interval values in the pooled safety analysis set (nor in the other core psoriasis studies or the completed studies in other indications or populations).

8.4.10. Vital signs and clinical examination findings

8.4.10.1. *Integrated safety analyses*

No clinically meaningful changes in posttreatment values in any treatment group.

8.4.11. Immunogenicity and immunological events

8.4.11.1. *Integrated safety analyses*

Key findings concerning analysis of the impact of antibodies to guselkumab on the observed safety in the Phase II (PSO2001) and Phase III (PSO3001, PSO3002 and PSO3003) core psoriasis studies are as follows:

- A total of 1,730 subjects across the Phase II and III core psoriasis studies (PSO2001, PSO3001, PSO3002, and PSO3003) who received guselkumab had posttreatment serum samples that were evaluable for antibodies to guselkumab. The overall incidence of antibodies to guselkumab after exposure to guselkumab was 5.5% (n=96).Titres of antibodies to guselkumab were generally low, with the majority (79.2%) being ≤ 1:160
- No apparent impact of antibodies to guselkumab on the PK of guselkumab was observed between subjects who were positive for antibodies to guselkumab and subjects who were negative for antibodies to guselkumab (that is, between-subject comparison), before and after the development of antibodies to guselkumab (that is, within-subject comparison), and by the time when the antibodies to guselkumab were developed.
- Antibodies to guselkumab and titre levels of antibodies to guselkumab had no discernible impact on development of ISRs.
- Seven (7.3%) of 96 subjects who were positive for antibodies to guselkumab from the Phase II and 3 core psoriasis studies had antibodies that were able to neutralize the bioactivity of guselkumab in vitro. Thus, the overall incidence of neutralizing antibodies to guselkumab in subjects who received guselkumab and had samples that were evaluable for antibodies to guselkumab was 0.4% (7/1,730 subjects).

8.4.12. Serious skin reactions

8.4.12.1. *Integrated safety analyses*

No serious skin reactions were reported in the pooled analysis.

[12] There were no other clinically meaningful changes from baseline or differences between groups in the frequency of abnormalities in laboratory tests in PSO3001/3002 through Week 48.

8.4.13. Injection-site reactions

8.4.13.1. *Integrated safety analyses*

- The proportion of subjects with ISRs following guselkumab injection through Week 16 or Week 48 was low (2.6%) and lower than the corresponding proportion of subjects reporting ISRs following adalimumab injection for both analysis periods.
- The proportion of guselkumab or adalimumab injections associated with an ISR was 0.7% for guselkumab and 1.3% for adalimumab through Week 48 (rate of placebo injections with ISRs was 0.3% through Week 48).
- Almost all of the ISRs reported following guselkumab injection were assessed as mild, none were severe or considered serious, and none resulted in study drug discontinuation.

8.5. Other safety issues

8.5.1. Safety in special populations

There was no evidence that comparisons of the safety profile for the guselkumab group with the placebo group (Week 16) or adalimumab groups (Weeks 16, 28, or 48) differed as a function of prior use of non-biologic systemic products or biologics.

As of 04 July 2016, 21 reports of pregnancy were identified in studies of guselkumab in completed studies in plaque psoriasis, RA or PPP, including 9 pregnancies in female subjects exposed to guselkumab participating in these studies (that is, maternal pregnancies) and 12 pregnancies in female partners of male subjects exposed to guselkumab participating in these studies (that is, paternal pregnancies).Therefore, there is no data to support safety in pregnancy.

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

The likelihood of therapeutic proteins-drug interactions between guselkumab and CYP substrates is low.

8.6. Post marketing experience

Guselkumab is not currently marketed in any country.[13]

8.7. Evaluator's overall conclusions on clinical safety

Across the single Phase II and three Phase III core psoriasis studies with guselkumab, a total of 1,748 subjects representative of the target patient group with moderate to severe plaque psoriasis received SC guselkumab, most (91%) at a dose of 100 mg. Subjects from the 2 placebo- and active comparator-controlled Phase III studies comprised the primary safety analysis set for this application. In this pooled safety analysis set, there was adequate exposure to guselkumab, with 1,367 subjects receiving the proposed dose regimen (SC injection of 100 mg at Weeks 0, 4, and then q8w), including 592 subjects who were exposed for 1 year.

Guselkumab was well tolerated at the dose used in pivotal Phase II studies. Despite the theoretical concerns for increased infection risk, guselkumab showed no imbalance versus placebo in total AEs, with the exception for gastroenteritis. This difference reached significance only in the first pivotal study through Week 48 treatment.[14]Injection site reactions were more frequent compared to placebo but reactions were generally mild and did not necessitate

[13] Since this evaluation was finalised, Tremfya has been approved and marketed in the USA.
[14] With guselkumab in comparison with adalimumab.

discontinuation. No serious opportunistic infections were reported. No tuberculosis or viral hepatitis reactivation was observed in any psoriasis trial[15].5.9% and 8.1% of subjects entering the Studies PSO3001 and PSO3002 were treated for latent tuberculosis identified during screening.

Treatment related AEs were comparable for treatment periods through to Week 16 for guselkumab compared to placebo.

Adverse drug reactions (ADRs) classified as were gastroenteritis and injection site erythema. Uncommon ADRs included injection site pain.

SAEs and discontinuations due to AEs were infrequent in the first 16 weeks of treatment and showed no differences among guselkumab, placebo and adalimumab. Over 48 weeks, SAEs remained comparable across the treatment groups. Guselkumab was comparable to adalimumab in AEs leading to discontinuation over 48 weeks. The rate of AEs causing discontinuation was low and comparable for the guselkumab, placebo and adalimumab groups through Week 16.

In pooled analyses, the rate of cardiovascular events was very low through Week 48.

The incidence of malignancies for guselkumab was similar to what would be expected in the general population. There was no cluster of specific malignancies in any treatment group.

Guselkumab specific treatment emergent anti-drug antibodies (ADA) were detected across the Phase II and III program (5.5% of subjects) but titres were generally low. Treatment emergent ADAs were not associated with a loss of efficacy or alteration of PK in patients with assessable data. No severe or serious hypersensitivity reactions or administration reactions were reported in any patients with treatment emergent ADA.

Hypersensitivity AEs were rare with only one subject in the PPP2001 study discontinuing guselkumab due to urticaria, although the dose used in this study was higher (200 mg).

The most common haematology abnormality through Week 48 in the guselkumab group was low lymphocyte counts, which occurred in 2.5% of subjects (n=31; maximum grade of 2 in 29 subjects and maximum grade of 3 in 2 subjects).This did not appear to lead to drug discontinuation or be associated with adverse clinical outcomes.

There was no indication that guselkumab was linked to hepatic transaminase elevations versus placebo or adalimumab.

There were no clinically relevant effects associated with use of guselkumab in vital signs or electrocardiogram (ECG).

No subpopulation treated with guselkumab showed an increased risk of any safety parameter compared to the overall population.

In conclusion, guselkumab 100 mg has an acceptable safety profile for intended use in adult patients with moderate to severe plaque psoriasis. Guselkumab 100 mg showed comparable safety to placebo (over 16 weeks) and adalimumab (over 48 weeks) of treatment.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of guselkumab in the proposed usage are:

[15] Sponsor clarification: In the guselkumab treated subjects.

- The 2 pivotal trials showed consistent results demonstrating superiority of guselkumab to placebo for PASI 75, PASI 90, PASI 100 and IGA 0 and 0/1 at 16 weeks. In both pivotal studies, superiority was also demonstrated against the active comparator adalimumab.
- The onset of clinical efficacy, measured by IGA 0/1 and PASI 90 response, occurred as early as Week 2 in both studies (PSO3001 and PS03002).Additionally, by Week 8 in both studies, guselkumab treatment responses also separated from those of adalimumab. The response separation between guselkumab and adalimumab continued to increase and reached a maximum around Week 16 and 20 for IGA 0/1 and PASI 90 response, respectively, and was maintained through Week 24.
- Assessed by complete psoriasis clearance (PASI 100 response and IGA 0), guselkumab demonstrated a high level of efficacy as evident at Week 48 with 47.4% and 50.5% of subjects in the guselkumab group achieving a PASI 100 response and IGA 0, respectively.
- The improvement in skin scores were associated with the best chance to not only improve, but to achieve normal quality of life (DLQI 0/1) and 57.6%-60.9% of the patients treated with guselkumab 100 mg were able to achieve this important goal at Week 24 compared with 39.5-41.1% with the active comparator adalimumab.
- Subjects in Study PSO3002 also reported significantly less anxiety and depression (measured by HADS) as well as less impairment and increased productivity at work (as measured by WLQ).
- The benefits demonstrated for guselkumab versus placebo extended to all subgroups studied (age, gender, race, region, weight, baseline disease severity, exposure to previous systemic psoriasis therapy, and comorbid psoriatic arthritis).

9.2. First round assessment of risks

The risks of guselkumab in the proposed usage are:

- Guselkumab has not yet been studied in patients less than 18 years of age, in patients with hepatic impairment or renal impairment or in pregnant women.
- Live vaccines cannot be given concurrently with guselkumab.
- Possible increased risk of gastroenteritis.
- Potential for serious infection including reactivation of latent tuberculosis and other serious opportunistic infections.
- Local injection site reactions which are generally mild and transient and do not result in permanent discontinuation from USK.
- Potential for increased risk of malignancy.
- Formation of anti-guselkumab antibodies that may result in loss or lack of efficacy.
- Lack of long term efficacy and safety data with the PFS as Studies PSO3001 and PSO3002.

9.3. First round assessment of benefit-risk balance

Although there are many new biologic agents approved for the treatment of psoriasis, many of the patients still do not achieve optimal efficacy when one considers clinically meaningful measures such as clear/almost clear skin (and demonstrated by PASI 90 and PASI 100).Other limitations such as diminishing efficacy over time and drug-specific safety concerns (for example, infection including tuberculosis, malignancies including lymphoma, and demyelinating neurologic events).Thus, there remains a significant unmet patient need for new agents with

unique mechanisms that can provide a rapid onset of effect, improved and sustained symptom clearance, and a safety profile that allows for chronic use.

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda (IgG1lambda) monoclonal antibody (mAb) that binds to the p19 protein subunit of interleukin-23 (IL-23) with high specificity and affinity. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses and plays a key role in the pathogenesis of plaque psoriasis. Guselkumab was evaluated in a large clinical program which complied with CHMP guidelines for evaluation of treatments for psoriasis. The clinical studies involved adequate number of the target patient population. It was demonstrated that guselkumab is a highly efficacious treatment with the most pronounced benefits seen with the 100 mg dose, particularly at the more difficult to achieve measures of clear/almost clear skin (PASI 90, PASI 100, IGA 0 or 0/1).The superior efficacy of guselkumab versus placebo was consistent in all subgroups of body weight, age, race, disease severity, and previous exposure or failure to systemic psoriasis therapy (including subjects with an inadequate response to ustekinumab).

The majority of patients attained clear or nearly clear skin as evidenced by PASI 90 (PSO3001 73.3%, PSO3002 70.0%) by Week 16 with guselkumab 100 mg. This high level of response is maintained over at least 48 weeks (for example PSO3001 76.3%).

Patient reported outcome data were consistent with the quantitative data showing the advantage with guselkumab.

The risk profile of guselkumab is based on 624 patients in pooled analysis treated with the proposed dose of 100 mg through 48 weeks. In the clinical program, there was no evidence of an imbalance of serious events compared with either placebo or adalimumab. There was a probable imbalance in the overall incidence of gastroenteritis and injection site reactions compared to placebo, consistent with the mechanism of action, with no reports of chronic or systemic disease resulting from treatment in any treatment group.

No serious opportunistic infections were reported.

Malignancy may represent a theoretical risk with any immunosuppressive therapy, but there is no evidence that guselkumab confers an increased risk for malignancy.

Overall, the benefit-risk balance of guselkumab 100 mg for the proposed indication of use in adult patients with moderate to severe plaque psoriasis, who are candidates for systemic therapy or phototherapy, is favourable.

10. First round recommendation regarding authorisation

The evaluator recommends that guselkumab 100 mg be approved for the indication requested:

> *Tremfya is indicated for the treatment of moderate to severe plaque psoriasis, scalp, nail, and hand and foot psoriasis and improvement of health related quality of life in adult patients who are candidates for systemic therapy or phototherapy.*

11. Clinical questions

11.1. Pharmacokinetics

No questions.

11.2. Pharmacodynamics

1. *Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 to mediate the efficacy of guselkumab?*
2. *Is there an ongoing strategy to identify long-term immunogenicity in open label studies and a potential role of neutralising antibodies in secondary non-responders?*

11.3. Efficacy

None.

11.4. Safety

Has the effect of guselkumab on live vaccination been assessed in preclinical toxicology studies?

11.5. PI and CMI

None.

12. Second round evaluation

12.1. Pharmacokinetics

No questions.

12.2. Pharmacodynamics

1. *Has the sponsor evaluated the potential for polymorphisms in the IL-23/Th-17 to mediate the efficacy of guselkumab?*

12.2.1. Sponsor response:

The Applicant has not performed any in vitro or mechanistic studies to evaluate the potential impact of polymorphisms associated with IL-23 or with IL-23 receptors on the efficacy of guselkumab. The applicant is currently generating SNP (single nucleotide polymorphism) data from subjects in studies CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003 and analyses have not yet been initiated.

12.2.2. Evaluator comment

The response has been noted. The effect of genetic polymorphisms associated with IL-23 or with IL-23 receptors is currently unknown and should be investigated. The sponsor has stated that this would be undertaken in the studies listed above.

'Effects of genetic polymorphisms associated with IL-23 or with IL-23 receptors' (or a term to that effect) should be added to the list of Missing Information items and the related study results be reported in PBRERs/PSURs.

2. *Is there an ongoing strategy to identify long-term immunogenicity in open label studies and a potential role of neutralising antibodies in secondary non-responders?*

12.2.3. Sponsor response

The long-term immunogenicity of guselkumab will be evaluated in the open-label period through Year 5 in the ongoing studies CNTO1959PSO3001 and CNTO1959PSO3002.The neutralising

antibodies (NAb) to guselkumab will also be evaluated in the open-label period through Year 5 in the ongoing studies CNTO1959PSO3001 and CNTO1959PSO3002.However, due to low incidence of anti-drug antibodies (ADA) to guselkumab (the overall incidence of ADA through up to Week 48 was 6.1% [83 of 1,361 subjects who received guselkumab and had post-treatment serum samples evaluable for ADA]) and even lower incidence of NAb to guselkumab (only 7 of 83 ADA-positive subjects had positive NAb to guselkumab through up to Week 48), an informative assessment of the role of NAb in secondary non-responders may not be possible.

12.2.4. Evaluator comment

The response has been noted. In absolute terms, the proportion of subjects with ADAs and also NAbs was low, in particular when compared to information from the literature with regard to other monoclonal antibodies used for treatment of psoriasis or similar conditions. However, given the large variety of methods to measure antibodies/immunogenicity (potentially leading to a large measurement variability), and given that these methods evolve over time, the absolute number/proportion of subjects with ADAs/NAbs may not be meaningful. It would have been advantageous to measure anti-adalimumab Abs in the active control arm as well (for example to compare those to the results reported in the literature), in order to put the result of anti-guselkumab Abs into context. This may be undertaken in future studies.

It would be prudent to continue monitoring ADAs/NAbs and the sponsor plans to do so.

'Effects of immunogenicity' (or a term to that effect) should be added to the list of Missing Information items and the related study results be reported in PBRERs/PSURs.

12.3. Efficacy

None.

12.4. Safety

3. Has the effect of guselkumab on live vaccination been assessed in preclinical toxicology studies?

12.4.1. Sponsor response

There were no specific nonclinical studies conducted to assess the effect of guselkumab on live vaccinations. However, targeted immunotoxicology assessments were conducted during the toxicology study in cynomolgus monkeys that included T-cell dependent antibody response to keyhole limpet hemocyanin immunization (KLH).Guselkumab treatment had no effect on responses to KLH immunization. Furthermore, there was no evidence of an increase in the incidence of infections during the nonclinical toxicology studies with guselkumab.

Labeling

In addition to the following responses, the annotated PI includes proposed modifications to other TGA requested revisions with rationale.

12.4.2. Evaluator comment

The response has been noted.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Tremfya (guselkumab) in the proposed usage are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Tremfya (guselkumab) in the proposed usage are unchanged from those identified in Section 9.2.

'Major adverse cardiovascular events (MACE)' was added as an Important Potential Risk in the RMP to align with the final EU-RMP.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Tremfya (guselkumab), given the proposed usage, is favourable. This assessment is based on the clinical data evaluated from a clinical point of view. The assessment was made by weighing up the risks and benefits as outlined in this evaluation report.

14. Second round recommendation regarding authorisation

Approval of Tremfya (guselkumab) is recommended for the following indications (as per proposed Tremfya product information):

> *Tremfya is indicated for the treatment of moderate to severe plaque psoriasis, scalp, nail, and hand and foot psoriasis and improvement of health related quality of life in adult patients who are candidates for systemic therapy or phototherapy.*

15. References

Nil.

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