Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Guselkumab

Proprietary Product Name: Tremfya / Janssen Guselkumab

Sponsor: Janssen-Cilag Pty Ltd

November 2018

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.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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 event
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 PsO
ESR	Erythrocyte sedimentation ratio
FDA	Food and Drug Administration
f-PGA	Fingernail Physician's global Assessment
GCP	Good Clinical Practice
GPP	Generalized pustular PsO
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 Conference on Harmonisation
IGA	Investigator's Global Assessment
IgG1λ	Immunoglobulin G1 lambda
IL	Interleukin
ISR	Injection site reaction
IV	Intravenous
mAb	Monoclonal antibody
MTX	Methotrexate
NAPSI	Nail PsA Area and Severity Index
NMSC	Non-melanoma skin cancer
NSAID	Non-steroidal anti-inflammatory drug
NK	Natural killer

Abbreviation	Meaning
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 100% improvement in the PASI from baseline
PD	Pharmacodynamic
PFS	Pre-filled syringe
PGA	Physician' Global Assessment
PK	Pharmacokinetic
PPP	Palmoplantar pustulosis
PPSI	Palmoplantar PsO Area and Severity Index
PPPASI	Palmoplantar Pustular PsO Area Severity Index
PPPASI-50	Proportion of patients achieving an improvement from baseline of ≥ 50%
PsA	Psoriatic Arthritis
PSSD	PsO Symptom and Sign Diary
PSSI	PsO 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
SC	Subcutaneous

Abbreviation	Meaning
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

I. Introduction to product submission

Submission details

Type of submission:	New Biological Entity
Decision:	Approved
Date of decision:	8 March 2018
Date of entry onto ARTG:	15 March 2018
ARTG numbers:	286019, 286020
Active ingredient:	Guselkumab
Product name:	Tremfya/Janssen Guselkumab
Sponsor's name and address:	Janssen-Cilag Pty Ltd 1-5 Khartoum Rd Macquarie Park NSW 2113
Dose form:	Solution for Injection
Strength:	100 mg
Container:	Single use 1 mL pre-filled (glass) syringe (PFS) in carton
Pack size:	Pack of 1 pre-filled syringe (PFS)
Approved therapeutic use:	*Tremfya is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy*.
Route of administration:	Subcutaneous (SC)
Dosage:	The recommended dose is 100 mg to be given as subcutaneous injection at week 0, week 4 and every 8 weeks thereafter.

Product background

This AusPAR describes the application by the sponsor to register a new biological entity, guselkumab, as Tremfya/Janssen Guselkumab, a solution for injection for the proposed indication of:

> *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.*

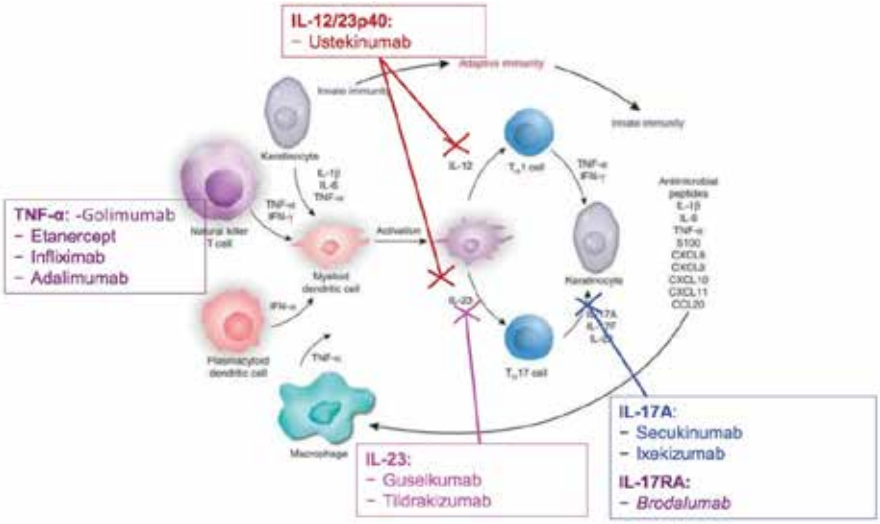
Skin psoriasis (PsO) is a chronic, immunologically mediated, inflammatory condition that affects 2 to 3% of the population. Approximately 30% of patients with skin PsO develop psoriatic arthritis and 85% to 90% of patients have chronic plaque PsO. Some 10% of these have severe disease. Its onset is typically between the ages of 30 and 55 years and it affects men and women equally. PsO 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 PsO. 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 and are often on visible skin. 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.

In addition to this PsO indication, guselkumab is also being investigated for safety and efficacy in the treatment of rheumatoid arthritis and palmoplantar pustulosis.

Guselkumab is a human immunoglobulin G1 lambda (IgG1 lambda) monoclonal antibody (mAb) that binds selectively to the IL-23 protein with high specificity and affinity, resulting in the inhibition of the biological effects of IL-23. A variety of biologic systemic therapies have been developed and approved for the treatment of PsO, including anti-tumour necrosis factor alpha (TNFα) agents, an IL-12/23 antagonist and more recently, IL-17A inhibitors. Figure 1 describes the cytokine targeting of biologicals for plaque PsO.

Figure 1: Cytokine targeting of biologics for plaque PsO



Modified from www.accessdata.fda.gov

The pro-inflammatory cytokine interleukin IL-23 and its resulting T helper 17 (Th17) pathway play perhaps a more important role in mediating PsO than IL-12. IL-23 induces differentiation and maintenance of Th17 cells, which produce the effector cytokines IL-17, IL-22 and 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 ribonucleic acid (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 PsO 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.

Current treatment options

The traditional paradigm for the treatment of PsO was a stepwise approach to treatment starting with topical agents, followed by phototherapy and 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 treatments such as potent topical corticosteroids to reduce scaling. If potent topical corticosteroids are insufficient, calcipotriol with betamethasone dipropionate is indicated for chronic stable plaque type PsO 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 psoralen plus ultraviolet therapy (PUVA) therapy are widely used for treatment of PsO. 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 (UV) light burns. Narrow band UV B (UVB) is also used and has similar efficacy.

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 and methotrexate) and biologics, including TNF-α antagonists (adalimumab, etanercept and infliximab), anti-IL-17A (secukinumab) and anti-IL-12/IL-23 (ustekinumab) have been approved for the treatment of PsO. Many of these treatments are associated with certain safety concerns (including, organ toxicity, and infections including tuberculosis, malignancies including lymphoma, immunogenicity and demyelinating neurologic events) which limits their value in the long term management of PsO. Few achieve the goal of clear/almost clear skin for a majority of patients.

Historically, approved SC biologic agents have shown maximum response rates of 70% to 80% of subjects achieving ≥ 75% improvement in the PsO 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 also have significant limitations. Many patients with PsO 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.

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 single packs (1 syringe packs).

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

Regulatory status

This is an application for registration of a new biological entity in Australia.

The tradename Tremfya is proposed for this product. At the time the TGA approved this application, the tradename had also received approval in the US, Canada and European Union (EU).

Applications to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the indication of treatment of moderate to severe plaque PsO were submitted in November 2016. The FDA approved Tremfya for the treatment of adults with moderate to severe plaque PsO on 13 July 2017, and EU approval was granted on 10 November 2017.

At the time the TGA considered this application, similar applications were under consideration in Argentina, Chile, Columbia, Dominican Republic, Hong Kong, Israel, Japan, Korea, Peru, Singapore, South Africa, Switzerland and Taiwan.

Secukinumab, an IL-17A inhibitor, was approved for the treatment of plaque PsO in January 2015 and placed on the Australian Register of Therapeutic Goods (ARTG) in August 2015. Ustekinumab (IL-12/ IL-23 inhibitor) was approved in Australia in August 2010. The TNFα antagonists approved for the treatment of PsO in Australia are infliximab, adalimumab and etanercept.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR and Attachment 2.

Description	Date
Submission dossier accepted and first round evaluation commenced	31 March 2017
First round evaluation completed	31 August 2017
Sponsor provides responses on questions raised in first round evaluation	2 November 2017

Description	Date
Second round evaluation completed	4 January 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 January 2018
Sponsor's pre-Advisory Committee response	16 January 2018
Advisory Committee meeting	1-2 February 2018
Registration decision (Outcome)	8 March 2018
Completion of administrative activities and registration on ARTG	15 March 2018
Number of working days from submission dossier acceptance to registration decision*	194

* Statutory time frame for a standard application is 255 working days

Evaluations included under *Quality findings* and *Nonclinical findings* incorporate both the first and second round evaluations.

III. Quality findings

Introduction

Tremfya is a solution for injection to be administered SC. The product will be supplied in a single use 1 mL PFS containing 100 mg guselkumab.

Drug substance (active ingredient)

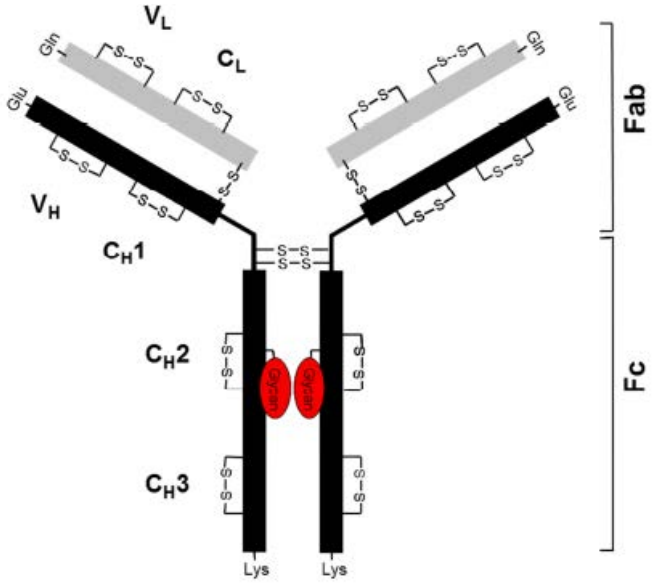
General properties

The recommended International Proprietary Name (INN) is guselkumab (CAS 1350289-85-8). The chemical name of the drug product is Immunoglobulin G1-lambda2, anti-[*Homo sapiens* IL-23 (interleukin 23, IL-23)].

The intact molecule contains 2 identical heavy chains (HC) of 447 amino acids (approximately 49 kilo Daltons (kDa) each) and 2 identical light chains (LC) of 217 amino acids (approximate 23 kDa each). The 4 chains are linked together by covalent disulphide bonds and non-covalent protein-protein interactions.

The structure of guselkumab is shown schematically in Figure 2 below.

Figure 2: Structural features of guselkumab



The HCs (black) and LCs (gray) are shown with intra- and inter-chain disulphides. The Fab and Fc regions of the IgG, the amino- and carboxy-terminal residues of heavy chain and the general location of N-linked glycosylation sites in the Fc region are noted.

As illustrated in Figure 3, IL-23 mediates cellular activity through sequential binding to 2 receptor chains expressed as the IL-12Rβ1/IL-23R receptor complex on the surface of T cells and natural killer (NK) cells. Guselkumab binds to the p19 subunit of human IL-23, blocks binding to the IL-23R and inhibits IL-23-mediated signalling. Guselkumab specifically inhibits IL-23-mediated signalling and does not impact IL-12-mediated signalling.

Figure 3: Illustration of IL-23 and the IL-23 receptor complex and the mechanism of action of guselkumab

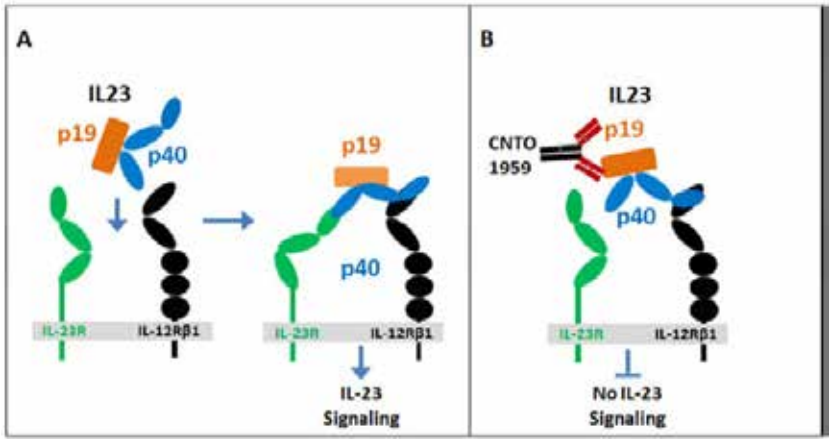


Figure 3A (left): Heterodimeric cytokine IL-23 (p19 + p40) is shown binding to the IL-12Rβ1/IL-23R two chain receptor complex expressed on the surface of NK or T cells. The IL-23 receptor complex is comprised of IL-12Rβ1 partnered with the signaling chain IL-23R. Figure 3B (right): Guselkumab is shown with the Fab fragment in red and Fc fragments in solid black. Guselkumab binds to human IL-23 via the p19 subunit of IL-23 and prevents IL-23-IL-23R complex formation and subsequent intracellular signaling of the partner receptor chains (Adapted from Floss et al., 2015). CNTO 1959 = guselkumab; Fab = fragment antigen binding; Fc = fragment crystallisable; IL-12Rβ1 = interleukin-12 receptor beta-1; IL-23 = interleukin-23; IL-23R = interleukin-23 receptor; NK = natural killer

Source and generation of the cell substrate

Guselkumab drug substance (DS) is manufactured in an 11 stage process consisting of fed batch cell culture followed by purification and formulation.

The current cell line is a CHO (Chinese hamster ovary) cell line transfected with an expression construct. The CHO cell line was used to produce the drug product (DP) for all clinical trials and will be used to produce commercial product.

The sponsor states that the characterisation of the expression constructs used for the production of guselkumab by the cell line was performed according to the International Conference on Harmonisation (ICH) Q5B: *Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of rDNA Derived Protein Products.*

Preparation and storage of master cell banks and working cell banks

The sponsor states that to be consistent with the ICH guideline *Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* (Q5D) recommendations.

Testing performed for the MCB and WCBs

Appropriate tests were chosen (as per ICH guidelines Q5A and Q5D) and designed to detect adventitious and endogenous viruses based on the lineage of the cell line, exposure to raw materials and humans during early cell line development, and exposure to humans during Good Manufacturing Practices (GMP) cell banking operations.

The sponsor has provided acceptable in house methods and acceptance criteria for the non-compendial raw materials.

Elucidation of structure and other characteristics

The protein structure of guselkumab was fully characterised The analytical characterisation included a comprehensive analysis of the biochemical, biophysical and biological properties of guselkumab. The batch used was representative of the Phase III process and used for clinical studies.

These tests are in accordance with the European Union (EU) guideline *EMEA/CHMP/BWP/157653/2007 Guidelines on Development, Characterisation and Specifications for Monoclonal Antibodies and Related Products.*

Control of impurities

A combination of manufacturing and reduced scale data demonstrated the consistent and robust removal of process and product related impurities. Tests for DNA and residual Protein A were routinely performed during commercial-scale batch manufacture and were consistently demonstrated to be reduced to safe levels in the DS.

Viral clearance studies demonstrated robust removal and inactivation of model adventitious and endogenous viruses.

Consistency of DS

The validation batches demonstrated consistency of quality attributes and the ability of the DS manufacturing process to produce DS batches that meet release specifications.

Control of DS

Aside from the compendia tests, the sponsor states that validation of the identity were performed in accordance with the ICH Tripartite guideline Q2(R1) *Validation of Analytical Procedures: Text and Methodology.*

Drug product

The 100 mg/syringe drug product (DP) is supplied as a sterile solution in a single-use, PFS which is assembled into an UltraSafe Plus passive needle guard.

The drug product contains the active ingredient as well as the excipients listed in Table 1 below.

Table 1: Ingredients included in Tremfya

Active ingredient	Excipients
Guselkumab	Sucrose
	Histidine
	Histidine monohydrochloride monohydrate
	Polysorbate 80 (PS 80)
	Water for injections

Recommended shelf-life

24 months stored at 2 to 8 degrees Celsius and protected from light. There are no temperature excursions or in use conditions requested.

Formulation development

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 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 PS 80 for the PFS formulation and slight differences in histidine concentration. The sponsor states these changes would not be expected to adversely impact the safety and efficacy of guselkumab.

Consistency of DP

The consistency of DP was examined by comparing results for 15 release and characterization tests from the 100 mg/syringe DP process validation batches. DP produced in the validation batches had consistent biochemical, biological, biophysical, and syringe functionality properties.

DP Specifications

All excipients in the drug product conform to US Pharmacopeia (USP/NF), European Pharmacopeia (Ph. Eur.) and/or Japanese Pharmacopeia (JP) compendia specifications.

No excipients of human or animal origin are used in the drug product.

DP Batch analyses

Release tests, acceptance criteria, and test results for PFS and product assembled into the UltraSafe Plus Passive Needle Guard (PFS-U) were included.

All of the batches (both Phase III process and process validation) are representative of the commercial manufacturing and assembly process.

All results met the acceptance criteria for proposed commercial specifications.

DP stability summary and conclusion

The sponsor proposed a DP shelf life of 24 months when stored at the recommended temperature of 2 to 8°C and protected from light. The shelf life claim is based on an ongoing stability program for Phase III process and process validation (PV) batches of DP. The sponsor states that the stability program follows ICH guidelines for stability of drug product; ICH Q1A (R2): *Stability Testing of New Drug Substances and Products*, ICH Q5C: *Stability Testing of Biotechnological/Biological Products)*..

The requested shelf life of 24 months when stored at 2 to 8°C protected from light is acceptable, provided the TGA requested data for ongoing studies is provided.

Post approval stability protocol and stability commitment

The sponsor commits to continuing the stability studies on various process batches through 36 months at 2 to 8°C in order to confirm the stability profiles. In addition, the stability program will include the accelerated (25°C/60% RH) and stressed (40°C/75% RH) storage conditions.

Evaluator's comment/assessment and conclusions

The proposed shelf life is 24 months however, the sponsor has only supplied 12 months data after return to shelf life. Furthermore the temperature cycling study was performed after 3 months storage at 2 to 8°C not at the beginning of shelf life as per relevant TGA Guideline.[1]

Based on the information provided, the temperature excursions recommended to the Delegate will be:

a. 24 months stored at 2 to 8°C and protected from light, with no allowable temperature excursions

b. If any Tremfya batches are subjected to an excursion within -0.5°C to 1.0°C for 10 days and/or +9°C to +25°C for 10 days, the sponsor must reduce the shelf life to 12 months.

The sponsor has acknowledged that at the completion of the temperature cycling studies, a new application will be required to extend the shelf life/approved excursions beyond that approved in this application. This response is acceptable.

[1] 14.4 Stability testing for prescription medicines Biological medicines: specific requirements

IV. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was generally adequate and consistent with the appropriate guideline.[2] Pivotal safety studies were conducted under Good Laboratory Practice (GLP) conditions.

Guselkumab belongs to a similar pharmacological class as ustekinumab (Stelara), approved by the TGA for similar indications as sought here. Ustekinumab is a monoclonal antibody against IL-12/IL-23.

Pharmacology

Primary pharmacology

Mechanism of action

PsO is a chronic skin disease caused by the excessive secretion of inflammatory cytokines.[3] IL-23, levels of which are elevated in the skin of patients with PsO, induces the differentiation and expansion of naïve CD4+ T cells into helper Th17/ThIL-17 that produce IL-17, IL-17F, IL6 and TNFα.[4] Th17/ThIL-17 cells are considered to play a role in the development of inflammatory conditions such as PsO. Inhibition of IL-23 by guselkumab is expected to ameliorate the effects of PsO in affected patients.

In vitro

IL-23 is a member of the IL-12 family of heterodimeric cytokines. IL-23 shares the p40 subunit with IL-12. However, in contrast to IL-12, which is comprised of a p40/p35 heterodimer, the p40 subunit is paired with a p19 subunit to form IL-23.[5] Guselkumab bound to the p19 subunit of human IL-23 with picomolar affinity (3.3 pM). Guselkumab did not bind to IL-23 when it was bound to the IL-23 receptor on cells. In an IL-23 responsive NK cell line, guselkumab inhibited STAT3 phosphorylation (part of the IL-23 signalling pathway) and inhibited IL10 production induced by human IL-23 (50% inhibitory concentration (IC_{50}) values 0.2 nM and 1.4 nM, respectively). Guselkumab also inhibited human IL-23 induced IL-17A and IL-17F production in mouse splenocytes (IC_{50} 16 to 80 pM) and anti-CD3/anti-CD28 activated T cells. The anti-IL-23 potency (in terms of cytokine release) was modestly higher for guselkumab (2 to 14 fold, depending on the in vitro assay) when compared to ustekinumab.

Guselkumab did not bind to human IL-12 or IL-12/23p40 and had no significant inhibitory activity on IL-12-mediated interferon gamma (IFNγ) production in a human NK cell line, suggesting guselkumab is an IL-23-specific antibody with a slightly different mode of action to ustekinumab.

Guselkumab had minimal inhibitory activity on mouse and rat IL-23 and only partial inhibitory activity on dog IL-23 suggesting species typically used in toxicity studies are not pharmacologically-responsive to guselkumab. Complete inhibition (with similar potency to that seen on human IL-23) was observed on guinea pig and cynomolgus monkey IL-23

[2] ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
[3] Wasilewska, A. *et al.* (2016) interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. *Adv. Dermatol. Allergol.* **XXXIII:** 247-252.
[4] Iwakura, Y. & H. Ishigame (2006). The IL-23/IL-17 axis in inflammation. J. Clin. Invest. 116: 1218-1222.
[5] Oppmann, B. *et al.* (2000) Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as wekk as distinct from IL-12. *Immunity* 13: 715-725.

(based on receptor binding and cytokine release assays); suggesting these species are suitable animal models to assess the toxicity of guselkumab from a pharmacological perspective.

In vivo

Studies to assess the in vivo efficacy of guselkumab were limited. In mice, guselkumab (at 0.4 mg/kg intraperitoneally (IP)) had some inhibitory effect on human IL-23-induced cytokine release, specifically IL1α and Granulocyte-colony stimulating factor (G-CSF). Exposures at this level were approximately 2.5 fold the anticipated minimum drug concentration (C_{trough}) levels in patients. As the elevation of IL-17A was small in mice treated with human IL-23, an assessment on the effect of IL-17A production could not be made. Overall, there was no compelling in vivo evidence in the nonclinical data to support the indication and efficacy will need to rely solely on clinical data.

Secondary pharmacodynamics and safety pharmacology

Guselkumab did not demonstrate complement dependent cytotoxicity (CDC) in an in vitro bioassay. As guselkumab does not bind to IL-23 bound to cells, guselkumab is not expected to induce antibody dependent cellular cytotoxicity (ADCC).

Specialised safety pharmacology studies assessed effects on the cardiovascular system in monkeys. Effects on the respiratory and central nervous system were assessed in repeat-dose toxicity studies in monkeys (in accordance with ICH S6[R1]).[6] No electrocardiogram (ECG) abnormalities were seen in monkeys treated with 50 mg/kg IV guselkumab (exposure ratio based on the peak plasma concentration (C_{max}) (ERC_{max}) was 168).[7] There were no overt signs of effects on the respiratory or central nervous system in monkeys following a 50 mg/kg IV dose (ERC_{max} 174). No adverse effects on the cardiovascular, respiratory and central nervous systems are predicted during clinical use.

Pharmacokinetics

The pharmacokinetic (PK) profile of guselkumab was consistent with the class of monoclonal antibodies. Following SC dosing, the rate of absorption was slow with peak serum levels reached 1 to 6 days following dosing in guinea pigs, monkeys and humans. This is typical for a SC administered antibody as systemic absorption via this route occurs primarily through the lymphatic system.[8] The SC bioavailability was high to very high in monkeys (72 to 101%) and moderate in humans (approximately 50%). The volume of distribution was less than total body water in monkeys and humans (98 to 175 mL/kg in monkeys and 270 mL/kg in humans), suggesting limited extravascular distribution. The clearance was low (7.7 to 16 mL/kg/day in monkeys and approximately10 mL/kg/day in humans) with very long elimination half-lives observed in guinea pigs (5 to 6 days), monkeys (7 to 12 days) and humans (18 days).

No distribution, metabolism or excretion studies were submitted (in accordance with ICH S6[R1]).[6]

Overall the pharmacokinetic profile of guselkumab in cynomolgus monkeys support the use of this species in the toxicity studies, taking into account the shorter half-life in this species compared to human subjects.

[6] ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.
[7] Estimated based on a Cmax of 1363 µg/mL for a 50 mg/kg IV dose in monkeys from Study CP2008T-034.
[8] Lobo, E.D., R.J. Hansen and J.P. Balthasar (2004). Antibody pharmacokinetics and pharmacodynamics. J. Pharm. Sci. 93: 2645-2668.

Pharmacokinetic drug interactions

The sponsor provided an in vitro study to evaluate the potential for IL-12 and IL-23 (separately and in combination) to alter the functional activity and mRNA expression of various cytochrome P450 (CYP450) isoforms (CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4). Similar to what was stated in a previous evaluation for ustekinumab:

The submitted study clearly demonstrated that IL-12 and IL-23, either alone or in combination, had no effect on the regulation or activity of CYP450 enzymes in vitro (or in isolated hepatocytes). However, this study does not address the effect of guselkumab on CYP450 activity or expression; and it provides no information on the potential indirect effects of IL-23 on CYP450 levels/activity. IL-23 stimulates the production of other inflammatory cytokines, including IL6 and TNFα.[9] As guselkumab inhibits IL-23 activity (but not levels), it is also expected that there would be a subsequent decrease in both IL6 and TNFα levels. As both IL6 and TNFα affect CYP450 activity and/or expression (as shown by the submitted study), guselkumab may indirectly have an effect on the plasma kinetics of co administered CYP450 substrates. Therefore, the submitted study with IL-23 in isolated hepatocytes cannot be considered representative of the potential effect of guselkumab in vivo and the proposed text relating to dose adjustments in patients should not be included in the Product Information document. Furthermore, the Stelara Product Information (PI) document should be amended to remove any mention of this study as it is potentially misleading. This was the original recommendation when the study was evaluated in 2011.

Toxicology

Acute toxicity

One non-GLP single dose toxicity study was submitted. Post-mortem analyses were not performed so no target organs for toxicity could be identified. The maximum non-lethal dose was 50 mg/kg IV and SC (ERC_{max} at least 36), suggesting a low order of toxicity in this species.

Repeat-dose toxicity

A repeat-dose toxicity study was conducted in cynomolgus monkeys (up to 24 weeks). This species is pharmacologically responsive to guselkumab and is considered an appropriate species from a pharmacological perspective. As tissue cross-reactivity studies demonstrated a similar pattern in monkeys and humans and given the serum kinetic profile of guselkumab, monkeys are considered an appropriate species from a pharmacokinetic perspective. A 3 week tolerability study was conducted in guinea pigs but as this is a non-standard species for toxicity assessments the full suite of analyses was not performed in this study and this study is excluded from the discussion below. The use of a single species is considered acceptable given guselkumab is not pharmacologically active in other standard species used in toxicity studies.[6] The duration of the pivotal study and the group sizes are both considered adequate for a biotechnology product according to the appropriate guideline. Overall, the conduct of the study is considered adequate to have revealed the toxicity of guselkumab.

Relative exposure

As monkeys were dosed weekly (compared to the maintenance 8 weekly clinical dose), area under the concentration versus time curve from Week 0 to Week 1 ($AUC_{0\text{-}1w}$) values in

[9] Koutruba, N., J. Emer and M. Lebwohl (2010). Review of ustekinumab, an interleukin-12 and interleukin-23 inhibitor used for the treatment of plaque psoriasis. Ther. Clin. Risk Management 6: 123-141.

monkeys were multiplied by 8 to achieve an AUC over 8 weeks ($AUC_{0\text{-}8wks}$) for exposure comparisons. Relative exposures were very high in treated monkeys, as shown below in Table 2.

Table 2: Relative exposure in the pivotal repeat-dose toxicity study

Species	Study duration [Study no.]	Dose mg/kg/ week SC	AUC_{0-1wk}^ µg·day/ mL	AUC_{0-8wks} µg·day/ mL	Exposure ratio#
Monkey (cynomolgus)	24 weeks [Study T-2008-007]	10	951	7608	31
		50	5412	43296	179
Human	Steady state Population PK Report Weight < 90kg	[100 mg]	–	242	–

= animal: human plasma $AUC_{0\text{-}8wks}$; ^ = data are for the sexes combined at the last sampling occasion

Major toxicities

No drug-related toxicities were observed in the pivotal study. This is consistent with findings in IL-23 knockout mice and the toxicity profile of the related compound, ustekinumab.[10]

Genotoxicity

No genotoxicity studies were conducted. Given the protein nature of the drug[6] this is considered acceptable.

Carcinogenicity

No carcinogenicity studies were submitted. As guselkumab is not pharmacologically-active in species typically used for carcinogenicity studies, and such studies are not normally expected for a drug of this chemical class.[11] The absence of such studies is acceptable. However, guselkumab is an immunosuppressive agent and immunosuppressants have been reported to increase the risk of malignancies. It is noted that the PI document for the related compound, ustekinumab (Stelara) contains warnings regarding the potential for an increased risk of malignancies. The sponsor conducted a risk assessment on the carcinogenic potential of guselkumab. Published data regarding the carcinogenic potential of IL-23 blockade (for example by guselkumab) is inconclusive. Both pro- and anti-carcinogenic actions were indicated. While there were no overt signs of pre-neoplastic lesions in the 24 week repeat-dose toxicity study in cynomolgus monkeys, the study is rather short for clear signs of carcinogenicity to be seen. Furthermore, group sizes were rather small (n=3/sex for the main part of the study), thus limiting the power of the study to detect potential carcinogenic effects. At this stage the carcinogenic potential of guselkumab is inconclusive. Therefore, it is considered appropriate that malignancy has been identified as an important potential risk in the Nonclinical Safety Specification of Risk Management Plan (RMP). Appropriate warnings could be warranted in the Tremfya PI document (similar to those seen in the Stelara PI) if any clinical signals are apparent.

[10] Ghilardi, N. et al. (2004) Compromised humoral and delayed-type hypersensitivity responses in IL23-deficient mice. J. Immunol. 172: 2827-2833.
[11] ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Reproductive toxicity

Reproductive toxicity studies consisted of fertility studies in guinea pigs and an enhanced pre-/postnatal (ePPND) study in cynomolgus monkeys. While the guinea pig is not a traditional animal model to assess fertility, guselkumab is pharmacologically active in this species (unlike mice and rats which are typically used for these studies) and protocols for the assessment of fertility parameters have been devised.[12] However, it should be noted that the historical control database for this model is limited. Dosing was more frequent in animals (twice weekly in guinea pigs and weekly in monkeys) as compared to the proposed human dose. This is considered acceptable given the shorter half-life of the drug in animals as compared to humans. The clinical route was used in all studies.

Male and female fertility were assessed in separate studies. Adequate animal numbers were used in the pivotal studies. Dosing in male guinea pigs commenced approximately7 weeks prior to mating, which was stated by the sponsor to cover a full spermatogenesis cycle in this species (approximately38 days).[13] Dosing of female guinea pigs commenced 21 days prior to mating and ceased on gestation day (GD) 7 (after implantation which occurs on GD 6 in this species);[14] though given the half-life of guselkumab (5 to 6 days), pregnant females would still be exposed during some of the post implantation period. The dosing periods are considered appropriate for this species.

The design of the ePPND study was consistent with the guideline and published literature.[15,16] Potential embryofetal development effects were determined by assessment of infants at birth and during the 6 month post-partum period as recommended by the relevant guideline. Dosing in the ePPND study commenced on GD 20 to 22 (the beginning of the organogenesis period) and continued until parturition. A sufficient number of infants were available for postnatal evaluations (11 to 15). Appropriate examinations were performed on infants to assess potential adverse effects.

Overall, the chosen species, study designs and doses used (see *Relative exposure* below) are considered acceptable.

Relative exposure

Exposure ratios were determined based on both AUC and C_{max}, as adverse embryofetal development effects can be associated with exposures on a single day. Exposure ratios were very large, as shown in Table 3, below.

Table 3: Relative exposure in reproductive toxicity studies

Species	Study	Dose mg/ kg SC	AUC# µg·day /mL	AUC_{0-8wks} µg·day /mL	C_{max} µg/ mL	Exposure ratio based on	
						AUC	C_{max}
Guinea pig Hartley	Male fertility	25	640	10240	243	42	30
		100	2639	42224	1004	174	124

[12] Rocca, M.S. & N.G. Wehner. (2009) The guinea pig as an animal model for developmental and reproductive toxicology studies. *Birth Defects Res (Part B)* **86:** 92-97.
[13] Russell, LD. *et al.* (1990). Histological and histopathological evaluation of the testes. 1st Ed. St Louis, MO: Cache River Press. Cited in Study T-2011-031.
[14] Ecobichon, D.J. Reproductive Toxicology. In: Derelanko, M.J. & M.A. Hollinger (ed) CRC Handbook of Toxicology. CRC Press, Inc (1995).
[15] ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
[16] Weinbauer, G.F. et al. (2011). The enhanced pre- and postnatal study for nonhuman primates: update and perspectives. Birth Defects Res (Part C) 93: 324-333.

Species	Study	Dose mg/	AUC# µg·day /mL	AUC0-8wks	Cmax µg/ mL	Exposure ratio based on	
		100	2734	43744	1009	181	125
	Female fertility	25	327	5232	132	22	16
		100	1273	20368	510	84	63
Monkey Cynomolgus	ePPND	10	896	7168	153	30	19
		50	3930	31440	733	130	90
Human	[100 mg]	–	242*	8.1**	–		

guinea pig, $AUC_{0-4days}$, multiplied by 16 to achieve AUC_{0-8wks}; monkey, $AUC_{0-7days}$, multiplied by 8 to achieve AUC_{0-8wk}

No adverse effects on male or female fertility were seen in treated guinea pigs. While an apparent increase in post implantation loss was observed in one study when treated males (at 100 mg/kg) were mated with untreated females (when compared with the concurrent negative control), the findings were not reproduced in two additional studies (at the same dose and similar AUC exposure level), suggesting the finding is incidental. As stated earlier, the historical control dataset is limited. The lack of an effect on fertility is consistent with findings in IL-23 deficient mice.[17]

Minimal placental transfer of guselkumab occurred in guinea pigs when it was administrated during early gestation (<GD 30). However, this is misleading as transplacental transfer of IgG antibodies primarily occurs during late gestation (after GD 35) in this species, similar to what occurs in primates.[18,19] Consistent with this, serum levels of guselkumab were 71 to 83% maternal levels in infant monkeys likely as a result of placental transfer during gestation (milk levels were negligible). The results indicate that placental transfer of guselkumab would likely occur in pregnant women. While no adverse embryofetal development effects were seen in monkeys (consistent with IL-23 knockout mice), the presence of guselkumab in the serum of infants at appreciable levels, indicates the drug could have pharmacological activity in the neonate until serum levels are sufficiently reduced. Therefore, given that exposure during human pregnancy (in terms of the risk management plan (RMP)) is missing information, the potential immunosuppressive action of guselkumab on neonates should be monitored as part of the pharmacovigilance plan.

No adverse effects on postnatal development were seen in monkeys following maternal exposure. Minimal excretion of guselkumab into milk was seen in monkeys, suggesting infant exposure via breast-feeding is expected to be extremely low.

[17] Ghilardi, N. et al. (2004). Compromised humoral and delayed-type hypersensitivity responses in IL23-deficient mice. J. Immunol. 172: 2827-2833.
[18]Struble, E.B. et al. (2012). Human antibodies can cross guinea pig placenta and bind its neonatal Fc receptor: implications for studying immune prophylaxis and therapy during pregnancy. Clin. Develop. Immunol. Doi:10.1155/2012/538701.
[19] Leissring, J.C. & J.W. Anderson (1961). The transfer of serum proteins from mother to young in the guinea pig. I. prenatal rates and routes. Am. J. Anatomy109: 149-155.

Pregnancy classification

The sponsor has proposed Pregnancy Category B1;[20] which is the same as ustekinumab and is acceptable.

Local tolerance

Injection site reactions were examined in the repeat-dose toxicity study in cynomolgus monkeys. The clinical formulation was used in the study. There were no notable test item-related findings.

Immunotoxicity

IL-23 has been shown to have important roles on the activity of memory T cells and macrophages, suggesting a possible role in immune responses.[21,22] In monkeys treated with ≤ 50 mg/kg/week SC guselkumab, there was no effect on the T cell-dependent antibody response to keyhole limpet hemocyanin (KLH) (noting different IgG isotypes were not examined and immune-phenotyping was not performed in this study). The sponsor conducted a literature review of the potential effect of guselkumab on immunocompetence in patients. The following points were made:

- In animal disease models, IL-23 plays a role in immunity to pathogens, including Klebsiella pneumonia, Cryptococcus neoformans, Candida albicans, Listeria monocytogenes, Helicobacter pylori, Pneumocystis carinii, and influenza A and Staphylococcus aureus co-infection.
- Individuals (human) deficient in both IL-12 and IL-23 demonstrate susceptibility to certain infections including: weakly virulent mycobacterial infections, Bacille Calmette-Guérin (BCG), environmental Mycobacteria species, recurring Salmonella species infections, recurrent or systemic Candida, Paracoccidioides, Histoplasma, and Toxoplasma gondii infections.

Based on the data above, serious infections should be considered a potential risk with guselkumab.

Delayed type hypersensitivity reactions were impaired in an IL-23-knockout mouse model.[23] These data suggest guselkumab may affect other immune-associated responses.

Anti-drug antibodies (ADAs) were detected in one treated female monkey in the ePPND study. The presence of ADAs correlated with an accelerated decrease in serum guselkumab levels. Therefore, ADAs in patients may result in reduced guselkumab exposures and possibly reduced efficacy.

Paediatric use

Guselkumab is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

[20] Australian Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have not shown evidence of an increased occurrence of fetal damage.
[21] Cua, D.J. et al. (2003) Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature421: 744-748.
[22] Ghilardi, N. *et al.* (2004) Compromised humoral and delayed-type hypersensitivity responses in IL-23-deficient mice. *J. Immunol.* **172:** 2827-2833.
[23] Ghilardi, N. et al. (2004) Compromised humoral and delayed-type hypersensitivity responses in IL-23-deficient mice. J. Immunol. 172: 2827-2833.

Nonclinical summary and conclusions

- The overall quality of the nonclinical dossier was generally adequate, consistent with the appropriate guideline. Pivotal safety studies were conducted under GLP conditions.
- In vitro, guselkumab bound to the p19 subunit of human IL-23 with picomolar affinity, inhibited IL-23 receptor signalling and IL-23-induced cytokine production in IL-23-responsive cells. Guselkumab did not bind to IL-23 when it was bound to the IL-23 receptor on cells. Guselkumab did not bind to human IL-12 or IL-12/23p40 and had no significant inhibitory activity on IL-12-mediated IFNγ production in a human NK cell line, suggesting guselkumab is an IL-23-specific antibody with a slightly different mode of action to ustekinumab. Guselkumab had similar pharmacological activity on guinea pig and cynomolgus monkey IL-23 to the human IL-23.
- There was no compelling in vivo nonclinical evidence to support the proposed indication.
- Guselkumab is not expected to induce complement dependent cytotoxicity or antibody dependent cellular cytotoxicity. Based on safety studies in cynomolgus monkeys, no adverse effects on the cardiovascular, respiratory and central nervous systems are predicted during clinical use.
- The pharmacokinetics of guselkumab in mice and human subjects was generally consistent with the protein nature of the drug: long half-lives and limited extravascular distribution.
- A repeat-dose toxicity study in cynomolgus monkeys (up to 24 weeks) at very high exposures revealed no drug-related toxicities.
- No genotoxicity studies were conducted. Given the protein nature of the drug this is considered acceptable.
- No carcinogenicity studies were submitted. A literature review indicated the carcinogenic potential of guselkumab as inconclusive.
- Reproductive toxicity studies consisted of fertility studies in guinea pigs and an enhanced pre-/postnatal (ePPND) study in cynomolgus monkeys. No adverse effects on male or female fertility were seen in treated guinea pigs. No adverse embryofetal or postnatal effects were evident in monkeys. However, serum levels of guselkumab were 71 to 83% maternal levels in infant monkeys likely as a result of placental transfer during gestation. Therefore, the drug is likely to have significant pharmacological action in the neonate until serum levels are sufficiently reduced. Of particular concern is the immunosuppressive action of guselkumab, suggesting neonates from mothers who received guselkumab during pregnancy may be more prone to infections.
- There were no notable injection site reactions in monkeys following SC administration.
- Based on the mode of action of guselkumab, patients may be at risk of serious infections.
- The presence of ADAs in a treated monkey correlated with an accelerated decrease in serum guselkumab levels. Therefore, ADAs in patients may result in reduced guselkumab exposures and possibly reduced efficacy.

Nonclinical conclusions and recommendation

- No comment can be made from a nonclinical perspective regarding efficacy for the proposed indication.

- The combined safety studies revealed the following as potential risks in patients:
  - Increased risk of infections
- While no adverse embryofetal development effects were seen in monkeys (consistent with IL-23 knockout mice), the presence of guselkumab in the serum of infants at appreciable levels, indicates the drug could have pharmacological activity in the neonate until serum levels are sufficiently reduced. Therefore, given that exposure during human pregnancy (in terms of the RMP) is missing information, the potential immunosuppressive action of guselkumab on neonates should be monitored as part of the pharmacovigilance plan.
- There are no objections to the registration of Tremfya. Amendments to the draft PI were also recommended but these are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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 PsO, erythrodermic PsO (EP), generalised pustular PsO (GPP), palmoplantar pustulosis (PPP), inflammatory bowel disease (IBD), ankylosing spondylitis and PsA.

Susceptibility to PsO, PsA, and IBD has been shown to be associated with genetic polymorphisms 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 antagonises the activities of both IL-12 and IL-23, guselkumab only antagonises the activity of IL-23 via its p19 subunit. Therefore, guselkumab utilises 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 PsO 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 PsO 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 PsO.

Guidance

This submission was consistent with the pre-submission planning advice given to the sponsor by the TGA. 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.

Contents of the clinical dossier

Scope of the clinical dossier

The pharmacokinetic profiles of guselkumab were assessed in 4 studies:

Study CNTO1959NAP1001

- Phase I, open label, randomised, parallel study to assess the pharmacokinetic comparability of 2 formulations and to evaluate pharmacokinetic comparability of guselkumab delivered by 2 different devices in 141 healthy subjects.

Study CNTO1959NAP1002

- Phase I open label, single dose study to characterise the elimination of guselkumab glycoform variants in 8 healthy subjects.

Study CNTO1959PSO1001

A randomised, double blind, placebo controlled, ascending dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of CNTO 1959 following a single IV or a single SC administration in 47 healthy subjects and 24 subjects with moderate to severe PsO.

Study 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 PsO.

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

Two Phase I studies:

Study CNTO1959PSO1001 (referred to as Study 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 PsO.

Study CNTO1959PSO1002 (referred to as Study 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 PsO.

One Phase II study:

Study CNTO1959PSO2001 (X-PLORE, Study PSO2001)

- A Phase II multicentre, 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 PsO (X-PLORE)

Three Phase III studies:

Study CNTO1959PSO3001 (VOYAGE 1, Study PSO3001)

- A Phase III, multicentre, 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 PsO (VOYAGE-1)

Study CNTO1959PSO3002 (VOYAGE 2, Study PSO3002)

- A Phase III, multicentre, 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 PsO with randomized withdrawal and retreatment.

CNTO1959PSO3003 (NAVIGATE, Study PSO3003)

- A Phase III, multicentre, 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 PsO and an inadequate response to ustekinumab

The safety of guselkumab was evaluated primarily in the PsO population in a total of 1,748 subjects with moderate to severe plaque PsO 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 Harmonisation (ICH) requirements.

In addition to the 6 core PsO studies, 4 completed studies (Studies CNTO1959NAP1001, CNT01959NAP1002, CNTO1275ARA2001, CNTO1959PPP2001), 5 ongoing studies (Studies CNTO1959PSO1003, CNTO1959PSA2001, CNTO1959PPP3001, CNTO1959PSO3004, CNTO1959PSO3005) with guselkumab in other indications (PPP, PsO), 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.

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 PsO was agreed with the US FDA on 21 November 2014.[24]

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.

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

Pharmacokinetics

Studies providing pharmacokinetic data

A list of the studies that provided pharmacokinetic information is given in Table 4 below.

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Synopsis
PK in healthy adults	General PK Single dose	CNTO1959NAP1002	Characterization of the elimination of guselkumab glycoform variants following a single IV administration of guselkumab at 10 mg/kg dose in healthy subjects
		CNTO1959PS01001	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)
	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	CNTO1959PS001	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)
		CNTO1959NPS01002	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, Randomized, Placebo- and Active-Comparator-Controlled, Dose-Ranging Trial to Evaluate CNTO 1959 for the Treatment of Subjects with Moderate to Severe Plaque-type PsO
		CNTO1959PS03001	A Phase III, Multicenter, Randomized, 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 PsO
		CNTO1959PS03002	A Phase III, Multicenter, Randomized, 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 PsO with Randomized Withdrawal and Retreatment
		CNTO1959PS03003	A Phase III, Multicentre, Randomized, 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)

PK topic	Subtopic	Study ID	Synopsis
		CNTO1275AR 2001	Efficacy/safety Ctrough and steady-state PK Immunogenicity of SC: 90 mg ustekinumab, 50 mg guselkumab, 200 mg guselkumab, or placebo in 274 patients with Rheumatoid Arthritis
	Other special populations	CNTO1959PP P2001	Efficacy/safety Ctrough 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 PsO 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)		

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

Preclinical studies showed some staining of striated cardiac or skeletal myocytes but no cross reactivity of guselkumab with non-IL-23 proteins such as human or porcine heavy chain myosin.

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 (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 apparent volume of distribution (Vz/F) and apparent total systemic clearance of drug (CL/F) values were reported in healthy subjects compared with subjects with PsO. T_{max} was similar.

The lyophilised presentation and PFS forms of guselkumab were bioequivalent.

Absorption, distribution, metabolism and excretion in target population

In subjects with PsO, 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 half-life ($t_{1/2}$) values ranged from approximately 14.7 to 17.6 days after a single SC administration in subjects with PsO (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 PsO (PSO1001 Part 2 and PSO1002)

The PK profiles of guselkumab from the Phase II and Phase III PsO studies were adequately described by a one-compartment linear model with first-order absorption and first-order elimination; the population CL/F and 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.

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 PsO 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.

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.

Pharmacodynamics

Studies providing pharmacodynamic data

Studies that provided pharmacodynamic (PD) data are listed in the Table 5 below.

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 PsO and the IL-23/Th17 and Th22 pathways from serum samples from all subjects randomized into the study.	CNTO1959PS02001	*	A Phase II multicentre, randomised, placebo and active comparator controlled, dose-ranging trial to evaluate CNTO 1959 for the treatment of subjects with moderate to severe plaque-type PsO
		CNTO1959PS03001	*	A Phase III, multicentre, randomized, 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 PsO
	Effect of guselkumab on histological analysis and gene expression profiles of skin	CNTO1959PS01001	*	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.

Evaluator's conclusions on pharmacodynamics

- Treatment with guselkumab resulted in improvement in histological characteristics of PsO 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 PsO-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.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

The Phase I study, Study PSO1001, demonstrated proof-of-concept of guselkumab efficacy in PsO 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.

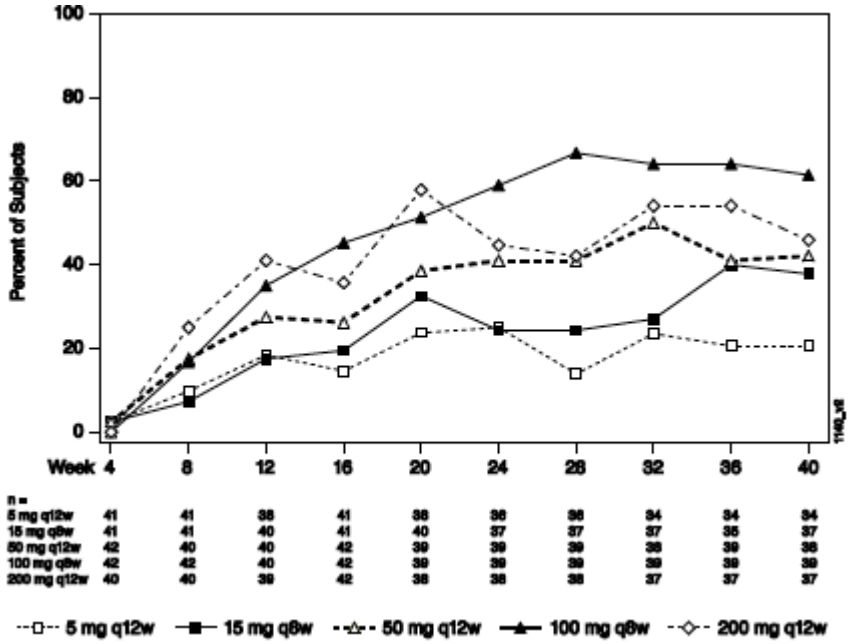
Phase II dose finding studies

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

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 that were not apparent among subjects receiving q8w dosing.

A clear dose-response in efficacy was observed across several clinically important PASI and Investigators Global Assessment (IGA) measures of response from the 5 mg 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 (see Figure 4, below). 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 4: Percentage of subjects achieving a PGA score of cleared (0) through Week 40 by Visit; randomized subjects in Study CNTO1959PSO2001



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 PsO.

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 PsO and used data from Study 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.

Efficacy

Studies providing efficacy data

The overview of the efficacy of guselkumab 100 mg SC in moderate to severe plaque PsO 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 PsO. In addition, efficacy results from Study PSO3003 are presented.

Evaluator's conclusions on 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 PsO. 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 PsO 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 Study 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 Study 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.

Limitations

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

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

No pivotal studies assess safety as the sole primary outcome.

Pivotal and/or main efficacy studies

The safety database from the core PsO Phase II study (Study CNTO1959PSO2001) and 3 Phase III (Studies CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003) clinical studies includes 1,748 subjects with moderate to severe plaque PsO 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 Study PSO3001;[25] and Study PSO3002 and 52 weeks in Study PSO2001.

Other studies

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), Study CNTO1959PPP2001(24 subjects receiving a single 200 mg guselkumab dose), and Study CNTO1959PSO3005 (21 subjects receiving 50 to 100 mg guselkumab q8w for up to 52 weeks).

Patient exposure

Tables 6 and 7 describe patient exposure to guselkumab.

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

Table 6: 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 5 TP 100 mg 5 TP 100 mg 5 TP 300 mg				
PSO1002	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					

Study type/ Indication	Controlled studies				Uncontrolled studies
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	
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 7: Summary of duration of guselkumab exposure and total guselkumab dose through the end of the reporting period; subjects treated with guselkumab in PsO 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.

Adapted from: TSIEXP01B.RTF [CNTO1959\Z_SCS\DBR_2016_06\RE_PSO_BLA\PROD\TSIEXP01B.SAS] 30JUN2016, 10:49

Safety issues with the potential for major regulatory impact

Infections

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 adverse drug reaction (ADR).

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.[26]

Liver function and liver toxicity

Integrated safety analyses

- ALT elevations (reported in 2 subjects) were the only Common Terminology Criteria for Adverse Events (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.

[26]Initially the sponsor also added injection site erythema and injection site pain as ADRs.

Haematology and haematological toxicity

Integrated safety analyses

For each haematology laboratory parameter (haemoglobin, red blood cells (RBC), platelets, white blood cells (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).

Immunogenicity and immunological events

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 PsO studies are as follows:

- A total of 1,730 subjects across the Phase II and III core PsO studies (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 (between-subject comparison), before and after the development of antibodies to guselkumab (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 III core PsO studies had antibodies that were able to neutralise 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).

Postmarketing data

Guselkumab is not currently marketed in any country.[27]

Evaluator's conclusions on safety

Across the single Phase II and three Phase III core PsO studies with guselkumab, a total of 1,748 subjects representative of the target patient group with moderate to severe plaque PsO 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

[27] Since the clinical evaluation report was finalised, Tremfya has been approved and marketed in the USA.

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.[28] Injection site reactions were more frequent compared to placebo but reactions were generally mild and did not necessitate discontinuation. No serious opportunistic infections were reported. No tuberculosis or viral hepatitis reactivation was observed in any PsO trial. 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.

ADRs classified as were gastroenteritis and injection site erythema. Uncommon ADRs included injection site pain.

Serious AEs (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 ADA were detected across the Phase II and III study 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 2 in 29 subjects and maximum Grade 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 ECGs.

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 PsO. Guselkumab 100 mg showed comparable safety to placebo (over 16 weeks) and adalimumab (over 48 weeks) of treatment.

[28] With guselkumab in comparison with adalimumab.

First round benefit-risk assessment

First round assessment of benefits

The benefits of guselkumab in the proposed usage are:

- 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 PsO 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% to 60.9% of the patients treated with guselkumab 100 mg were able to achieve this important goal at Week 24 compared with 39.5 to 41.1% with the active comparator adalimumab.
- Subjects in Study PSO3002 also reported significantly less anxiety and depression (measured by Hospital Anxiety and Depression Scale (HADS)) as well as less impairment and increased productivity at work (as measured by Work Limitation Questionnaire (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 PsO therapy and comorbid psoriatic arthritis).

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 treatment.
- 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.

First round assessment of benefit-risk balance

Although there are many new biologic agents approved for the treatment of PsO, 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 TB, malignancies, including lymphoma, and demyelinating neurologic events) are also known. 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 is a fully human immunoglobulin G1 lambda (IgG1λ) 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 PsO. Guselkumab was evaluated in a large clinical program which complied with CHMP guidelines for evaluation of treatments for PsO. 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 PsO therapy (including subjects with an inadequate response to ustekinumab).

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

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.*

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

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 report.

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 the first round evaluation report.

It is noted that the sponsor had become aware of a minor discrepancy between the number of investigator-reported major adverse cardiovascular events (MACE) in Study CNTO1959PSO2001 (Study PSO2001) and the number reported in the adjudicated data that has been investigated and corrected. MACE was added as an Important Potential Risk in the RMP to align with the EU RMPv1.2.

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.

Second round recommendation regarding authorisation

Approval of Tremfya (guselkumab) is recommended for the following indications:

> *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.*

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation

The sponsor submitted EU-RMP version 1.0 (dated 21 November 2016; data lock point (DLP) 30 June 2016) and Australian Specific Annex (ASA) version 1.0 (dated 6 February2017) in support of this application. In their response, the sponsor has submitted EU-RMP version 1.2 (dated 8 August 2017; DLP 30 June 2016) and ASA version 1.1 (dated 19 October 2017) in support of this application.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (see Table 8) with changes made at the second round (EU-RMP version 1.2).[29]

Table 8: Summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	None	–	–	–	–
Important potential risks	Serious infection	ü	ü	ü	–
	Malignancy	ü	ü	–	–
	Serious hypersensitivity reactions (including anaphylaxis and serum sickness)	ü	ü	ü	–
	Major adverse cardiovascular events (MACE)	ü	ü	–	–
Missing information	Use in paediatric patients	ü	ü	ü	–
	Exposure during pregnancy	ü	ü	ü	–
	Exposure during lactation	ü	ü	ü	–
	Use in patients ≥65 years of age	ü	ü	ü	–
	Use in patients with severe hepatic impairment	ü	–	ü	–
	Use in patients with severe renal impairment	ü	–	ü	–
	Long-term safety beyond 1 year in patients with	ü	ü	–	–

[29] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	moderate to severe plaque psoriasis				

Additional pharmacovigilance activities include:

- Two Phase III, multicentre, randomised, double-blind, placebo and active comparator controlled trials (Studies CNTO1959PSO3001 and CNTO1959PSO3002) to assess long-term safety
- A Paediatric Investigation Plan (PIP) (EMEA-001523-PIP02-14) use in paediatric patients.
- A planned observational study to assess long-term safety.

At second round, the following additional pharmacovigilance activities have been added to assess 'Exposure during pregnancy, 'Long term safety', 'Major adverse cardiovascular events (MACE)' and 'Use in patients ≥ 65 years of age':

- German PsO Registry (PsoBEST Registry)/observational PASS cohort study;

In addition, the following study is an additional pharmacovigilance activity for 'Exposure during pregnancy and lactation'

- Electronic Administrative Health Claims Databases Review/observational PASS cohort study

There are no additional risk minimisation activities and this is considered acceptable.

New and outstanding recommendations

At the second round, there are three new recommendations. The sponsor should address the following comment from the nonclinical evaluator under 1 below. Recommendations 2 and 3 below are considered to be editorial and the changes can be incorporated when the next revised ASA is submitted.

1. The potential immunosuppressive action of guselkumab on neonates should be monitored as part of the pharmacovigilance plan.
2. The additional pharmacovigilance activities listed in the ASA v1.1do not align with EU-RMP for the following safety concerns: Use in paediatric patients, exposure during pregnancy, exposure during lactation, use in patients that are ≥ 65 years of age and long-term safety beyond 1 year in patients with moderate to severe plaque PsO. This should be corrected when the ASA is next updated.
3. The sponsor has committed to collecting demographic information specific to Australia as part of its routine AE reporting and follow-up process. The sponsor should add this commitment to the ASA when next updated, noting that all targeted questionnaire forms except the pregnancy collection form include a tick box to collect Aboriginal/ATSI ethnicity.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement EU-RMP (version 1.2, dated 8 August 2017, data lock point 30 June 2016) with Australian Specific Annex (version 1.1, dated 19 October 2017) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections on quality grounds to the approval of Tremfya Guselkumab 100 mg solution for injection and Janssen Guselkumab (guselkumab) 100 mg solution for injection.

Nonclinical

There are no nonclinical objections to the registration.

The nonclinical evaluator has noted that in vitro, guselkumab bound to the p19 subunit of human IL-23 with picomolar affinity, inhibited IL-23 receptor signalling and IL-23-induced cytokine production in IL-23-responsive cells. Guselkumab did not bind to IL-23 when it was bound to the IL-23 receptor on cells. Guselkumab did not bind to human IL-12 or IL-12/23p40 and had no significant inhibitory activity on IL-12-mediated IFNγ production in a human NK cell line, suggesting guselkumab is an IL-23-specific antibody with a slightly different mode of action to ustekinumab. Guselkumab had similar pharmacological activity on guinea pig and cynomolgus monkey IL-23 to the human IL-23.

Guselkumab is not expected to induce complement dependent cytotoxicity or antibody dependent cellular cytotoxicity. Based on safety studies in cynomolgus monkeys, no adverse effects on the cardiovascular, respiratory and central nervous systems are predicted during clinical use.

No genotoxicity studies were conducted. Given the protein nature of the drug this is considered accept acceptable. No carcinogenicity studies were submitted. A literature review indicated the carcinogenic potential of guselkumab as inconclusive. Serum levels of guselkumab were 71 to 83% maternal levels in infant monkeys likely as a result of placental transfer during gestation, therefore, significant pharmacological action would be expected in the neonate until serum levels are sufficiently reduced. Of particular concern is the immunosuppressive action of guselkumab, suggesting neonates from mothers who received guselkumab during pregnancy may be more prone to infections.

The presence of anti-drug antibodies (ADAs) in a treated monkey correlated with an accelerated decrease in serum guselkumab levels. There were no animal models for efficacy in the management of PsO.

Clinical

Pharmacology

Guselkumab is a human mAb directed against the p19 subunit of IL-23 and thus, specifically targets IL-23. 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 an upstream regulator of IL-17A, a central pro-inflammatory effector

cytokine implicated in PsO 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 T-cells. Therefore, inhibition of IL-23 blocks downstream production of IL-17A and IL-22 by Th17 cells and other cell types.

Analyses of a subset of subjects from Phase II and Phase III PsO studies showed that exposure to guselkumab reduced disease and mechanism related serum biomarkers IL-17A, IL-17F, and IL-22 compared to subjects exposed to placebo. In the dose-finding study, Study CNTO1959PSO2001 samples for assessment of biomarkers were obtained from all 280 subjects at intervals to Week 40 of the study. Baseline levels of serum IL-17A and IL-17F were shown to be higher in the PsO study population than in an independent cohort of healthy control subjects. Additionally, serum IL-22 was also elevated at baseline in the PsO study population compared to healthy control subjects. Baseline levels of serum IL-17A, IL-17F and IL-22 were shown to be higher in the moderate to severe PsO study population than in an independent cohort of healthy control subjects. Baseline levels of serum IL-17A, IL-17F, IL-22 and CCL22/MDC levels positively correlated with disease severity as determined by baseline PsO Area and Severity Index (PASI) scores. Guselkumab consistently decreased IL-17A, IL-17F and IL- 22 serum levels compared with placebo and compared with adalimumab.

Study PSO1001 was a Phase I study, summarised in the CER Attachment 2. In that study, 20 subjects with PsO received guselkumab and 4 received placebo. Histological analysis of skin biopsy was performed. While it was stated that treatment with guselkumab resulted in improvement in histological measures of PsO at Week 12 including reductions in epidermal thickness, T-cell density, and dendritic cells those histology results were not included in the study report.

After SC administration guselkumab is slowly absorbed, most likely via lymphatic circulated based on its molecular weight. Median time to C_{max} (T_{max}) after a single 100 mg SC dose was between 5.0 and 5.5 days. Mean bioavailability is estimated to be approximately48 – 55%, consistent with other IgG1 mAbs. In subjects with PsO 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 Vz/F values were approximately 16.1 to 28.0 L (177 to 288 mL/kg) and mean $t_{1/2}$ ranged from approximately 14.7 to 17.6 days after a single SC dose. The percent coefficient of variance (CV%) of C_{max}) values ranged from approximately 26% to 46% and the CV% of AUCinf values ranged from approximately 34% to 50%, indicating a large inter-subject variability in systemic exposure to guselkumab.

The exact metabolic pathway for guselkumab has not been characterised. As a fully human IgG1λ 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.

In vitro testing using cryopreserved human hepatocytes suggested guselkumab is unlikely to modulate the expression or activity of multiple cytochrome (CYP) P450 enzymes so interactions between guselkumab and CYP450 substrates are unlikely. A clinical study to evaluate whether guselkumab will alter the metabolism of probe substrates metabolised by CYP450 isozymes (midazolam (CYP3A4), warfarin (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and caffeine (CYP1A2)) was ongoing at the time of submission.

No studies have been performed in subjects with hepatic or renal impairment.

Immunogenicity was assessed in 1730 subjects who received up to 52 weeks of exposure. In that population 5.5% (n=96) had guselkumab antibody. Titres were generally low (79.2% were ≤ 1:160) and 7.3% (7/96) of these were positive for neutralising antibody to

guselkumab. Clinical studies did not detect an effect of neutralising antibodies on the clearance of guselkumab.

Efficacy

Study PSO2001 is described in the CER (see Attachment 2). In this study subjects received one of 5 dose regimens of guselkumab. Of these the 100 mg q8w had the largest reduction in PSA score to 0. Additionally subjects with trough serum guselkumab concentrations ≥ 0.67 µg/mL at Week 40 achieved the highest levels of efficacy with PGA 0 (70.0%), PGA 0/1 (90.0%), and PASI 75 (96.7%) responses. The 100 mg q8w dose regimen provided the highest trough concentrations of the 5 dose regimens assessed.

There were 2 pivotal Phase III studies. Studies 3001 and 3002 are ongoing randomised, double blind, placebo and active comparator controlled studies to evaluate efficacy and safety of guselkumab in subjects with moderate to severe plaque-type PsO, defined as an Investigator's Global Assessment (IGA) ≥ 3, PsO Area and Severity Index (PASI) ≥ 12, and involved body surface area (BSA) ≥ 10%. In both studies the active comparator was adalimumab given at the recommended dose regimen. Both studies were international and included centres in Australia.

Study 3001 compared placebo and adalimumab with guselkumab. The co-primary endpoints were for the guselkumab/ placebo comparison:

- Proportion of subjects who achieved IGA 0/1 and
- Proportion of subjects who achieved PASI 90 response at Week 16

There were 13 additional endpoints listed as major secondary endpoints and 16 analyses listed as major secondary analyses. The first 6 major secondary endpoints compared guselkumab with adalimumab. In order to control the overall Type 1 error rate, the primary analysis and major secondary analyses were to be tested in a fixed sequence, with the first major secondary endpoint tested only if the co-primary endpoints are positive, and the subsequent endpoint(s) tested only if the preceding endpoint in the sequence was positive. Of note, for the proposed regional PsO claims in the indication only a scalp PsO score was included in the group of major secondary endpoints (at number 11). This endpoint was: The proportion of subjects who achieve an ss-IGA score of absence of disease (0) or very mild disease (1) and have at least a 2 grade improvement from baseline at Week 16, comparing the guselkumab group and placebo group among randomised subjects with scalp PsO and an ss-IGA score ≥ 2 at baseline.
Nail PsO was assessed in the 6th and 7th endpoints from a list of other secondary endpoints. These were:

- The percent improvement from baseline in Nail PsO Area and Severity Index (NAPSI) at Week 16 among randomised subjects with nail PsO at baseline.
- The proportion of subjects who achieve a fingernail Physician Global Assessment (f-PGA) score of clear (0) or minimal (1) and have at least a 1 grade improvement from baseline at Week 16 among randomised subjects with an f-PGA score ≥ 2 at baseline.

Planto-palmar PsO was assessed in the 12th endpoint in the list of other secondary endpoints as:

- The proportion of subjects who achieve an hf-PGA score of clear (0) or almost clear (1) and a reduction of at least 2 grades on the hf-PGA scale from baseline at Week 16 among randomised subjects with hand and/or foot PsO and an hf-PGA score ≥ 2 at baseline.

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 PsO of 80 mg at Week 0 then 40 mg at Week 1 and every 2 weeks through to Week 47.

An open-label guselkumab treatment period was to begin after Week 48 and extend through Week 160. That segment of the study is ongoing. Subjects in Groups 1 and 2 will continue to receive guselkumab 100 mg at Week 52 and q8w thereafter through Week 148. Subjects in Group 3 initially randomised to adalimumab will enter a washout period after their final dose of adalimumab at Week 47 and commence guselkumab 100 mg at Week 52 and then q8w thereafter through Week 148.

Study subjects were required to meet the criteria for moderate to severe plaque PsO for at least 6 months prior to the first administration of study drug. Important exclusion criteria were: history of lymphoproliferative disease; current or recent malignancy; uncontrolled infections disease; recent anti-TNF treatment or treatment with other biologics; and expected to receive any live virus vaccination.

A total of 836 subjects were treated. Among all randomised subjects at baseline, the majority were white (81.7%) and male (72.6%). Median weight was 86.5 kg, and median age was 44.0 years. The median duration of PsO 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.

174 subjects were randomised to placebo, 329 to guselkumab and 333 to adalimumab. All but 1 subject received at least one dose of study medication. At Week 16 165 (94.8%) of the placebo treated subjects switched to guselkumab.

There was clear superiority of guselkumab over placebo for the 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). Selected efficacy endpoints for the guselkumab versus placebo and adalimumab comparisons are shown in the CER Attachment 2. All show superiority of guselkumab over placebo and adalimumab for each endpoint (IGA 0, IGA 0/1, PASI100, PASI 90 and PASI75 at Weeks 16 and 24). Similarly for the regional PsO endpoints superiority of guselkumab over placebo was demonstrated at Week 16 for ss-IGA, f-PGA, NAPSI and hf-PGA was reported and results are shown in the CER (see Attachment 2).

Efficacy results were sustained at Week 24. No 48 week endpoints were considered as major secondary efficacy endpoints where the comparison was between guselkumab and adalimumab with no subjects continuing to receive placebo. Results in the table (Table 9) below show continuing similar response rates to Weeks 16 and 24 and superiority of guselkumab over adalimumab at Week 48. Figure 3 in the CER shows response rates over time to Week 48 (see Attachment 2).

Table 9: Number of Subjects with IGA Scores of Cleared (0), Cleared (0) or Minimal (1) and Number of PASI 90 Responders at Week 48; Subjects Randomised at Week 0 (Study PSO3001)

	Guselkumab	Adalimumab
Analysis set: Subjects Randomized at Week 0	329	334
IGA score of cleared (0)	166 (50.5%)	86 (25.7%)
p-value[a]		< 0.001
IGA score of cleared (0) or minimal (1)	265 (80.5%)	185 (55.4%)
p-value[a]		< 0.001
PASI 90 responders	251 (76.3%)	160 (47.9%)
p-value[a]		< 0.001

[a] Based on the Cochran-Mantel-Haenszel chi-square test stratified by investigator site (pooled).

Improvements in the quality of life measure Dermatology Quality of Life Index (DLQI) scores were observed in the guselkumab group compared with the placebo group at Week 16 ($p<0.001$) and numerically greater improvements compared with the adalimumab group at Week 24.

Study 3002 had the same design as 3001 for the first 24 weeks of study then there was randomised withdrawal from Week 28 through to Week 72 to assess whether maintenance therapy was needed. Retreatment with guselkumab was also assessed in that study period after which all subjects were to receive open-label guselkumab to Week 160. Data to Week 48 was provided for evaluation.

This study had the same co-primary endpoints as Study 3001 and compared guselkumab with placebo. The first 3 major secondary endpoints were for the Week 24 comparisons between guselkumab and adalimumab. The fourth major secondary endpoint assessed time to loss of response on withdrawal of treatment. The endpoint was '*The time to loss of PASI 90 response through Week 48, comparing subjects randomized to placebo and subjects randomized to continue guselkumab 100 mg q8w at Week 28*'. The fifth major secondary endpoint was a comparison of Week 16 DLQI between guselkumab and placebo groups. Additional endpoints assessed continuous guselkumab treatment versus guselkumab withdrawal. These were:

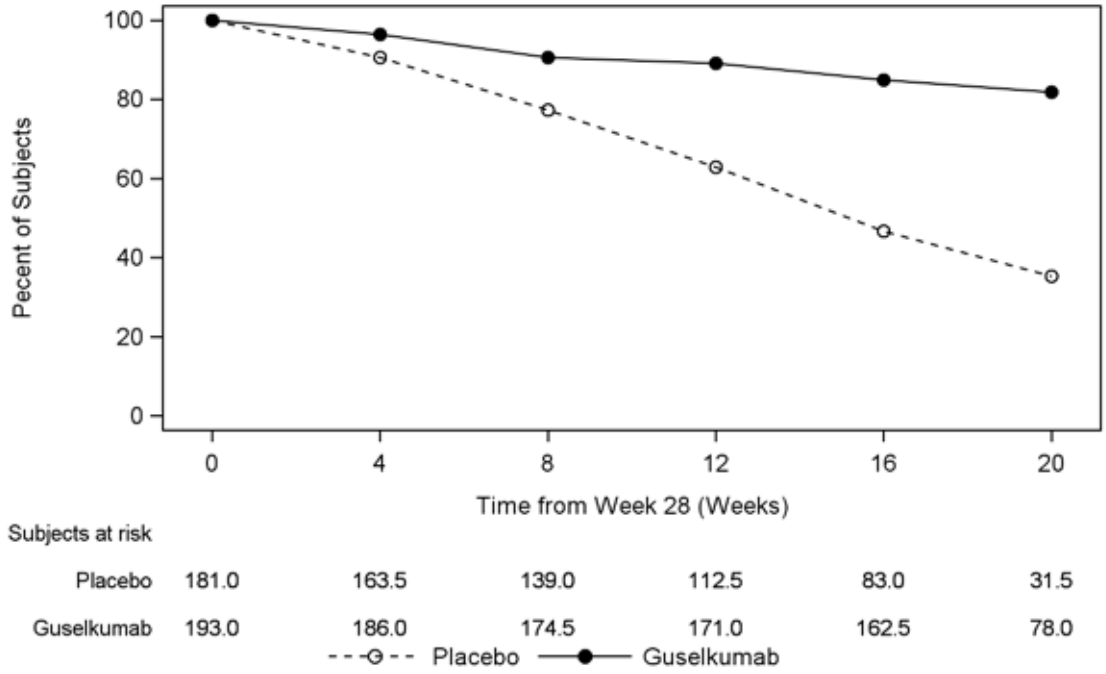
- The proportion of subjects who achieve an IGA score of cleared (0) or minimal (1) at Week 48
- The proportion of subjects who achieve a PASI 90 response at Week 48
- The proportion of subjects who achieve a PASI 90 response at Week 76.

The inclusion and exclusion criteria were as for Study 3001. A total of 992 subjects were randomised, 496 to guselkumab, 248 to placebo and 248 to adalimumab. 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. The median duration of PsO 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. 54.3% had previously received phototherapy, 61.8% had received non-biologic systemic therapies and 20.9% a biologic therapy. 32.1% of subjects were naïve to all prior non-biologic systemic and biologic therapies.

The effect of commencing treatment is seen clearly in Figure 4 in the CER in Attachment 2. At Week 16 84.1% of the guselkumab group and 8.5% of the placebo group had an IGA score of 0. ($p < 0.001$). Similarly at Week 16, 70.0% of the guselkumab group and 2.4% of the placebo group had a PASI90 response ($p < 0.001$). There was a gradual loss of

response when guselkumab was withdrawn as shown in the figure below (see Figure 5; extracted from the study report).

Figure 5: Life-table estimate of percent of subjects maintaining PASI 90 response; subjects randomised at Week 28 (Study PSO3002)



A significantly greater proportion of subjects receiving continuous guselkumab maintenance therapy 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. 40% of subjects maintained a PASI90 response 20 weeks after ceasing treatment with guselkumab.

Most other efficacy measures were not assessed during the randomised withdrawal period. The PsO Symptom and Sign Diary (PSSD) was recorded for all but 18.2% of patients and can provide another estimate of the extent of loss of effect. The change from baseline in median symptom PSSD score at Week 48 i.e. 20 weeks after withdrawal of guselkumab was -32.2 compared with -45.8 for subjects maintained on guselkumab during those 20 weeks. Similarly the median sign PSSD which was -33 for the withdrawn group and -49 for the continuing guselkumab group.

Study 3003, is described in the CER Attachment 2. Subjects commenced the study on ustekinumab at the recommended dose and at Week 16 subjects with an 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 through to Week 44.

The primary endpoint was 'The number of visits at which subjects achieve an IGA response of cleared (0) or minimal (1) and at least a 2-grade improvement (from Week 16) from Week 28 through Week 40, among randomized subjects with an inadequate (IGA ≥ 2) response to ustekinumab at Week 16.

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). For the 268 randomised subjects, the mean number of visits at which subjects had an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement (from Week 16) between Week 28 and Week 40 was (1.5 visits for the guselkumab group and 0.7 visits for the ustekinumab group ($p < 0.001$). Additionally, 32.6% of subjects given guselkumab and 14.3% given ustekinumab had an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement at 3 or 4 visits. Figure 5 in the CER (see Attachment 2) shows the percentage of subjects who achieved an IGA score of cleared (0) or minimal (1) and at least a 2 grade improvement from Week 16 through Week 40 by visit.

Safety

The core PsO Studies PSO2001, PSO3001, PSO3002 and PSO3003 included 1,748 subjects with moderate to severe plaque PsO who were exposed to guselkumab. Of these 1,393 were exposed for at least 6 months and 728 for at least 1 year (that is, treated through at least 48 weeks. Studies in pustuloplantar PsO (n=25), pustular PsO (n=21) and rheumatoid arthritis (n=110) were not included in the core safety database.
Safety data from the 2 Phase III studies (Studies 3001 and 3002) were pooled and were the primary safety analysis set. Table 13 in the CER (see Attachment 2) shows the number of subjects in each treatment group with one of more TEAEs through to Week 16 of these studies. Adverse events were reported in 46.7% of subjects given placebo, 49.2% of those given guselkumab and 49.9% of subjects given adalimumab. SAEs were reported in 1.4% of subjects given placebo, 1.9% given guselkumab and 2.1% given adalimumab.

Infections were reported in 21.3%, 23.3% and 24.6% of subjects given placebo, guselkumab and adalimumab respectively. Serious infections were reported in 1 subject each given placebo and guselkumab and 4 subjects given adalimumab. There were no reports of active TB or an opportunistic infection in any guselkumab treated subject through Week 48 in Studies PSO3001 or PSO3002. Active TB was reported for 2 subjects in the adalimumab group.

At Week 28 the AE rates in subjects given guselkumab and adalimumab were similar at 60.8% and 64.4% respectively. Infections were the most frequently reported AE in both groups with nasopharyngitis and upper respiratory tract infection (URTI) the most frequently reported infections. Through the end of the reporting period (through Week 48) for the pooled safety analysis set, the average duration of follow-up was similar (approximately 41 weeks) for subjects in the guselkumab and adalimumab. Of the 1,221 subjects in the guselkumab group, 823 had received study treatment only with guselkumab from Week 0 through Week 48 or until termination of study participation and 398 had been randomised to placebo and crossed over to guselkumab. The 581 subjects in the adalimumab group included 333 subjects from Study PSO3001 who received study treatment with adalimumab from Week 0 through Week 48 or until termination of study participation, plus the 248 subjects from Study PSO3002 who received treatment with adalimumab from Week 0 until their first dose of guselkumab or until termination of study participation.

There was no evidence for an increase in the reporting rate for SAEs over time through to Week 48 in subjects treated with guselkumab. Most SAEs reported in subjects exposed to guselkumab were single events.

There was one death in a subject given guselkumab across all studies up to the 30 June 2016 cut-off for reporting. This was due to myocardial infarction (MI) in a subject with multiple CV risk factors. After the 30 June 2016 cut-off a further 2 deaths were reported, a man with carcinoma planoepitheliale of unknown origin (squamous cell carcinoma (SCC) on biopsy) and a man with a history of depression who died of apparent suicide.

The event rate for adjudicated MACE based on the pooled Phase II (Study PSO2001) and Phase III (Studies PSO3001 and PSO3002) data through to Week 28 was 0.68/100 subject-years for guselkumab and 0.65 per 100 subject-years for adalimumab. This was based on few reports. Similarly for all adjudicated CV events, these were reported at 1.37 per 100 subject-years for guselkumab and 1.63 per 100-subject years for adalimumab. Through to Week 48 there was also no indication of a stronger association with CV events for guselkumab than with adalimumab.

9 malignancies were reported in subjects given guselkumab; 6 non-melanoma skin cancer (NMSC), 2 prostate cancer, 1 micro papillary variant of infiltrating carcinoma Grade 3 right breast. In the adalimumab group, there was 1 report of NMSC through Week 48, and no reports of malignancy other than NMSC. The sponsor compared these rates with those from the Surveillance, Epidemiology, and End Results (SEER) database. Comparison of the number of malignancies (other than cervical cancers in situ or NMSC) in the guselkumab group with data from the SEER database (adjusted for age, sex, and race) indicated that the rate of these events in subjects with moderate to severe PsO treated with guselkumab for up to 1 year was no higher than that expected for the general US population (standardi ratio = 0.72 (95% CI: 0.15, 2.11)). SEER is a program of the US National Cancer Institute and provides information on cancer statistics from approximately 28% of the US population [30].

There was no evidence of increased suicidal ideation or suicide associated with guselkumab. Across all completed or ongoing Phase I, Phase II, or Phase III studies in plaque PsO or other indications, no event of completed suicide or suicide attempt was reported in guselkumab-treated subjects; 1 nonserious event of suicidal ideation was reported. Adjudicated Suicidal ideation and behavior (SIB) analysis by Columbia Classification Algorithm of Suicide Assessment (C-CASA) showed an incidence rate of 0.10/100 subject-years for guselkumab in the pooled safety analysis set through Week 48.

One subject developed severe thrombocytopenia which resolved without intervention on discontinuation of guselkumab. One case of hypersensitivity was reported as a SAE in a subject given guselkumab.

Risk management plan

The RMP evaluator noted as important potential risks serious infection, malignancy, serious hypersensitivity reactions (including anaphylaxis and serum sickness) and MACE. In addition to routine pharmacovigilance activities the RMP evaluator has noted that the sponsor proposes the following activities:

- Two Phase III, multicenter, randomised, doubleblind, placebo and active comparator controlled trials (Studies CNTO1959PSO3001 and CNTO1959PSO3002) to assess long-term safety
- A PIP (EMEA-001523-PIP02-14) for use in paediatric patients
- An observational study to assess long term safety
- A German PsO Registry (PsoBEST Registry)/observational PASS cohort study
- Electronic Administrative Health Claims Databases Review/observational PASS cohort study.

The RMP evaluator also highlighted that the recommendation from the nonclinical evaluator be addressed. This was that the potential immunosuppressive action of

[30] https://seer.cancer.gov/about/overview.html

guselkumab on neonates be monitored as part of the pharmacovigilance plan. Editorial amendments have also been requested for subsequent Risk Management Plan updates.

The suggested condition of registration pertaining to the Risk Management Plan is the sponsor implement EU-RMP (version 1.2, dated 8 August 2017, data lock point 30 June 2016) with Australian Specific Annex (version 1.1, dated 19 October 2017) and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

The dose above which no further improvement in PsO signs and symptoms is likely has not been established. Study PSO2001 examined 5 dose regimens but higher doses at the q8w frequency proposed have not been examined. However using the proposed dose regimen 60% of subjects achieved clearance of their PsO with maximal response seen by Week 26. These results are similar to those of secukinumab and ustekinumab.

Study 3001 was quite complex with a large number of efficacy endpoints which were to be determined in a fixed sequence so as to control for multiplicity effects. The results were not reported in that sequence. The Delegate seeks reassurance from the sponsor that the results were statistically significant in fixed sequence specified in the statistical plan. If this is not the case then all statistical comparisons below the first non-significant comparison should not be included as statistically significant in any description of that study.

However it is clear that guselkumab is a very effective treatment for moderate to severe plaque PsO. It is superior to adalimumab with IGA scores of 0/1 at Week 16 in 85.1% of subjects given guselkumab and in 65.9% given adalimumab in Study 3001 and 84.1% guselkumab versus 67.7% adalimumab in Study 3002. A similar separation persisted throughout 48 weeks of treatment. Other efficacy measures also showed similar superiority of guselkumab over adalimumab. For those patients who do not adequately respond to ustekinumab, another sponsor sponsored mAb for the treatment of plaque PsO, cross study comparison suggests an additional 15% of these patients may achieve a clinically significant improvement on switching to guselkumab compared with maintaining ustekinumab.

Response commences within 2 weeks of the first dose and stabilises around Week 12 to 16. Median time to loss of excellent response (PASI90) was about 16 weeks. Loss of effect for regional PsO was not recorded in Study 3002 so it is not clear how quickly and to what extent scalp, nail or planto-palmar PsO signs and symptoms recur on cessation of treatment. The median PSSD sign and symptoms diary scores showed only a small median increase in signs and symptoms in the 20 weeks after withdrawal of guselkumab in Study 3002. 40% of study subjects withdrawn from guselkumab continued to have PASI90 responses at 20 weeks after withdrawal. It is not clear whether all patients will require ongoing treatment to maintain an acceptable response or whether intermittent treatment may be sufficient for the many patients.

With ustekinumab, an IL-12 and IL-23 inhibitor the major safety concerns are increased risk of serious infections and malignancy, and hypersensitivity reactions including anaphylaxis. Live vaccines should not be administered with ustekinumab. Exfoliative dermatitis or pustular PsO may develop in patients with plaque PsO when given ustekinumab. For guselkumab the concerns are similar. There may be an increased in the incidence of NMSC associated with guselkumab.

The RMP evaluator has recommended MACE (defined as CV death, non-fatal MI and non-fatal stroke) be considered an important potential risk from guselkumab. The basis for this

was not clear. While the safety analysis showed fewer adverse CV events with placebo than with guselkumab there was considerably less follow-up duration for subjects given placebo than for those given either of the active treatments.

Summary of issues

- Guselkumab has been investigated in adults only. The safety and efficacy of guselkumab has not been investigated in patients aged < 18 years so its use in that population is not recommended.
- The optimum dose regimen for guselkumab in the treatment of plaque PsO has not been established.
- It is not clear whether continuous treatment is required or advised for the majority of patients with moderate to severe plaque PsO or with regional PsO.
- The long term safety of guselkumab will require careful long term observation.

Proposed action

The Delegate had no reason to say, at this time, that the application for Tremfya/ Janssen Guselkumab 100 mg solution for injection, pre-filled syringe should not be approved for registration, subject to negotiation of the PI and other conditions of registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. The proposed indication is cumbersome and not consistent with the indication of other mAbs currently approved for the treatment of PsO. Does the committee consider the proposed revision is appropriate?
2. The data on recurrence of signs and symptoms of PsO on ceasing treatment with guselkumab is quite limited. Available evidence suggests that while continuous treatment is required for maximal response an acceptable response may be achieved with intermittent treatment for many patients. Does the committee consider this approach would be worthwhile given the unknown long term safety effects of guselkumab?
3. A portion of patients with moderate to severe PsO who had an inadequate response to ustekinumab responded to guselkumab. Does the committee consider the proposed description of this information clearly describes the extent of benefit that may be achieved?
4. Does the committee consider the long term safety follow up provisions in the RMP are sufficient or should other follow up procedures be put instituted?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor's response to the second round clinical evaluation is provided below.

Response to comments in the TGA second round clinical evaluation

Comment 1

'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.

Sponsor response

The sponsor acknowledges the request and agrees to provide a summary of single nucleotide polymorphism (SNP) minor allele frequencies associated with the IL-23/Th17 axis in study participants from the global Phase III Studies CNTO1959PSO3001, CNTO1959PSO3002 and CNTO1959PSO3003, including associations with baseline phenotypes or response to guselkumab, when data analysis is completed and the study report is finalised. However, the sponsor considers that the effects of genetic polymorphism associated with IL-23 or IL-23 receptors should not be added to the list of missing information in the RMP. The rationale for this opinion is provided below.

The sponsor's core position is aligned with the EMA Guideline on good pharmacovigilance practices (GVP) Module V (Rev 2) 28 March 2017 for identification, classification and characterisation of risks in the RMP. In line with the guideline, the sponsor considers that effects of genetic polymorphisms associated with IL-23 or with IL-23 receptors does not meet the definition of missing information in the RMP. Specifically, this topic is not included in the EU-RMP for guselkumab as the absence of information on genetic polymorphisms associated with IL-23 or with IL-23 receptors does not constitute a major 'safety' concern. While the effect of genetic polymorphisms associated with IL-23 or with IL-23 receptors may be relevant to efficacy results, there is very limited information available on the effects of genetic polymorphisms in treatment of PsO in general and the available information does not indicate any major concerns in terms of safety risks, including lack of efficacy that could impact the benefit-risk balance in the PsO population. This approach is consistent with the RMPs for other biologics (anti TNFs, anti-IL-17 agents and anti-IL-12/23) that are approved for treatment for PsO.

> *EMA Guideline on good pharmacovigilance practices (GVP) – Module V (Rev 2) 28 March 2017: Missing information relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far. The absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile. A scientific rationale is needed for the inclusion of that population as missing information in the RMP.*

The sponsor would like to highlight that Deoxyribonucleic acid (DNA) single nucleotide polymorphism (SNP) tests are not routinely performed in real world clinical practice; therefore, it is unlikely that postmarketing/spontaneous cases would provide more information on effects of genetic polymorphisms associated with IL-12 or IL-23 receptors. However, the sponsor confirms that if a new safety signal is identified in the analysis from the global Phase III studies with respect to the effects of polymorphisms associated with IL-23 or IL-23 receptors, an evaluation of these signals will be provided in the Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR).

Comment 2

'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.

The sponsor respectfully disagrees with the request to add effects of immunogenicity as missing information in the RMP as the sponsor has considerable information on

immunogenicity from the completed and ongoing studies and these results do not indicate any safety concerns due to immunogenicity.

In the initial submission, the sponsor evaluated the effects of immunogenicity on PK, efficacy and safety, with a focus on data through Week 48 from the global PSO Studies PSO3001 and PSO3002). Based on these data, the sponsor agrees with the evaluator's assessment that no safety concerns were identified given that the overall incidence of antibodies to guselkumab was low (5.5%) and there was no apparent impact of antibodies to guselkumab on the PK, efficacy or safety of guselkumab. In addition to the above information, the sponsor is now able to provide the cumulative information from all completed and ongoing studies, including updates through Week 100 from global PsO Studies PSO 3001 and PSO 3002. As described below, these data demonstrate that no safety concerns were observed due to immunogenicity.

The immunogenicity data from the completed Phase I to III studies (Studies CNTO1959PSO1001, CNTO1959PSO1002, CNTO1959PSO1003, CNTO1959NAP1001, CNTO1959NAP1002, CNTO1959PSO2001, CNTO1959PSO3003, CNTO1959PSA2001, CNTO1275ARA2001, and CNTO1959PPP2001) and the ongoing

Phase III studies (CNTO1959PSO3001 and CNTO1959PSO3002) show a generally low incidence of antibodies to guselkumab (approximately 0% to 8% in PsO, 5% in PsA, 11% in RA, 8% in PPP and 0% to 3% in healthy subjects).

A total of 2,086 subjects in Phase II and III PsO studies (Studies CNTO1959PSO2001, CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003) who received guselkumab had posttreatment serum samples that were evaluable for antibodies to guselkumab. The overall incidence of antibodies to guselkumab through up to Week 100 (approximately 2 years) after exposure to guselkumab was 8.0% (N=167). Titres of antibodies to guselkumab were generally low with the majority (129 of 167; 77.2%) having titres ≤1:160. Nine (5.4%) of 167 subjects who were positive for antibodies to guselkumab had antibodies that were able to neutralize the bioactivity of guselkumab in vitro; therefore, the overall incidence of neutralising antibodies (NAbs) to guselkumab in subjects who received guselkumab was approximately 0.4% (9/2086 subjects).

Further, in Study CNTO1959PSO3002, the incidence of antibodies to guselkumab was also evaluated specifically during the retreatment period with guselkumab. Among the 313 subjects who were withdrawn and retreated with guselkumab prior to Week 100, 310 subjects had appropriate samples for immunogenicity assessment obtained after retreatment. Only 3 (1.0%) of the 310 subjects newly developed antibodies to guselkumab after retreatment with guselkumab.

No apparent impact of antibodies to guselkumab on the pharmacokinetics of guselkumab was observed between subjects who were positive for antibodies to guselkumab and subjects who were negative for antibodies to guselkumab in any of the studies conducted for guselkumab so far.

Overall, the development of antibodies to guselkumab did not appear to be associated with a reduction in the clinical efficacy of guselkumab, and had no discernible impact on injection-site reactions or possible serious hypersensitivity reactions. The sponsor also would like to highlight that antibody testing is not routinely performed in real world clinical practice; therefore, it is unlikely that postmarketing/spontaneous cases would provide more information on immunogenicity. However, the sponsor acknowledges the request from the evaluator to provide information on immunogenicity from ongoing studies and commits to providing this information in the Clinical Study Reports and Investigator's Brochure, if applicable and when the studies are completed and the documents are updated. If a new safety signal is identified with respect to immunogenicity, an evaluation of these signals will be provided in the PBRER/PSUR.

Response to questions in the TGA Delegate's overview

The applicant's response to the Delegate's request for advice is provided below.

Question 1

The proposed indication is cumbersome and not consistent with the indication of other MABs currently approved for the treatment of PsO. Does the committee consider the proposed revision appropriate?

Sponsor response

The sponsor agrees to the Delegate's proposed changes to the indication as follows:

Tremfya is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Question 2

The data on recurrence of signs and symptoms of PsO on ceasing treatment with guselkumab is quite limited. Available evidence suggests that while continuous treatment is required for maximal response an acceptable response may be achieved with intermittent treatment for many patients. Does the committee consider this approach would be worthwhile given the unknown long-term safety effects of guselkumab?

Sponsor response

The available results from the randomised withdrawal phase of VOYAGE-2 (Study PSO3002) demonstrate definitively that subjects that continue q8w dosing maintain better responses relative to those who discontinue guselkumab. A loss of PASI 90 response was evident as early as 4 weeks after the next dose of guselkumab would have been due (based on the recommended 8 week dosing interval) among those who discontinued treatment. While the available withdrawal data do suggest that many subjects may maintain their response for longer than 8 weeks following withdrawal of guselkumab, to date the sponsor has been unable to define clinical or biomarker parameters for predicting with any degree of certainty which patients will be able to sustain response with intermittent or extended dosing. Furthermore, it is also clear that most, if not all, will eventually lose response over time without additional treatment.

Defining an 'acceptable' sub-maximal response in PsO is not straightforward. Available quality of life data demonstrate that patients perceive benefit from complete clearance relative to lower level responses. A treatment approach that would require patients with underlying moderate to severe PsO to undergo intermittent relapse of their disease does not, in our view, align with the prevailing sentiment that most patients desire high levels of sustained clearance.

While all new therapies lack long term safety data by definition, to date, no safety concerns are evident within the available guselkumab safety data set, which includes subjects that have received up to 2 years of continuous treatment at 100 mg q8w. Ultimately, the sponsor does not currently believe that theoretical concerns due to a lack of longer-term safety data justify the exploration of inherently less effective guselkumab treatment regimens.

Question 3

A portion of patients with moderate to severe PsO who had an inadequate response to ustekinumab responded to guselkumab. Does the Committee consider the proposed description of this information in the 'Review of Product Information' clearly describes the extent of benefit that may be achieved?

Sponsor response

The following information is included in the Clinical trials section of the proposed PI. The sponsor believes that this explanation provided clearly describes the results achieved and is consistent with the EU Summary of Product Characteristics (SmPC).

NAVIGATE

> *The NAVIGATE study examined the efficacy of guselkumab in patients who had an inadequate response (that is, who had not achieved a 'cleared' or 'minimal' response defined as IGA ≥ 2) to ustekinumab at Week 16. All patients (N=871) received open-label ustekinumab (45 mg ≤100 kg and 90 mg >100 kg) at Weeks 0 and 4. At Week 16, 268 patients with an IGA ≥ 2 score were randomised to either continue ustekinumab treatment (N=133) q12w, or to initiate guselkumab treatment (N=135) at Weeks 16, 20, and q8w thereafter. Baseline characteristics for randomised subjects were similar to those observed in VOYAGE 1 and 2.*
>
> *After randomisation, the primary endpoint was the number of post-randomisation visits between Weeks 12 and 24 at which patients achieved an IGA score 0/1 and had ≥ 2 grade improvement. Patients were examined at four week intervals for a total of four visits. Among patients who inadequately responded to ustekinumab at the time of randomisation, significantly greater improvement of efficacy was observed in patients who switched to guselkumab treatment compared to patients who continued ustekinumab treatment. Between 12 and 24 weeks after randomisation, guselkumab patients achieved an IGA score 0/1 with ≥ 2 grade improvement twice as often as ustekinumab patients (mean 1.5 vs 0.7 visits, respectively, p < 0.001). Additionally, at 12 weeks after randomisation a higher proportion of guselkumab patients compared to ustekinumab patients achieved an IGA score 0/1 and ≥ 2 grade improvement (31.1% vs. 14.3%, respectively; p = 0.001) and a PASI 90 response (48% vs 23%, respectively, p < 0.001). Differences in response rates between guselkumab and ustekinumab treated patients were noted as early as 4 weeks after randomisation (11.1% and 9.0%, respectively) and reached a maximum 24 weeks after randomisation (see Figure 2). No new safety findings were observed in patients who switched from ustekinumab to guselkumab.*

Question 4

Does the committee consider the long-term safety follow up provisions in the RMP are sufficient or should other follow up procedures be put instituted?

Sponsor response

The following long-term safety follow-up studies are either ongoing or proposed:

- VOYAGE 1 (Study CNTO1959PSO3001) and VOYAGE 2 (Study CNTO1959PSO3002); both Phase III, multicentre, randomised, double blind, placebo and active comparator controlled trials
- Company-sponsored Observational Cohort Study PASS
- Electronic Administrative Health Claims Databases Review/observational PASS
- German PsO Registry (PsoBEST Registry)/observational PASS
- Paediatric Investigation Plan (EMEA-001523-PIP02-14) randomised controlled trial

The long-term extensions of two pivotal Phase III PsO trials, VOYAGE 1 and VOYAGE 2, are ongoing. Data from these clinical trials are available through Week 100. The available safety data suggest no increase in rates of adverse events between Week 48 and Week 100 in either trial. Rates of serious adverse events remained stable. There have been no

reports of TB, opportunistic infections, or serious hypersensitivity reactions, and no new safety concerns were identified from Week 48 through Week 100.

The sponsor believes the long-term safety provisions listed above and included in the RMP/ASA are sufficient to address any safety concerns with the use of Tremfya.

Advisory Committee Considerations[31]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Tremfya(guselkumab; pre-filled syringe containing 100 mg of guselkumab) to have an overall positive benefit-risk profile for the Delegate's amended indication:

> *Tremfya is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.*

Sponsor application indication:

> *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.*

In making this recommendation the ACM expressed concern that:

- There were no data on the interaction of Tremfya with live vaccines.
- It was not appropriate to include extensive reporting on regional PsO results in the PI based on scalp data alone. Comment on scalp PsO is appropriate as response patterns at this site of involvement may vary between biologic agents for PsO.

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- Live vaccines in the Contraindication sections of the PI since they were not assessed in the clinical trials.

[31] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

The committee is requested to provide advice on the following specific issues:

1. *The proposed indication is cumbersome and not consistent with the indication of other MABs currently approved for the treatment of PsO. Does the committee consider the proposed revision is appropriate?*

The ACM considers the proposed revised indication to be appropriate.

2. *The data on recurrence of signs and symptoms of PsO on ceasing treatment with guselkumab is quite limited. Available evidence suggests that while continuous treatment is required for maximal response an acceptable response may be achieved with intermittent treatment for many patients. Does the committee consider this approach would be worthwhile given the unknown long term safety effects of guselkumab?*

The current safety data for guselkumab and long-term safety data for ustekinumab (as best surrogate) do not support treatment cessation on the grounds of patient safety. Intermittent treatment is more likely to result in a rapid loss of response with older biologic agents. This is less common with newer agents (such as ustekinumab) allowing for temporary cessation ('treatment holidays'). Nevertheless, the ACM advised that intermittent treatment be the exception and not recommended as the standard regimen.

3. *A portion of patients with moderate to severe PsO who had an inadequate response to ustekinumab responded to guselkumab. Does the committee consider the proposed description of this information clearly describes the extent of benefit that may be achieved?*

The ACM did not address this question specifically but proposed that there was no reason to modify the current presentation of results from the NAVIGATE study (which concluded that patients derived significant benefit by switching to guselkumab after an inadequate response to ustekinumab). It was also noted, however, that there exists significant response heterogeneity due to genetic and non-genetic factors that precludes a definitive prediction of a positive response.

4. *Does the committee consider the long term safety follow up provisions in the RMP are sufficient or should other follow up procedures be put instituted?*

The ACM concluded that the long-term safety follow-up provisions in the Risk Management Plan are sufficient. This position is supported by the TGA evaluator's response to the sponsor's RMP which the ACM considers reasonable.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tremfya/Janssen Guselkumab 100 mg solution for injection, prefilled syringe, indicated for:

> *Tremfya/Janssen Guselkumab is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.*

Specific conditions of registration applying to these goods

1. Tremfya and Janssen Guselkumab (Guselkumab) are to be included in the Black Triangle Scheme. The PI and CMI for Tremfya and Janssen Guselkumab must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
2. The EU Risk Management Plan (RMP) (version 1.2, dated 8 August 2017, data lock point 30 June 2016) with Australian Specific Annex (version 1.1, dated 19 October 2017), included with submission PM-2017-00552-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Tremfya or Janssen Guselkumab approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>. The PI for all tradenames are identical except for the product name.

Attachment 2. Extract from the Clinical Evaluation Report

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