Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Guselkumab

Proprietary Product Name: Tremfya

Sponsor: Janssen-Cilag Pty Ltd

March 2021

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 abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20 criteria
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AusPAR	Australian Public Assessment Report
bDMARD	Biological disease-modifying antirheumatic drug
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	Confidence interval
CL	Clearance
CMH	Cochran-Mantel-Haenszel
CO	Placebo crossover
CRF	Case report form
CRP	C-reactive protein
cDMARD	Conventional synthetic disease-modifying antirheumatic drug

Abbreviation	Meaning
C_{trough}	Trough concentration
$C_{trough,ss}$	Trough concentration at steady state
DAS28-CRP	Disease Activity Score 28 with C reactive protein
DBL	Database lock
DILI	Drug-induced liver injury
DLP	Data lock point
DMARD	Disease-modifying antirheumatic drug
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EE	Early escape
E-R	Exposure-response
EU	European Union
GUS	Guselkumab
GVP	Good pharmacovigilance practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HCQ	Hydroxychloroquine
IGA	Investigator's Global Assessment
IL	Interleukin
ISR	Injection site reaction
JAK	Janus kinase
LEF	Leflunomide
LEI	Leeds Enthesitis Index
MACE	Major adverse cardiovascular events
MCS	Mental Component Score
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PASI 75	Psoriasis Area and Severity Index 75 response

Abbreviation	Meaning
PBO	Placebo
PCS	Physical Component Score
PD	Pharmacodynamic(s)
PE	Primary endpoint
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PsA	Psoriatic arthritis
PSUR	Periodic safety update report
PT	Preferred Term
PY	Patient-years
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RMP	Risk management plan
SAA	Serum amyloid A
SAE	Serious adverse event
SC	Subcutaneous(ly)
SD	Standard deviation
SDC	Smallest detectable difference
SF-36	36-Item Short form Health Survey
SOC	System Organ Class
SSZ	Sulfasalazine
TB	Tuberculosis
TSS	Total Sharp Score
TEAE	Treatment emergent adverse events
TGA	Therapeutic Goods Administration

Abbreviation	Meaning
Th	T helper
TNF	Tumour necrosis factor
URTI	Upper respiratory tract infection
US(A)	United States (of America)
VD	Volume of distribution
vdHS	Van der Heijde-Sharp

I. Introduction to product submission

Submission details

Type of submission:	Extension of indication
Product name:	Tremfya
Active ingredient:	Guselkumab
Decision:	Approved
Date of decision:	21 January 2021
Date of entry onto ARTG:	29 January 2021
ARTG numbers:	321410, 286020
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
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
Containers:	Pre-filled pen, pre-filled syringe
Pack sizes:	1 pre-filled pen 1 pre-filled syringe
Approved therapeutic use:	*Psoriatic arthritis* *Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to prior DMARD therapy*
Route of administration:	Subcutaneous
Dosage:	Psoriatic arthritis The recommended dose of Tremfya is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	Tremfya may be administered alone or in combination with a conventional synthetic disease-modifying antirheumatic drug (cDMARD), for example methotrexate. For further information regarding dosage, refer to the Product Information.
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. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Janssen-Cilag Pty Ltd (the sponsor) to register Tremfya (guselkumab) 100 mg, solution for injection for the following extension of indications:

> *Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to, prior DMARD therapy.*

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with skin psoriasis. It affects men and women equally. The prevalence of PsA in the general population is approximately 1 to 2 per 1000 of the general population, and estimates in the population of patients with psoriasis have varied between 4% and 30%. In the majority of PsA patients, psoriasis precedes the onset of arthritis with a median time between the diagnosis of skin and joint disease of seven to eight years.

Clinically PsA may manifest with one or more arthritic patterns, including as distal arthritis characterised by involvement of the distal interphalangeal joints; asymmetric oligoarthritis in less than five small and/or large joints; symmetric polyarthritis, similar to rheumatoid arthritis; highly deforming and destructive arthritis mutilans; and as a spondyloarthropathy affecting the sacroiliac joints and/or the spine. Additional periarticular clinical manifestations of PsA include enthesitis, dactylitis, and skin and nail disease. Since 2006, the diagnosis of PsA in a patient with an inflammatory musculoskeletal disease (peripheral arthritis, spondylitis or enthesitis), for research purposes, has been based on achieving a total of at least three points on the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (see Figure 1).[2]

[2] Gladman DD, Ritchlin C (2020) Clinical manifestations and diagnosis of psoriatic arthritis *UpToDate*, last updated May 01 2020, accessed August 12 2020.

Figure 1: Classification Criteria for Psoriatic Arthritis (CASPAR) criteria

CASPAR criteria[3]
To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories: – Skin psoriasis that is: § Present (2 points); or § Previously present by family history (1 point); or § A family history of psoriasis if patient is unaffected (1 point). – Nail lesions (1 point) – Dactylitis (1 point) – Negative rheumatoid factor (1 point) – Juxta-articular bone formation on radiographs (1 point)

This submission requests an extension of the registered treatment indications in Australia for guselkumab (GUS), an interleukin (IL)-23 inhibitor currently approved for the treatment of moderate to severe plaque psoriasis in adults, to include the treatment of adults with psoriatic arthritis. GUS is the first anti-IL-23 therapy proposed for the treatment of active PsA in Australia, although several alternative biological and non-biological therapies have been registered over the last few years.

The treatment choices for PsA depend on several factors, including the presence or absence and severity of psoriatic skin disease; whether the arthropathy involves only one or a few joints or is polyarticular; whether the arthritis is associated with extra-articular features; and comorbidities, allergies and drug-drug interactions. The initial treatment of PsA usually involves managing pain and inflammation, particularly in the peripheral joints, with oral non-steroidal anti-inflammatory drugs (NSAIDs). Intra-articular steroid injections may be considered for oligoarthritis. Generally, patients will be commenced on a disease modifying antirheumatic drug (DMARD), for example the conventional DMARD (cDMARD) drugs such as methotrexate, sulfasalazine and leflunomide amongst others. Biological DMARD (bDMARD) therapies to date have been approved only as second line therapies following failure of or intolerance to cDMARDs.

In Australia, the approved bDMARDs for PsA currently include:

- Tumour necrosis factor (TNF)-inhibitors adalimumab, certolizumab pegol, golimumab, infliximab and etanercept, for the following indications:

  Adalimumab is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

  Cimzia (certolizumab pegol)[4] is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease modifying antirheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.

[3] Taylor, W., et al. (2006), Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. Arthritis & Rheumatism, 54: 2665-2673.
[4] Cimzia was registered in Australia on 10 February 2017, ARTG 281317.

Simponi (golimumab)[5], alone or in combination with methotrexate, is indicated for: The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.

Infliximab is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy. Infliximab may be administered in combination with methotrexate.

Etanercept is indicated for the treatment of the signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Etanercept has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

- The IL-17 inhibitor, secukinumab, for the following indication:

  Cosentyx;[6] is indicated for the treatment of adult patients with active psoriatic arthritis when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

- The IL-12/23 inhibitor, ustekinumab, for the following indication:

  Stelara,[7] alone or in combination with methotrexate, is indicated for the treatment of signs and symptoms of active psoriatic arthritis in adult patients (18 years and older) where response to previous non-biological DMARD therapy has been inadequate.

- Additionally, a non-conventional, non-biological selective Janus kinase (JAK) inhibitor tofacitinib has also been recently approved for PsA, for the following indication::

  Xeljanz;[8] in combination with conventional synthetic DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response to a prior DMARD therapy.

Tremfya (guselkumab) was first registered in Australia for the treatment of plaque psoriasis in March 2018. A subset of patients included in the pivotal and supporting trials for psoriasis had PsA.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 15 March 2018 for the below indication,

Plaque psoriasis,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.

At the time the TGA considered this application, similar applications had been approved in United States of America (USA) on13 July 2020, in Canada on 4 September 2020 and received a Committee for Medicinal Products for Human Use (CHMP of European Union (EU)) post-authorisation summary of positive opinion on 15 October 2020. Application

[5] Simponi was registered in Australia on 13 November 2009, ARTG 153181
[6] Cosentyx was registered in Australia on 12 January 2015, ARTG 218798
[7] Stelara was registered in Australia on 28 July 2009, ARTG 149549
[8] Xeljanz was registered in Australia on 5 February 2015, ARTG 196987

were under consideration in Switzerland (submitted on 28 January 2020) and in Singapore (submitted on 16 July 2020).

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
USA	13 September 2019	Approved on 13 July 2020	*Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis*
Canada	30 September 2019	Approved on 4 September 2020	*Tremfya/Tremfya One-Press (guselkumab injection) is indicated for the treatment of adult patients with active psoriatic arthritis.* *Tremfya/Tremfya One-Press can be used alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD) (e.g. methotrexate).*
EU, via centralised procedure Rapporteur: Hungary Co-rapporteur: Ireland	16 October 2019	Received CHMP post-authorisation summary of positive opinion on 15 October 2020	*Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1)*
Switzerland	28 January 2020	Under consideration	Under consideration
Singapore	16 July 2020	Under consideration	Under consideration

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 timeline

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

Table 2: Timeline for Submission PM-2019-05350-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	18 December 2019
First round evaluation completed	29 June 2020
Sponsor provides responses on questions raised in first round evaluation	3 August 2020
Second round evaluation completed	9 September 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	20 October 2020
Sponsor's pre-Advisory Committee response	2 November 2020
Advisory Committee meeting	3 and 4 December 2020
Registration decision (Outcome)	21 January 2021
Completion of administrative activities and registration on the ARTG	29 January 2021
Number of working days from submission dossier acceptance to registration decision*	210

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

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

The Delegate referred to the below guidelines and guidance documents in this AusPAR:

- Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. CPMP/EWP/438/04 (effective 5 February 2008).

- Guideline on the Clinical Investigation of Medicinal Products indicated for the Treatment of Psoriasis. CPMP/EWP/2454/02
- European Medicines Agency Guideline on good pharmacovigilance practices, Module V- Risk Management Systems.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier consists of

- two Phase III efficacy and safety studies (Studies PSA3001 and PSA3002);
- one Phase II study (Study PSA2001);
- one population pharmacokinetic (PopPK) analysis; and
- pooled safety data from the placebo-controlled and active open-label periods of the pivotal studies.

Pharmacology

Pharmacokinetics

The pharmacokinetic characteristics of GUS in patients with PsA are substantially similar to those reported in patients with plaque psoriasis.

In the Phase II Study PSA2001, participants received 100 mg guselkumab subcutaneously (SC) at Weeks 0 and 4, then every 8 weeks (Q8W). In the Phase III Study PSA3001, in adults who had inadequate response to cDMARDS with/without bDMARDS, 126 participants were randomised to the same Q8W regimen as described in Study PSA2001, and 127 were randomised to receive 100 mg guselkumab SC every four weeks (Q4W group). In the second Phase III study (Study PSA3002), in adults with PsA who had an inadequate response to cDMARDS and were all bDMARD naïve, 247 participants were randomised to Q8W regimen and 240 to Q4WQ4W regimen. Steady state trough concentrations ($C_{trough,ss}$) were achieved earlier in Q4WQ4W arms, and were three to four times higher than in the Q8W arms (as summarised in Table 2). In Study PSA2001, $C_{trough,ss}$ were maintained at Week 44, and patients who crossed over from placebo (PBO) to GUS therapy at Week 24 recorded similar $C_{trough,ss}$ at comparable time points.

Table 2: Studies PSA2001, PSA3001, PSA3002 Guselkumab trough concentrations at steady state

Study ID	PSA2001	PSA3001		PSA3002	
N	90	127	126	240	247
regimen	Q8w	Q4w	Q8w	Q4w	Q8w
Time to steady state (week)	20	12	20	12	20
$C_{trough,ss}$ (µg/mL) median mean ± SD n	 0.94 1.15±0.82 85	 3.90 4.08±1.88 110	 0.95 1.12±0.77 112	 3.35 3.70±1.92 208	 1.05 1.28±1.03 215

$C_{trough,ss}$ = trough concentration at steady state; SD = standard deviation

The GUS C_{trough} appeared slightly lower with increasing body weight; the concomitant use of MTX had no apparent impact on serum GUS concentrations in all three studies.

Population pharmacokinetic data

Serum GUS concentration data through to Week 24 from the Phase III studies were utilised to perform a population pharmacokinetic (PK) analysis using a nonlinear mixed-effect modelling approach. The GUS concentration-time profiles in adults with PsA were adequately described by a one compartment linear model with first-order absorption and first-order elimination. The final model identified that increased body weight was associated with increased clearance (CL) and volume of distribution (V_D) of GUS. Model-predicted steady state C_{trough} and area under the concentration-time curve (AUC) during one dose interval (8 weeks or 4 weeks) were about 30 to 35% lower in participants who weighed ≤ 100kg compared to those who weighed > 100kg, in both regimens. Comorbid diabetes was associated with increased CL (about 15%). The model-derived elimination half-life was approximately 18.1 days, which was consistent with that in patients with psoriasis.

The sponsor states that there was no clinically meaningful difference in clinical responses over different body weight strata with either of the dosage regimens, and that therefore the effect of body weight on exposure does not require dose adjustment. Similarly, there was no consistent impact of diabetes comorbidity on efficacy with either GUS regimen.

A total of 15 of 746 (2%) adults with results included in the population PK analysis developed anti-drug antibodies (ADA) during the respective studies. In the population PK covariate analysis, the presence of ADA had no apparent impact on exposure to GUS. Small patient numbers in the ADA positive dataset make interpretations inconclusive at present.

Pharmacodynamics

In the Phase III studies, the effects of GUS on serum inflammatory markers, particularly those that affect the T helper (Th) 17 effector cytokine IL-17A, were assessed as part of a biomarker analysis. In both studies, 21 serum proteins were measured from a sub-population of 50 participants per treatment group per study (n = 300 participants in total) at Week 0 (pre-treatment), 4 and 24. The biomarker levels were compared to levels in serum samples from 34 healthy adults matched to reflect the demographics (age, sex, and race/ethnicity) of the treatment population.

In the biomarker analysis, serum levels at Baseline of the acute phase proteins CRP, serum amyloid A (SAA) and IL-6, as well as the Th17 effector cytokines IL-17A and IL-17F, were 40% higher (geometric mean values) in adults with active PsA compared with healthy controls. In Study PSA3001 the subpopulation of participants that had previously been treated with one or more anti-TNF drugs had significantly higher levels of SAA, IL-6, IL-17A, and IL-17F compared to those participants without prior exposure to anti-TNF therapy (geometric mean > 40% higher), although these proteins were significantly upregulated in both PsA groups when compared with the healthy control set.

Treatment with GUS resulted in decreases in serum CRP, SAA, IL-6, IL-17A, IL-17F and IL-22 as early as Week 4, while in the PBO arms there were no significant changes in inflammatory markers from Baseline. Expression of these proteins continued to decrease further over time regardless of the GUS dose regimen. At Week 24, IL-17A and IL-17F expression were no different for GUS treated participants (both dose regimens) compared to demographically matched healthy volunteers. No discernible dose-dependent biomarker differences were observed over 24 weeks of therapy.

The American College of Rheumatology (ACR) response is a composite endpoint that is used to quantify the clinical response to therapy in patients with rheumatoid arthritis or PsA. An ACR20 response is defined as a 20% decrease in the combined number of swollen (maximum of 66) and tender (maximum of 68) joint counts, as well as a 20% improvement in any three of five core measures. When the primary endpoint of the ACR20 response at Week 24 was assessed against quartiles of steady state C_{trough} GUS at Week 20, no apparent exposure-response (E-R) relationship was observed in either Study PSA3001 or PSA3002. For the major secondary endpoint of ACR50 response at Week 24 assessed against C_{trough} quartiles at Week 20, a weak E-R relationship was observed in both Phase III PsA studies.

A definitive conclusion on the impact of ADA on clinical efficacy is limited by the small number of ADA positive participants. No apparent relationship was observed between safety outcomes (adverse events (AE), serious adverse events (SAE), AEs leading to discontinuation, infections, and serious infections) and C_{trough} quartiles at Week 20/24.

Efficacy

Study PSA3001

Study PSA3001 was a randomised double-blind, PBO controlled three arm trial evaluating the efficacy and safety of GUS in adults with active PsA who had an inadequate response or were intolerant to cDMARDs (≥ 3 months treatment), apremilast (≥ 4 months treatment) and/or NSAIDs (≥ 4 weeks treatment). About one third of participants also had inadequate response or intolerance to up to two anti-TNF bDMARDs. The study included a screening phase of up to six weeks, an active treatment phase of 52 weeks, and a safety follow up phase of 12 weeks after the last dose of study medication (at 48 weeks).

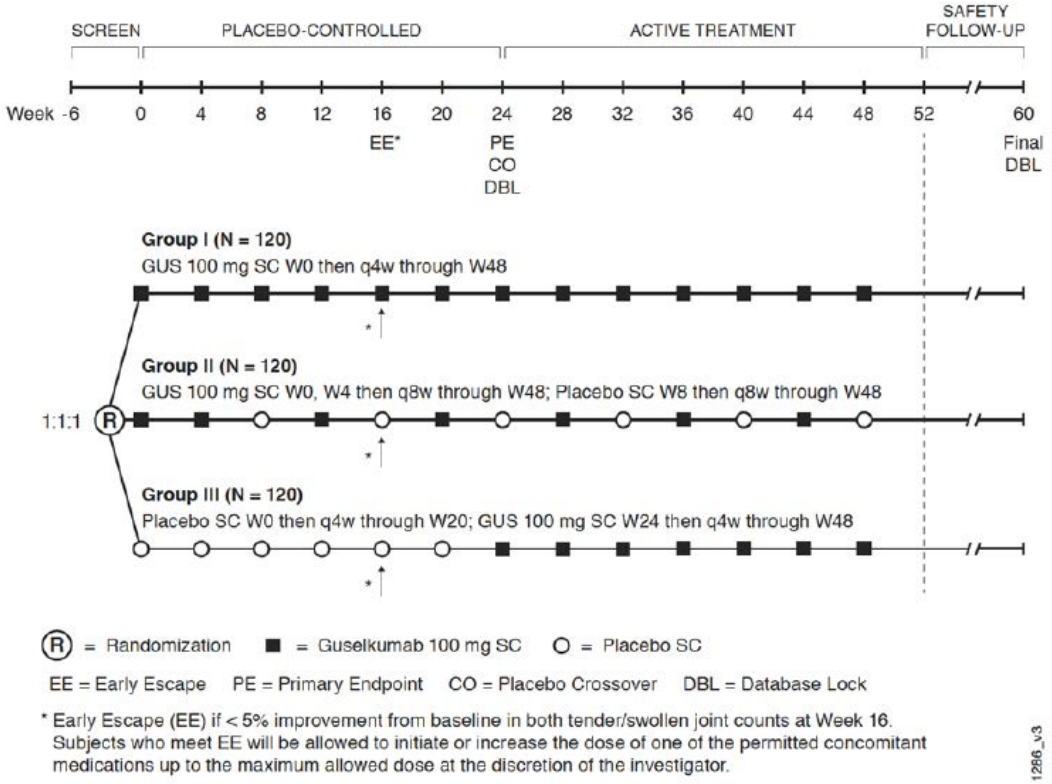
Participants were allowed to continue on stable doses of NSAIDs, oral corticosteroids (≤ 10 mg/day prednisone, or equivalent) and one of the cDMARDs MTX, ≤ 25 mg/week, sulfasalazine (SSZ) ≤ 3g/day, hydroxychloroquine (HCQ) ≤ 400 mg/day or leflunomide (LEF) ≤ 20 mg/day during the trial. Those participants who had not achieved a minimum 5% improvement from Baseline in both tender and swollen joint counts by Week 16 satisfied early escape (EE) criteria and were permitted to initiate or increase the dose of one permitted concomitant PsA medication, which had to be stabilised by Week 24, while remaining on the allocated treatment regimen.

The key inclusion criteria were a clinical diagnosis of PsA according to CASPAR at least six months prior to first dose of study drug, and current active PsA. Active PsA was defined as at least three swollen and tender joints and CRP ≥ 0.3 mg/dL at screening and Baseline.

The participants were randomised in a 1:1:1 ratio to receive GUS 100 mg every 4 weeks (Q4W) from Week 0 to Week 48; GUS 100 mg at Weeks 0 and 4 and Q8W to Week 48; or PBO injections every four weeks from Week 0 to 20 followed by a cross-over from PBO to GUS 100 mg at Week 24 and Q4W to Week 48, as shown in Figure 2. Randomisation was stratified by baseline non-biological DMARD use (yes/no) and prior exposure to anti-TNF drugs (yes/no).

The primary endpoint of this study was the proportion of participants who achieved an ACR20 response at Week 24.

Figure 2: Study PSA3001 Schematic diagram of the study design



The major secondary endpoints included:

- proportion of participants with psoriasis involving at least 3% body surface area (BSA) and an Investigator's Global Assessment (IGA) of psoriasis score of ≥ 2 at Baseline that achieve a response in psoriasis severity according to the IGA at Week 24,
- mean change from Baseline in the Disease Activity Score-28 with C-reactive protein (DAS28-CRP) at Week 24,
- mean change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 24,
- mean change from Baseline in the 36-Item Short form Health Survey (SF-36) Physical Component Score (PCS) at Week 24,
- proportion of participants achieving ACR20 response at Week 16,
- proportion of participants achieving ACR50 response at Week 24,
- proportion of participants achieving ACR50 response at Week 16,
- proportion of participants achieving ACR70 response at Week 24,
- proportion of participants with enthesitis at Baseline that achieve resolution of enthesitis at Week 24,

- change from Baseline in enthesitis score (based on the Leeds Enthesitis Index (LEI)) at Week 24, in those who had enthesitis,
- proportion of participants with dactylitis at Baseline that achieve resolution of dactylitis at Week 24,
- change from Baseline in dactylitis scores at Week 24, in those who had dactylitis
- change from Baseline in SF-36 Mental Component Score (MCS) at Week 24.

Figure 3: Study PSA3002 Schematic summarising sequential endpoint testing procedure

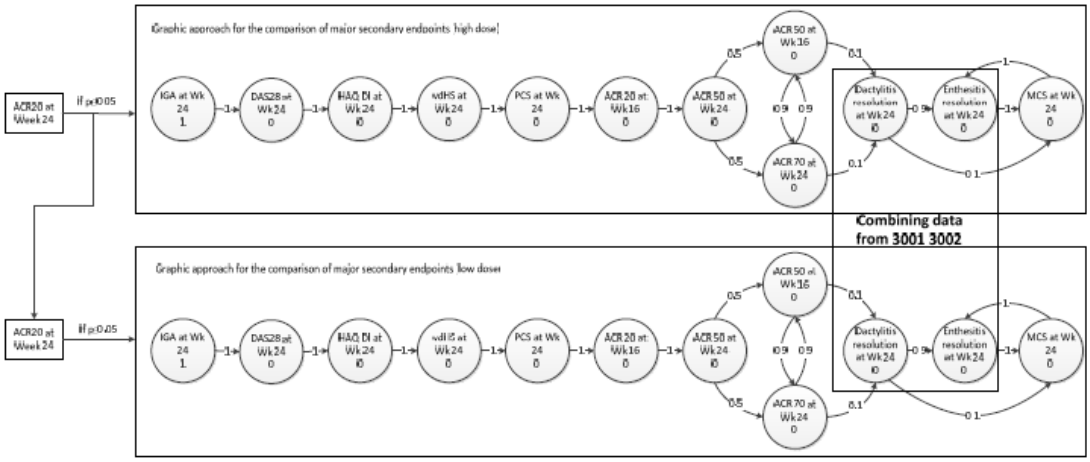


Figure 3 provides a schematic of the sequential testing procedure in Study PSA3002. The same order was applied in Study PSA3001, however Study PSA3001 did not include a radiographic study endpoint in the sequential endpoint testing procedure (van der Heijde-Sharp (vdHS) at Week 24), and MCS at Week 24.

In Study PSA3001, 382 participants were randomised and 381 received at least one dose of study treatment: 128 in the Q4W arm, 127 in the Q8W arm and 126 in the PBO arm. At Week 16, three (2.3%) participants in the Q4W group, four (3.1%) in the Q8W arm and 24 (19.0%) in the PBO arm were eligible for concomitant medication adjustments. Through to Week 24, three (2.3%) participants in the Q4W group, four (3.1%) in the Q8W arm and 12 (9.5%) in the PBO group ceased study treatment. The most common reasons for study drug discontinuation were AEs in GUS treated groups (three in the Q8W group and one in the Q4W arm, versus two in the PBO group) and lack of efficacy in the PBO group (four, versus no participants in either GUS treatment arm). Through to Week 24, major protocol deviations were recorded for 44 participants (11.5%). Among the pre-specified categories of major protocol violations, the percentage of affected individuals in each of the treatment groups was similar.

Demographic characteristics at Baseline were similar in the three treatment groups. The participants had a median age of 49 years (range: 19 to 74 years) with more than half (55.6%; 212 out of 381) aged 45 to < 65 years of age and 7.6% (29 out of 381) aged between 65 and 74 years. Just over half were male and more than 90% were of Caucasian background. The overall population had a mean body mass index (BMI) of 29.8 kg/m^2 (range: 17 to 52 kg/m^2). The proportion of participants with BMI ≥ 30 kg/m^2 (obese) at Baseline was slightly greater (48.4%) in the Q4W group, compare to 40.9% in the Q8W arm and 41.3% in the PBO group. The treatment groups were reasonably well balanced with respect to baseline PsA features and PsA activity, which reflected moderate to severe disease activity, however participants in the Q4W arm tended to have more severe psoriasis and less severe PsA. Evidence of dactylitis varied among the treatment arms (29.7% in Q4W group, 38.9% in Q8W group and 43.7% in PBO group) as did the baseline mean dactylitis scores (9.4 out of 10 in Q4W group, 8.2 in Q8W group and 6.6 in PBO

group). Evidence of enthesitis and mean enthesitis scores were similar at Baseline in the treatment groups.

Prior to enrolment in Study PSA3001, most patients had received cDMARDs (90.3%); with the most common drugs being MTX (80.8%), SSZ (29.4%) and LEF (17.6%). In addition, 41.5% of participants had previously used systemic corticosteroids and 85.3% of participants had taken NSAIDs. At Baseline 64.8% of participants were currently using a cDMARD. Concomitant medication use was well balanced across the treatment groups up to Week 24.

The primary efficacy outcome was achieved in both the Q4W and Q8W treatment groups. At Week 24, 76 (59.4%) participants in the Q4W arm and 66 (52.0%) in the Q8W arm achieved an ACR20 response, compared with 28 (22.2%) participants in the PBO group. The treatment related difference for Q4W versus PBO was 37.1 (95% CI 26.1, 48.2, $p < 0.001$) and for Q8W versus PBO was 29.8 (95% CI 18.6, 41.1, $p < 0.001$). No comparison was performed between Q4W and Q8W arms, and sensitivity analyses were consistent with primary analysis findings. ACR20 responses rose above Baseline from four weeks after the first dose.

Statistically significant improvements over PBO were achieved in both the Q4W and Q8W arms for the major secondary endpoints up to and including the ACR50 response at Week 24. Statistically significant improvements over PBO were achieved in the Q4W arm for secondary endpoints ACR50 at Week 16 and ACR70 at Week 24. In the Q8W arm, numerical improvements over PBO treatment for these two outcomes were not statistically significant, or hierarchical endpoint testing rules prohibited further formal testing. No formal testing for statistical significance of numerically better results in change from Baseline in SF-36 MCS at Week 24 was performed, owing to hierarchical testing rules.

Study PSA3002

Study PSA3002 was also a randomised double-blind, PBO controlled three arm trial evaluating the efficacy and safety of guselkumab in adults with active PsA who had an inadequate response or were intolerant to cDMARDs (≥ 3 months treatment), apremilast (≥ 4 months treatment) and/or NSAIDs (≥ 4 weeks treatment).

The following major features differentiated Study PSA3002 from Study PSA3001:

- The active treatment phase of PSA3002 runs from Week 24 to Week 104, and the safety follow-up phase concludes at 112 weeks.
- All participants in this study were naïve to biologic therapies, including anti-TNF drugs.
- All participants had more severely active PsA, defined as at least five swollen and tender joints and CRP ≥ 0.6 mg/dL at Baseline.
- An additional radiographic secondary outcome was included in the statistical analysis (Figure 3): assessment of the change in joint structural damage from Baseline to Week 24 according to the modified vdHS Total Sharp Score (modified vdH-S TSS). The maximum modified vdH-S score is 528. In general, the smallest detectable difference (SDC) in the vdH-S score is thought to be between 5 to 8 points; in Study PSA3002 the SDC was calculated to be 2.18.
- Stratification factors during randomisation were baseline non-biological DMARD use (yes/no) and most recent available CRP prior to randomisation (< 2.0 mg/dL versus ≥ 2.0 mg/dL).

In this study, a total of 741 participants were randomised and 739 participants received at least one dose of study drug: 245 were allocated to the Q4W arm, 248 to the Q8W arm and 246 to PBO. At Week 16, 12 (4.9%) participants in the Q4W arm, 13 (5.2%) in the Q8W

arm and 38 (15.4%) in the PBO arm met EE criteria. Through to Week 24, nine (3.7%) in the Q4W arm, eight (3.2%) in the Q8W arm and six (2.4%) in the PBO arm ceased study treatment. The most common reasons for discontinuation of study treatment were AEs (six in the Q4W arm, two in the Q8W arm, four in the PBO arm) followed by lack of efficacy (three participants in each GUS treatment group, versus zero in the PBO arm). Through to Week 24, major protocol variations were recorded for 58 participants (7.8%). Among the pre-specified categories of major protocol violations, the percentage of affected individuals in each of the treatment groups was similar.

There were no clinically significant differences between the treatment groups with respect to demographic characteristics at Baseline. The participants had a median age of 46 years (range: 19 to 75 years) with almost half (49.5%) aged 45 to < 65 years of age and 4.5% aged 65 years or more at Baseline. Just over half were male and 98.0% were of Caucasian background. The overall population had a mean BMI of 28.9 kg/m^2 (range: 16 to 56 kg/m^2).

The treatment groups were also reasonably well balanced with respect to baseline PsA features and PsA severity. The PsA disease activity scores recorded at Baseline were consistent with severe activity in patients at a significant risk of functional impairment and damage over time. Some variability in baseline CRP levels between groups was noted. The mean (median) CRP levels were similar in the PBO (2.116 (1.155) mg/dL) and Q8W (2.036 (1.31) mg/dL) treatment arms and higher than in the GUS Q4W arms (1.807 (1.16) mg/dL). Evidence of dactylitis and enthesitis varied between the treatment arms. The overall proportion of participants with enthesitis at Baseline was higher in the PBO arm (72.7%) compared to the Q8W arm (63.7%) and the Q4W arm (69.4%), although enthesitis scores were similar. More participants in the Q4W arm (49.4%) had dactylitis at Baseline compared to 44.8% in the Q8W arm and 40.4% in the PBO group. With regard to characteristics of plaque psoriasis, the proportion of participants with a baseline IGA score > 2 was higher in the PBO (85.3%) and Q4W groups (82.0%) compared to the Q8W arm (78.6%).

Most participants had received conventional DMARDs (90.8%): most frequently MTX (85.0%), then SSZ (21.7%) and LEF (12.9%). In addition, 47.0% of participants had previously used systemic corticosteroids and 93.2% had taken NSAID medication. At Baseline, 69.3% were currently using MTX, SSZ or LEF. Additionally, around one in five (19.6%) were taking oral corticosteroids (at a median dose of 5 mg/day of prednisone in the 2 GUS groups and 10 mg/day in the PBO arm) and 68.2% were taking NSAID. Concomitant medication use was well balanced across the 3 treatment groups up to Week 24.

The primary efficacy outcome was achieved in both the Q4W and Q8W treatment groups. At Week 24, 156 (63.7%) participants in the Q4W arm and 159 (64.6%) in the Q8W arm achieved an ACR20 response compared with 81 (32.9%) participants in the PBO group. The treatment related difference for Q4W versus PBO was 30.8 (95% CI 22.4, 39.1, $p < 0.001$) and for Q8W versus PBO was 31.2 (95% CI 22.9, 39.5, $p < 0.001$). No comparison was performed between Q4W and Q8W arms, and sensitivity analyses were consistent with primary analysis findings. ACR20 responses increased from Week 4 after the first dose of GUS.

Statistically significant improvements over PBO were achieved in both the Q4W and Q8W arms for the major secondary endpoints up to and including change from Baseline in HAQ-DI score at Week 24.

A key focus of Study PSA3002 was assessing whether GUS was able to slow the radiographic progression of PsA. The inclusion criteria were selected to try and enhance the population most likely to show radiographic changes over 24 weeks. Radiographic progression was assessed using the change from Baseline in modified vDH-S at Week 24.

Mean (median) modified vdH-S scores at Baseline were 23.75 (10.50) in the PBO group, 23.04 (11.50) in the Q8W group and 27.17 (10.00) in the Q4W group, respectively. Statistically significant improvements over PBO were achieved in the Q4W arm for change from Baseline in vdH-S at Week 24. The mean standard deviation (SD) change from Baseline modified vdH-S score in the PBO group was 0.90 (3.142); in the Q8W group was 0.45 (2.376) and in the Q4W group was 0.25 (2.521). In the Q8W arm, the apparent numerical advantage over PBO was not statistically significant.

Statistically significant improvements over PBO were achieved in the Q4W arm for all of the remaining secondary endpoints. Numerically higher scores in the Q8W arm compared to PBO were not formally tested, based on the hierarchical testing rules.

Secondary endpoints (pooled data)

Statistically significant improvements over PBO were achieved in the pooled (Studies PSA3001 plus PSA3002) Q4W group with regard to changes in enthesitis and dactylitis. Numerically higher improvements over PBO in the pooled Q8W group were not formally tested for statistical significance.

Study PSA2001

In this supportive Phase II study, a total of 149 participants were randomised in a 2:1 ratio to receive SC GUS 100 mg at Weeks 0 and 4, then Q8W (Weeks 12, 20, 28, 36 and 44) as well as a single SC PBO injection at Week 24 (Group 1, n = 100); or PBO injections at Weeks 0, 4, 12 and 20, followed by SC GUS 100 mg at Weeks 24, 28, 36 and 44 (Group 2, n = 49). At Week 16, participants in both treatment arms who recorded < 5% improvement from Baseline in both swollen and tender joint counts qualified for EE and switched to open-label therapy with SC ustekinumab.

The primary efficacy outcome evaluated in Study PSA2001 was the proportion of participants in each treatment group achieving an ACR20 response at Week 24. The major secondary efficacy endpoints were: proportion of participants achieving Psoriasis Area and Severity Index 75 (PASI 75)skin response at Week 24, the mean change from Baseline in HAQ-DI score at Week 24, percentage of participants recording ACR20 response at Week 16, proportion of participants achieving ACR50 response at Week 24, percentage improvement in enthesitis score at Week 24 (among participants with enthesitis at Baseline) and the percentage improvement in dactylitis scores at Week 24 (among participants with dactylitis at Baseline).

The pre-specified primary and secondary efficacy outcomes were met. At Week 24, the proportion of participants who achieved ACR20 response was significantly higher in the GUS Q8W arm (58.0%) compared to the PBO group (18.4%; $p < 0.001$ by Cochran-Mantel-Haenszel (CMH) test). The treatment related difference was 39.7% (95% CI: 25.3%, 54.1%). The likelihood (risk ratio) of achieving an ACR20 response at Week 24 in GUS treated group versus PBO was 3.2 (95% CI: 1.7, 5.9). Five sensitivity analyses supported the primary efficacy analysis result.

For those adults randomised to the GUS treatment arm, further improvements in ACR20, ACR50 and ACR70 response rates from Week 24 were observed and these improvements were maintained through to Week 44 (77.4%, 46.4%, and 26.2%, respectively for ACR20/50/70 responses) and also at 12 weeks after the last study drug administration.

For participants in the PBO to GUS crossover treatment group, improvements in ACR20, ACR50 and ACR70 response rates were observed four weeks after the first dose of GUS. Improvements in ACR response rates continued over time in these participants and by Week 44, the ACR20, ACR50 and ACR70 response rates in the PBO to GUS crossover group were 75.0%, 46.4% and 25.0%, respectively. The proportions of participants achieving the respective ACR response were numerically comparable to those observed in the originally randomised GUS treatment group.

The sponsor has requested that both Q4W and Q8W regimens be approved for use in Australia. The clinical evaluator disagrees, noting that although the Study PSA3001 indicated a potential dose-response efficacy effect (specifically in the ACR50 and ACR70 responses), this was not supported by the larger Study PSA3002 in patients at higher risk of radiographic progression, nor by the pooled analysis of both studies. While there was a small but statistically significant difference in radiographic outcomes in Q4W population compared to PBO, which was not seen with the Q8W regimen, the clinical relevance of this finding was considered unclear.

Safety

Safety and tolerability data for GUS in the pivotal Phase III PsA studies were pooled for the 24 week placebo controlled periods, and additionally up to the data cut at 1 May 2019. Through to the data cut-off date, a total of 1100 participants with active PsA were exposed to GUS, including 978 (88.9%) individuals treated for at least six months and 518 (47.1%) individuals treated for at least one year.

Safety data included all AEs including injection site and allergic reactions; adverse events of special interest (AESI) including serious and opportunistic infections, malignancy, major adverse cardiovascular events (MACE), anaphylaxis and serum sickness. Safety information was collected by case report form (CRF) every four weeks, vital signs every four weeks and/or physical examination at Weeks 24 and 52, and clinical laboratory tests every four weeks. Medications, assessments for potential tuberculosis (TB) exposure and validated assessment for suicidal behaviour (electronic Columbia Suicide Severity Rating Scale, eC-SSRS) were also regularly reviewed.

The safety analysis set of Study PSA2001 contained a total of 129 adults with active PsA who were exposed to at least 1 dose of GUS therapy, including 115 (89.1%) treated for at least six months and 70 (54.3%) treated for at least one year. Data from Study PSA2001 included adverse event reports for up to 56 weeks exposure.

Safety data collected for up to three years of treatment from two studies in psoriasis were also included in the safety dataset, for comparison. In the Phase III psoriasis studies a total of 823 adults with moderate to severe psoriasis were exposed to GUS Q8W regimen. Approximately 20% of patients in the psoriasis studies had a history or current diagnosis of PsA.

Table 3: Studies PSA3001, PSA3002 Summary of treatment emergent adverse events through the placebo-controlled period (Week 24)

	Placebo-Controlled Period Through Week 24[a]			
		Guselkumab		
	Placebo[b]	100 mg q8w	100 mg q4w	Combined
Analysis set: Safety Analysis Set	372	375	373	748
Avg duration of follow up (weeks)	24.2	24.1	24.1	24.1
Avg number of study agent admins	5.9	5.9	5.9	5.9
Avg number of placebo admins	5.9	2.0	0.0	1.0
Avg number of guselkumab admins	-	3.9	5.9	4.9
Subjects with 1 or more				
AEs	176 (47.3%)	182 (48.5%)	182 (48.8%)	364 (48.7%)
SAEs	12 (3.2%)	7 (1.9%)	8 (2.1%)	15 (2.0%)
AEs leading to discontinuation of study agent	7 (1.9%)	5 (1.3%)	8 (2.1%)	13 (1.7%)
AEs with severe intensity	6 (1.6%)	3 (0.8%)	2 (0.5%)	5 (0.7%)
Infections	77 (20.7%)	73 (19.5%)	80 (21.4%)	153 (20.5%)
Serious infections	3 (0.8%)	1 (0.3%)	3 (0.8%)	4 (0.5%)
Injection site reactions	1 (0.3%)	5 (1.3%)	4 (1.1%)	9 (1.2%)
Events of malignancy	1 (0.3%)	2 (0.5%)	0	2 (0.3%)
Opportunistic infections	0	0	0	0
Anaphylactic reactions or serum sickness reactions	0	0	0	0
Events leading to death	2 (0.5%)	0	0	0

Note: Adverse events are coded using MedDRA Version 21.1. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

a: For subjects in all treatment groups who discontinued study treatment early, with the last study treatment (placebo or guselkumab) administered before Week 24 and who did not receive any study agent (placebo or guselkumab) at or after Week 24, all data including the final safety follow-up visit collected through data cut were included in this period.

b: For subjects in the placebo group who changed treatment from placebo to guselkumab due to crossover, only data before the first administration of guselkumab were included in this group. Data on and after the first administration of guselkumab were not included in this group.

Table 3 (shown above)summarises the treatment emergent adverse events (TEAE) reported in the pooled Phase III PSA studies during the 24 week placebo-controlled period. Total reports of one or more AE were approximately equal in PBO, Q8W and Q4W groups, and reports of one or more serious adverse events (SAE) were slightly higher in the PBO group. In all groups, infections were the most frequently reported adverse events.

The most frequently reported types of infectious AE through to Week 24 were nasopharyngitis (4.6%, 6.9% and 5.1% respectively in the PBO, Q8W, and Q4W groups), upper respiratory tract infection (URTI, 4.6%, 3.5% and 6.2% in the PBO, Q8W and Q4W groups, respectively) and bronchitis (1.1%, 1.6% and 2.9% in the PBO, Q8W and Q4W groups, respectively). All other infections were reported in < 2% of both GUS groups. Other System Organ Classses (SOC) with AEs reports in > 10% of participants in either GUS treatment group included abnormal investigations (7.0% with PBO, 13.6% with GUS Q8W, 11.5% with GUS Q4W) and musculoskeletal and connective tissue disorders (12.6% with PBO, 9.9% with GUS Q8W, 10.2% with GUS Q4W).

Through to Week 24, few participants reported injection site reactions (ISR), one in the PBO pool, five in the Q8W pool and four in the Q4W pool. All ISRs were mild in intensity and none resulted in permanent treatment discontinuation. Through to Week 24, a total of four suicidal ideation events were reported, two in the PBO group and one in each GUS dose group. Three of the four participants had a history of suicidal ideation.

Through to Week 24, similar proportions of participants in each pool experienced at least one treatment related AE, 10.0% (37) in the PBO group, 11.5% (43) in the Q8W group and 10.7% (40) in the Q4W group. By Preferred Term (PT), the most common treatment related AEs were raised serum alanine aminotransferase (ALT) (6.5% in Q4W therapy versus 2.4% in the other two groups), raised serum AST (2.0 to 2.4% in the two GUS treatment groups versus 0.8% with PBO), nasopharyngitis (2.0% with Q4W therapy versus < 1.0% in the two other groups), URTI (1.6% with Q4W therapy versus < 1.0% in

the two other groups) and neutropenia (2.0% with Q8W versus < 1.0% in the two other treatment groups).

Infections and infestations constituted the SAEs in the first 24 weeks. Three severe infections were reported with Q4W therapy (all in Study PSA3002): acute hepatitis B, pneumonia (influenza) and oophoritis. Two serious infections were reported in the PBO group (both in Study PSA3001): URTI and limb abscess. No patients died in the GUS treatment groups in the first 24 weeks, one participant in the PBO group died with cardiac failure (unrelated to treatment). Through to Week 24, the overall rates of AEs leading to study drug discontinuation per 100 patient-years (PY) of follow-up were 4.05, 2.88, and 6.97 respectively for the PBO group, GUS Q8W, and GUS Q4W group. Four participants in GUS arms recorded infections that led to treatment discontinuation. Bronchitis was reported in one patient treated with GUS Q8W, and single reports of acute hepatitis B, pneumonia (influenza) and rhinovirus infection were recorded in the GUS Q4W arm. A low number of participants experienced an AE leading to interruption of study medication: seven (1.7%) in the PBO group, nine (2.4%) in Q8W group and ten (2.7%) in the Q4W group. Various types of infection and raised serum transaminases were the two most common AE resulting in the interruption of GUS therapy in both dose regimens.

Through to Week 24, Grade 1 or higher post-baseline increases in serum ALT were reported more frequently in the GUS Q4W group (38.8%) compared with the Q8W (30.1%) and PBO (32.3%) arms. Similarly, Grade 1 or higher post-baseline increases in serum aspartate aminotransferase (AST) were reported slightly more frequently in the Q4W group (24.8%) compared with the Q8W (20.9%) and PBO (21.7%) groups. Most post-baseline increases in serum transaminases were transient, did not result in study drug interruption or discontinuation and were not associated with clinically significant increases in bilirubin. Grade 2 or higher increases in ALT or AST were also generally transient and did not result in drug discontinuation. Exceptions were three participants in the Q4W group of Study PSA3002. One participant had a history of alcohol use and MTX use at Baseline, and study drug was interrupted owing to increased AST and ALT, chronic cholecystitis, pancreatitis and fatty liver disease. This person discontinued the study after the Week 24 visit. In the second person, study drug was discontinued owing to drug-induced liver injury (DILI) related to isoniazid for treatment of latent TB, and the third person discontinued treatment with a SAE of acute hepatitis B virus infection. No significant renal related AEs or post-baseline laboratory changes in renal function were recorded.

Through to Week 24, the proportion of participants with a Grade 1 or higher post-baseline decrease in neutrophil count was higher in the GUS Q4W (7.8%) and Q8W (7.2%) groups compared with the PBO arm (4.3%). Few Grade 2 or higher decreases in neutrophil counts were reported in the combined GUS (1.7%; 13/748) cohort, however the reports were still more frequent compared with PBO (1.1%; 4/370). There was a single case of Grade 4 decrease in neutrophil count in a person treated with GUS Q4W and etoricoxib. Grade 2 or higher decreases in white blood cell counts also occurred more frequently in GUS treatment groups (1.5%, 11 out of 744 combined) than in the PBO group (0.8%, 3 out of 370).

Through to Week 24, patients treated with GUS showed a greater mean reduction from Baseline in platelet counts compared with the PBO group. At Week 24, the mean change in platelet count from Baseline was -3.4 x 10^9/L in the PBO group compared to -21.7 x 10^9/L in the GUS Q8W group, and -21.0 x 10^9/L in the GUS Q4W arm. The sponsor considered these changes to be consistent with a decrease in inflammatory response following active treatment.

Through to Week 24, the incidence of positive ADA to GUS was low at 1.6% (6 out of 373) with Q8W therapy and 2.4% (9 out of 371) with Q4W regimen. Although the incidence of ADA was low overall, it was somewhat lower in patients that received a concomitant

cDMARD (1.6%; 8 out of 501 with cDMARD versus 2.9%; 7 out of 243 without cDMARD). The clinical relevance for safety outcomes in participants who developed ADA is yet to be defined; with no discernible link to the risk of infection, or injection related reactions.

Table 4: Studies PSA3001, PSA3002 Summary of treatment emergent adverse events through to 1 May 2019 (data cut-off)

	Reporting Period Through the Data Cut (01 May 2019)				
	Guselkumab				
	100 mg q8w	100 mg q4w	Placebo → 100 mg q4w[a]	100 mg q4w Combined[a]	All Combined[a]
Analysis set: Safety Analysis Set	375	373	352	725	1100
Avg duration of follow up (weeks)	51.9	51.9	28.7	40.6	44.5
Avg number of study agent admins	13.2	13.2	7.5	10.4	11.4
Avg number of placebo admins	5.9	0.0	0.0	0.0	2.0
Avg number of guselkumab admins	7.3	13.2	7.5	10.4	9.4
Subjects with 1 or more					
AEs	243 (64.8%)	239 (64.1%)	133 (37.8%)	372 (51.3%)	615 (55.9%)
SAEs	20 (5.3%)	18 (4.8%)	14 (4.0%)	32 (4.4%)	52 (4.7%)
AEs leading to discontinuation of study agent	8 (2.1%)	10 (2.7%)	6 (1.7%)	16 (2.2%)	24 (2.2%)
AEs with severe intensity	8 (2.1%)	10 (2.7%)	9 (2.6%)	19 (2.6%)	27 (2.5%)
Infections	127 (33.9%)	116 (31.1%)	68 (19.3%)	184 (25.4%)	311 (28.3%)
Serious infections	5 (1.3%)	4 (1.1%)	5 (1.4%)	9 (1.2%)	14 (1.3%)
Injection site reactions	8 (2.1%)	11 (2.9%)	4 (1.1%)	15 (2.1%)	23 (2.1%)
Events of malignancy	2 (0.5%)	0	1 (0.3%)	1 (0.1%)	3 (0.3%)
Opportunistic infections	0	0	0	0	0
Anaphylactic reactions or serum sickness reactions	0	0	0	0	0
Events leading to death	0	0	0	0	0

Note: Adverse events are coded using MedDRA Version 21.1. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.

a: For subjects in the placebo group who changed treatment from placebo to guselkumab due to crossover, only data on and after first administration of guselkumab were included in this group. Data prior to the first administration of guselkumab were not included.

In general, all of the pooled safety data provided in the Phase III PsA studies through to the data cut-off date including from patients switched from PBO to GUS protocols from Week 24 (Table 4), the safety data from Study PSA2001, and the safety data from the pooled psoriasis studies reflected the safety profile identified during the 24 week PBO-controlled period in the two pivotal studies.

Reports of MACE across the pooled studies included one non-fatal ischaemic stroke in the Q4W arm, one cardiac failure before Week 24 in the PBO group, one myocardial infarction in a GUS treated patient with multiple cardiovascular risk factors enrolled in Study PSA2001 and one MACE in a GUS treated patient in the psoriasis studies. Through to data cut-off, two participants treated with GUS Q4W recorded pulmonary embolism. Two GUS treated patients developed skin malignancies, including one case of malignant melanoma *in situ*.

Overall, through to Week 24 and through to the data cut-off date, evaluation by sub-groups (for example, baseline demographic or disease characteristics, medication history) revealed no substantial differences between the GUS and placebo groups or between the GUS Q8W and Q4W groups in the proportions of participants with AEs, SAEs, AEs leading to discontinuation of study agent, infections, or serious infections. Low numbers of participants in certain subgroups (for example participants ≥ 65 years, race other than white) or the low overall number of participants with certain types of events (that is SAEs, AEs leading to discontinuation of study agent, and serious infections) limit interpretation of the subgroup data.

The clinical evaluator concluded that the safety profile of GUS in adult patients with active PsA was as expected for an anti-IL-23 therapy and was consistent with previous GUS experience in adult patients with moderate to severe psoriasis. However, four additional adverse reactions were identified in the PsA studies:

- Respiratory tract infection (replacing upper respiratory tract infection), to include bronchitis and respiratory tract infections
- Bronchitis
- Transaminases increased
- Neutrophil count decreased

The clinical evaluator recommends that the risks of raised transaminases and neutropenia should be included in the risk management plan (RMP), however, the sponsor responded that including references to these risks in the PI is sufficient. The sponsor proposes to include an updated table of AE frequency in the PI, based on the additional data from the PsA studies and post marketing experience, shown in Table 5. The adverse reactions are classified by MedDRA[9] SOC and frequency, using the following convention: very common (≥ 1 out of 10), common (≥ 1 out of 100 to < 1 out of 10), uncommon (≥ 1 out of 1,000 to < 1 out of 100), rare (≥ 1 out of 10,000 to < 1 out of 1,000), very rare (< 1 out of 10,000), not known (cannot be estimated from the available data).

Table 5: Summary of adverse reactions for Product Information

System Organ Class	Frequency	Adverse drug reaction
Infections and infestations	Very common	Respiratory tract infections
	Uncommon	Herpes simplex infections
	Uncommon	Tinea infections
	Uncommon	Gastroenteritis
Investigations	Common	Transaminases increased
	Uncommon	Neutrophil count decreased
Immune system disorders	Uncommon	Hypersensitivity
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria
	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Injection site erythema
	Uncommon	Injection site pain

[9] MedDRA = Medical Dictionary for Regulatory Affairs

Clinical evaluator's recommendation

The clinical evaluator recommended approval of the submission.

The clinical evaluator recommended that this approval be subject to regular periodic safety update reports (PSUR) and the provision to the TGA of the final reports for Studies PSA3001 and PSA3002 when available.

Risk management plan

The pharmacovigilance plan and RMP are considered acceptable by the RMP evaluator.

In support of the extended indications, the sponsor submitted EU-RMP version 5.1 (dated 1 October 2019; data lock point (DLP) 12 July 2019) and Australia Specific Annex (ASA) version 3.0 (dated 14 October 2019). In response to TGA questions, the sponsor provided EU-RMP version 5.3 (dated 26 May 2020, DLP 12 September 2019) and ASA version 4.0 (dated 20 July 2020). In response to second round RMP evaluation report, the sponsor has provided ASA version 5.0 (dated 17 September 2020).

The summary of safety concerns in the RMP is included as Table 6. No new safety concerns were identified in association with the extension of indication to include PsA. Specifically, the RMP evaluator considered that the risks of elevated serum transaminases and decreased neutrophil count did not need to be included in the RMP. Routine pharmacovigilance includes targeted questionnaires for all risks. The follow-up and completion of Study PSA3002 has been included in the RMP as an additional pharmacovigilance activity.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 6.[10]

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Serious infection	ü[1]	ü[2,3]	ü	–
	Malignancy	ü[1]	ü[2,3]	ü	–
	Serum sickness	ü[1]	ü[2,3]	ü	–
	Major adverse cardiovascular events (MACE)	ü[1]	ü[2,3]	ü	–
Missing information	Exposure during pregnancy	ü[4]	ü[3,5]	ü	–

[10] *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 labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Use in patients ≥ 65 years of age	ü	ü [3]	ü	–
	Long-term safety of guselkumab	ü	ü [2,3]	ü	–

[1]Targeted follow-up questionnaires, [2]Clinical trials, [3]Patient registries, [4]Specific pregnancy follow-up forms, [5]Electronic Administrative Health Claims Databases Review/ observational PASS

Recommended conditions of registration

The RMP evaluator has recommended the following 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:

> *The Tremfya EU-Risk Management Plan (RMP) (version 5.3, dated 26 May 2020, data lock point 12 September 2019), with Australian Specific Annex (version 5.0, dated 17 September 2020), included with submission PM-2019-05350-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.*

The following wording is recommended for the PSUR requirement:

> *An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).*
>
> *Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration*

Risk-benefit analysis

Delegate's considerations

Proposed indication

The original submission from the sponsor proposed an extended indication for Tremfya to include '*the treatment of adult patients with active psoriatic arthritis*'. After reviewing the submitted dossier, the clinical evaluator recommended that the indication should be limited to use after failure of or intolerance to a trial of cDMARD. The recommendation was based on the inclusion criteria for the Phase III clinical studies, both of which only enrolled participants who had been treated with one or more cDMARDs for at least three months, or apremilast for at least four months, and/or NSAIDs. In both studies, over 90% of participants had trialled cDMARDs, and between 60 and 70% were using cDMARDs at Baseline. While in Study PSA3001 about one third of participants also had inadequate

response or intolerance to up to two anti-TNF bDMARDs, no participant in Study PSA3002 had trialled a biological therapy before agreeing to participate. The sponsor proposed an amended indication, which was supported by the clinical evaluator:

'*Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to prior DMARD therapy*'.

The Delegate agrees that the amended indication accurately reflects the population included in the pivotal studies.

Dosing regimen

The clinical evaluator noted that '*the most overt difference between Studies PSA3001 and PSA3002 was the relative efficacy observed with the 2 GUS dose regimens*'.

Study PSA3001 enrolled participants with active PsA with a median of eight swollen joints and 14.2 tender joints, and median CRP of 0.666 mg/dL. Over 90% had received prior treatment with cDMARDs, immunosuppressives or apremilast and 31% had received anti-TNF therapies (see Table 7, below). At Week 24, 76 (59.4%) participants in the Q4W arm and 66 (52.0%) in the Q8W arm achieved an ACR20 response, compared with 28 (22.2%) participants in the PBO group. These results may suggest a modest dose-effect response, supporting more frequent dosing of GUS. However, in this study, ACR characteristics at Baseline were slightly more favourable in the Q4W population (see Table 8, below); conversely the features of psoriasis in the Q4W group were nominally more severe than in the other two groups.

Table 7: Studies PSA3001, PSA 3002 Baseline demographics and disease characteristics

	CNTO1959PSA3001	CNTO1959PSA3002
Subjects randomized at Week 0	381	739
Demographic characteristics		
Age (years), median	49.0	46.0
Sex, male	195 (51.2%)	388 (52.5%)
Race, white	349 (91.6%)	724 (98.0%)
Weight (kg), median	85.0	83.0
≤90 kg	228 (59.8%)	466 (63.1%)
>90 kg	153 (40.2%)	273 (36.9%)
BMI (kg/m^2), median	29.3	28.1
Baseline disease characteristics		
PsA duration (yrs), median	5.00	3.43
Psoriasis duration (yrs), median	14.0	12.0
Percent BSA affected with psoriasis, median	6.0	9.0
Subjects with ≥3% BSA	281 (73.9%)	600 (81.5%)
PASI score, median	5.3	6.2
PsA subtype		
Polyarticular arthritis with absence of rheumatoid nodules	166 (43.6%)	281 (38.0%)
Asymmetric peripheral arthritis	110 (28.9%)	147 (19.9%)
Spondylitis with peripheral arthritis	75 (19.7%)	258 (34.9%)
Distal interphalangeal joint involvement	28 (7.3%)	47 (6.4%)
Arthritis mutilans	2 (0.5%)	6 (0.8%)
Number of swollen joints (0-66), median	8.0	10.0
Number of tender joints (0-68), median	14.2	18.0
HAQ-DI score (0-3), median	1.250	1.250
CRP (mg/dL), median	0.666	1.200
Dactylitis, N	380	738
Subjects with dactylitis	142 (37.4%)	331 (44.9%)
Dactylitis score (1-60), median	4.0	5.0
Enthesitis, N	380	738
Subjects with enthesitis	222 (58.4%)	506 (68.8%)
Enthesitis score (based on LEI) (1-6), median	2.0	2.0[a]
Prior/concomitant medications for PsA or psoriasis		
Prior medications for PsA	381 (100.0%)	739 (100.0%)
Any DMARDs, immunosuppressives, or apremilast	348 (91.3%)	672 (90.9%)
MTX	308 (80.8%)	628 (85.0%)
MTX use ≥3 years [b]	122 (39.6%)	215 (34.2%)
Immunosuppressives	17 (4.5%)	25 (3.4%)
Systemic corticosteroids	158 (41.5%)	347 (47.0%)
NSAIDs	325 (85.3%)	689 (93.2%)
Apremilast	12 (3.1%)	13 (1.8%)
Anti-TNFα	118 (31.0%)	0
1 therapy [b]	102 (86.4%)	0
2 therapies [b]	16 (13.6%)	0
Prior medications for psoriasis	246 (64.6%)	469 (63.5%)
Topicals	234 (61.4%)	453 (61.3%)
UVB	40 (10.5%)	70 (9.5%)
PUVA	23 (6.0%)	43 (5.8%)
Baseline medications for PsA	247 (64.8%)	512 (69.3%)
Non-biologic DMARDs (MTX, HCQ, SSZ, and LEF)	247 (64.8%)	512 (69.3%)
MTX	211 (55.4%)	443 (59.9%)
Oral corticosteroids	54 (14.2%)	145 (19.6%)
NSAIDs	217 (57.0%)	504 (68.2%)

BMI=body mass index; BSA=body surface area; CRP=C-reactive protein; DMARD=disease-modifying antirheumatic drug; HAQ-DI=Disability Index of the Health Assessment Questionnaire; HCQ= hydroxychloroquine; LEF=leflunomide; LEI=Leeds Enthesitis Index; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; PASI=Psoriasis Area Severity Index; DAS28 (CRP)=Disease Activity Index Score 28 (CRP); PsA=psoriatic arthritis; PUVA=psoralens ultraviolet A; SSZ=sulfasalazine; TNF=tumor necrosis factor; UVB=ultraviolet B; vdH-S=van der Heijde-Sharp (score); W=Week.

a: Number of subjects with enthesitis = 498.

b: The number of subjects with the indicated previous medication or therapy was the denominator for the percentage of subjects.

Table 8: Study PSA3001 Summary of psoriatic arthritis disease characteristics for American College of Rheumatology components at Baseline

		Guselkumab	
	Placebo	100 mg q8w	100 mg q4w
Analysis set: Full Analysis Set 1	126	127	128
Median number of swollen joints (0-66)	8.0	8.0	7.0
Median number of tender joints (0-68)	15.0	15.0	13.0
Number of subjects with dactylitis	55 (43.7%)	49 (38.9%)	38 (29.7%)
Median HAQ disability index (0-3)	1.375	1.375	1.125
Median CRP (mg/dL)	0.787	0.663	0.571

Study PSA3002 enrolled participants with active PsA with a median of ten swollen joints and 18 tender joints, and median CRP of 1.200 mg/dL. Compared to Study PSA3001 group, more patients in PSA3002 had active enthesitis and/or dactylitis, the median BSA affected by psoriasis was greater, and baseline use of cDMARDs, corticosteroids and NSAIDs were all slightly higher reflecting a moderately more severely affected group. At Week 24, 156 (63.7%) participants in the Q4W arm and 159 (64.6%) in the Q8W arm achieved an ACR20 response compared with 81 (32.9%) of participants in the PBO group. Compared to the outcomes of Study PSA3001, this larger study in a more severely affected population does not suggest a dose-dependent effect of GUS.

The pharmacodynamics (PD) data from the same study populations appear to support a modest dose effect. Although there was no apparent E-R effect when the primary endpoint of the ACR20 response at Week 24 was assessed against quartiles of $C_{trough,ss}$ GUS at Week 20 in either Study PSA3001 or PSA3002, a weak E-R effect was seen in both studies when the arguably more difficult to achieve ACR50 response at Week 24 was assessed against C_{trough} quartiles at Week 20.

With regard to safety, while overall adverse event reports in the GUS treated groups were generally low, there was a tendency for more adverse events to occur in the Q4W group.

Clinical significance of radiographic changes

The sponsor states that patients naïve to biologic therapies with more severe symptoms and signs of PsA (and psoriasis) at Baseline were enrolled in PSA3002 to capture a population more likely to experience radiographically detectable progression, and subsequently a radiographic response to GUS, over 24 weeks. The change from Baseline vdH-S endpoint at Week 24 was included as a secondary endpoint relatively early in the sequential statistical testing procedure. Statistically significant improvements over PBO in change from Baseline in vdH-S at Week 24 were achieved in the Q4W arm. The mean (SD) change from Baseline modified vdH-S score in the PBO group was 0.90 (3.142); in the Q8W group was 0.45 (2.376) and in the Q4W group was 0.25 (2.521). The higher positive number in the PBO group indicate more progression. In the Q8W arm, the apparent numerical advantage over PBO was not statistically significant.

Change from Baseline radiographic data have been included in the PI of several TNF-inhibitors where the approved indications have included statements such as 'reducing the rate of progression of joint damage in PsA'. While direct comparisons between studies cannot be made, data from studies of etanercept and golimumab included in the respective PIs indicate ≤ 0 mean changes in TSS scores over time with active treatment compared to > 0 changes (indicating progression) in PBO groups. The Australian adalimumab PI reports TSS change from Baseline at Week 24 of 1.0 vs 1.6 with PBO.

Based on the data provided in the submission, the relative advantage of the Q4W GUS regimen over the Q8W regimen appears to be a potentially better effect on radiographic progression, although the relative differences were small. This needs to be balanced

against a relatively small, but consistently higher safety risk with the Q4W regimen over the Q8W regimen.

Proposed action

Guselkumab is the first in class anti-IL-23 therapy proposed for the treatment of active psoriatic arthritis (PsA) in Australia, although several alternative biological and non-biological therapies have been registered over the last few years. Notwithstanding the range of treatment options, a significant proportion of patients still develop intolerance to or poor responses to these options. Noting this continuing gap in treatment, including medicines that act via different immunomodulatory pathways in the ARTG would contribute to the treatment options for patients with this frequently poorly responsive disease.

Pending advice from the Advisory Committee on Medicines (ACM) and the sponsor's pre-ACM response, the Delegate considers the benefit/risk profile to be positive and recommends approval for the indication:

> *Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to prior DMARD therapy.*

In conclusion, the Delegate had no reason to say, at the time, that the application for guselkumab should not be approved for registration.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. Please advise the indication and dosage regimen for TREMFYA approved by the EU on 15 October 2020.

The sponsor has received a positive Committee for Medicinal Products for Human use (CHMP) Opinion on 15 October 2020 for the Type II variation for a new therapeutic indication, psoriatic arthritis. The European Commission (EC) Decision expected in December 2020. The proposed indication and dosage regimen in the EU for the psoriatic arthritis indication is as follows

> **Therapeutic indications**
>
> *Psoriatic arthritis*
>
> *Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).*
>
> **Posology and method of administration**
>
> Psoriatic arthritis
>
> The recommended dose of Tremfya is 100 mg by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered (see section 5.1).

Advisory committee considerations[11]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the delegate

1. What is the opinion of the Committee regarding the evidence supporting the efficacy of a 4 weekly dosage regimen of guselkumab for the treatment of psoriatic arthritis?

The ACM acknowledges that a 4 weekly dosage regimen of guselkumab 100 mg for the treatment of psoriatic arthritis is effective. However, based on the efficacy and safety data presented, the ACM supports the approval of the 8 weekly dosage regimen, owing to lack of data to demonstrate the superiority of the 4 weekly regimen. The ACM also acknowledges that the 4 weekly regimen may be beneficial to a sub-group of PsA patients with a higher acute-phase response, however it will be up to the treating physician to decide on the optimal dosing regimen for each patient.

2. 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.

The ACM did not provide advice on any other pertinent issue.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to, prior DMARD therapy.*
>
> *Dosage: 100 mg by subcutaneous injection at Week 0, Week 4, and every 8 weeks thereafter.*
>
> *Tremfya may be administered alone or in combination with a conventional synthetic disease modifying antirheumatic drug (csDMARD) (e.g. methotrexate)*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Tremfya (guselkumab) 100 mg, solution for injection, pre-filled pen, pre-filled syringe indicated for the following extension of indications:

> *Psoriatic arthritis*

[11] 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.

Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to prior DMARD therapy

As such, the full indications at this time were:

Plaque psoriasis

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.

Psoriatic arthritis

Tremfya is indicated for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to prior DMARD therapy

Specific conditions of registration applying to these goods

- The Tremfya EU-RMP (version 5.3, dated 26 May 2020, DLP 12 September 2019), with Australian specific annex (version 5.0, dated 17 September 2020), included with submission PM-2019-05350-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- The final reports from studies PSA3001 and PSA3002 should be submitted to the TGA when completed.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Tremfya 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>.

Therapeutic Goods Administration

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