▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

TREMFYA®

guselkumab

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Guselkumab.

TREMFYA (guselkumab) 100 mg solution for injection in pre-filled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg pre-filled syringe contains 100 mg of guselkumab per 1 mL.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds selectively to the extracellular human interleukin 23 (IL-23) protein with high specificity and affinity. Guselkumab is produced in a mammalian cell line using recombinant DNA technology.

For a full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Solution for injection in a prefilled syringe.

TREMFYA is a clear, colourless to light yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage (dose and interval)

The recommended dose of TREMFYA is 100 mg to be given as subcutaneous injection at week 0, week 4 and every 8 weeks thereafter.

Method of Administration

TREMFYA is administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

TREMFYA is intended for use under the guidance and supervision of a physician. TREMFYA may be administered by a health care professional, or a patient may self-inject after proper training in subcutaneous injection technique.

After removing the pre-filled syringe from the refrigerator, keep the pre-filled syringe inside the carton and allow to reach room temperature by waiting for 30 minutes before injecting TREMFYA. The pre-filled syringe should not be shaken.

Comprehensive instructions for the subcutaneous administration of TREMFYA are given in the Instructions for Use leaflet. Patients should be instructed to inject the full amount of TREMFYA according to the directions provided in this leaflet.

TREMFYA is for single use in one patient only. Following administration of TREMFYA, discard any unused portion. The syringe should be disposed of using accepted medical practices for used syringes. The syringe and needle must never be re-used.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Special Populations

Renal or hepatic impairment

Specific studies of TREMFYA have not been conducted in patients with renal or hepatic insufficiency.

Elderly (>65 years of age)

No dose adjustment is required (see sections 5.1 Pharmacodynamic Properties – Clinical Trials and 5.2 Pharmacokinetic Properties - Special Populations).

Paediatrics (< 18 years of age)

The safety and efficacy of TREMFYA in paediatric patients (< 18 years of age) have not been evaluated.

4.3 CONTRAINDICATIONS

Serious hypersensitivity to guselkumab or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

Infections

TREMFYA may increase the risk of infection. In clinical trials, infections occurred in 23% of subjects in the TREMFYA group versus 21% of subjects in the placebo group through 16 weeks of treatment. The rate of serious infections for the TREMFYA group and the placebo group were ≤ 0.2%. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Instruct patients treated with TREMFYA to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TREMFYA until the infection resolves.

Pre-treatment evaluation for tuberculosis

In clinical studies, subjects with latent tuberculosis (TB) who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop TB. Evaluate patients for TB infection prior to initiating treatment with TREMFYA. Initiate treatment of latent TB prior to

administering TREMFYA. Patients receiving TREMFYA should be monitored for signs and symptoms of active TB during and after treatment. Do not administer TREMFYA to patients with active TB infection. Consider anti-TB therapy prior to initiating TREMFYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Immunisations

Prior to initiating therapy with TREMFYA, complete all appropriate immunisations according to current immunisation guidelines. Live vaccines should not be used concurrently in patients treated with TREMFYA. No data are available on the response to live or inactive vaccines.

Before live viral or live bacterial vaccination, treatment with TREMFYA should be withheld for at least 12 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Prescribing Information of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Use in the elderly

Of the 1748 plaque psoriasis subjects exposed to TREMFYA in Phase 2 and Phase 3 clinical trials, a total of 93 subjects were 65 years or older, and 4 subjects were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger patients who received TREMFYA in clinical studies. However, the number of patients aged 65 years and older was not sufficient to determine whether they respond differently from younger patients (see PHARMACOLOGY – SPECIAL POPULATIONS).

Paediatric use

The safety and efficacy of TREMFYA in paediatric patients (< 18 years of age) have not been evaluated.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In a Phase 1 study in subjects with moderate to severe plaque psoriasis, changes in systemic exposures (C_{max} and AUC_{inf}) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant (see Pharmacokinetic Properties), indicating that drug interactions between guselkumab and substrates of various CYP enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely. There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates

Live vaccines should not be given while a patient is undergoing therapy with TREMFYA (see section 4.4 Special Warnings and Precautions for Use - Immunisations).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The effect of TREMFYA on human fertility has not been evaluated.

No effects on fertility parameters were identified in female and male fertility studies conducted in guinea pigs. Results from the studies indicated no effects on male or female reproductive parameters. Safety margins for C_{max} and AUC_{last} at the 100 mg/kg twice-weekly NOAEL dose were at least 60-fold and 80-fold higher, respectively than those following a single administration of a 100 mg SC dose to psoriasis subjects.

Use in Pregnancy – Category B1

The use of TREMFYA in pregnant women has not been studied and the effect of TREMFYA on human pregnancy is unknown.

No maternal, embryo or fetal toxicity was observed in cynomolgus monkeys after administration of weekly 50 mg/kg doses of guselkumab. Safety margins for C_{max} and AUC_{last} at the 50 mg/kg weekly NOAEL dose were at least 90-fold and 130-fold higher, respectively than those following administration of a 100 mg SC dose to psoriasis subjects. As with other IgG antibodies, guselkumab crosses the placenta and was detectable in newborn cynomolgus monkey serum samples indicating transplacental transfer of drug.

TREMFYA should only be used during pregnancy under the advice of a physician if the potential benefit outweighs the potential risk.

Use in Lactation

There are no data on the presence of guselkumab in human milk, the effects on a breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA.

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Tremfya has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably causally associated with the use of TREMFYA based on the comprehensive assessment of the available adverse event information. A causal relationship with TREMFYA cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trials Experience

The safety profile of TREMFYA in subjects with moderate to severe plaque psoriasis is based on data from the Phase 2 (PSO2001) and Phase 3 (VOYAGE 1, VOYAGE 2, NAVIGATE) studies. Of the 1748 TREMFYA-treated subjects, 1393 subjects were exposed for at least 6 months (24 weeks) and 728 subjects were exposed for at least 1 year (i.e., treated through Week 48). Most subjects (n=1583) received a dosage regimen of 100 mg TREMFYA as subcutaneous injection every 8 weeks.

The adverse reaction profile of TREMFYA in 823 patients with moderate to severe plaque psoriasis is based on pooled data from two 16-week placebo-controlled phase III studies. Table 1 provides a summary of adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA group than in the placebo group during the 16-week, placebo- controlled period of the pooled clinical trials, VOYAGE 1 and VOYAGE 2.

Table 1: Adverse reactions reported by ≥1% of patients through Week 16 in VOYAGE 1 and VOYAGE 2

	Placebo N = 422 n (%)	TREMFYA[a] N = 823 n (%)	Adalimumab[b] N = 581 n (%)
Gastrointestinal disorders			
Diarrhoea	4 (0.9%)	13 (1.6%)	7 (1.2%)
General disorders and administration site conditions			
Injection site reactions[c]	12 (2.8%)	37 (4.5%)	42 (7.2%)
Infections and Infestations			
Upper respiratory infections[d]	54 (12.8%)	118 (14.3%)	80 (13.8%)
Gastroenteritis[e]	4 (0.9%)	11 (1.3%)	8 (1.4%)
Herpes simplex infections[f]	2 (0.5%)	9 (1.1%)	8 (1.4%)
Tinea infections[g]	0	9 (1.1%)	3 (0.5%)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (2.1%)	22 (2.7%)	11 (1.9%)
Nervous system disorders			
Headache[h]	14 (3.3%)	38 (4.6%)	18 (3.1%)

[a] Subjects received 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter;

[b] Subjects received adalimumab at 80 mg Week 0, 40 mg week 1 then 40 mg q2w thereafter

[c] Injection site reactions include injection site erythema, bruising, haematoma, haemorrhage, swelling, oedema, pruritus, pain, discolouration, induration, inflammation, and urticaria.

[d] Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.

[e] Gastroenteritis includes gastroenteritis and viral gastroenteritis

[f] Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

[g] Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.

[h] Headache includes headache and tension headache.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse reactions that occurred at rates < 1% in the TREMFYA group and at a higher rate than in the placebo group through Week 16 in VOYAGE 1 and VOYAGE 2 were:

Infections and Infestations: candida infections

Nervous system disorders: migraine

Skin and subcutaneous tissue disorders: urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Single intravenous doses of TREMFYA up to 987 mg (10 mg/kg) have been administered in healthy volunteers and single subcutaneous doses of TREMFYA up to 300 mg have been administered in subjects with plaque psoriasis in clinical trials without dose-limiting toxicity. In

the event of overdose, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC16.

Mechanism of Action

Guselkumab is a human IgG1λ monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL-23) protein with picomolar affinity. IL-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalise production of these cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In in vitro models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signalling, activation and cytokine cascades. Guselkumab is considered to exert its clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway.

Pharmacodynamic effects

In a Phase 1 study, treatment with guselkumab resulted in reduced expression of IL-23/Th17 pathway genes and psoriasis-associated gene expression profiles, as shown by analyses of mRNA obtained from lesional skin biopsies of psoriatic subjects at Week 12 compared to baseline. In the same Phase 1 study, treatment with guselkumab resulted in improvement of histological measures of psoriasis at Week 12, including reductions in epidermal thickness and T-cell density. In addition, reduced serum IL-17A, IL-17F and IL-22 levels compared to placebo were observed in guselkumab treated subjects in Phase 2 and Phase 3 studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The immunogenicity of TREMFYA was evaluated using a sensitive and drug-tolerant immunoassay. In pooled Phase 2 and Phase 3 analyses, fewer than 6% of subjects treated with TREMFYA developed antidrug antibodies in up to 52 weeks of treatment. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralising which equates to 0.4% of all subjects treated with TREMFYA. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to TREMFYA with the incidences of antibodies to other products may be misleading.

Clinical Trials

Three multicentre, randomised, double-blind trials (VOYAGE 1, VOYAGE 2, and NAVIGATE) enrolled subjects 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥12, and a minimum affected body surface area (BSA) of 10%. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

VOYAGE 1 and VOYAGE 2

In VOYAGE 1 and VOYAGE 2, 1829 subjects were randomised to either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), placebo or adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter).

Both trials assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an IGA score of 0 ("cleared") or 1 ("minimal");
- the proportion of subjects who achieved at least a 90% reduction from baseline in the PASI composite score (PASI 90).

Comparisons between TREMFYA and adalimumab were secondary endpoints at the following time points:

- at Week 16 (VOYAGE 1 and VOYAGE 2), the proportions of subjects who achieved an IGA score of 0 or 1, a PASI 90, and a PASI 75 response;
- at Week 24 (VOYAGE 1 and VOYAGE 2), and at Week 48 (VOYAGE 1), the proportions of subjects achieving an IGA score of 0, an IGA score of 0 or 1, and a PASI 90 response.

Other evaluated outcomes included improvement in psoriasis symptoms assessed on the Psoriasis Symptoms and Signs Diary (PSSD) and improvements in psoriasis of the scalp at Week 16.

Baseline disease characteristics were consistent for the study populations in VOYAGE 1 and 2 with a median BSA of 22% and 24%, a median baseline PASI score of 19 for both studies, a median baseline DLQI score of 14 and 14.5, a baseline IGA score of severe for 25% and 23% of patients, and a history of psoriatic arthritis for 19% and 18% of patients, respectively.

Overall skin disease

TREMFYA demonstrated superiority to adalimumab on PASI 75, PASI 90 and IGA cleared or minimal (0 or 1) at Week 16 in both studies ($p < 0.001$ for all comparisons). TREMFYA also demonstrated superiority to adalimumab on PASI 75, PASI 90, PASI 100, IGA cleared (0), and IGA cleared or minimal (0 or 1) at Week 24 in both studies and at Week 48 in VOYAGE 1 ($p < 0.001$ for all comparisons)

The key efficacy results for the primary and major secondary study endpoints are shown in Table 2 below.

Table 2: Summary of Clinical Responses in VOYAGE 1 and VOYAGE 2

	Number of patients (%)					
	VOYAGE 1			VOYAGE 2		
	Placebo (N=174)	Guselkumab (N=329)	Adalimumab (N=334)	Placebo (N=248)	Guselkumab (N=496)	Adalimumab (N=248)
IGA response of 0/1 (cleared or minimal)						
Week 16	12 (6.9)	280 (85.1)[c]	220 (65.9)[b]	21 (8.5)	417 (84.1)[c]	168 (67.7)[b]
Week 24	-	277 (84.2)	206 (61.7)[b]	-	414 (83.5)	161 (64.9)[b]
Week 48	-	265 (80.5)	185 (55.4)[b]	-	-	-
IGA response of 0 (cleared)						
Week 16	2 (1.1)	157 (47.7)[a]	88 (26.3)[d]	2 (0.8)	215 (43.3)[a]	71 (28.6)[d]
Week 24	-	173 (52.6)	98 (29.3)[b]	-	257 (51.8)	78 (31.5)[b]
Week 48	-	166 (50.5)	86 (25.7)[b]	-	-	-
PASI 75 response						
Week 16	10 (5.7)	300 (91.2)[a]	244 (73.1)[b]	20 (8.1)	428 (86.3)[a]	170 (68.5)[b]
Week 24	-	300 (91.2)	241 (72.2)[e]		442 (89.1)	176 (71.0)[e]
Week 48	-	289 (87.8)	209 (62.6)[e]	-	-	-
PASI 90 response						
Week 16	5 (2.9)	241 (73.3)[c]	166 (49.7)[b]	6 (2.4)	347 (70.0)[c]	116 (46.8)[b]
Week 24	-	264 (80.2)	177 (53.0)[b]	-	373 (75.2)	136 (54.8)[b]
Week 48	-	251 (76.3)	160 (47.9)[b]	-	-	-
PASI 100 response						
Week 16	1 (0.6)	123 (37.4)[a]	57 (17.1)[d]	2 (0.8)	169 (34.1)[a]	51 (20.6)[d]
Week 24	-	146 (44.4)	83 (24.9)[e]	-	219 (44.2)	66 (26.6)[e]
Week 48	-	156 (47.4)	78 (23.4)[e]	-	-	-

[a] $p < 0.001$ for comparison between guselkumab and placebo.
[b] $p < 0.001$ for comparison between guselkumab and adalimumab for major secondary endpoints.
[c] $p < 0.001$ for the comparisons between guselkumab and placebo for the co-primary endpoints.
[d] comparisons between guselkumab and adalimumab were not performed.
[e] $p < 0.001$ for comparison between guselkumab and adalimumab.

Response over time

Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 ($p < 0.001$). The percentage of subjects achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the difference reaching a maximum around Week 20 (VOYAGE 1 and 2) and maintained through Week 48 (VOYAGE 1).

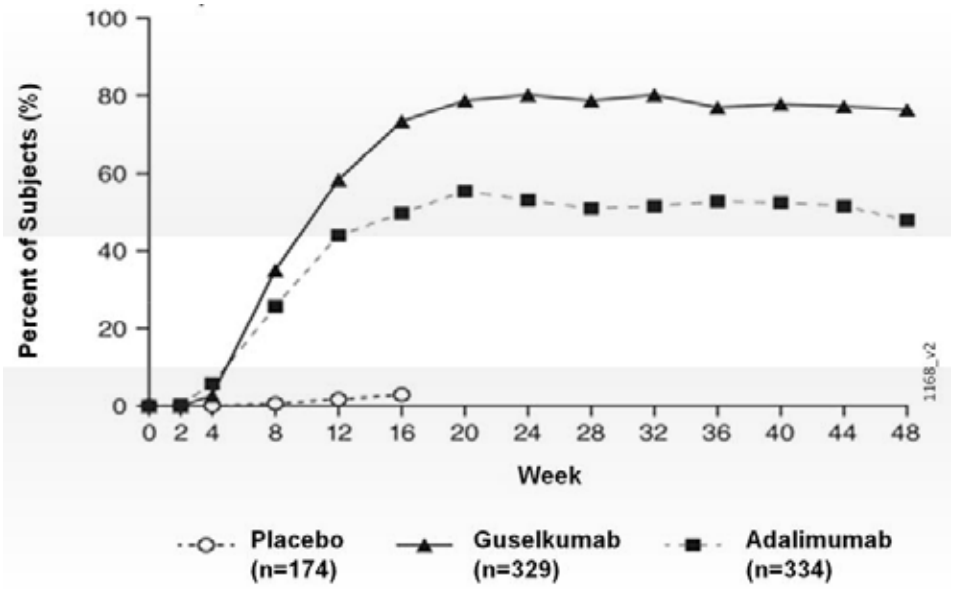

Figure 1: Percent of Subjects Who Achieved PASI 90 Response Through Week 48 by Visit (Subjects Randomised at Week 0) in VOYAGE 1

The efficacy and safety of guselkumab was demonstrated regardless of age, gender, race, body weight, plaques location, PASI baseline severity, concurrent psoriatic arthritis, and previous treatment with a biologic therapy. Guselkumab was efficacious in conventional systemic-naive, biologic-naive, and biologic-exposed patients.

In VOYAGE 2, 88.6% of patients receiving guselkumab maintenance treatment at Week 48 were PASI 90 responders compared to 36.8% of patients who were withdrawn from treatment at Week 28 ($p < 0.001$). Loss of PASI 90 response was noted as early as 4 weeks after withdrawal of guselkumab treatment with a median time to loss of PASI 90 response of approximately 15 weeks.

In VOYAGE 2, among 112 adalimumab subjects who failed to achieve a PASI 90 response at Week 28, 66% achieved a PASI 90 response after 20 weeks of treatment with guselkumab. No new safety findings were observed in patients who switched from adalimumab to guselkumab.

Regional disease

In VOYAGE 1 and 2, significant improvements were seen in scalp, hand and foot, and nail psoriasis (as measured by the Scalp-specific Investigator Global Assessment [ss-IGA], Physician's Global Assessment of Hands and/or Feet [hf-PGA], Fingernail Physician's Global Assessment [f-PGA] and Nail Psoriasis Severity Index [NAPSI], respectively) in guselkumab treated patients compared to placebo treated patients at Week 16 ($p < 0.001$, Table 3). Guselkumab demonstrated superiority compared to adalimumab for scalp and hand and foot psoriasis at Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1) ($p \leq 0.001$, except for hand and foot psoriasis at Week 24 [VOYAGE 2] and Week 48 [VOYAGE 1], $p < 0.05$).

Table 3: Summary of Regional Disease Responses in VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	Guselkumab	Adalimumab	Placebo	Guselkumab	Adalimumab
ss-IGA (N)[a]	145	277	286	202	408	194
ss-IGA 0/1[b], n (%)						
Week 16	21 (14.5)	231 (83.4)[c]	201 (70.3)[d]	22 (10.9)	329 (80.6)[c]	130 (67.0)[d]
hf-PGA (N)[a]	43	90	95	63	114	56
hf-PGA 0/1[b], n (%)						
Week 16	6 (14.0)	66 (73.3)[e]	53 (55.8)[d]	9 (14.3)	88 (77.2)[e]	40 (71.4)[d]
f-PGA (N)[a]	88	174	173	123	246	124
f-PGA 0/1, n (%)						
Week 16	14 (15.9)	68 (39.1)[e]	88 (50.9)[d]	18 (14.6)	128 (52.0)[e]	74 (59.7)[d]
NAPSI (N)[a]	99	194	191	140	280	140
Percent Improvement, mean (SD)						
Week 16	-0.9 (57.9)	34.4 (42.4)[e]	38.0 (53.9)[d]	1.8 (53.8)	39.6 (45.6)[e]	46.9 (48.1)[d]

[a] Includes only subjects with ss-IGA, f-PGA, hf-PGA score ≥ 2 at baseline or baseline NAPSI score > 0.

[b] Includes only subjects achieving ≥ 2-grade improvement from baseline in ss-IGA and/or hf-PGA.

[c] $p < 0.001$ for comparison between guselkumab and placebo for the major secondary endpoint.

[d] comparisons between guselkumab and adalimumab were not performed.

[e] $p < 0.001$ for comparison between guselkumab and placebo.

Health-related quality of life / Patient reported outcomes

Greater improvements in symptoms of psoriasis (itch, pain, stinging, burning and skin tightness) at Week 16 in TREMFYA compared to placebo were observed in both trials based on the Psoriasis Symptoms and Signs Diary (PSSD). Greater proportions of subjects on TREMFYA compared to adalimumab achieved a PSSD symptom score of 0 (symptom-free) at Week 24 in both trials.

NAVIGATE

The NAVIGATE study examined the efficacy of guselkumab in patients who had an inadequate response (i.e., 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 start to become apparent at 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.

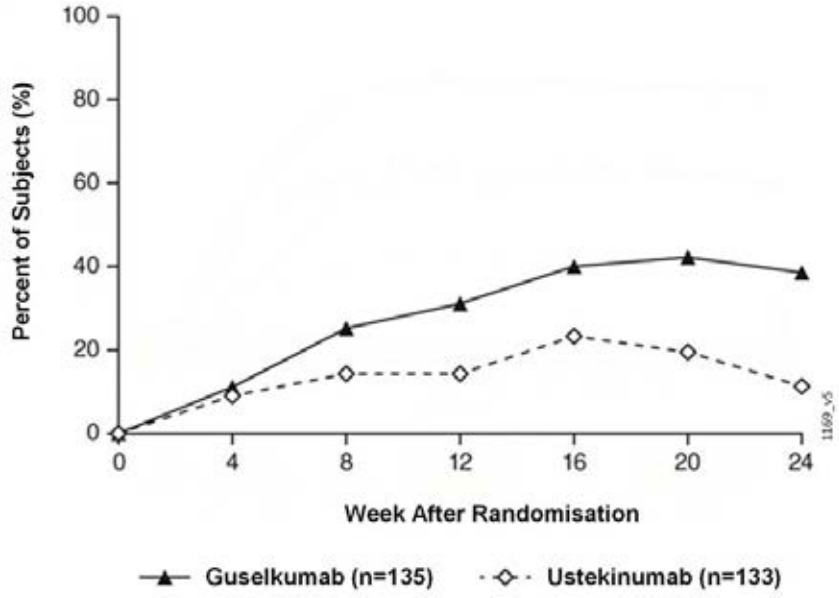

Figure 2: Percent of Subjects Who Achieved an IGA Score of Cleared (0) or Minimal (1) and at least a 2-grade improvement in IGA from Week 0 Through Week 24 by Visit After Randomisation in NAVIGATE

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (Cmax) of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose.

Steady state serum guselkumab concentrations were achieved by Week 20 following subcutaneous administrations of 100 mg guselkumab at Weeks 0 and 4, and every 8 weeks thereafter. The mean (± SD) steady state trough serum guselkumab concentrations in two Phase 3 studies were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. Serum guselkumab concentrations did not appear to accumulate over time when given subcutaneously every 8 weeks.

The absolute bioavailability of guselkumab following a single 100 mg subcutaneous injection was estimated to be approximately 49% in healthy subjects.

Distribution

Mean volume of distribution during the terminal phase (V_z) following a single intravenous administration to healthy subjects ranged from approximately 7 to 10 L (98 to 123 mL/kg) across studies.

Metabolism

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

Excretion

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day (3.6 to 6.0 mL/day/kg) across studies.

Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in subjects with plaque psoriasis across studies.

Dose Linearity

The systemic exposure of guselkumab (Cmax and AUC) increased in an approximately dose-proportional manner following a single subcutaneous injection at doses ranging from 10 mg to 300 mg in healthy subjects or subjects with plaque psoriasis.

Population Pharmacokinetic Analysis

In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.516 L/d and 13.5 L, respectively, and the $T_{1/2}$ was approximately 18 days in subjects with psoriasis.

In the population pharmacokinetic analysis, the effects of baseline demographics (weight, age, sex, and race), immunogenicity, baseline disease characteristics, comorbidities (past and current history of diabetes, hypertension, and hyperlipidaemia), past use of therapeutic biologics, past use of methotrexate or cyclosporine, concomitant medications (ibuprofen, paracetamol, acetylsalicylic acid, and isoniazid), use of alcohol, or current smoking status, on pharmacokinetics of guselkumab was evaluated. Only the effects of body weight on CL/F and V/F were found to be significant, with a trend towards higher CL/F in heavier subjects. However, subsequent exposure-response modelling analysis suggested that no dose adjustment would be warranted for body weight.

Cytochrome P450 Substrates

The effects of guselkumab on the pharmacokinetics of representative probe substrates of CYP isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]) were evaluated in subjects with moderate to severe plaque psoriasis. Results from this study indicate that changes in C_{max} and AUC_{inf} of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates.

SPECIAL POPULATIONS

Elderly Patients (>65 years of age and older)

Of the 1384 plaque psoriasis subjects exposed to TREMFYA and included in the population pharmacokinetic analysis, 70 subjects were 65 years of age or older, including 4 subjects who were 75 years of age or older. Population pharmacokinetic analyses indicated there were no apparent changes in CL/F estimate in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Patients with Renal or Hepatic Impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of guselkumab.

Renal elimination of intact guselkumab, an IgG mAb, is expected to be low and of minor importance; similarly, hepatic impairment is not expected to influence clearance of guselkumab as IgG mAbs are mainly eliminated via intracellular catabolism.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Guselkumab has not been evaluated for genotoxic potential.

Carcinogenicity

Guselkumab has not been evaluated for carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injection.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not shake.

Keep the pre-filled syringe in original carton until time of use in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

TREMFYA is supplied as a single-use sterile solution in a pre-filled 1mL glass syringe with a fixed 27G, half inch needle assembled in a passive needle guard delivery system.

TREMFYA is available in cartons containing 1 pre-filled syringe.

TREMFYA does not contain preservatives.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:

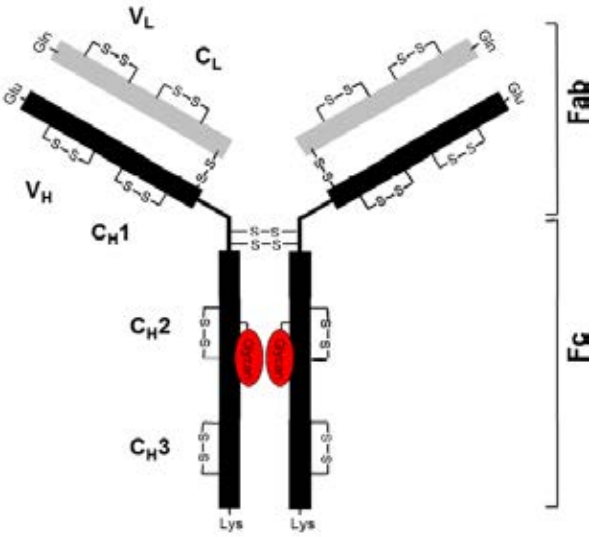

Figure 3. General structure of guselkumab

CAS No.: 1350289-85-8

7 MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

JANSSEN-CILAG Pty Ltd
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Macquarie Park NSW 2113 Australia

9 DATE OF FIRST APPROVAL

15 March 2018

10 DATE OF REVISION

15 March 2018

Summary table of changes

Section	Summary of changes
	New