▼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.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TREMFYA contains guselkumab and is available in the following presentations:

Solution for subcutaneous injection

Pre-filled syringe

- 100 mg / 1 mL
- 200 mg / 2 mL

Pre-filled pen

- 100 mg / 1 mL
- 200 mg / 2 mL

Solution for intravenous infusion

Single-dose vial

- 200 mg / 20 mL (10 mg/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

For Subcutaneous Injection

Solution for injection in a prefilled syringe or a pre-filled pen (One-Press® patient-controlled injector or auto-injector).

For Intravenous Infusion

Concentrated solution for infusion in a single-dose vial.

TREMFYA is a clear, colourless to light yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.

Ulcerative colitis

TREMFYA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, a biologic treatment, or a Janus kinase (JAK) inhibitor.

Crohn's disease

TREMFYA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

TREMFYA is administered by intravenous infusion or subcutaneous injection.

Dosage (Dose and Interval)

Plaque psoriasis

The recommended dose of TREMFYA is 100 mg at Week 0, Week 4 and every 8 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment.

Psoriatic arthritis

The recommended dose of TREMFYA is 100 mg at week 0, week 4, and every 8 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.

TREMFYA may be administered alone or in combination with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) (e.g. methotrexate).

Ulcerative colitis

Induction:

The recommended induction dosage of TREMFYA is 200 mg administered by intravenous infusion over a period of at least one hour at Week 0, Week 4 and Week 8.

Maintenance:

The recommended maintenance dosage of TREMFYA is 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.

Crohn's Disease

Induction:

The recommended induction dosage of TREMFYA is:

- 200 mg administered by intravenous infusion over a period of at least one hour at Week 0, Week 4 and Week 8.

or

- 400 mg administered by subcutaneous injection (given as two consecutive injections of 200 mg each) at Week 0, Week 4 and Week 8

Maintenance:

The recommended maintenance dosage of TREMFYA is 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter. For some patients, a dosage of 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, may be used.

Immunomodulators and/or corticosteroids may be continued during treatment with TREMFYA. In patients who have responded to treatment with TREMFYA, corticosteroids may be reduced or discontinued in accordance with standard of care.

Method of Administration

Subcutaneous 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 or pre-filled pen from the refrigerator, keep the pre-filled syringe or pen inside the carton and allow to reach room temperature by waiting for 30 minutes before injecting TREMFYA. The pre-filled syringe or pre-filled pen 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 or pen should be disposed of using accepted medical practices for used syringes. The syringe or pen and its needle must never be re-used.

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

Intravenous infusion (Ulcerative Colitis and Crohn's Disease)

TREMFYA 200 mg vial is for IV infusion only. Intravenous infusion of TREMFYA should be administered by qualified healthcare professionals.

<u>Instructions for dilution of TREMFYA 200 mg for IV infusion (Ulcerative colitis and Crohn's Disease)</u>

TREMFYA solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique. TREMFYA does not contain preservatives. Each vial is for single use only.

Inspect TREMFYA visually for particulate matter and discolouration prior to administration. TREMFYA is a clear and colourless to light yellow solution that may contain small translucent particles. Do not use if the liquid contains large particles, is discoloured or cloudy.

Add TREMFYA to a 250 mL intravenous infusion bag of 0.9% Sodium Chloride Injection as follows:

1. Withdraw and then discard 20 mL of the 0.9% Sodium Chloride Injection from the 250 mL infusion bag which is equal to the volume of TREMFYA to be added.
2. Withdraw 20 mL of TREMFYA from the vial and add it to the 250 mL intravenous infusion bag of 0.9% Sodium Chloride Injection for a final concentration of 0.8 mg/mL. Gently mix the diluted solution. Discard the vial with any remaining solution.
3. Visually inspect the diluted solution for particulate matter and discolouration before infusion. Infuse the diluted solution over a period of at least one hour.
4. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein binding filter (pore size 0.2 micrometre).
5. Do not infuse TREMFYA concomitantly in the same intravenous line with other medicinal products.
6. Dispose any unused medicinal product in accordance with local requirements.

Storage of diluted infusion solution:

- To reduce microbiological hazard, use as soon as practical after dilution. If storage is necessary, the diluted infusion solution may be kept at room temperature up to 25°C for up to 10 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 10 hours after the dilution in the infusion bag.
- Do not freeze.
- Discard any unused portion of the infusion solution.

Missed Dose

Patients who miss a dose of TREMFYA should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

Special Populations

Renal or hepatic impairment

Specific studies of TREMFYA have not been conducted in patients with renal or hepatic insufficiency. No dose adjustments are considered necessary (see section 5.2 Pharmacokinetic Properties - Special Populations).

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. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Infections have been observed in clinical trials in plaque psoriasis (23% vs 21% placebo: ≤0.2% serious infections in both groups) and psoriatic arthritis (21% in both TREMFYA and placebo groups: ≤0.8% serious infections in both groups). A similar risk of infection was seen in the placebo-controlled trials in subjects with ulcerative colitis and Crohn's disease.

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.

Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing setting. Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnea. If a serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of TREMFYA should be discontinued.

Use in the Elderly

Of the 5926 plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease patients exposed to TREMFYA in Phase 2 and Phase 3 clinical trials, a total of 339 patients were 65 years or older, and 34 patients 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 section 5.2 Pharmacokinetic properties – 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

Interactions with Cyp450 Substrates

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 section 5.2 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/ Therapeutic Infectious Agents

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).

Concomitant Immunosuppressive Therapy or Phototherapy

In psoriasis studies, the safety and efficacy of Tremfya in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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

No guselkumab-related effects on fertility parameters were identified in female and male fertility studies conducted in guinea pigs. Exposures (AUC) at the 100 mg/kg twice-weekly subcutaneous no observed adverse effect level (NOAEL) dose were at least 17-fold higher than those following administration of a 200 mg intravenous dose in patients.

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 guselkumab related maternal, embryo or fetal toxicity was observed in cynomolgus monkeys after administration of weekly 50 mg/kg subcutaneous doses of guselkumab. Safety margins at the 50 mg/kg weekly NOAEL dose were approximately 26 times the clinical exposure (AUC) following a dose of 200 mg given intravenously. 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 guselkumab based on the comprehensive assessment of the available adverse event information. A causal relationship with guselkumab 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 is based on data from the Phase 2 (PSO2001, PSA2001, QUASAR induction dose-ranging study, GALAXI 1) and Phase 3 (VOYAGE 1, VOYAGE 2, NAVIGATE, ORION, ECLIPSE, DISCOVER 1, DISCOVER 2, QUASAR induction study (IS) and QUASAR maintenance study (MS), GALAXI 2 and 3, and GRAVITI) studies in 5926 subjects, including 2711 with plaque psoriasis, 1229 subjects with psoriatic arthritis, 897 subjects with ulcerative colitis, and 1089 subjects with Crohn's disease. The duration of exposure to TREMFYA is presented in Table 1.

Table 1: Long-Term Exposure to TREMFYA in Phase 2 and Phase 3 studies

Duration of exposure	Number of subjects
≥ 1 year	4632[a]
≥ 2 years	1953[b]
≥ 3 years	1482[b]
≥ 4 years	1393[b]
≥ 5 years	950[b]

[a] plaque psoriasis, psoriatic arthritis, ulcerative colitis and Crohn's disease studies
[b] plaque psoriasis and psoriatic arthritis studies

Plaque Psoriasis

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 2 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 2: 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.

Psoriatic Arthritis

Table 3 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 24-week, placebo-controlled period of the pooled clinical trials, DISCOVER 1 and DISCOVER 2.

Table 3: Adverse reactions reported by ≥1% of patients through Week 24 in DISCOVER 1 and DISCOVER 2

	Placebo N = 372 n (%)	TREMFYA Q8W[a] N = 375 n (%)	TREMFYA Q4W[b] N = 373 n (%)
Gastrointestinal disorders			
Diarrhoea	3 (0.8%)	6 (1.6%)	4 (1.1%)
General disorders and administration site conditions			
Injection site reactions[c]	1 (0.3%)	5 (1.3%)	3 (0.8%)
Infections and Infestations			
Respiratory tract infections[d]	45 (12.1%)	46 (12.3%)	52 (13.9%)
Investigations			
Transaminases increased[e]	17 (4.6%)	31 (8.3%)	32 (8.6%)
Neutrophil count decreased	0	1 (0.3%)	6 (1.6%)
Nervous system disorders			
Headache[f]	3 (0.8%)	8 (2.1%)	7 (1.9%)

[a] Subjects received 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter;
[b] Subjects received 100 mg of TREMFYA at Week 0, and every every 4 weeks thereafter
[c] Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, oedema, pruritus, pain, discolouration, induration, inflammation, and urticaria.
[d] Respiratory tract infections include nasopharyngitis, upper respiratory tract infection (URTI), bronchitis, pharyngitis, and viral URTI.
[e] Transaminases increased includes: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia
[f] Headache includes headache and tension headache.

Ulcerative Colitis

TREMFYA was studied up to 12 weeks in patients with moderately to severely active ulcerative colitis in a randomised, double-blind, placebo-controlled induction study (QUASAR IS-2) and a randomised, double-blind, placebo-controlled, induction dose-finding study (QUASAR IS-1). Long term safety up to 44-weeks was evaluated in patients who responded to induction therapy in a randomised, double-blind, placebo-controlled maintenance study (QUASAR MS) (see sections 5.1 Pharmacodynamic Properties – Clinical Trials).

In the two induction studies (QUASAR IS-1 and QUASAR IS-2), 1014 patients were enrolled of whom 522 patients received at least one dose of TREMFYA 200 mg by intravenous infusion up to Week 12. In the maintenance study (QUASAR MS), 568 patients were randomised of whom 376 patients received either TREMFYA 100 mg every 8 weeks or TREMFYA 200 mg every 4 weeks by subcutaneous (SC) injection.

The overall safety profile in patients treated with TREMFYA is similar for patients with psoriasis, psoriatic arthritis and ulcerative colitis.

Adverse reactions that occurred in ≥2% of patients in the TREMFYA group and at a higher rate than placebo in the induction studies (QUASAR IS-1 and QUASAR IS-2) were rash (2.1% vs. 1.6%).

Adverse reactions that occurred in ≥3% of patients in the TREMFYA group and at a higher rate than placebo in the maintenance study (QUASAR MS) are shown in Table 4.

Table 4: Adverse Reactions Occurring in ≥3% of Patients through Week 44 in QUASAR MS

	TREMFYA[a] 100 mg Subcutaneous Injection N=186 n (%)	TREMFYA[a] 200 mg Subcutaneous Injection N=190 n (%)	Placebo N=192 n (%)
Arthralgia	8 (4.3)	15 (7.9)	13 (6.8)
Upper respiratory tract infection	6 (3.2)	13 (6.8)	8 (4.2)
Injection site reaction	0	7 (3.7)	0

[a] Patients receiving TREMFYA 100 mg at Week 16 and every 8 weeks thereafter or TREMFYA 200 mg at Week 12 and every 4 weeks thereafter

Crohn's Disease

The safety of TREMFYA was evaluated up to 48 weeks in four trials in patients with moderately to severely active Crohn's disease: two identically designed randomised, double-blind, placebo and active-controlled parallel group trials (GALAXI 2, GALAXI 3); one randomised, double-blind, dose ranging trial (GALAXI 1) [NCT03466411]; and one randomised, double-blind, and placebo-controlled subcutaneous induction trial (GRAVITI) (see sections 5.1 Pharmacodynamic Properties – Clinical Trials).

The overall safety profile in patients treated with TREMFYA is similar for patients with psoriasis, psoriatic arthritis, and Crohn's disease.

GALAXI 1, GALAXI 2 and GALAXI 3

In clinical trials, GALAXI 1, GALAXI 2 and GALAXI 3, 1349 patients were enrolled of whom 649 patients were randomised to receive TREMFYA 200 mg by intravenous infusion at Week 0, 4 and 8 followed by a maintenance dose of either TREMFYA 200 mg subcutaneous (SC) injection at Week 12 and every 4 weeks thereafter or TREMFYA 100 mg SC at Week 16 and every 8 weeks thereafter.

Adverse reactions that occurred in ≥3% of patients in the TREMFYA groups and at a higher rate than placebo from Week 0 to Week 48 (GALAXI 1, GALAXI 2 and GALAXI 3) are shown in Table 5.

Table 5: Adverse Reactions Occurring in ≥3% of Patients through Week 48[a] in GALAXI 1, GALAXI 2 and GALAXI 3

	TREMFYA 200 mg Intravenous Induction→ 100 mg q8w Subcutaneous Injection N=353 n (%)	TREMFYA 200 mg Intravenous Induction→ 200 mg q4w Subcutaneous Injection N=296 n (%)	Placebo N=211 n (%)
Respiratory tract infections[b]	95 (26.9%)	100 (33.8%)	30 (14.2%)
Arthralgia	29 (8.2%)	25 (8.4%)	8 (3.8%)
Headache	17 (4.8%)	24 (8.1%)	6 (2.8%)
Diarrhoea	12 (3.4%)	8 (2.7%)	3 (1.4%)
Rash	6 (1.7%)	9 (3.0%)	3 (1.4%)

[a] For the Week 0 to Week 12 period (GALAXI 1, GALAXI 2 and GALAXI 3), adverse reactions that occurred in ≥2% of patients in the TREMFYA group and higher than placebo were respiratory tract infections (COVID-19 and nasopharyngitis), arthralgia, and headache.

[b] Respiratory tract infections include COVID-19, upper respiratory tract infection, nasopharyngitis, influenza, and respiratory tract infection.

GRAVITI

In clinical trial, GRAVITI, 347 patients were evaluated of whom 230 patients were randomised to receive TREMFYA 400 mg subcutaneous induction at Week 0, 4 and 8 followed by a maintenance dose of either TREMFYA 200 mg SC at Week 12 and every 4 weeks thereafter or TREMFYA 100 mg SC at Week 16 and every 8 weeks thereafter.

The overall safety profile observed in patients treated with TREMFYA in GRAVITI is generally consistent with the safety profile in patients treated with TREMFYA in the combined studies GALAXI 1, GALAXI 2 and GALAXI 3, with the addition of gastroenteritis which in the 48-week treatment period in GRAVITI occurred in 3.5% of patients in the 100 mg SC q8w group, 1.7% of patients in the 200 mg q4w group, compared to 0.9% of patients in the placebo group.

Transaminases Increased

In two Phase 3 psoriatic arthritis clinical studies, through the placebo-controlled period, adverse events of increased transaminases (includes alanine aminotransferase (ALT) Increased, aspartate aminotransferase (AST) Increased, Hepatic Enzyme Increased, Transaminases Increased, Liver Function Test Abnormal, Hypertransaminasemia) were reported more frequently in the TREMFYA-treated groups (8.6% in the 100 mg q4w group and 8.3% in the 100 mg q8w group) than in the placebo group (4.6%). Through 1-year, adverse events of increased transaminases (as above) were reported in 12.9% of patients in the q4w group and 11.7% of patients in the q8w group.

Based on laboratory assessments, an increased incidence of liver enzyme elevations was observed in patients treated with TREMFYA q4w compared to patients treated with TREMFYA q8w or placebo. Most transaminase (ALT and AST) increases were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency (Table 6). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase 3 psoriatic arthritis clinical study. In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

Table 6: Frequency of Patients with Transaminase Increases Post-Baseline in Two Phase 3 Psoriatic Arthritis Clinical Studies

	Through Week 24[a]			Through 1 Year[b]	
	Placebo N=370[c]	TREMFYA 100 mg q8w N=373[c]	TREMFYA 100 mg q4w N=371[c]	TREMFYA 100 mg q8w N=373[c]	TREMFYA 100 mg q4w N=371[c]
ALT					
>1 to ≤3 x ULN	30.0%	28.2%	35.0%	33.5%	41.2%
>3 to ≤ 5 x ULN	1.4%	1.1%	2.7%	1.6%	4.6%
>5 x ULN	0.8%	0.8%	1.1%	1.1%	1.1%
AST					
>1 to ≤3 x ULN	20.0%	18.8%	21.6%	22.8%	27.8%
>3 to ≤ 5 x ULN	0.5%	1.6%	1.6%	2.9%	3.8%
>5 x ULN	1.1%	0.5%	1.6%	0.5%	1.6%

[a] placebo-controlled period

[b] patients randomised to placebo at baseline and crossed over to TREMFYA are not included

[c] number of patients with at least one post-baseline assessment for the specific laboratory test within the time period

In pooled Phase 2/3 Crohn's disease clinical studies, through the reporting period of approximately one-year, adverse events of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, hepatic function abnormal, and liver function test increased) were reported in 3.4% of patients in the TREMFYA 200 mg SC q4w treatment group and 4.1% of patients in the TREMFYA 100 mg SC q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase 2/3 Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase 3 clinical studies. In pooled Phase 2/3 Crohn's disease clinical studies, through the reporting period of approximately one-year, ALT or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the TREMFYA 200 mg SC q4w treatment group and 2.6% of patients in the TREMFYA 100 mg SC q8w treatment group compared to 1.9% in the placebo group. In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

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

Adverse reactions that occurred at rates < 1% in the TREMFYA group during the placebo controlled- period of the pooled plaque psoriasis and psoriatic arthritis clinical trials were:

Infections and Infestations: candida infections, gastroenteritis, herpes simplex infections, tinea infections

Nervous system disorders: migraine

Skin and subcutaneous tissue disorders: urticaria.

Postmarketing Data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 7). Because these reactions were reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data

Table 7: Adverse Reactions Identified During Postmarketing Experience with Guselkumab

System Organ Class Adverse Reaction	**Frequency Category Estimated from Clinical Trials with TREMFYA[a]**
Immune System Disorders	
Hypersensitivity	Rare
Anaphylaxis[b]	Rare
Skin and Subcutaneous Tissue Disorders	
Rash[c]	Common
General disorders and administration site conditions	
Injection Site Reactions[d]	Uncommon

[a] Postmarketing adverse reaction frequency is derived from the placebo-controlled portion of the clinical trials. Clinical Trials include: Psoriasis (0-16 weeks): CNTO1959PSO3001 and CNTO1959PSO3002; Psoriatic arthritis (0-24 weeks): CNTO1959PSA3001 and CNTO1959PSA3002; Ulcerative colitis (0-12 weeks): Includes subjects with modified Mayo score 5-9 from CNTO1959UCO3001 Induction Study 1 and Induction Study 2. Crohn's disease (0-12 weeks): Includes subjects with a screening SES-CD score ≥6 [or ≥4 for subjects with isolated ileal disease] from CNTO1959CRD3001 GALAXI 1, GALAXI 2, GALAXI 3 and CNTO1959CRD3004 GRAVITI

[b] Anaphylaxis: Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Type I hypersensitivity

[c] Rash: Rash, Rash erythematous, Rash papular, Rash pruritic

[d] Injection site reactions: Injection site erythema, Injection site pain, Injection site reaction

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

TREMFYA intravenous doses up to 1200 mg as well as subcutaneous doses up to 400 mg at a single dosing visit have been administered in clinical studies 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 through the antigen binding site. 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 patients with ulcerative colitis, and Crohn's Disease, levels of IL-23 are elevated in the colon tissue. 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, psoriatic arthritis, ulcerative colitis, and Crohn's Disease through blockade of the IL-23 cytokine pathway.

Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, Crohn's disease, and ulcerative colitis. Guselkumab has demonstrated *in vitro*: blocking of IL-23 and binding to CD64. These results indicate that guselkumab is able to neutralise IL-23 at the cellular source of inflammation.

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 in plaque psoriasis. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In Phase 3 studies in psoriatic arthritis, evaluated subjects had elevated serum levels of acute phase proteins C-reactive protein, serum amyloid A and IL-6, and Th17 effector cytokines IL-17A, IL-17F and IL-22 at baseline. Guselkumab decreased levels of these proteins within 4 weeks of initiation of treatment. By Week 24, guselkumab further reduced the levels of these proteins compared to baseline and also to placebo. In guselkumab-treated subjects, serum IL-17A and IL-17F levels were similar to those observed in a demographically matched healthy cohort at Week 24.

In patients with ulcerative colitis and Crohn's disease, guselkumab treatment led to a decrease in inflammatory markers including CRP and faecal calprotectin through induction Week 12, which were sustained through one year of maintenance treatment. Serum protein levels of IL-17A, IL-22 and IFNγ were reduced as early as Week 4, and continued to decrease through induction Week 12. Guselkumab also reduced colon mucosal biopsy RNA levels of IL-17A, IL-22 and IFNγ at Week 12.

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. 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.

Plaque psoriasis

In pooled Phase 2 (PSO2001) and Phase 3 (VOYAGE 1, VOYAGE 2 and NAVIGATE) 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. In pooled Phase 3 analyses, approximately 15% of patients treated with TREMFYA developed antidrug antibodies in up to 264 weeks of treatment. Of the subjects who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising which equates to 0.76% of all subjects treated with TREMFYA. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

Psoriatic arthritis

In pooled Phase 3 (DISCOVER 1 and DISCOVER 2) analyses up to Week 52, 4.5% (n=49) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 5 had antibodies that were classified as neutralising antibodies, and 3 developed injection site reactions through Week 52. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics and efficacy of guselkumab.

Ulcerative Colitis

In a pooled Phase 2/3 (QUASAR) analyses up to Week 56 (n=501), 12% (n=58) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects who developed antidrug antibodies, 16% (n=9) had antibodies that were classified as neutralising which equates to 2% of all subjects treated with TREMFYA. Most of the patients who were positive for antibodies to guselkumab had low titers. Antibodies to guselkumab were not associated with changes in pharmacokinetics, clinical efficacy or development of injection-site reactions.

Crohn's Disease

In pooled Phase 2/3 (GALAXI) analyses up to Week 48, 5% (30/634) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects who developed antidrug antibodies, 7% (2/30) had antibodies that were classified as neutralising antibodies, which equates to 0.3% (2/634) of TREMFYA-treated subjects.

In a Phase 3 (GRAVITI) analysis up to Week 48, 9% (24/273) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects who developed antidrug antibodies, 13% (3/24) had antibodies that were classified as neutralising antibodies, which equates to 1% (3/273) of TREMFYA-treated subjects.

Most of the patients who were positive for antibodies to guselkumab had low titers. Antibodies to guselkumab were not associated with changes in pharmacokinetics, clinical efficacy or development of injection-site reactions.

Clinical Trials

Plaque Psoriasis

Four multicentre, randomised, double-blind, placebo and/or active controlled trials (VOYAGE 1, VOYAGE 2, NAVIGATE and ORION) 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- Placebo- and adalimumab-controlled studies

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 through Week 47. All subjects, including those randomised to adalimumab at Week 0, received TREMFYA 100 mg at Week 52 and every 8 weeks 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 8 below.

Table 8: 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). In VOYAGE 1, for subjects receiving continuous guselkumab treatment, PASI 90 response was maintained from Week 52 to Week 252 with 84.1% (329/391) of patients continuing to achieve a PASI 90 response at Week 252.

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

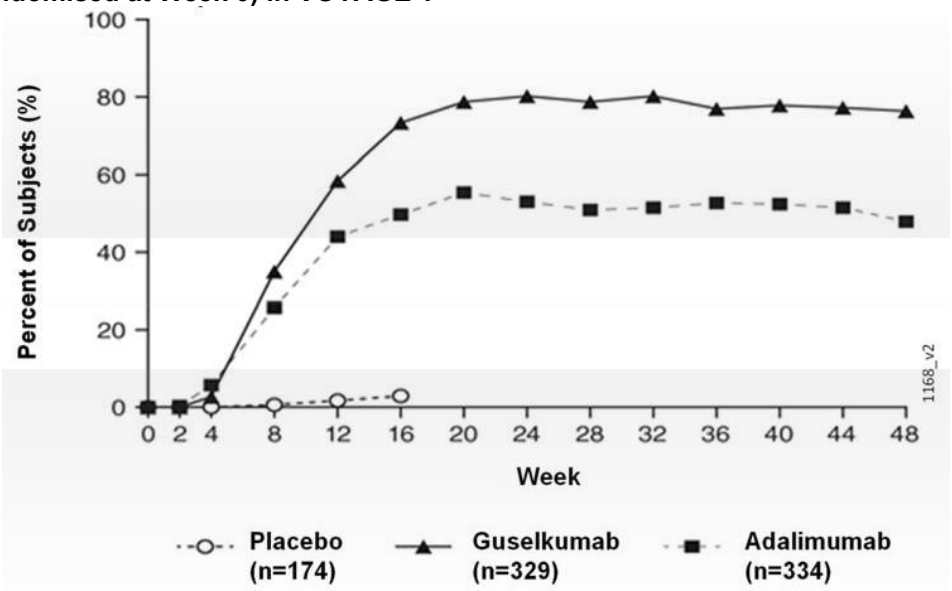
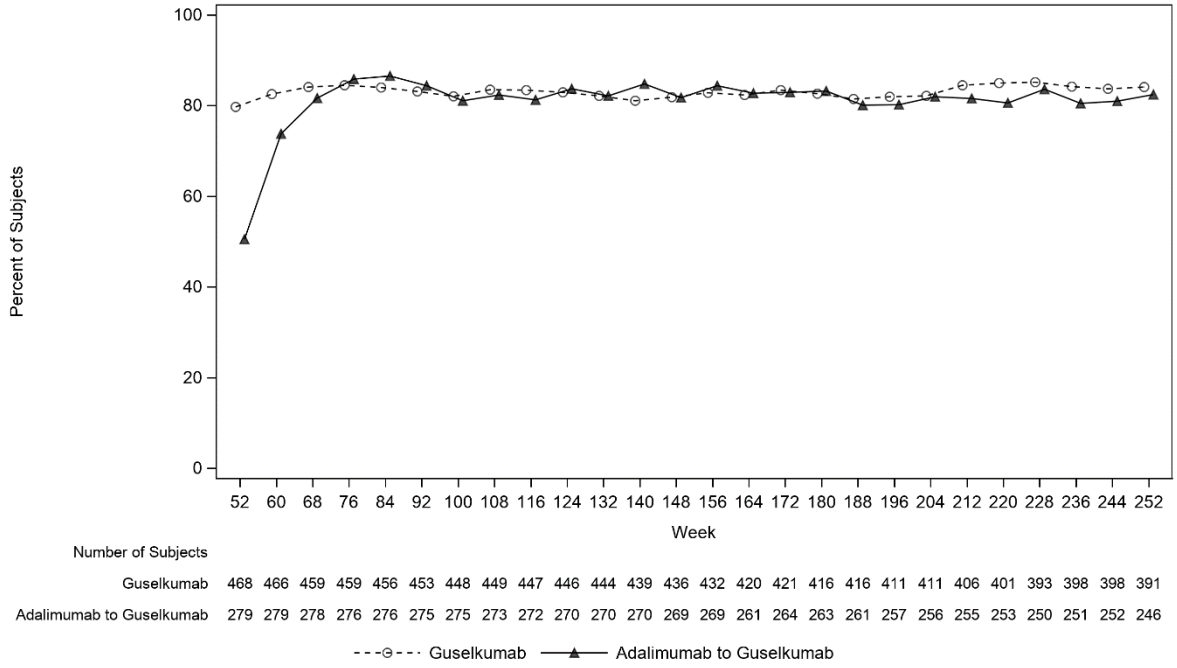


Figure 2: Percent of Subjects Achieving PASI 90 Response From Week 52 Through Week 252 by Visit in VOYAGE 1



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. Among patients who were withdrawn from treatment and subsequently re-initiated guselkumab, 80% regained a PASI 90 response when assessed 20 weeks after initiation of retreatment.

In VOYAGE 2, among 112 adalimumab subjects who failed to achieve a PASI 90 response at Week 28, 66% and 76% achieved a PASI 90 response after 20 and 44 weeks of treatment with guselkumab respectively. 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 9). 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 9: 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 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1).

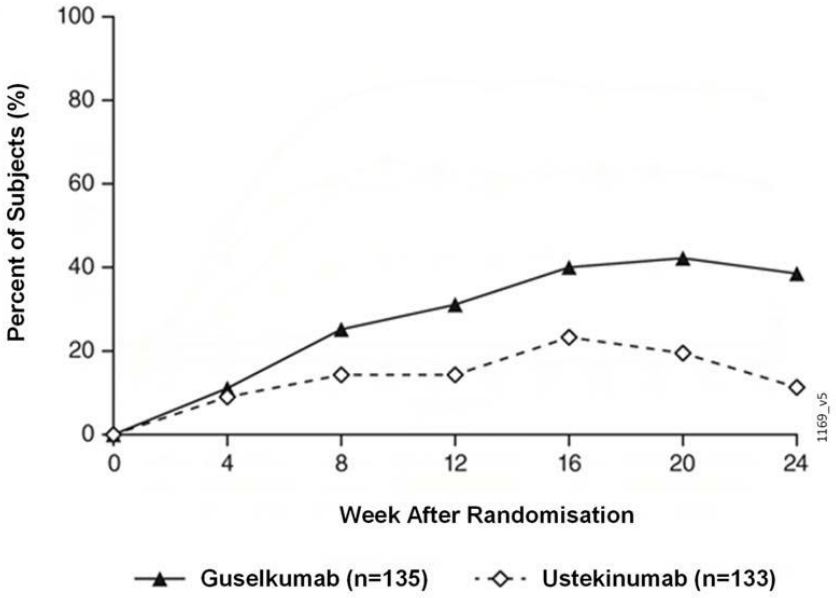
In VOYAGE 1, for subjects receiving continuous guselkumab treatment, improvements in PSSD scores were maintained from Week 52 through Week 252.

NAVIGATE - Active-controlled study in ustekinumab inadequate responders

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 3). No new safety findings were observed in patients who switched from ustekinumab to guselkumab.

Figure 3: 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



ORION - Placebo-controlled study with pre-filled pen

ORION evaluated the efficacy, safety, PK, immunogenicity, usability, and acceptability of guselkumab delivered with a pre-filled pen. In this study, 78 subjects were randomised to receive either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), or placebo. Baseline characteristics for randomised subjects were comparable to those observed in VOYAGE 1 and VOYAGE 2. The co-primary endpoints were the proportion of subjects who achieved an IGA score of 0 or 1 at Week 16 and the proportion of subjects who achieved a PASI 90 response at Week 16. The secondary endpoints included the proportion of subjects who achieved an IGA score 0 at Week 16 and the proportion of subjects who achieved a PASI 100 response at Week 16.

A significantly greater proportion of subjects in the guselkumab group achieved an IGA score of 0 or 1 or a PASI 90 response at Week 16 (80.6% and 75.8%, respectively, $p<0.001$ for both endpoints) than in the placebo group (0% for both endpoints). The proportion of subjects who achieved an IGA score of 0 at Week 16 was significantly higher in the guselkumab group compared to the placebo group (56.5% vs. 0%; $p < 0.001$). The proportion of subjects who

achieved a PASI 100 response at Week 16 was significantly higher in the guselkumab group compared to the placebo group (50.0% vs. 0%; p < 0.001).

Patient Experience

Subject experience with the pre-filled pen was assessed on a scale of 0 (worst) to 10 (best) using a validated Self-Injection Assessment Questionnaire (SIAQ) based on subject responses across 6 domains (feelings about injections, self-image, self-confidence, pain and skin reactions during or after the injection, ease of use of the self-injection device, and satisfaction with self-injection) at weeks 0, 4 and 12. At week 12, the mean score for "Satisfaction with Self Injection" was 9.18 (with 10 indicating "Very Satisfied") and the mean score for "Ease of Use" was 9.24 (with 10 indicating "Very Easy"). The mean scores for the other domains at week 12 ranged from 8.43 to 9.84.

Active-controlled study with secukinumab – ECLIPSE

The efficacy and safety of TREMFYA were also investigated in a double-blind study compared to secukinumab. Patients were randomised to receive TREMFYA (N=534; 100 mg at Week 0, 4 and every 8 weeks thereafter) or secukinumab (N=514; 300 mg at Week 0, 1, 2, 3, 4, and every 4 weeks thereafter). The last dose was at Week 44 for both treatment groups. Demographic and disease characteristics were similar between the two treatment groups and consistent with those of the subjects enrolled in the pivotal Phase 3 psoriasis studies for TREMFYA and secukinumab. The primary endpoint was the proportion of subjects who achieved a PASI 90 response at Week 48. Major secondary endpoints were the proportion of subjects who achieved a PASI 75 response at both Week 12 and Week 48, a PASI 90 response at Week 12, PASI 75 response at Week 12, a PASI 100 response at Week 48, an IGA score of cleared (0) at Week 48, and an IGA score of cleared (0) or minimal (1) at Week 48.

TREMFYA was superior to secukinumab as measured by the primary endpoint of PASI 90 response at Week 48 (84.5% versus 70.0%, p<0.001). Comparative clinical response rates are presented in Table 10.

Table 10: Summary of Clinical Response Rates in ECLIPSE

	Number of patients (%)	
	TREMFYA (N=534)	Secukinumab (N=514)
Primary Endpoint		
PASI 90 response at Week 48	451 (84.5%)[a]	360 (70.0%)
Major Secondary Endpoints		
PASI 75 response at both Week 12 and Week 48	452 (84.6%)[b]	412 (80.2%)
PASI 75 response at Week 12	477 (89.3%)[c]	471 (91.6%)
PASI 90 response at Week 12	369 (69.1%)[c]	391 (76.1%)
PASI 100 response at Week 48	311 (58.2%)[c]	249 (48.4%)
IGA score of cleared (0) at Week 48	332 (62.2%)[c]	259 (50.4%)
IGA score of cleared (0) or minimal (1) at Week 48	454 (85.0%)[c]	385 (74.9%)

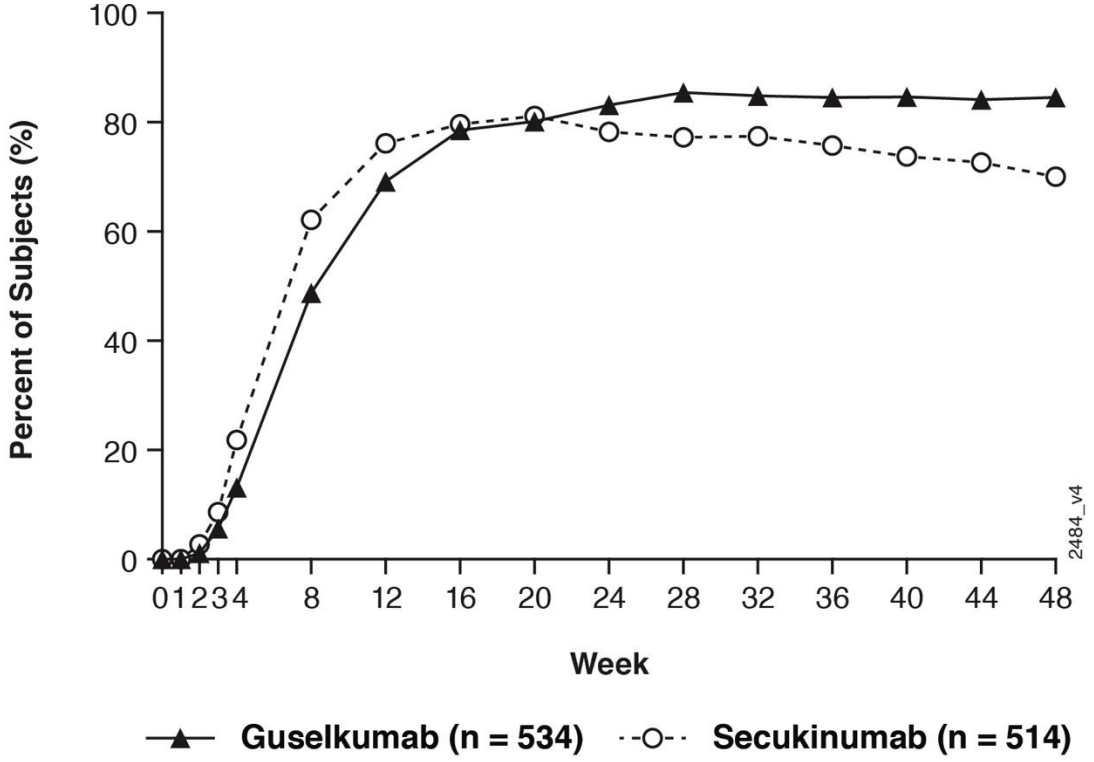
[a] p<0.001 for both non-inferiority and superiority

[b] p<0.001 for non-inferiority, p=0.062 for superiority

[c] formal statistical testing was not performed

TREMFYA and secukinumab PASI 90 response rates through Week 48 are presented in Figure 4.

Figure 4: Percent of Subjects Who Achieved a PASI 90 Response from Week 0 Through Week 48 by Visit (Subjects Randomised at Week 0) in ECLIPSE



Psoriatic Arthritis (PsA)

DISCOVER 1 and DISCOVER 2

The safety and efficacy of TREMFYA were assessed in 1120 patients in 2 randomised, double-blind, placebo-controlled studies (DISCOVER 1 and DISCOVER 2) in adult patients with active PsA (≥3 swollen joints, ≥3 tender joints, and a C-reactive protein (CRP) level of ≥0.3 mg/dL in DISCOVER 1 and ≥5 swollen joints, ≥5 tender joints, and a CRP level of ≥0.6 mg/dL in DISCOVER 2) who had inadequate response to standard therapies. Patients in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and a median duration of PsA of 4 years at baseline.

In DISCOVER 1 approximately 30% of subjects had been previously treated with up to 2 anti-tumor necrosis factor alpha (anti-TNFα) agents whereas in DISCOVER 2 all subjects were biologic naïve. Approximately 58% of subjects from both studies had concomitant methotrexate (MTX) use. Patients with different subtypes of PsA were enrolled in both studies, including polyarticular arthritis with the absence of rheumatoid nodules (40%), spondylitis with peripheral arthritis (30%), asymmetric peripheral arthritis (23%), distal interphalangeal involvement (7%) and arthritis mutilans (<1%). At baseline, over 65% and 42% of the patients had enthesitis and dactylitis, respectively and over 75% had ≥3% body surface area (BSA) psoriasis skin involvement.

DISCOVER 1 evaluated 381 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and every 8 weeks (q8w) thereafter, or TREMFYA 100 mg SC every 4 weeks (q4w). DISCOVER 2 evaluated 739 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and q8w thereafter, or TREMFYA 100 mg SC q4w. At Week 24, placebo subjects in both studies crossed over to receive TREMFYA 100 mg SC q4w.

The primary endpoint in both studies was the percentage of patients achieving an ACR20 response at Week 24. Secondary endpoints included change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI), IGA, ACR 50, ACR 70, SF-36 PCS, SF-36 MCS and change from baseline in total modified van der Heijde-Sharp score (DISCOVER 2), at Week 24. Additionally, resolution of enthesitis and dactylitis based on the pooled data from DISCOVER 1 and DISCOVER 2 was assessed as a secondary endpoint in DISCOVER 2.

Signs and symptoms

In both studies, patients treated with TREMFYA 100 mg q8w or 100 mg q4w demonstrated a greater clinical response including ACR20, ACR50, and ACR70 compared to placebo at Week 24 (Table 11). These responses were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2. Responses were seen regardless of prior anti-TNFα exposure (DISCOVER 1) and concomitant csDMARD use (DISCOVER 1 and DISCOVER 2). Additionally, in both studies, examination of age, gender, race, body weight, and previous treatment with csDMARDs did not identify differences in response to TREMFYA among these subgroups.

Table 11: Clinical Responses in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			**DISCOVER 2**		
	Placebo (N=126)	TREMFYA 100 mg q8w (N=127)	TREMFYA 100 mg q4w (N=128)	Placebo (N=246)	TREMFYA 100 mg q8w (N=248)	TREMFYA 100 mg q4w (N=245)
ACR 20 response						
Week 16	25.4%	52.0%[b]	60.2%[b]	33.7%	55.2%	55.9%[c]
Week 24	22.2%	52.0%[a]	59.4%[a]	32.9%	64.1%[a]	63.7%[a]
ACR 50 response						
Week 16	12.7%	22.8%	26.6%[c]	9.3%	28.6%	20.8% [c]
Week 24	8.7%	29.9% [b]	35.9%[b]	14.2%	31.5%	33.1% [c]
ACR 70 response						
Week 24	5.6%	11.8%	20.3%[b]	4.1%	18.5%	13.1% [c]
DAS 28 (CRP) LS Mean Change from baseline (adjusted mean)						
Week 24	-0.70	-1.43 [b]	-1.61 [b]	-0.97	-1.59 [b]	-1.62 [b]
Minimal Disease Activity (MDA)						
Week 24	11.1%	22.8% [d]	30.5% [e]	6.1%	25.0% [e]	18.8% [e]
Modified PsA Responder Criteria (PsARC)						
Week 24	31.0%	59.8%[e]	72.7%[e]	44.7%	72.6%[e]	68.6%[e]

[a] multiplicity adjusted p<0.001 for comparison between TREMFYA and placebo for primary endpoint

[b] multiplicity adjusted p<0.001 for comparison between TREMFYA and placebo for major secondary endpoint

[c] multiplicity adjusted p=0.006 for comparison between TREMFYA and placebo for major secondary endpoint

[d] nominal p=0.012 for comparison between TREMFYA and placebo

[e] nominal p<0.001 for comparison between TREMFYA and placebo

Clinical response was maintained up to Week 52 as assessed by ACR 20/50/70, DAS 28 (CRP), MDA, IGA and PASI 90 response rates (see Table 12).

Table 12: Clinical Responses in DISCOVER 1 and DISCOVER 2 at Week 52[a]

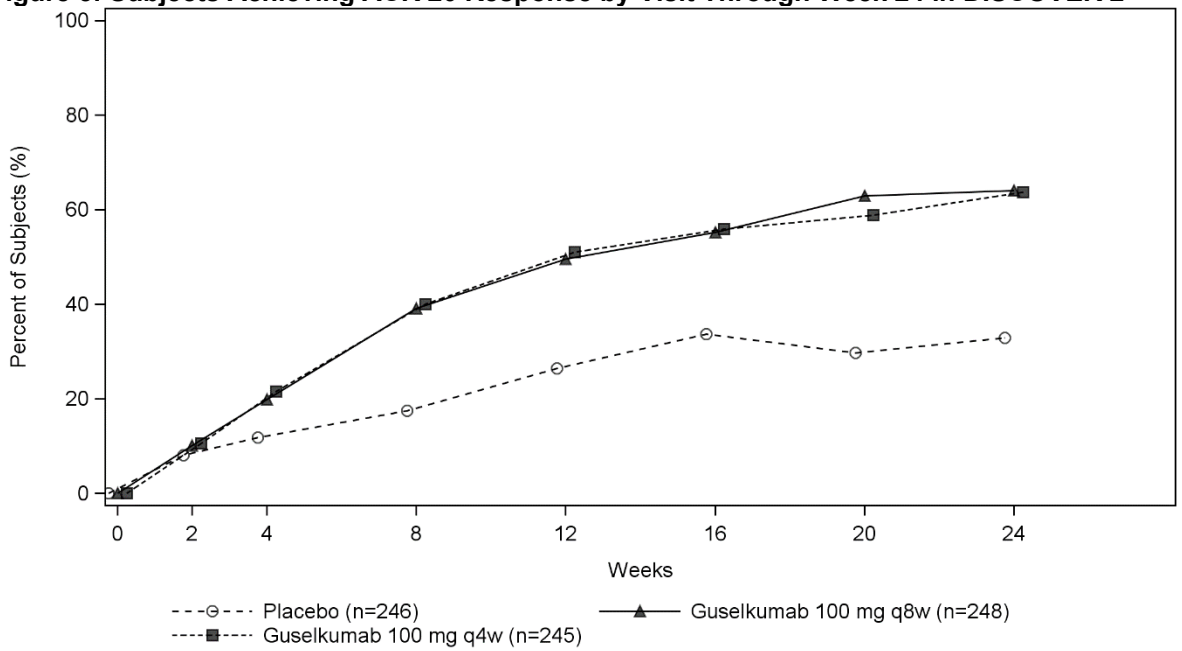
	DISCOVER 1		DISCOVER 2	
	Guselkumab 100 mg q8w	Guselkumab 100 mg q4	Guselkumab 100 mg q8w	Guselkumab 100 mg q4
ACR 20				
N[b]	112	124	234	228
% Response	67.9%	75.8%	79.1%	75.9%
ACR 50				
N[b]	113	124	234	228
% Response	43.4%	55.6%	51.3%	49.1%
ACR 70				
N[b]	114	124	234	228
% Response	28.9%	29.8%	29.5%	28.1%
DAS28 (CRP) change from baseline				
N[c]	112	123	234	227
Mean (SD)	-2.03 (1.250)	-1.99 (1.062)	-2.08 (1.121)	-2.11 (1.128)
MDA				
N[b]	112	124	234	228
% Response	33.9%	40.3%	32.9%	36.8%
Patients with ≥ 3% BSA and IGA ≥ 2 at baseline				
IGA Response				
N[b]	75	88	170	173
% Response	69.3%	83.0%	77.1%	84.4%
PASI 90				
N[b]	75	88	170	173
% Response	66.7%	76.1%	77.1%	81.5%

[a] There was no placebo arm beyond Week 24.
[b] Evaluable subjects with an observed response status.
[c] Subjects have an observed change from baseline.

In DISCOVER 1 and 2, patients treated with TREMFYA who had spondylitis with peripheral arthritis as their primary presentation, demonstrated greater improvement from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) compared to placebo at Week 24. Improvement in BASDAI was maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

In DISCOVER 2, a greater ACR 20 response was observed in both TREMFYA dose groups compared with the placebo group as early as Week 4 and the treatment difference continued to increase over time through Week 24 (Figure 5).

Figure 5: Subjects Achieving ACR 20 Response by Visit Through Week 24 in DISCOVER 2



In DISCOVER 2, for subjects receiving continuous guselkumab treatment at week 24, ACR 20 response was maintained from Week 24 to Week 52 (see Figure 6). For subjects receiving continuous guselkumab treatment at week 52, ACR 20 response was maintained from Week 52 to Week 100 (see Figure 7).

Figure 6: Subjects Achieving ACR 20 Response by Visit from Week 24 Through Week 52 in DISCOVER 2

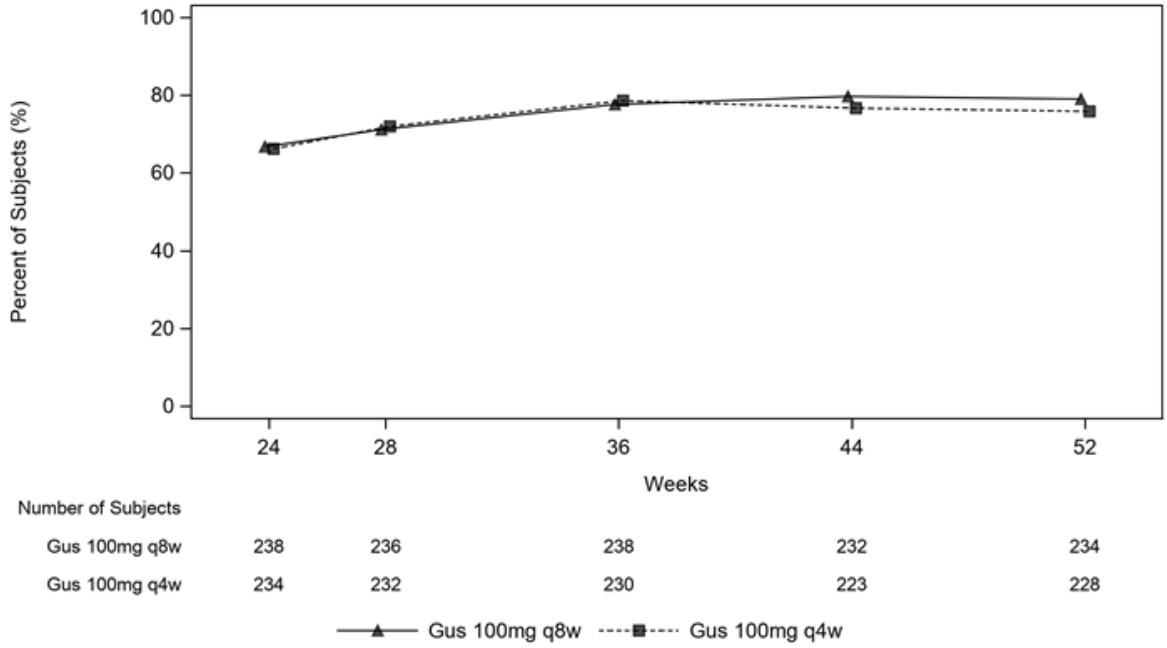
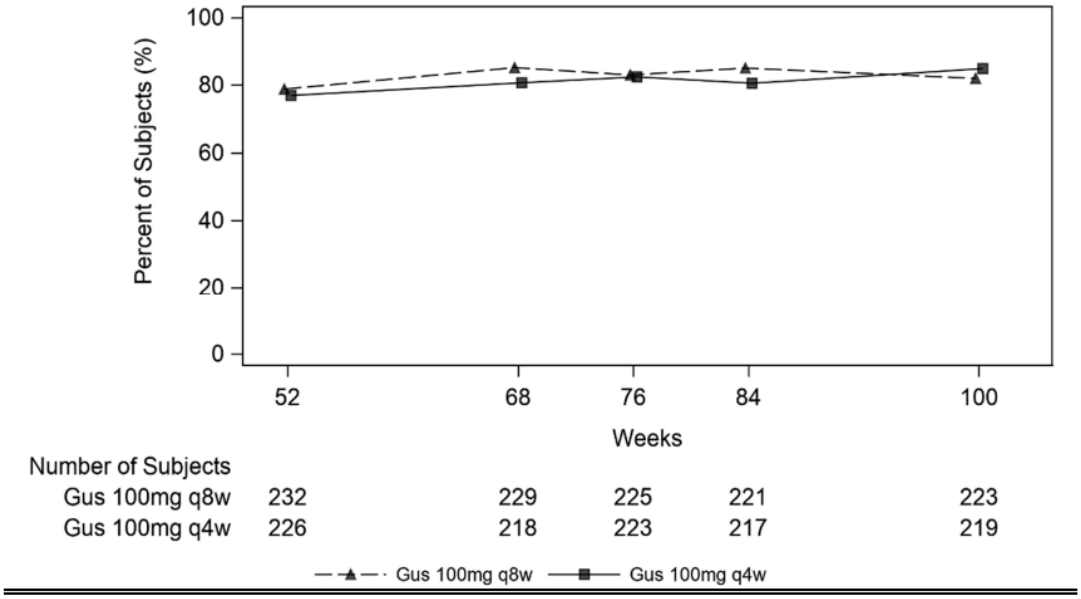


Figure 7: Subjects Achieving ACR 20 Response by Visit from Week 52 Through Week 100 in DISCOVER 2



In DISCOVER 1 and DISCOVER 2, median percent improvement from baseline was observed in all components of the ACR response criteria.

Psoriasis Skin Response

In DISCOVER 1 and DISCOVER 2, among subjects with mild to severe psoriasis (BSA ≥3% and IGA ≥2) at baseline, a greater proportion of subjects in both TREMFYA dose groups achieved a psoriasis response, defined as an IGA of 0 (cleared) or 1 (minimal) and a ≥2-grade reduction from baseline, compared with the placebo group at Week 24. Results from psoriasis skin response endpoints in DISCOVER 1 and DISCOVER 2 are presented in Table 13. Responses for both IGA and PASI endpoints were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Table 13: Psoriasis Skin Response in Subjects with ≥ 3% BSA and IGA ≥ 2 at Baseline

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo (n=78)	100 mg q8w (n=82)	100 mg q4w (n=89)	Placebo (n=183)	100 mg q8w (n=176)	100 mg q4w (n=184)
IGA response *IGA 0/1 and ≥2 grade improvement*						
Week 24	15.4%	57.3%[a]	75.3%[a]	19.1%	70.5%[a]	68.5%[a]
PASI 90 response						
Week 16	10.3%	45.1%[b]	52.8%[b]	8.2%	55.1%[b]	53.8%[b]
Week 24	11.5%	50.0%[b]	62.9%[b]	9.8%	68.8%[b]	60.9%[b]
PASI 100 response						
Week 16	7.7%	23.2%[c]	32.6%[b]	3.8%	27.3%[b]	33.2%[b]
Week 24	6.4%	25.6%[b]	44.9%[b]	2.7%	45.5%[b]	44.6%[b]

[a] $p < 0.001$ (major secondary endpoint)

[b] nominal $p < 0.001$

[c] nominal $p=0.006$

Enthesitis and Dactylitis

Enthesitis and dactylitis were assessed based on pooled data from DISCOVER 1 and DISCOVER 2. Among subjects with dactylitis at baseline, a greater proportion of subjects in both the TREMFYA 100 mg q8w and the TREMFYA 100 mg q4w groups achieved dactylitis resolution at Week 24 compared with the placebo group (Table 14). Among subjects with enthesitis at baseline, a greater proportion of subjects in both the TREMFYA 100 mg q8w group and q4w group achieved enthesitis resolution at Week 24 compared with the placebo group (Table 14). Based on the combined data from DISCOVER 1 and DISCOVER 2, resolution of dactylitis and enthesitis were maintained from Week 24 to Week 52. In DISCOVER 2, among subjects with dactylitis and enthesitis at baseline, resolution of dactylitis and enthesitis were maintained at Week 100.

Table 14: Dactylitis and Enthesitis Resolution at Week 24; Pooled Data from DISCOVER 1 and DISCOVER 2

		TREMFYA	
	Placebo	**100 mg q8w**	**100 mg q4w**
Dactylitis			
Subjects with dactylitis at baseline (n)	154	160	159
Dactylitis resolution at Week 24	42.2%	59.4% [b]	63.5%[a]
Enthesitis			
Subjects with enthesitis at baseline (n)	255	230	243
Enthesitis resolution at Week 24	29.4%	49.6% [c]	44.9%[a]

[a] p=0.006 (major secondary endpoint)

[b] not formally tested based on hierarchical order in testing procedure, nominal p=0.001 (major secondary endpoint)

[c] not formally tested based on hierarchical order in testing procedure, nominal p<0.001 (major secondary endpoint)

Radiographic response

In DISCOVER 2, inhibition of structural damage progression was measured radiographically and expressed as the mean change from baseline in the total modified van der Heijde-Sharp (vdH-S) score at Week 24.

TREMFYA q4w inhibited the progression of structural damage compared to placebo at Week 24. TREMFYA q8w showed numerically less, but not statistically significant, progression of structural damage compared to placebo. These results are shown in Table 15.

Table 15: Change from Baseline in vdH-S score at Week 24 in DISCOVER 2

	N	**LS Mean change from baseline in vdH-S score at Week 24**
Placebo	246	0.95
TREMFYA 100 mg q4w	245	0.29[a]
TREMFYA 100 mg q8w	248	0.52[b]

[a] multiplicity adjusted p=0.006 for comparison between TREMFYA and placebo for major secondary endpoint

[b] multiplicity adjusted p=0.069 for comparison between TREMFYA and placebo for major secondary endpoint

The mean change from baseline in total modified vdH-S was similar in the guselkumab q8w and q4w groups at Week 52 (0.97 and 1.07, respectively) and at Week 100 (1.50 and 1.68 respectively).

Physical function and health-related quality of life

TREMFYA-treated patients in both the 100 mg q8w and q4w dose groups in both DISCOVER 1 and DISCOVER 2 showed greater mean improvement from baseline in physical function compared to patients treated with placebo as assessed by HAQ-DI at Weeks 16 and 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52. In both studies, the proportion of HAQ-DI responders (≥0.35 improvement in HAQ-DI score) was greater in both TREMFYA dose groups compared to placebo at weeks 16 and 24. The proportion of HAQ-DI

responders was maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Table 16: HAQ-DI Response at Weeks 16 and 24 in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo (N=126)	100 mg q8w (N=127)	100 mg q4w (N=128)	Placebo N=246	100 mg q8w (N=248)	100 mg q4w (N=245)
HAQ-DI Mean change from baseline[f]						
Baseline	1.2391	1.2057	1.0938	1.2949	1.2848	1.2490
Mean change at Week 16	-0.1131	-0.2620[d]	-0.3393[c]	-0.1167	-0.3177[c]	-0.3442[c]
Mean change at Week 24	-0.0743	-0.3225[a]	-0.3968[a]	-0.1300	-0.3672[a]	-0.4004[a]
HAQ-DI Responders (≥ 0.35 improvement from baseline)						
Week 16	30.9%	46.4%[e]	57.3%[c]	30.9%	50.0%[c]	51.8%[c]
Week 24	29.1%	50.9%[b]	57.3%[c]	31.4%	50.0% [c]	56.1% [c]

[a] p<0.001 (major secondary endpoint)

[b] nominal p=0.001

[c] nominal p<0.001

[d] nominal p=0.008

[e] nominal p=0.019

[f] adjusted mean change

At Week 24, subjects in both the TREMFYA 100 mg q8w and q4w dose groups in both DISCOVER 1 and DISCOVER 2 showed greater improvement from baseline in the SF-36 PCS with no worsening in the SF-36 MCS compared with placebo. At Week 24 there was consistent evidence of effect in the physical functioning, role-physical, bodily-pain, general health, social-functioning and vitality domains but not in the role-emotional and mental health domains. At Week 24, a greater mean increase from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score was observed in guselkumab treated patients compared to placebo in both DISCOVER 1 (5.609, 5.841 and 2.206 in the 100 mg q8w, 100 mg q4w and placebo groups, respectively; both nominal p<0.001) and DISCOVER 2 (7.550, 7.111 and 3.559 in the 100 mg q8w, 100 mg q4w and placebo groups, respectively; both nominal p<0.001). In DISCOVER 2, greater improvements in health-related quality of life as measured by mean change from baseline in the Dermatology Life Quality Index (DLQI) were observed in guselkumab treated patients compared to placebo at Week 24 (-8.954, -8.853, and -2.129 in the 100 mg q8w, 100 mg q4w and placebo groups, respectively; both nominal p<0.001). In DISCOVER 2, greater improvements were also observed in overall work impairment and activity impairment as assessed by the Work Productivity and Activity Impairment (WPAI)-PsA questionnaire compared to placebo at Week 24. Improvements in SF-36 PCS, SF-36 MCS, FACIT-F, DLQI and WPAI-PsA scores were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Ulcerative Colitis (UC)

The efficacy and safety of TREMFYA were evaluated in two Phase 3 multicentre, randomised, double-blind, placebo-controlled studies (QUASAR induction study and QUASAR maintenance study) in adult patients with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to corticosteroids, conventional immunomodulators, biologic therapy (TNF blockers, vedolizumab), and/or a Janus kinase (JAK) inhibitor. In addition, efficacy and safety of TREMFYA were evaluated in a randomised, double-blind, placebo controlled, Phase 2b induction dose-finding study (QUASAR induction dose-ranging study).

Disease activity was assessed by the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the sum of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally reviewed endoscopy (ES). Moderately to severely active ulcerative colitis was defined as a mMS between 5 and 9, a RBS $\geq$1, and an ES of 2 (defined by marked erythema, absent vascular pattern, friability, and/or erosions) or an ES of 3 (defined by spontaneous bleeding and ulceration).

QUASAR Induction Study: QUASAR IS

In the induction study QUASAR IS, patients were randomised 3:2 to receive either TREMFYA 200 mg or placebo by intravenous infusion at Week 0, Week 4, and Week 8. A total of 701 patients were evaluated. At baseline the median mMS was 7, with 35.5% of patients having a baseline mMS of 5 to 6 and 64.5% having a mMS of 7 to 9, and 67.9% of patients with a baseline ES of 3. The median age was 39 years (ranging from 18 to 79 years); 43.1% were female; and 72.5% identified as White, 21.4% as Asian, 1% as Black, 0.1% as American Indian or Alaskan Native, and 0.1% as multiple racial groups.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, methotrexate, 6-MP, AZA and/or oral corticosteroids. At baseline, 72.5% of patients were receiving aminosalicylates, 20.8% of patients were receiving immunomodulators (MTX, 6-MP, or AZA), and 43.1% of patients were receiving corticosteroids. Concomitant biologic therapies or JAK inhibitors were not permitted.

A total of 49.1% of patients had previously failed at least one biologic therapy, and/or JAK inhibitor. Of these patients, 88%, 54% and 18% had previously failed a TNF blocker, vedolizumab or a JAK inhibitor, respectively, and 47% had failed treatment with 2 or more of these therapies. A total of 48.4% of patients were biologic and JAK inhibitor naïve, and 2.6% had previously received but had not failed a biologic or JAK inhibitor.

The primary endpoint was clinical remission as defined by the mMS at Week 12. Secondary endpoints at Week 12 included symptomatic remission, endoscopic healing, clinical response, histologic endoscopic mucosal healing, and fatigue response (see Table 17).

Significantly greater proportions of patients were in clinical remission in the TREMFYA treated group compared to the placebo group at Week 12.

Table 17: Proportion of Patients Meeting Efficacy Endpoints at Week 12 in QUASAR IS

Endpoint	Placebo (N=280)	TREMFYA 200 mg Intravenous Infusion[a] (N=421)	Treatment Difference (95% CI)
Clinical remission[b]			
Total Population	22 (8%)	95 (23%)	15% (10%, 20%)[c]
Biologic and JAK inhibitor naïve[d]	16/137 (12%)	64/202 (32%)	
Prior biologic and/or JAK inhibitor failure[e]	5/136 (4%)	26/208 (13%)	
Symptomatic remission[f]			
Total Population	58 (21%)	210 (50%)	29% (23%, 36%)[c]
Biologic and JAK inhibitor naïve[d]	36/137 (26%)	122/202 (60%)	
Prior biologic and/or JAK inhibitor failure[e]	19/136 (14%)	80/208 (38%)	
Endoscopic healing[g]			
Total Population	31 (11%)	113 (27%)	16% (10%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	23/137 (17%)	77/202 (38%)	
Prior biologic and/or JAK inhibitor failure[e]	7/136 (5%)	31/208 (15%)	
Clinical response[h]			
Total Population	78 (28%)	259 (62%)	34% (27%, 41%)[c]
Biologic and JAK inhibitor naïve[d]	48/137 (35%)	144/202 (71%)	
Prior biologic and/or JAK inhibitor failure[e]	27/136 (20%)	107/208 (51%)	
Histologic endoscopic mucosal healing[i]			
Total Population	21 (8%)	99 (24%)	16% (11%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	15/137 (11%)	66/202 (33%)	
Prior biologic and/or JAK inhibitor failure[e]	6/136 (4%)	28/208 (13%)	
Fatigue response[j]			
Total Population	60 (21%)	173 (41%)	20% (13%, 26%)[c]
Biologic and JAK inhibitor naïve[d]	40/137 (29%)	84/202 (42%)	
Prior biologic and/or JAK inhibitor failure[e]	18/136 (13%)	80/208 (38%)	

[a] TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8
[b] A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy
[c] p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method (adjusted for stratification factors: biologic and/or JAK-inhibitor failure status and concomitant use of corticosteroids at baseline)
[d] An additional 7 subjects in the placebo group and 11 subjects in the TREMFYA group were previously exposed to but did not fail a biologic or JAK inhibitor
[e] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis
[f] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.
[g] An endoscopy subscore of 0 or 1 with no friability present on the endoscopy
[h] Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
[i] A combination of histologic healing [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system] and endoscopic healing as defined above
[j] Fatigue was assessed using the PROMIS-Fatigue Short form 7a. Fatigue response was defined as a ≥ 7-point improvement from baseline which is considered clinically meaningful

QUASAR IS and QUASAR induction dose-ranging study also enrolled patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥1. In these patients, TREMFYA efficacy relative to placebo, as measured by clinical remission, clinical response, and endoscopic healing at Week 12, was consistent with the total moderately to severely active UC population.

Rectal Bleeding Subscore and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with TREMFYA and continued to decrease through Week 12.

Maintenance Study: QUASAR MS

The maintenance study (QUASAR MS) evaluated 568 patients who achieved clinical response at Week 12 following the intravenous administration of TREMFYA in either QUASAR IS or from the QUASAR induction dose-ranging study. These patients were randomised to receive a subcutaneous maintenance regimen of either TREMFYA 100 mg every 8 weeks, TREMFYA 200 mg every 4 weeks or placebo for 44 weeks.

The primary endpoint was clinical remission as defined by mMS at Week 44. Secondary endpoints at Week 44 included but were not limited to symptomatic remission, endoscopic healing, corticosteroid-free clinical remission, histologic endoscopic mucosal healing, and fatigue response (see Table 18).

Significantly greater proportions of patients were in clinical remission in both TREMFYA treated groups compared to the placebo group at Week 44.

Table 18: Proportion of Patients Meeting Efficacy Endpoints at Week 44 in QUASAR MS

Endpoint	Placebo N=190	TREMFYA 100 mg q8w Subcutaneous Injection[a] N=188	TREMFYA 200 mg q4w Subcutaneous Injection[b] N=190	Treatment Difference vs Placebo (95% CI)	
				TREMFYA 100 mg	TREMFYA 200 mg
Clinical remission[c]					
Total population[d]	36 (19%)	85 (45%)	95 (50%)	25% (16%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	28/108 (26%)	53/105 (50%)	56/96 (58%)		
Prior biologic and/or JAK-inhibitor failure[g]	6/75 (8%)	31/77 (40%)	35/88 (40%)		
Symptomatic remission[h]					
Total population[d]	71 (37%)	132 (70%)	131 (69%)	32% (23%, 41%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	50/108 (46%)	78/105 (74%)	73/96 (76%)		
Prior biologic and/or JAK-inhibitor failure[g]	18/75 (24%)	50/77 (65%)	53/88 (60%)		
Corticosteroid-free clinical remission[i]					
Total population[d]	35 (18%)	85 (45%)	93 (49%)	26% (17%, 34%)[e]	29% (20%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	28/108 (26%)	53/105 (50%)	54/96 (56%)		
Prior biologic and/or JAK-inhibitor failure[g]	5/75 (7%)	31/77 (40%)	35/88 (40%)		
Endoscopic healing[j]					
Total population[d]	36 (19%)	93 (49%)	98 (52%)	30% (21%, 38%)[e]	31% (22%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	28/108 (26%)	56/105 (53%)	57/96 (59%)		
Prior biologic and/or JAK-inhibitor failure[g]	6/75 (8%)	35/77 (45%)	37/88 (42%)		
Histologic endoscopic mucosal healing[k]					
Total population[d]	32 (17%)	82 (44%)	91 (48%)	26% (17%, 34%)[e]	30% (21%, 38%)[e]

Biologic and JAK-inhibitor naïve[f]	25/108 (23%)	52/105 (50%)	54/96 (56%)		
Prior biologic and/or JAK-inhibitor failure[g]	6/75 (8%)	29/77 (38%)	34/88 (39%)		
Clinical response[l]					
Total population[d]	82 (43%)	146 (78%)	142 (75%)	34% (25%, 43%) [e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	58/108 (54%)	87/105 (83%)	78/96 (81%)		
Prior biologic and/or JAK-inhibitor failure [g]	21/75 (28%)	54/77 (70%)	59/88 (67%)		
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population[d]	20/59 (34%)	40/66 (61%)	50/69 (72%)	26% (9%, 43%) [m]	38% (23%, 54%) [e]
Biologic and JAK-inhibitor naïve [f]	14/41 (34%)	28/43 (65%)	38/48 (79%)		
Prior biologic and/or JAK-inhibitor failure [g]	4/15 (27%)	12/20 (60%)	10/18 (56%)		
Endoscopic normalisation[n]					
Total population[d]	29 (15%)	65 (35%)	64 (34%)	18% (10%, 27%) [e]	17% (9%, 25%) [e]
Biologic and JAK-inhibitor naïve [f]	22/108 (20%)	40/105 (38%)	40/96 (42%)		
Prior biologic and/or JAK-inhibitor failure [g]	6/75 (8%)	24/77 (31%)	21/88 (24%)		
Fatigue response[o]					
Total population[d]	56 (29%)	95 (51%)	82 (43%)	20% (11%, 29%) [e]	13% (3%, 22%) [m]
Biologic and JAK-inhibitor naïve[f]	39/108 (36%)	54/105 (51%)	51/96 (53%)		
Prior biologic and/or JAK-inhibitor failure [g]	14/75 (19%)	36/77 (47%)	28/88 (32%)		

[a] TREMFYA 100 mg as a subcutaneous injection every 8 weeks after the induction regimen
[b] TREMFYA 200 mg as a subcutaneous injection every 4 weeks after the induction regimen
[c] A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy
[d] Patients who achieved clinical response 12 weeks following the intravenous administration of TREMFYA in either QUASAR induction study or QUASAR induction dose-ranging study
[e] p <0.001, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomisation stratification factors
[f] An additional 7 subjects in the placebo group, 6 subjects in the TREMFYA 100 mg group, and 6 subjects in the TREMFYA 200 mg group were previously exposed to but did not fail a biologic or JAK inhibitor
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase [JAK] inhibitor for ulcerative colitis
[h] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.
[i] Not requiring any treatment with corticosteroids for at least 8 weeks prior to Week 44 and also meeting the criteria for clinical remission at Week 44
[j] An endoscopy subscore of 0 or 1 with no friability present on the endoscopy
[k] A combination of histologic healing [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system] and endoscopic healing as defined above
[l] Decrease from induction baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
[m] p <0.01, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomisation stratification factors
[n] An endoscopy subscore of 0
[o] Fatigue was assessed using the PROMIS-Fatigue Short form 7a. Fatigue response was defined as a ≥ 7-point improvement from induction baseline which is considered clinically meaningful.

In QUASAR IS and QUASAR MS, the efficacy and safety of TREMFYA was consistently demonstrated regardless of age, sex, race, body weight, and previous treatment with a biologic therapy or JAK inhibitor. TREMFYA was efficacious in biologic and JAK inhibitor naïve patients, as well as in patients who previously failed a biologic and/or JAK inhibitor.

In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from TREMFYA 200 mg SC q4w compared to the 100 mg SC q8w. Clinically meaningful numerical differences were observed between the two TREMFYA dose groups among patients with a CRP level of >3 mg/L after completion of induction dosing for the following endpoints at Week 44: clinical remission (48% 200 mg q4w vs. 30% 100 mg q8w), maintenance of clinical remission (88% 200 mg q4w vs. 50% 100 mg q8w), corticosteroid-free clinical remission (46% 200 mg q4w vs. 30% 100 mg q8w), endoscopic healing (52% 200 mg q4w vs. 35% 100 mg q8w), and histologic-endoscopic mucosal healing (46% 200 mg q4w vs. 29% 100 mg q8w).

In QUASAR MS, patients with extensive disease at induction baseline derived additional benefit from TREMFYA 200 mg SC q4w compared to the 100 mg SC q8w. Clinically meaningful numerical differences were observed between the two TREMFYA dose groups among patients with extensive disease at induction baseline for the following endpoints at Week 44: clinical remission (63% 200 mg q4w vs. 49% 100 mg q8w), maintenance of clinical remission (83% 200 mg q4w vs. 68% 100 mg q8w), corticosteroid-free clinical remission (60% 200 mg q4w vs. 49% 100 mg q8w), endoscopic healing (64% 200 mg q4w vs. 52% 100 mg q8w), and histologic-endoscopic mucosal healing (58% 200 mg q4w vs. 44% 100 mg q8w).

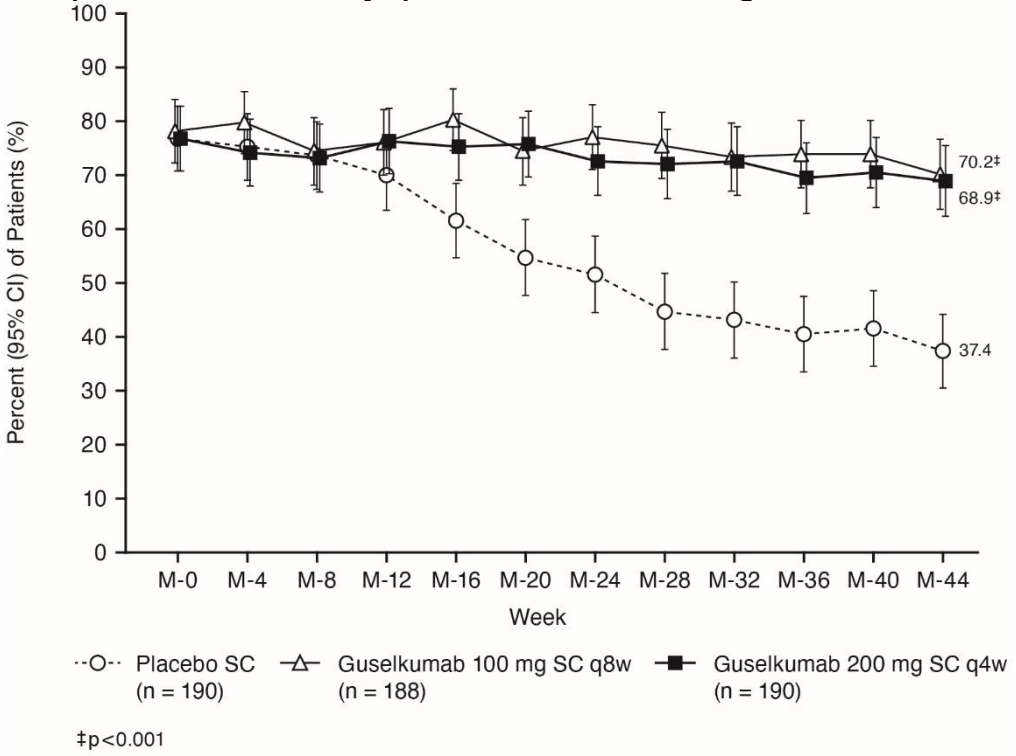
QUASAR MS also enrolled patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥1 who achieved clinical response 12 weeks following the intravenous administration of TREMFYA in QUASAR IS or QUASAR induction dose-ranging study. In these patients, TREMFYA showed efficacy relative to placebo as measured by clinical remission, clinical response, and endoscopic healing at Week 44 was consistent with the total population.

Remission over time

In QUASAR MS, symptomatic remission as defined as a stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0 was sustained

through Week 44 in both TREMFYA treatment groups, while a decline was observed in the placebo group (Figure 8).

Figure 8: Proportion of Patients in Symptomatic Remission Through Week 44 in QUASAR MS



Week 24 Responders to TREMFYA

TREMFYA treated patients who were not in clinical response at induction Week 12, received TREMFYA 200 mg SC at induction Weeks 12, 16 and 20. In QUASAR IS, 66/120 (55%) TREMFYA treated patients who were not in clinical response at induction Week 12 achieved clinical response at induction Week 24. Week 24 responders to TREMFYA entered QUASAR MS and received TREMFYA 200 mg SC every 4 weeks. At Week 44 of QUASAR MS, 83/123 (68%) of these patients maintained clinical response and 37/123 (30%) achieved clinical remission.

Recapture of efficacy after loss of response to TREMFYA

Nineteen patients receiving 100 mg TREMFYA SC every 8 weeks who experienced a first loss of response (10%) between Week 8 and 32 of QUASAR MS received blinded TREMFYA dosing with 200 mg TREMFYA SC every 4 weeks and 11 of these patients (58%) achieved symptomatic response and 5 patients (26%) achieved symptomatic remission after 12 weeks.

Histologic and Endoscopic Assessment

Histologic remission was defined as a Geboes histologic score ≤2 B.0 (absence of neutrophils from the mucosa [both lamina propria and epithelium], no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system). At Week 12 of QUASAR IS, histologic remission was achieved in 40% of patients treated with TREMFYA and 19% of patients in the placebo group. At Week 44 of QUASAR MS, histologic remission was achieved in 59% and 61% of patients treated with TREMFYA 100 mg SC every 8 weeks and TREMFYA 200 mg SC every 4 weeks and 27% of patients in the placebo group.

Normalisation of the endoscopic appearance of the mucosa was defined as ES of 0. At Week 12 of QUASAR IS, endoscopic normalisation was achieved in 15% of patients treated with TREMFYA and 5% of patients in the placebo group. At Week 44 of QUASAR MS, endoscopic normalisation was achieved in 35% and 34% of patients treated with TREMFYA 100 mg SC every 8 weeks and TREMFYA 200 mg SC every 4 weeks compared to 15% of patients on placebo.

Composite histologic-endoscopic mucosal outcomes

Combined endoscopic normalisation and histologic remission was achieved by a greater proportion of patients treated with TREMFYA 100 mg SC every 8 weeks or 200 mg SC every 4 weeks compared to placebo at Week 44 (31% and 33% vs 14% respectively).

Combined symptomatic remission, endoscopic healing, histologic healing, and faecal calprotectin ≤250 mg/kg was achieved by a greater proportion of patients treated with TREMFYA 100 mg SC every 8 weeks or 200 mg SC every 4 weeks compared to placebo at Week 44 (31% and 35% vs 11% respectively).

Combined symptomatic remission, endoscopic normalisation, histologic remission, and faecal calprotectin ≤250 mg/kg was achieved by a greater proportion of patients treated with TREMFYA 100 mg SC every 8 weeks or 200 mg SC every 4 weeks compared to placebo at Week 44 (22% and 28% vs 9% respectively).

Health Related Quality of Life

At Week 12 of QUASAR IS, patients receiving TREMFYA showed greater and clinically meaningful improvements from baseline when compared with placebo in IBD-specific quality of life assessed by IBDQ total score, all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function) and in fatigue by PROMIS Fatigue SF 7a. Clinically meaningful improvements in general health related quality of life were seen in all 7 domains of PROMIS-29 (i.e., depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities), as well as in summary scores of overall physical health and mental health. Improvements in general health status were also seen in the 5 dimensions of EQ-5D as well as EQ-5D-VAS. These improvements in health-related quality of life measures (IBDQ, PROMIS-Fatigue SF 7a, PROMIS-29, EQ-5D and EQ-5D VAS) were maintained in TREMFYA-treated patients in QUASAR MS through Week 44.

Patients receiving TREMFYA experienced greater improvements in overall work productivity and daily activity as assessed by the WPAI-GH questionnaire when compared to patients receiving placebo. These improvements in work productivity were maintained in TREMFYA treated patients in QUASAR MS through Week 44.

Ulcerative colitis (UC) related hospitalisations and surgeries

Through Week 12 of QUASAR IS, lower proportions of patients in the TREMFYA group compared with the placebo group had UC-related hospitalisations (1.9%, 8/421 vs. 5.4%, 15/280). The proportions of patients who underwent UC-related surgeries were 0.5% (2/421) in the TREMFYA group and 0.7% (2/280) in the placebo group.

Through Week 44 of QUASAR MS, the proportion of patients with UC-related hospitalisations were 1.6% (3/188) in patients treated with TREMFYA 100 mg SC every 8 weeks and 1.1% (2/190) in patients treated with 200 mg SC every 4 weeks compared to placebo 0.5% (1/190). There were no reported UC-related surgeries across the TREMFYA and placebo groups.

Crohn's Disease

The efficacy and safety of TREMFYA were evaluated in three trials in adult patients with moderately to severely active Crohn's disease who had an inadequate response, loss of response or intolerance to either oral corticosteroids, conventional immunomodulators (AZA, 6-MP, MTX), and/or biologic therapy (TNF blocker or vedolizumab): two identically designed 48-week multicentre, randomised, double-blind, placebo- and biologic active-controlled, parallel group trials (intravenous induction and subcutaneous (SC) maintenance: (GALAXI 2 and GALAXI 3 [NCT03466411]) and one 48-week multicentre, randomised, double-blind, placebo-controlled, parallel group trial (SC induction and SC maintenance: GRAVITI [NCT05197049]). All three trials had a treat-through study design: patients randomised to TREMFYA maintained that treatment assignment for the duration of the trial.

GALAXI 2 and GALAXI 3

In GALAXI 2 and GALAXI 3 trials, moderately to severely active Crohn's disease was defined as a Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 and a Simple Endoscopic Score for CD (SES-CD) of ≥6 (or ≥4 for patients with isolated ileal disease).

In GALAXI 2 and GALAXI 3 trials, patients were randomised in a 2:2:2:1 ratio to receive TREMFYA 200 mg intravenous induction at Weeks 0, 4 and 8 followed by TREMFYA 200 mg subcutaneous maintenance every 4 weeks; or TREMFYA 200 mg intravenous induction at Weeks 0, 4 and 8, followed by TREMFYA 100 mg subcutaneous maintenance every 8 weeks; or a biologic active control; or placebo. Placebo non-responders received the biologic active control starting at Week 12.

A total of 1021 patients were evaluated in GALAXI 2 (N=508) and GALAXI 3 (N=513). The median age was 34 years (ranging from 18 to 83 years); 42.4% were female; and 74.3% identified as White, 21.3% as Asian, and 1.5% as Black or African American.

In GALAXI 2, 52.8% of patients had previously failed treatment with at least one biologic therapy, 41.9% were biologic-naïve, and 5.3% had previously received but had not failed a biologic. At baseline, 37.4% of the patients were receiving oral corticosteroids and 29.9% of the patients were receiving conventional immunomodulators.

In GALAXI 3, 51.9% of patients had previously failed treatment with at least one biologic therapy, 41.5% were biologic-naïve, and 6.6% had previously received but had not failed a biologic. At baseline, 36.1% of the patients were receiving oral corticosteroids and 30.2% of the patients were receiving conventional immunomodulators.

In GALAXI 2 and GALAXI 3, the composite co-primary endpoints were (1) clinical response at Week 12 and clinical remission at Week 48 and (2) clinical response at Week 12 and endoscopic response at Week 48 compared to placebo (Table 19). Secondary endpoints included clinical and endoscopic outcomes with short-term (Week 12) and long-term (through Week 48) comparisons to placebo (Tables 20 and 21). For the composite endpoints in GALAXI 2 and GALAXI 3, the same patient had to achieve both components of the endpoint.

Table 19: Proportion of Patients Meeting Efficacy Co-Primary Endpoints in GALAXI 2 and GALAXI 3

GALAXI 2					
Endpoint	**Placebo (N=76)**	**TREMFYA IV Induction→ 100 mg q8w Subcutaneous Injection[a] (N=143)**	**TREMFYA IV Induction→ 200 mg q4w Subcutaneous Injection[b] (N=146)**	**Treatment Difference vs Placebo (95% CI)[c]**	
				TREMFYA 100 mg	**TREMFYA 200 mg**
Clinical response[d] at Week 12 and clinical remission[e] at Week 48					
Total population	9 (12%)	70 (49%)	80 (55%)	38% (27%, 49%)[f]	43% (32%, 54%)[f]
Biologic-naïve[g]	3/34 (9%)	35/58 (60%)	37/63 (59%)		
Prior biologic failure[h]	5/39 (13%)	30/77 (39%)	38/73 (52%)		
Clinical response[d] at Week 12 and endoscopic response[i] at Week 48					
Total population	4 (5%)	56 (39%)	56 (38%)	34% (24%, 43%)[f]	33% (24%, 42%)[f]
Biologic-naïve[g]	2/34 (6%)	26/58 (45%)	31/63 (49%)		
Prior biologic failure[h]	2/39 (5%)	28/77 (36%)	19/73 (26%)		
GALAXI 3					
Endpoint	**Placebo (N=72)**	**TREMFYA IV Induction→ 100 mg q8w Subcutaneous Injection[a] (N=143)**	**TREMFYA IV Induction→ 200 mg q4w Subcutaneous Injection[b] (N= 150)**	**Treatment Difference vs Placebo (95% CI)[c]**	
				TREMFYA 100 mg	**TREMFYA 200 mg**
Clinical response[d] at Week 12 and clinical remission[e] at Week 48[e]					
Total population	9 (13%)	67 (47%)	72 (48%)	34% (23%, 45%)[f]	35% (24%, 46%)[f]
Biologic-naïve[g]	4/27 (15%)	25/58 (43%)	33/65 (51%)		
Prior biologic failure[h]	5/39 (13%)	40/76 (53%)	35/74 (47%)		
Clinical response[d] at Week 12 and endoscopic response[i] at Week 48					
Total population	4 (6%)	48 (34%)	54 (36%)	28% (19%, 37%)[f]	31% (21%, 40%)[f]
Biologic-naïve[g]	2/27 (7%)	21/58 (36%)	25/65 (38%)		
Prior biologic failure[h]	2/39 (5%)	27/76 (36%)	27/74 (36%)		

a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8 followed by TREMFYA 100 mg as a subcutaneous injection every 8 weeks thereafter for up to 48 weeks.

b TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8 followed by TREMFYA 200 mg as a subcutaneous injection every 4 weeks thereafter for up to 48 weeks.

c The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No). CI = confidence interval

d Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150.

e Clinical remission is defined as CDAI score <150.

f $p < 0.001$

g An additional 9 patients in the placebo group and 17 patients in the TREMFYA 100 mg SC q8w group, and 21 patients in the TREMFYA 200 mg SC q4w group were previously exposed to but did not fail a biologic therapy.

h Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.

i Endoscopic response is defined as ≥ 50% improvement from baseline in SES-CD score or SES-CD Score ≤ 2.

Table 20: Proportion of Patients Meeting Short-Term Efficacy Endpoints in GALAXI 2 and GALAXI 3

GALAXI 2			
Endpoint	**Placebo (N=76)**	**TREMFYA IV Induction[a] (N=289)**	**Treatment Difference vs Placebo (95% CI)[b]**
Clinical remission[c] at Week 12			
Total population	17 (22%)	136 (47%)	25% (14%, 36%)[d]
Biologic-naïve[e]	6/34 (18%)	60/121 (50%)	
Prior biologic failure[f]	9/39 (23%)	67/150 (45%)	
Endoscopic response[g] at Week 12			
Total population	8 (11%)	109 (38%)	28% (19%, 36%)[d]
Biologic-naïve[e]	5/34 (15%)	62/121 (51%)	
Prior biologic failure[f]	2/39 (5%)	40/150 (27%)	
Fatigue response[h] at Week 12			
Total population	22 (29%)	131 (45%)	16% (5%, 28%)[i]
Biologic-naïve[e]	11/34 (32%)	58/121 (48%)	
Prior biologic failure[f]	10/39 (26%)	62/150 (41%)	
Clinical remission[c] at Week 12 and endoscopic response[g] at Week 12			
Total population	3 (4%)	62 (21%)	18% (11%, 24%)[d]
Biologic-naïve[e]	0/34	36/121 (30%)	
Prior biologic failure[f]	2/39 (5%)	22/150 (15%)	
GALAXI 3			
Endpoint	**Placebo (N=72)**	**TREMFYA IV Induction[a] (N=293)**	**Treatment Difference vs Placebo (95% CI)[b]**
Clinical remission[c] at Week 12			
Total population	11 (15%)	138 (47%)	31% (21%, 41%)[d]
Biologic-naïve[e]	4/27 (15%)	61/123 (50%)	
Prior biologic failure[f]	6/39 (15%)	71/150 (47%)	
Endoscopic response[g] at Week 12			
Total population	10 (14%)	106 (36%)	22% (12%, 32%)[d]
Biologic-naïve[e]	6/27 (22%)	51/123 (41%)	
Prior biologic failure[f]	3/39 (8%)	47/150 (31%)	
Fatigue response[h] at Week 12			
Total population	13 (18%)	127 (43%)	26% (15%, 36%)[d]
Biologic-naïve[e]	5/27 (19%)	56/123 (46%)	
Prior biologic failure[f]	7/39 (18%)	64/150 (43%)	
Clinical remission[c] at Week 12 and endoscopic response[g] at Week 12			
Total population	2 (3%)	64 (22%)	19% (12%, 25%)[d]
Biologic-naïve[e]	1/27 (4%)	33/123 (27%)	
Prior biologic failure[f]	1/39 (3%)	29/150 (19%)	

a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8. The two TREMFYA treatment groups were combined for this column as they received identical treatment.

b The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No). CI = confidence interval.

c Clinical remission is defined as CDAI score <150.

d $p < 0.001$

e An additional 9 patients in the placebo group and 38 patients in the TREMFYA 200 mg intravenous group, were previously exposed to but did not fail a biologic therapy.

f Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.

g Endoscopic response is defined as ≥ 50% improvement from baseline in SES-CD score or SES-CD Score ≤ 2.

h Fatigue response is defined as improvement of ≥ 7 points in PROMIS Fatigue Short Form 7a.

i $p < 0.05$

In GALAXI 2 and GALAXI 3, a greater proportion of patients achieved clinical response (assessed by CDAI) at Week 4 as well as endoscopic remission at Week 12 in patients treated with TREMFYA 200 mg intravenous induction compared to placebo.

Table 21: Proportion of Patients Meeting Long-Term Efficacy Endpoints in GALAXI 2 and GALAXI 3

GALAXI 2					
Endpoint	**Placebo (N=76)**	**TREMFYA IV Induction→ 100 mg q8w Subcutaneous Injection[a] (N=143)**	**TREMFYA IV Induction→ 200 mg q4w Subcutaneous Injection[b] (N=146)**	**Treatment Difference vs Placebo (95% CI)[c]**	
				TREMFYA 100 mg	**TREMFYA 200 mg**
Clinical response[d] at Week 12 and corticosteroid-free clinical remission[e] at Week 48					
Total population	7 (9%)	67 (47%)	74 (51%)	39% (28%, 49%)[f]	41% (31%, 52%)[f]
Biologic-naïve[g]	2/34 (6%)	34/58 (59%)	33/63 (52%)		
Prior biologic failure[h]	4/39 (10%)	28/77 (36%)	36/73 (49%)		
Clinical response[d] at Week 12 and endoscopic remission[i] at Week 48					
Total population	2 (3%)	38 (27%)	48 (33%)	24% (16%, 32%)[f]	30% (21%, 39%)[f]
Biologic-naïve[g]	1/34 (3%)	19/58 (33%)	27/63 (43%)		
Prior biologic failure[h]	1/39 (3%)	19/77 (25%)	15/73 (21%)		
GALAXI 3					
Endpoint	**Placebo (N=72)**	**TREMFYA IV Induction→ 100 mg q8w Subcutaneous Injection[a] (N=143)**	**TREMFYA IV Induction→ 200 mg q4w Subcutaneous Injection[b] (N=150)**	**Treatment Difference vs Placebo (95% CI)[c]**	
				TREMFYA 100 mg	**TREMFYA 200 mg**
Clinical response[d] at Week 12 and corticosteroid-free clinical remission[e] at Week 48					
Total population	9 (13%)	65 (45%)	67 (45%)	33% (22%, 44%)[f]	31% (20%, 43%)[f]
Biologic-naïve[g]	4/27 (15%)	23/58 (40%)	30/65 (46%)		
Prior biologic failure[h]	5/39 (13%)	40/76 (53%)	33/74 (45%)		
Clinical response[d] at Week 12 and endoscopic remission[i] at Week 48					
Total population	4 (6%)	34 (24%)	34 (23%)	18% (10%, 27%)[f]	17% (8%, 25%)[f]
Biologic-naïve[g]	2//27 (7%)	15/58 (26%)	19/65 (29%)		
Prior biologic failure[h]	2/39 (5%)	19/76 (25%)	14/74 (19%)		

a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8 followed by TREMFYA 100 mg as a subcutaneous injection every 8 weeks thereafter for up to 48 weeks
b TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8. Followed by TREMFYA 100 mg as a subcutaneous injection every 4 weeks thereafter for up to 48 weeks
c The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No). CI = confidence interval.
d Clinical response is defined as ≥100-point reduction from baseline in CDAI score or CDAI score <150.
e 90-day corticosteroid-free clinical remission is defined as CDAI score <150 and not receiving corticosteroids at least 90 days prior to the associated visit.
f $p < 0.001$
g An additional 9 patients in the placebo group and 21 patients in the TREMFYA 200 mg SC q4w group, and 17 patients in the TREMFYA 100 mg SC q8w group were previously exposed to but did not fail a biologic therapy.
h Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.
i Endoscopic remission (global definition) is defined as SES-CD Score ≤ 4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component.

In the pooled GALAXI Phase 3 studies subpopulation analysis, patients with high inflammatory burden after completion of induction dosing derived additional benefit from TREMFYA 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w. A clinically meaningful difference of 14 to 17 percentage points was observed between the two TREMFYA dose groups among patients with a CRP level of >5 mg/L after completion of induction, for the endpoints of clinical remission at Week 48 (100 mg subcutaneous q8w: 54% vs 200 mg subcutaneous q4w: 71%); and endoscopic response at Week 48 (100 mg subcutaneous q8w: 36% vs 200 mg subcutaneous q4w: 50%).

In the pooled GALAXI Phase 3 studies subpopulation analysis, patients with high disease severity at baseline (Week 0) derived additional benefit from TREMFYA 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w. A clinically meaningful difference of 8 to 13 percentage points was observed between the two TREMFYA dose groups in patients with a baseline CDAI >300 or a baseline SES-CD >12, for the endpoints of clinical remission at Week 48; endoscopic response at Week 48; and the composite of clinical remission at Week 48 and endoscopic response at Week 48.

Stool Frequency and Abdominal Pain

Reductions in stool frequency and abdominal pain subscores were observed as early as Week 4 in a greater proportion of patients treated with TREMFYA 200 mg intravenous compared to placebo, and continued improvement was observed through Week 48 with both maintenance dose regimens of TREMFYA.

Other Health-Related Outcomes

Fatigue was assessed in GALAXI 2 and GALAXI 3 with the Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Short Form-7a (PROMIS-Fatigue SF-7a). Treatment with TREMFYA 200 mg intravenously resulted in greater mean change from baseline and clinically meaningful (≥ 7 points) improvement in fatigue as measured by PROMIS-Fatigue SF-7a at Week 12 in GALAXI 2 and GALAXI 3 trials when compared with patients on placebo (45% vs. 29%, $p<0.05$ (GALAXI 2) and 43% vs. 18% $p<0.001$ (GALAXI 3). The improvement in fatigue response was maintained through Week 48.

GRAVITI

In the GRAVITI trial, moderately to severely active Crohn's disease was defined as a Crohn's Disease Activity Index (CDAI) score of ≥ 220 and ≤ 450 and a Simple Endoscopic Score for CD (SES-CD) of ≥6 (or ≥4 for patients with isolated ileal disease).

In GRAVITI, patients were randomised in a 1:1:1 ratio to receive TREMFYA 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by TREMFYA 200 mg subcutaneous maintenance every 4 weeks; or TREMFYA 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by TREMFYA 100 mg subcutaneous maintenance every 8 weeks; or placebo. All patients in the placebo group who met rescue criteria received treatment with TREMFYA 400 mg subcutaneous induction followed by TREMFYA 100 mg subcutaneous maintenance every 8 weeks.

A total of 347 patients were evaluated. The median age of patients was 36 years (ranging from 18 to 83 years); 41.5% were female; and 66% identified as White, 21.9% as Asian, and 2.6% as Black or African American.

In GRAVITI, 46.4% of patients had previously failed treatment with at least one biologic therapy, 46.4% were biologic-naïve, and 7.2% had previously received but had not failed a biologic. At baseline, 29.7% of the patients were receiving oral corticosteroids and 28.5% of the patients were receiving conventional immunomodulators.

In GRAVITI, the co-primary endpoints were clinical remission at Week 12 and endoscopic response at Week 12 compared to placebo (Table 22). Additional multiplicity-controlled endpoints at Week 12, Week 24, or Week 48 are included in Table 22 and Table 23.

Table 22: Proportion of Patients Meeting Efficacy Endpoints at Week 12 in GRAVITI

Endpoint	Placebo (N=117)	TREMFYA 400 mg Subcutaneous Injection[a] (N=230)	Treatment Difference vs Placebo (95% CI)[b]
Clinical Remission[c] at Week 12			
Total population	25 (21%)	129 (56%)	35% (25%, 45%)[d]
Biologic-naïve[e]	14/56 (25%)	52/105 (50%)	
Prior biologic failure[f]	9/53 (17%)	65/108 (60%)	
Endoscopic Response[g] at Week 12			
Total population	25 (21%)	95 (41%)	20% (10%, 30%)[d]
Biologic-naïve[e]	15/56 (27%)	51/105 (49%)	
Prior biologic failure[f]	9/53 (17%)	36/108 (33%)	
Clinical Response[h] at Week 12			
Total population	39 (33%)	169 (73%)	40% (30%, 51%)[d]
Biologic-naïve[e]	21/56 (38%)	71/105 (68%)	
Prior biologic failure[f]	15/53 (28%)	84/108 (78%)	

a TREMFYA 400 mg subcutaneous induction at Weeks 0, 4 and 8
b The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No). CI = confidence interval
c Clinical remission is defined as CDAI score <150.
d p<0.001
e An additional 8 patients in the placebo group and 17 patients in the TREMFYA 400 mg subcutaneous group, were previously exposed to but did not fail a biologic therapy.
f Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.
g Endoscopic response: ≥50% improvement from baseline in SES-CD score.
h Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150.

Onset of clinical response and clinical remission based on CDAI occurred as early as Week 4 in a greater proportion of patients treated with the TREMFYA induction regimen compared to placebo.

Table 23: Proportion of Patients Meeting Efficacy Endpoints at Week 24 or Week 48 in GRAVITI

Endpoint	Placebo (N=117)	TREMFYA 400 mg SC induction→ 100 mg Subcutaneous Injection q8w[a] (N=115)	TREMFYA 400 mg SC induction→ 200 mg Subcutaneous Injection q4w[b] (N=115)	Treatment difference vs Placebo (95% CI)[c]	
				TREMFYA 100 mg	TREMFYA 200 mg
Clinical Remission[d] at Week 24					
Total population	25 (21%)	70 (61%)	67 (58%)	39% (28%, 51%)[e]	37% (26%, 48%)[e]
Biologic-naïve[f]	14/56 (25%)	32/53 (60%)	33/52 (63%)		
Prior biologic failure[g]	10/53 (19%)	35/55 (64%)	28/53 (53%)		
Clinical Remission[d] at Week 48					
Total population	20 (17%)	69 (60%)	76 (66%)	43% (32%,54%)[e]	49% (38%, 60%)[e]
Biologic-naïve[f]	13/56 (23%)	33/53 (62%)	35/52 (67%)		
Prior biologic failure[g]	5/53 (9%)	32/55 (58%)	33/53 (62%)		
Endoscopic Response[h] at Week 48					
Total population	8 (7%)	51 (44%)	59 (51%)	37% (27%,48%)[e]	45% (34%,55%)[e]
Biologic-naïve[f]	7/56 (13%)	28/53 (53%)	26/52 (50%)		
Prior biologic failure[g]	0/53 (0%)	20/55 (36%)	29/53 (55%)		

a TREMFYA 400 mg SC induction at Weeks 0, 4 and 8 followed by TREMFYA 100 mg SC every 8 weeks
b TREMFYA 400 mg SC induction at Weeks 0, 4 and 8, followed by TREMFYA 200 mg SC maintenance every 4 weeks
c The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), BIO-Failure status (Yes or No). CI = confidence interval.
d Clinical remission is defined as CDAI score <150.
e p<0.001
f An additional 8 patients in the placebo group and 7 patients in the TREMFYA 100 mg SC q8w group, and 10 patients in the TREMFYA 200 mg SC q4w group were previously exposed to but did not fail a biologic therapy.
g Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.
h Endoscopic response: ≥50% improvement from baseline in SES-CD score.

Endoscopic Remission at Week 48

Endoscopic remission was observed at Week 48 in 38.3% (44/115) of patients treated with the TREMFYA 400 mg subcutaneous induction followed by TREMFYA 200 mg subcutaneous q4w maintenance regimen and 30.4% (35/115) of patients treated with TREMFYA 400 mg subcutaneous induction followed by TREMFYA 100 mg subcutaneous q8w maintenance regimen, compared to 6.0% (7/117) of patients treated with placebo.

Clinical Remission at Week 48 and Endoscopic Remission at Week 48

Clinical remission at Week 48 and endoscopic remission at Week 48 was observed in 33.9% (39/115) of patients treated with the TREMFYA 400 mg subcutaneous induction followed by TREMFYA 200 mg subcutaneous q4w maintenance regimen and 26.1% (30/115) of patients treated with TREMFYA 400 mg subcutaneous induction followed by TREMFYA 100 mg subcutaneous q8w maintenance regimen, compared to 4.3% (5/117) of patients treated with placebo.

Stool Frequency and Abdominal Pain

Reductions in stool frequency and abdominal pain subscores were observed as early as Week 4 in a greater proportion of patients treated with TREMFYA 400 mg subcutaneous compared to placebo, and these improvements during induction were maintained through Week 48.

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

In subjects with plaque psoriasis, following subcutaneous administrations of 100 mg guselkumab at Weeks 0 and 4, and every 8 weeks thereafter, steady state serum guselkumab concentrations were achieved by Week 20. The mean (± SD) steady state trough serum guselkumab concentrations in two Phase 3 studies in plaque psoriasis 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 pharmacokinetics of guselkumab in subjects with psoriatic arthritis was similar to that in subjects with plaque psoriasis. Following subcutaneous administration of 100 mg of guselkumab at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL. Following subcutaneous administration of 100 mg of guselkumab every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3.8 mcg/mL.

The pharmacokinetics of TREMFYA were similar in subjects with ulcerative colitis and Crohn's disease.

Following the recommended intravenous induction dose regimen of TREMFYA 200 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was 68.3 mcg/mL in subjects with ulcerative colitis and 70.5 mcg/mL in subjects with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of TREMFYA 400 mg at Weeks 0, 4, and 8, mean peak serum concentration was estimated to be 27.7 mcg/mL in subjects with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimens was similar following subcutaneous and intravenous induction.

Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks or 200 mg TREMFYA every 4 weeks in patients with ulcerative colitis, mean steady-state trough serum guselkumab concentrations were approximately 1.4 mcg/mL and 10.7 mcg/mL, respectively.

Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks or 200 mg TREMFYA every 4 weeks in subjects with Crohn's disease, mean steady-state trough serum guselkumab concentrations were approximately 1.2 mcg/mL and 10.1 mcg/mL, respectively.

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, approximately 15 to 18 days in subjects with plaque psoriasis across studies, and approximately 17 days in patients with ulcerative colitis and Crohn's disease.

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. Serum guselkumab concentrations were approximately dose proportional following IV administration in patients with ulcerative colitis or Crohn's disease.

Population Pharmacokinetic Analysis

In a population pharmacokinetic analysis, the apparent clearance and apparent volume of distribution were 0.516 L/d and 13.5 L, respectively, and the $T_{1/2}$ was approximately 18 days in subjects with psoriasis. The apparent clearance and apparent volume of distribution at steady-state were 0.531 L/d and 10.1 L, respectively, and the $T_{1/2}$ was approximately 17 days in subjects with ulcerative colitis. The apparent clearance and apparent volume of distribution at steady-state were 0.568 L/d and 11.4 L, respectively, and the $T_{1/2}$ was approximately 17 days in subjects with Crohn's disease.

In population pharmacokinetic analyses, 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 (NSAIDs, corticosteroids and conventional synthetic DMARDS such as methotrexate, azathioprine, 6-mercaptopurine), use of alcohol, or current smoking status, on pharmacokinetics of guselkumab was evaluated. Only the effects of body weight on clearance and volume of distribution were found to be significant, with a trend towards higher clearance 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 in phase III clinical studies and included in the population pharmacokinetic analysis (pop PK), 70 subjects were 65 years of

age or older, including 4 subjects who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to TREMFYA in phase III clinical studies and included in the pop PK analysis, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age and older. Of the 859 ulcerative colitis patients exposed to TREMFYA in clinical studies and included in the pop PK analysis, a total of 52 patients were 65 years of age or older, including 9 patients were 75 years of age or older. Of the 1009 Crohn's disease subjects exposed to TREMFYA in clinical studies and included in the pop PK analysis, a total of 39 subjects were 65 years of age or older, including 5 subjects who were 75 years of age or older. Population pharmacokinetic (pop PK) 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. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies. No dose adjustments are considered necessary.

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

200 mg vial

Disodium edetate

Histidine

Histidine hydrochloride monohydrate

Methionine

Polysorbate 80

Sucrose

Water for injections

100 mg pre-filled syringe, 200 mg pre-filled syringe, 100 mg pre-filled pen (One-Press® patient -controlled injector), 200 mg pre-filled pen (auto-injector)

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injections

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 or pre-filled pen in their original carton until time of use in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

For Subcutaneous Injection

TREMFYA is supplied as a single-use sterile solution in following packaging presentations:

- a pre-filled 1mL glass syringe with a fixed 27G, half inch needle assembled in a passive needle guard delivery system or in a pre-filled pen with a passive needle guard enclosed in a patient-controlled injector device
- a 2 mL glass syringe with a 27G, half inch fixed needle assembled in a passive needle guard system or in a pre-filled pen

TREMFYA is available in cartons containing 1 pre-filled syringe or 2 (2 packs of 1) pre-filled syringes:

- 100 mg (100 mg/mL in 1.0 mL syringe volume)
- 200 mg (100 mg/mL in 2.0 mL syringe volume)

TREMFYA is available in cartons containing 1 pre-filled pen or 2 (2 packs of 1) pre-filled pens:

- 100 mg (100 mg/mL in 1.0 mL pre-filled pen – One-Press® patient-controlled injector)
- 200 mg (100 mg/mL in 2.0 mL pre-filled pen – auto-injector)

For Intravenous Infusion

TREMFYA is supplied as a single-use sterile concentrated solution in a type I clear glass vial closed with a chlorobutyl rubber stopper, an aluminium seal and polypropylene flip top.

TREMFYA is available in cartons containing 1 vial:

- 200 mg (200 mg / 20 mL in a single-dose vial)

Not all presentations may be marketed.

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:

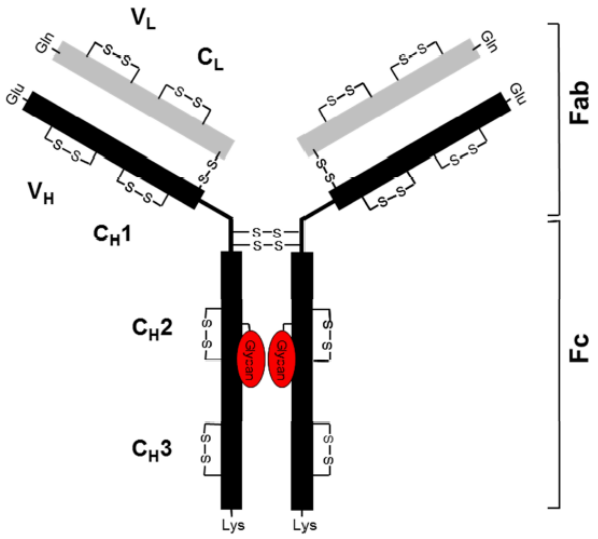


Figure 9: General structure of guselkumab

CAS No.: 1350289-85-8

7 MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia

9 DATE OF FIRST APPROVAL

15 March 2018

10 DATE OF REVISION

17 July 2025

Summary Table of Changes

Section	Summary Of Changes
2, 3, 6.1, 6.5	Updated for new strengths, new route of administration, new dosage form and new IV formulation (200 mg / 2 mL pre-filled syringe and pre-filled pen for subcutaneous injection and 200 mg / 20 mL single-dose vial for intravenous infusion)
4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2	Updated for new indications: Ulcerative colitis and Crohn's disease
4.9	Updated overdose information