ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 45 mg/0.45 mL solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 45 mg guselkumab in 0.45 mL. 1 mL solution contains 100 mg of guselkumab.

Each pre-filled pen can deliver 0.1 mL to 0.45 mL (corresponding to 10 mg to 45 mg guselkumab) in increments of 0.05 mL.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

This medicinal product contains 0.3 mg of polysorbate 80 (E433) in each pre-filled pen which is equivalent to 0.5 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection) in pre-filled pen (VarioJect)

The solution is clear and colourless to light yellow and may contain a few small white or clear particles, with target pH of 5.8 and approximate osmolarity of 367.5 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paediatric plaque psoriasis

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

4.2 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.

Posology

The 45 mg/0.45 mL pre-filled pen is for paediatric patients 6 years and older with a body weight less than 40 kg.
Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

Paediatric plaque psoriasis (6 to 17 years)
Children from the age of 6 years with a body weight less than 40 kg
The recommended dose is shown below in Table 1, up to a maximum of 45 mg, administered by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks (q8w).

Table 1: Recommended dose of guselkumab for subcutaneous injection in paediatric patients with body weight less than 40 kg

Body Weight (kg) (at time of dosing)	**Dose (mg)**
12-15 kg	20
16-19 kg	25
20-23 kg	30
24-26 kg	35
27-30 kg	40
31-39 kg	45

Children from the age of 6 years with a body weight of 40 kg or more
For children with a body weight of 40 kg, or more a 100 mg pre-filled syringe is available. For the posology and method of administration, see section 4.2 of the Tremfya 100 mg pre-filled syringe Summary of Product Characteristics.

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Renal or hepatic impairment
Tremfya has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies, and no dose adjustments are considered necessary. For further information on elimination of guselkumab, see section 5.2.

Paediatric population
The safety and efficacy of Tremfya in patients less than 6 years have not been established.
No data are available.

Method of administration

Subcutaneous use only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

Tremfya is not intended for self-administration by paediatric patients. After proper training in subcutaneous injection technique, a caregiver may inject Tremfya if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow-up of patients. Caregivers should be instructed to inject the prescribed amount of solution according to the 'Instructions for use' provided in the carton.
For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Guselkumab may increase the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with guselkumab should be instructed 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, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving guselkumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting (see section 4.8). Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately and appropriate therapy initiated.

Hepatic transaminase elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with guselkumab q4w compared to patients treated with guselkumab q8w or placebo (see section 4.8).

Immunisations

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

Before live viral or live bacterial vaccination, treatment 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 Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Excipients with known effect

Polysorbate 80 content
This medicinal product contains 0.3 mg of polysorbate 80 (E433) in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

In a Phase I study in patients 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, indicating that 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.

Concomitant immunosuppressive therapy or phototherapy

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are limited data from the use of guselkumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tremfya during pregnancy.

Breast-feeding

It is unknown whether guselkumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant during this period cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from Tremfya therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. See section 5.3 for information on the excretion of guselkumab in animal (cynomolgus monkey) milk.

Fertility

The effect of guselkumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was respiratory tract infections (approximately 8% of patients in ulcerative colitis studies, 11% of patients in the Crohn's disease studies, and 15% of patients in the psoriasis and psoriatic arthritis clinical studies).

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

Tabulated list of adverse reactions

Table 2 provides a list of adverse reactions from psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: List of adverse reactions

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

Description of selected adverse reactions

Transaminases increased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia) were reported more frequently in the guselkumab treated groups (8.6% in the 100 mg subcutaneous q4w group and 8.3% in the 100 mg subcutaneous q8w group) than in the placebo group (4.6%). Through 1-year, adverse reactions 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, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the guselkumab q4w group compared with the guselkumab q8w group (Table 3). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 3: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through Week 24[a]			Through 1 year[b]	
	Placebo N=370[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 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 guselkumab are not included.

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

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the guselkumab q8w dose was similar to that observed for the guselkumab q8w dose in the psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled induction period (Week 0-12), adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, and liver function test increased) were reported more frequently in the guselkumab treated groups (1.7% of patients) than in the placebo group (0.6% of patients). In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, adverse reactions 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 guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase II and Phase III Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies. In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled period (Week 12), ALT (< 1% of patients) and AST (< 1% of patients) elevations ≥ 3x ULN were reported in guselkumab treated patients. In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, ALT and/or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.6% of patients in the guselkumab 100 mg subcutaneous 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.

Neutrophil count decreased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, the adverse reaction of decreased neutrophil count was reported more frequently in the guselkumab treated group (0.9%) than in the placebo group (0%). Through 1 year, the adverse reaction of decreased neutrophil count was reported in 0.9% of patients treated with guselkumab. In most cases, the decrease in blood neutrophil count was mild, transient, not associated with infection and did not lead to discontinuation of treatment.

Gastroenteritis
In two Phase III psoriasis clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the guselkumab treated group (1.1%) than in the placebo group (0.7%). Through Week 264, 5.8% of all guselkumab treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of guselkumab through Week 264. Gastroenteritis rates observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies.

Injection site reactions
In two Phase III psoriasis clinical studies through Week 48, 0.7% of guselkumab injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 264, 0.4% of guselkumab injections were associated with injection site reactions. Injection site reactions were generally mild to moderate in severity; none were serious, and one led to discontinuation of guselkumab.

In two Phase III psoriatic arthritis clinical studies through Week 24, the number of patients that reported 1 or more injection site reactions was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) patients in the guselkumab q8w group, 4 (1.1%) patients in the guselkumab q4w group, and 1 (0.3%) patient in the placebo group. One patient discontinued guselkumab due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Through 1 year, the proportion of patients reporting 1 or more injection site reactions was 1.6% and 2.4% in the guselkumab q8w and q4w groups, respectively. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period was similar to rates observed in the psoriasis clinical studies.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group (guselkumab 200 mg was administered as two 100 mg injections in the Phase III ulcerative colitis maintenance clinical study) and no injection site reactions in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and none were serious.

In Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 4.1% (0.8% of injections) in the treatment group which received guselkumab 200 mg intravenous induction followed by 200 mg subcutaneous q4w, and 1.4% (0.6% of injections) of patients in the guselkumab 200 mg intravenous induction followed by 100 mg subcutaneous q8w group. Overall injection site reactions were mild; none were serious.

In a Phase III Crohn's disease clinical study through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7% (1.3% of injections) in the treatment group which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 4.3% (0.7% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Most injection site reactions were mild; none were serious.

Immunogenicity
The immunogenicity of guselkumab was evaluated using a sensitive and drug-tolerant immunoassay.

In pooled Phase II and Phase III analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 8% (n=12) had antibodies that were classified as neutralising, which equates to 0.4% of all patients treated with guselkumab. In pooled Phase III analyses in patients with psoriasis, approximately 15% of patients treated with guselkumab developed antidrug antibodies in up to 264 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising, which equates to 0.76% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

In the Phase III paediatric study, 18% (n=21) of paediatric psoriasis patients treated with guselkumab developed antidrug antibodies in up to week 44. Of the patients who developed antidrug antibodies, none had antibodies that were classified as neutralising. Antibodies to guselkumab were not associated with changes in pharmacokinetics, clinical efficacy or development of injection site reactions. However, the number of patients who were positive for antibodies to guselkumab is too small for definitive conclusions about the impact on efficacy and safety of guselkumab.

In pooled Phase II and Phase III analyses in patients with ulcerative colitis, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralising, which equates to 2% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or the development of injection site reactions.

In pooled Phase II and Phase III analyses up to Week 48 in patients with Crohn's disease who were treated with intravenous induction followed by subcutaneous maintenance dose regimen, approximately 5% (n=30) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 7% (n=2) had antibodies that were classified as neutralising antibodies, which equates to 0.3% of guselkumab treated patients. In a Phase III analysis up to Week 48 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of these patients, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

Paediatric population

Plaque psoriasis
The safety of guselkumab was assessed in a Phase III placebo- and active-controlled study in paediatric patients with moderate to severe plaque psoriasis. This clinical study evaluated safety for up to 52 weeks in 120 patients 6 to 17 years of age. The safety profile for guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe in paediatric patients 6 to 17 years was consistent with the safety profile reported in the adult plaque psoriasis studies (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Guselkumab intravenous doses up to 1 200 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, the patient must be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment must be administered immediately.

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 high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In *in vitro* models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signalling, activation and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis and psoriatic arthritis 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. 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 I 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 patients with plaque psoriasis at Week 12 compared to baseline. In the same Phase I 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 patients in Phase II and Phase III plaque psoriasis studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In psoriatic arthritis patients in Phase III studies, 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 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

Clinical efficacy and safety

Adult plaque psoriasis
The efficacy and safety of guselkumab was assessed in three randomised, double-blind, active controlled Phase III studies in adult patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic therapy.

VOYAGE 1 and VOYAGE 2
Two studies (VOYAGE 1 and VOYAGE 2) evaluated the efficacy and safety of guselkumab versus placebo and adalimumab in 1 829 adult patients. Patients randomised to guselkumab (N=825) received 100 mg at Weeks 0 and 4, and every 8 weeks (q8w) thereafter through Week 48 (VOYAGE 1) and Week 20 (VOYAGE 2). Patients randomised to adalimumab (N=582) received 80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week (q2w) through Week 48 (VOYAGE 1) and Week 23 (VOYAGE 2). In both studies, patients randomised to placebo (N=422) received guselkumab 100 mg at Weeks 16, 20 and q8w thereafter. In VOYAGE 1, all patients, including those randomised to adalimumab at Week 0, started to receive open-label guselkumab q8w at Week 52. In VOYAGE 2, patients randomised to guselkumab at Week 0 who were Psoriasis Area and Severity Index (PASI) 90 responders at Week 28 were re-randomised to either continue treatment with guselkumab q8w (maintenance treatment) or receive placebo (withdrawal treatment). Withdrawal patients re-initiated guselkumab (dosed at time of retreatment, 4 weeks later and q8w thereafter) when they experienced at least a 50% loss of their Week 28 PASI improvement. Patients randomised to adalimumab at Week 0

who were PASI 90 non-responders received guselkumab at Weeks 28, 32 and q8w thereafter. In VOYAGE 2, all patients started to receive open-label guselkumab q8w at Week 76.

Baseline disease characteristics were consistent for the study populations in VOYAGE 1 and 2 with a median body surface area (BSA) of 22% and 24%, a median baseline PASI score of 19 for both studies, a median baseline dermatology quality of life index (DLQI) score of 14 and 14.5, a baseline investigator global assessment (IGA) score of severe for 25% and 23% of patients, and a history of psoriatic arthritis for 19% and 18% of patients, respectively.

Of all patients included in VOYAGE 1 and 2, 32% and 29% were naïve to both conventional systemic and biologic therapy, 54% and 57% had received prior phototherapy, and 62% and 64% had received prior conventional systemic therapy, respectively. In both studies, 21% had received prior biologic therapy, including 11% who had received at least one anti-tumour necrosis factor alpha (TNFα) agent, and approximately 10% who had received an anti-IL-12/IL-23 agent.

The efficacy of guselkumab was evaluated with respect to overall skin disease, regional disease (scalp, hand and foot and nails) and quality of life and patient reported outcomes. The co-primary endpoints in VOYAGE 1 and 2 were the proportion of patients who achieved an IGA score of cleared or minimal (IGA 0/1) and a PASI 90 response at Week 16 versus placebo (see Table 4).

Overall skin disease
Treatment with guselkumab resulted in significant improvements in the measures of disease activity compared to placebo and adalimumab at Week 16 and compared to adalimumab at Weeks 24 and 48. The key efficacy results for the primary and major secondary study endpoints are shown in Table 4 below.

Table 4: 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)
Week 16						
PASI 75	10 (5.7)	300 (91.2)[a]	244 (73.1)[b]	20 (8.1)	428 (86.3)[a]	170 (68.5)[b]
PASI 90	5 (2.9)	241 (73.3)[c]	166 (49.7)[b]	6 (2.4)	347 (70.0)[c]	116 (46.8)[b]
PASI 100	1 (0.6)	123 (37.4)[a]	57 (17.1)[d]	2 (0.8)	169 (34.1)[a]	51 (20.6)[d]
IGA 0/1	12 (6.9)	280 (85.1)[c]	220 (65.9)[b]	21 (8.5)	417 (84.1)[c]	168 (67.7)[b]
IGA 0	2 (1.1)	157 (47.7)[a]	88 (26.3)[d]	2 (0.8)	215 (43.3)[a]	71 (28.6)[d]
Week 24						
PASI 75	-	300 (91.2)	241 (72.2)[e]	-	442 (89.1)	176 (71.0)[e]
PASI 90	-	264 (80.2)	177 (53.0)[b]	-	373 (75.2)	136 (54.8)[b]
PASI 100	-	146 (44.4)	83 (24.9)[e]	-	219 (44.2)	66 (26.6)[e]
IGA 0/1	-	277 (84.2)	206 (61.7)[b]	-	414 (83.5)	161 (64.9)[b]
IGA 0	-	173 (52.6)	98 (29.3)[b]	-	257 (51.8)	78 (31.5)[b]
Week 48						
PASI 75	-	289 (87.8)	209 (62.6)[e]	-	-	-
PASI 90	-	251 (76.3)	160 (47.9)[b]	-	-	-
PASI 100	-	156 (47.4)	78 (23.4)[e]	-	-	-
IGA 0/1	-	265 (80.5)	185 (55.4)[b]	-	-	-
IGA 0	-	166 (50.5)	86 (25.7)[b]	-	-	-

[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.

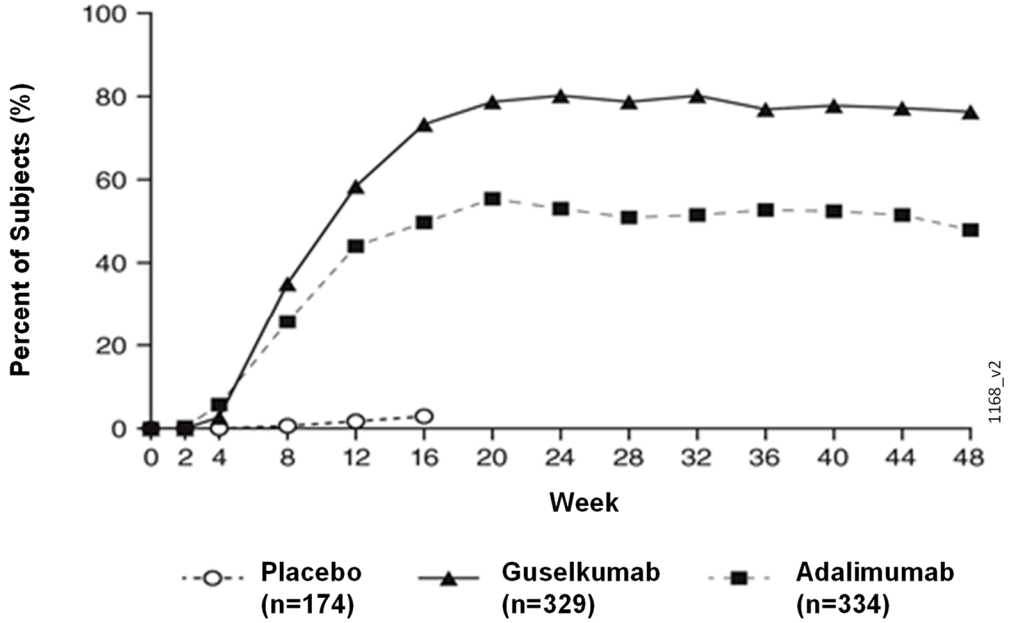
[d] comparisons between guselkumab and adalimumab were not performed.

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

Response over time

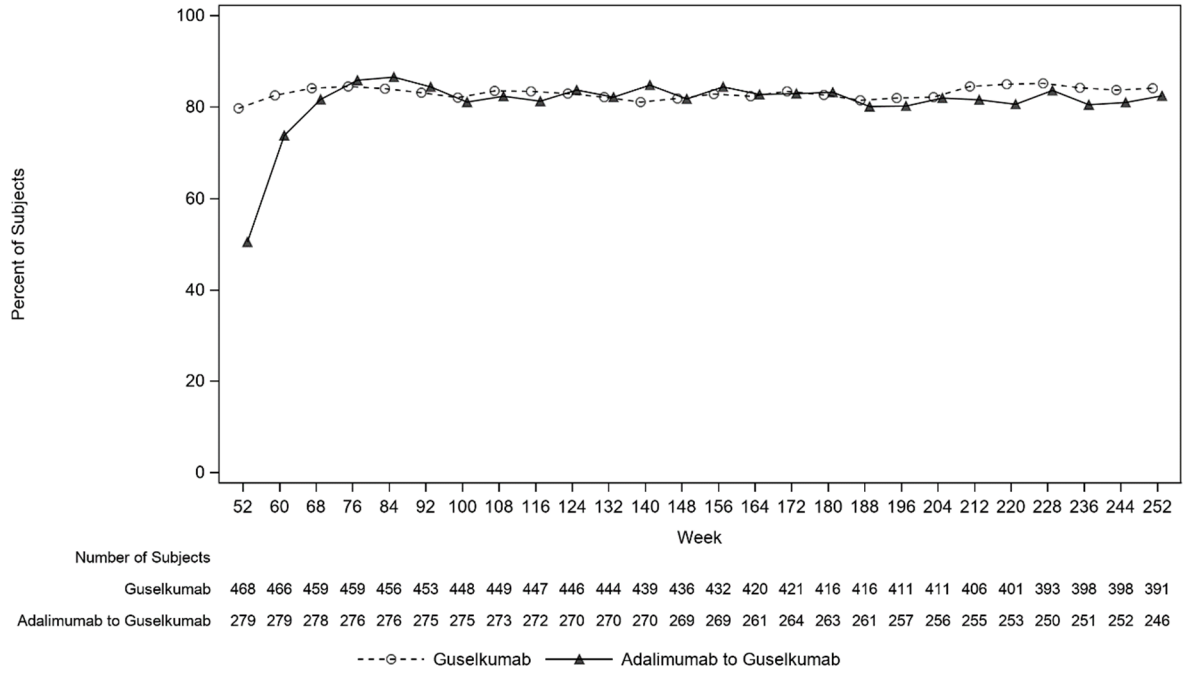
Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 ($p < 0.001$). The percentage of patients achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the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

Figure 1: Percent of patients who achieved a PASI 90 response through week 48 by visit (patients randomised at week 0) in VOYAGE 1



In VOYAGE 1, for patients receiving continuous guselkumab treatment, the PASI 90 response rate was maintained from Week 52 through Week 252. For patients randomised to adalimumab at Week 0 who crossed over to guselkumab at Week 52, the PASI 90 response rate increased from Week 52 through Week 76 and was then maintained through Week 252 (see Figure 2).

Figure 2: Percent of patients who achieved a PASI 90 response by visit in the open-label phase 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- naïve, biologic naïve, 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 patients randomised to adalimumab 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. In addition, among 95 patients randomised to guselkumab who failed to achieve a PASI 90 response at Week 28, 36% and 41% achieved a PASI 90 response with an additional 20 and 44 weeks of continued 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 5). 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 5: 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 patients with ss-IGA, f-PGA, hf-PGA score ≥ 2 at baseline or baseline NAPSI score > 0.

[b] Includes only patients 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

Across VOYAGE 1 and 2 significantly greater improvements in health-related quality of life as measured by Dermatology Life Quality Index (DLQI) and in patient-reported psoriasis symptoms (itching, pain, burning, stinging and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) as measured by the Psoriasis Symptoms and Signs Diary

(PSSD) were observed in guselkumab patients compared to placebo patients at Week 16 (Table 6). Signs of improvement on patient-reported outcomes were maintained through Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1). In VOYAGE 1, for patients receiving continuous guselkumab treatment, these improvements were maintained in the open-label phase through Week 252 (Table 7).

Table 6: Summary of patient reported outcomes at week 16 in VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	guselkumab	adalimumab	Placebo	guselkumab	adalimumab
DLQI, patients with baseline score	170	322	328	248	495	247
Change from baseline, mean (standard deviation)						
Week 16	-0.6 (6.4)	-11.2 (7.2)[c]	-9.3 (7.8)[b]	-2.6 (6.9)	-11.3 (6.8)[c]	-9.7 (6.8)[b]
PSSD Symptom score, patients with baseline score > 0	129	248	273	198	410	200
Symptom score = 0, n (%)						
Week 16	1 (0.8)	67 (27.0)[a]	45 (16.5)[b]	0	112 (27.3)[a]	30 (15.0)[b]
PSSD Sign score, patients with baseline score > 0	129	248	274	198	411	201
Sign score = 0, n (%)						
Week 16	0	50 (20.2)[a]	32 (11.7)[b]	0	86 (20.9)[a]	21 (10.4)[b]

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

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

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

Table 7: Summary of patient reported outcomes in the open-label phase in VOYAGE 1

	guselkumab			adalimumab-guselkumab		
	Week 76	Week 156	Week 252	Week 76	Week 156	Week 252
DLQI score > 1 at baseline, n	445	420	374	264	255	235
Patients with DLQI 0/1	337 (75.7%)	308 (73.3%)	272 (72.7%)	198 (75.0%)	190 (74.5%)	174 (74.0%)
PSSD Symptom Score, patients with baseline score > 0	347	327	297	227	218	200
Symptom score = 0, n (%)	136 (39.2%)	130 (39.8%)	126 (42.4%)	99 (43.6%)	96 (44.0%)	96 (48.0%)
PSSD Sign score, patients with baseline score > 0	347	327	297	228	219	201
Sign score = 0, n (%)	102 (29.4%)	94 (28.7%)	98 (33.0%)	71 (31.1%)	69 (31.5%)	76 (37.8%)

In VOYAGE 2, guselkumab patients had significantly greater improvement from baseline compared to placebo in health-related quality of life, anxiety and depression, and work limitation measures at Week 16, as measured by the 36-item Short Form (SF-36) health survey questionnaire, Hospital Anxiety and Depression Scale (HADS), and Work Limitations Questionnaire (WLQ), respectively. The improvements in SF-36, HADS and WLQ were all maintained through Week 48 and in the open-label phase through Week 252 among patients randomised to maintenance therapy at Week 28.

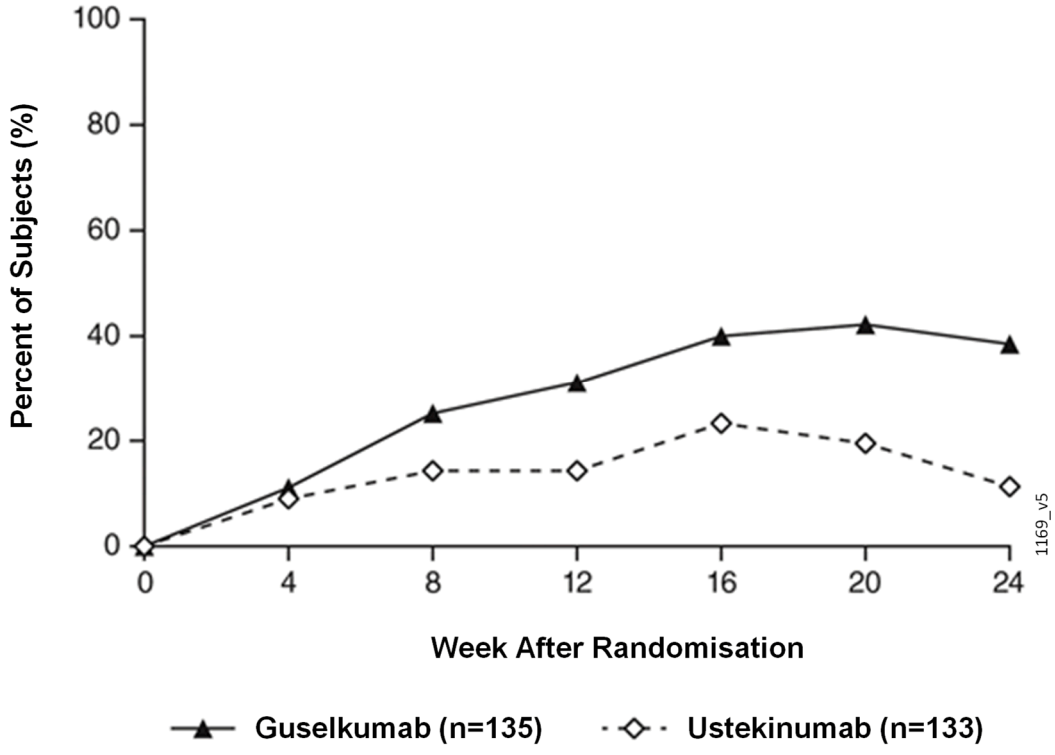
NAVIGATE

The NAVIGATE study examined the efficacy of guselkumab in patients who had an inadequate response (i.e., who had not achieved a 'cleared' or 'minimal' response defined as IGA ≥ 2) to

ustekinumab at Week 16. All patients (N=871) received open-label ustekinumab (45 mg ≤100 kg and 90 mg >100 kg) at Weeks 0 and 4. At Week 16, 268 patients with an IGA ≥ 2 score were randomised to either continue ustekinumab treatment (N=133) q12w, or to initiate guselkumab treatment (N=135) at Weeks 16, 20, and q8w thereafter. Baseline characteristics for randomised patients were similar to those observed in VOYAGE 1 and 2.

After randomisation, the primary endpoint was the number of post-randomisation visits between Weeks 12 and 24 at which patients achieved an IGA score 0/1 and had ≥ 2 grade improvement. Patients were examined at four-week intervals for a total of four visits. Among patients who inadequately responded to ustekinumab at the time of randomisation, significantly greater improvement of efficacy was observed in patients who switched to guselkumab treatment compared to patients who continued ustekinumab treatment. Between 12 and 24 weeks after randomisation, guselkumab patients achieved an IGA score 0/1 with ≥ 2 grade improvement twice as often as ustekinumab patients (mean 1.5 vs 0.7 visits, respectively, $p < 0.001$). Additionally, at 12 weeks after randomisation a higher proportion of guselkumab patients compared to ustekinumab patients achieved an IGA score 0/1 and ≥ 2 grade improvement (31.1% vs. 14.3%, respectively; $p = 0.001$) and a PASI 90 response (48% vs 23%, respectively, $p < 0.001$). Differences in response rates between guselkumab and ustekinumab-treated patients were noted as early as 4 weeks after randomisation (11.1% and 9.0%, respectively) and reached a maximum 24 weeks after randomisation (see Figure 3). No new safety findings were observed in patients who switched from ustekinumab to guselkumab.

Figure 3: Percent of patients 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



ECLIPSE
Efficacy and safety of guselkumab were also investigated in a double-blind study compared to secukinumab. Patients were randomised to receive guselkumab (N=534; 100 mg at Week 0, 4 and q8w thereafter), or secukinumab (N=514; 300 mg at Week 0, 1, 2, 3, 4, and q4w thereafter). The last dose was at week 44 for both treatment groups.

Baseline disease characteristics were consistent with a population of moderate to severe plaque psoriasis with a median BSA of 20%, a median PASI score of 18, and an IGA score of severe for 24% of patients.

Guselkumab 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 PASI response rates are presented in Table 8.

Table 8: PASI response rates in ECLIPSE

	Number of patients (%)	
	guselkumab (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%)

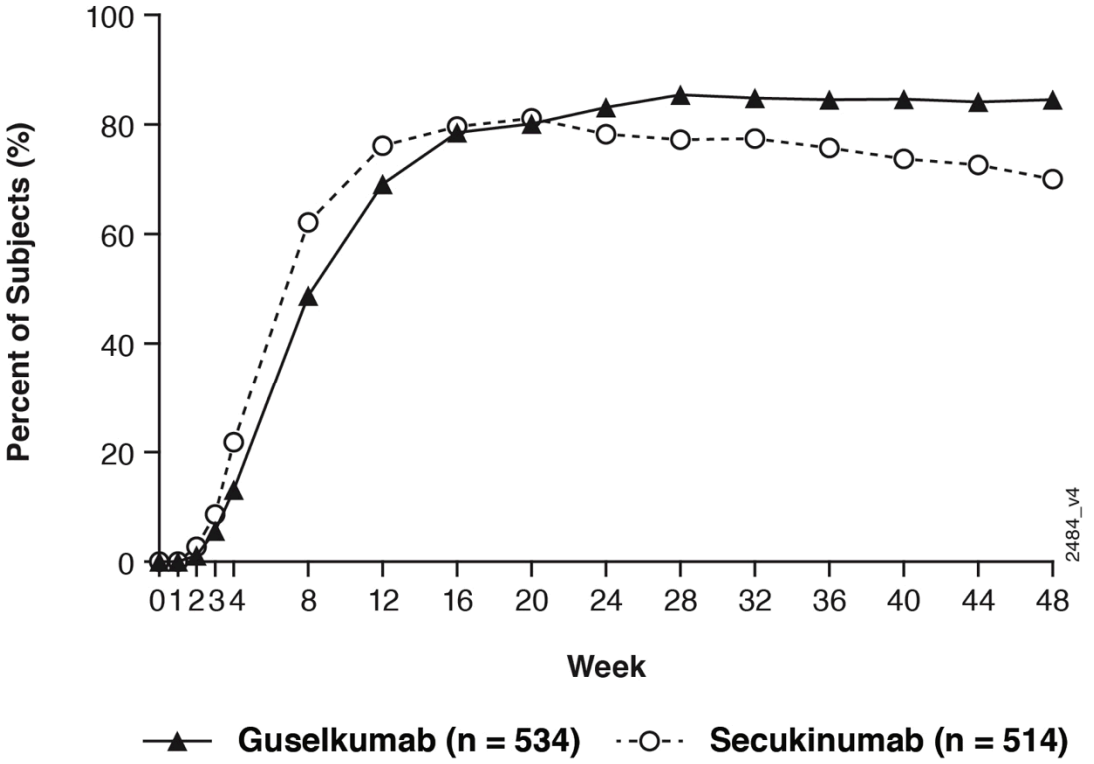
[a] $p < 0.001$ for superiority

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

[c] formal statistical testing was not performed

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

Figure 4: Percent of patients who achieved a PASI 90 response through week 48 by visit (Patients randomised at Week 0) in ECLIPSE



Paediatric population

Paediatric plaque psoriasis

The safety and efficacy of guselkumab were assessed in one multicentre, randomised, placebo- and active biological comparator-controlled study (PROTOSTAR) in 120 paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy and were inadequately controlled by phototherapy and/or topical therapies. PROTOSTAR was conducted in two parts. Part 1 consisted of a 16-week randomised, placebo and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of

treatment with guselkumab through Week 52. Part 2 consisted of an open-label guselkumab arm through Week 52.

Enrolled patients had an IGA score of ≥3 on a 5-point scale of overall disease severity, a PASI ≥12, and a minimum affected BSA of ≥10%, and at least one of the following: 1) very thick lesions, 2) clinically relevant facial, genital, or hand/foot involvement, 3) PASI ≥20, 4) BSA >20%, or 5) IGA=4. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

In Part 1, 92 patients 6 to 17 years of age were randomised to receive subcutaneous injection of either guselkumab (n=41) or placebo (n=25) at Week 0, 4, and 12, or an active biological comparator (n=26) weekly. In Part 2, 28 additional adolescent patients 12 to 17 years of age were enrolled to receive subcutaneous injection of guselkumab at Week 0, 4, and every 8 weeks thereafter. In the guselkumab group, patients with a body weight less than 70 kg received 1.3 mg/kg administered with the 45 mg/0.45 mL pre-filled pen, and patients with a body weight of 70 kg or more received 100 mg administered with the pre-filled syringe.

The co-primary endpoints were the proportion of patients who achieved a PASI 75 response and the proportion of patients who achieved an IGA score of 0 (“cleared”) or 1 (“minimal”) at Week 16. Secondary endpoints included but were not limited to the proportion of patients who achieved a PASI 90 response, an IGA score of 0 (“cleared”) or a PASI 100 response at Week 16.

Of the 92 patients in the controlled part of the study, baseline demographic characteristics were generally comparable across treatment groups. Overall, over 55% were male, 85% were white, the mean body weight was approximately 57.3 kg, and the mean age was 12.9 years with 33% of the patients less than 12 years.

The baseline disease characteristics were generally comparable across treatment groups with median baseline BSA of 20%, median baseline PASI score of approximately 17, and baseline IGA score of severe for 20% (placebo) and 24% (guselkumab) of patients, and a history of psoriatic arthritis for 3.3% of patients.

Overall skin disease
Treatment with guselkumab resulted in significant improvements in the outcome measures of disease activity compared to placebo at Week 16. The key efficacy results for the study endpoints are shown in Table 9 below.

Table 9: Summary of endpoints at week 16 in PROTOSTAR

	Placebo (N=25)	**Guselkumab (N=41)**	**P-value**
IGA scores of cleared (0) or minimal (1), n (%)	4 (16.0%)	27 (65.9%)	<0.001
IGA scores of cleared (0), n (%)	1 (4.0%)	16 (39.0%)	0.004
PASI 75 responders, n (%)	5 (20.0%)	31 (75.6%)	<0.001
PASI 90 responders, n (%)	4 (16.0%)	23 (56.1%)	0.003
PASI 100 responders, n (%)	0	14 (34.1%)	0.002
Change from baseline in CDLQI, LSMean (95% CI)[a]	-1.88 (-3.81, 0.05)	-7.28 (-8.87, -5.68)	<0.001

CDLQI = Children’s Dermatology Life Quality Index
[a] LSMean = least squares mean

Beyond the 16-week placebo-controlled period in Part 1 of PROTOSTAR, the guselkumab treated patients who achieved PASI 90 at Week 16 were withdrawn from treatment. Loss of PASI 90 response was noted as early as 12 weeks after withdrawal of guselkumab treatment with a median time to loss of PASI 90 response of approximately 24 weeks. Of the guselkumab treated patients who failed to achieve a PASI 90 response at Week 16, 72.2% of patients that received an additional 32 weeks of

continued guselkumab treatment were PASI 75 responders at Week 52, and 61.1% achieved a PASI 90 response at Week 52.

In patients randomised to placebo at Week 0 who failed to achieve a PASI 90 response at Week 16 and crossed over to receive guselkumab 95.0% and 65.0% achieved PASI 75 and PASI 90 response, respectively, at Week 52.

5.2 Pharmacokinetic properties

Paediatric population

Steady-state serum trough concentrations of guselkumab were achieved by Week 20 in paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis treated with guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe (see section 4.2), and were within the range of those observed in adults.

The recommended dosing regimen results in similar predicted serum guselkumab exposure in paediatric patients with plaque psoriasis as compared to adults across the body weight range.

Adult population

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) 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 patients with plaque psoriasis, following subcutaneous administrations of guselkumab 100 mg 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 III studies in patients with plaque psoriasis were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL.

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 across studies.

Biotransformation

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

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day across studies. Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and csDMARDs such as MTX, did not affect the clearance of guselkumab.

Linearity/non-linearity

The systemic exposure of guselkumab (C_{max} 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 patients with plaque psoriasis.

Patients with renal or hepatic impairment

No specific study has 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. Based on population pharmacokinetic analyses in adults, creatinine clearance or hepatic function did not have a meaningful impact on guselkumab clearance.

Body weight

Clearance and volume of distribution of guselkumab increases as body weight increases and doses are adjusted for body weight up 40 kg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, toxicity to reproduction and pre- and post-natal development.

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well tolerated via intravenous and subcutaneous routes of administration. A weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 23 times the maximum clinical exposures following a dose of 200 mg given intravenously. Additionally, there were no adverse immunotoxicity or cardiovascular safety pharmacology effects noted during the conduct of the repeat-dose toxicity studies or in a targeted cardiovascular safety pharmacology study in cynomolgus monkeys.

There were no preneoplastic changes observed in histopathology evaluations of animals treated up to 24-weeks, or following the 12-week recovery period during which active substance was detectable in the serum.

No mutagenicity or carcinogenicity studies were conducted with guselkumab.

Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.45 mL solution in a pre-filled glass syringe assembled in a single use, pre-filled pen with an automatic needle guard and an adjustable dose selection plunger.

Tremfya is available in packs containing one pre-filled pen.

6.6 Special precautions for disposal and other handling

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

Prior to use, a visual inspection of the pre-filled pen is recommended. The solution should be clear, colourless to light yellow, and may contain a few small white or clear particles. Tremfya should not be used if the solution is cloudy or discoloured, or contains large particles.

Each pack is provided with an 'Instructions for use' leaflet that fully describes the preparation and administration of the pre-filled pen.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/012 1 pre-filled pen

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal: 15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

This medicinal product contains 0.5 mg of polysorbate 80 (E433) in each pre-filled syringe which is equivalent to 0.5 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear and colourless to light yellow and may contain a few small white or clear particles, with target pH of 5.8 and approximate osmolarity of 367.5 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult plaque psoriasis

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Paediatric plaque psoriasis

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescents from the age of 6 years who are candidates for systemic therapy.

Psoriatic arthritis

Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

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, or a biologic treatment.

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 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

Posology

Adult plaque psoriasis
The recommended dose is 100 mg by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks (q8w).

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

Paediatric plaque psoriasis (6 to 17 years)
Children from the age of 6 years with a body weight of 40 kg or more
The recommended dose is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks (q8w).

Children from the age of 6 years with a body weight less than 40 kg
For children with a body weight less than 40 kg a 45 mg/0.45 mL pre-filled pen is available. For the posology and method of administration, see section 4.2 of the Tremfya 45 mg/0.45 mL pre-filled pen Summary of Product Characteristics.

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

Psoriatic arthritis
The recommended dose is 100 mg by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks (q4w) may be considered (see section 5.1).

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

Ulcerative colitis
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion at Week 0, Week 4 and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

or

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 200 mg dose, see SmPC for Tremfya 200 mg solution for injection.

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

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

Crohn's disease
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion at Week 0, Week 4, and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

or

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose regimen of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 200 mg dose, see SmPC for Tremfya 200 mg solution for injection.

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

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is required (see section 5.2).
There is limited information in patients aged ≥ 65 years and very limited information in patients aged ≥ 75 years (see section 5.2).

Renal or hepatic impairment
Tremfya has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies, and no dose adjustments are considered necessary. For further information on elimination of guselkumab, see section 5.2.

Paediatric population
The safety and efficacy of Tremfya in patients less than 18 years with ulcerative colitis, Crohn's disease and psoriatic arthritis and in patients less than 6 years with psoriasis have not been established. No data are available.

Method of administration

Subcutaneous use only. Sites for injection include the abdomen, thigh and back of the upper arm. Tremfya should not be injected into areas where the skin is tender, bruised, red, hard, thick or scaly. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, adult patients or caregivers may inject Tremfya if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow-up of patients. Adult patients or caregivers should be instructed to inject the full amount of solution according to the 'Instructions for use' provided in the carton. Tremfya is not intended for self-administration by paediatric patients.
For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g., active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Guselkumab may increase the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with guselkumab should be instructed 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, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving guselkumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting (see section 4.8). Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately and appropriate therapy initiated.

Hepatic transaminase elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with guselkumab q4w compared to patients treated with guselkumab q8w or placebo (see section 4.8).

When prescribing guselkumab q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter according to routine patient management. If increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, treatment should be temporarily interrupted until this diagnosis is excluded.

Immunisations

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

Before live viral or live bacterial vaccination, treatment 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 Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Excipients with known effect

Polysorbate 80 content
This medicinal product contains 0.5 mg of polysorbate 80 (E433) in each pre-filled syringe which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

In a Phase I study in patients 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, indicating that 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.

Concomitant immunosuppressive therapy or phototherapy

In psoriasis studies, the safety and efficacy of guselkumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of guselkumab.

In ulcerative colitis and Crohn's disease studies, concomitant use of immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP]) or corticosteroids did not appear to influence the safety or efficacy of guselkumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are limited data from the use of guselkumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tremfya during pregnancy.

Breast-feeding

It is unknown whether guselkumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant during this period cannot be excluded. A decision should

be made whether to discontinue breast-feeding or to abstain from Tremfya therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. See section 5.3 for information on the excretion of guselkumab in animal (cynomolgus monkey) milk.

Fertility

The effect of guselkumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was respiratory tract infections (approximately 8% of patients in ulcerative colitis studies, 11% of patients in the Crohn's disease studies, and 15% of patients in the psoriasis and psoriatic arthritis clinical studies).

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

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

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

Description of selected adverse reactions

Transaminases increased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia) were reported more frequently in the guselkumab treated groups (8.6% in the 100 mg subcutaneous q4w group and 8.3% in the 100 mg subcutaneous q8w group) than in the placebo group (4.6%). Through 1-year, adverse reactions 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, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the guselkumab q4w group compared with the guselkumab q8w group (Table 2). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 2: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through Week 24[a]			**Through 1 year[b]**	
	Placebo N=370[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 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 guselkumab are not included.

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

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the guselkumab q8w dose was similar to that observed for the guselkumab q8w dose in the psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled induction period (Week 0-12), adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, and liver function test increased) were reported more frequently in the guselkumab treated groups (1.7% of patients) than in the placebo group (0.6% of patients). In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, adverse reactions 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 guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase II and Phase III Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies. In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-

controlled period (Week 12), ALT (< 1% of patients) and AST (< 1% of patients) elevations ≥ 3x ULN were reported in guselkumab treated patients. In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, ALT and/or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.6% of patients in the guselkumab 100 mg subcutaneous 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.

Neutrophil count decreased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, the adverse reaction of decreased neutrophil count was reported more frequently in the guselkumab treated group (0.9%) than in the placebo group (0%). Through 1 year, the adverse reaction of decreased neutrophil count was reported in 0.9% of patients treated with guselkumab. In most cases, the decrease in blood neutrophil count was mild, transient, not associated with infection and did not lead to discontinuation of treatment.

Gastroenteritis
In two Phase III psoriasis clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the guselkumab treated group (1.1%) than in the placebo group (0.7%). Through Week 264, 5.8% of all guselkumab treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of guselkumab through Week 264. Gastroenteritis rates observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies.

Injection site reactions
In two Phase III psoriasis clinical studies through Week 48, 0.7% of guselkumab injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 264, 0.4% of guselkumab injections were associated with injection site reactions. Injection site reactions were generally mild to moderate in severity; none were serious, and one led to discontinuation of guselkumab.

In two Phase III psoriatic arthritis clinical studies through Week 24, the number of patients that reported 1 or more injection site reactions was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) patients in the guselkumab q8w group, 4 (1.1%) patients in the guselkumab q4w group, and 1 (0.3%) patient in the placebo group. One patient discontinued guselkumab due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Through 1 year, the proportion of patients reporting 1 or more injection site reactions was 1.6% and 2.4% in the guselkumab q8w and q4w groups respectively. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period was similar to rates observed in the psoriasis clinical studies.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group (guselkumab 200 mg was administered as two 100 mg injections in the Phase III ulcerative colitis maintenance clinical study) and no injection site reactions in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and none were serious.

In Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 4.1% (0.8% of injections) in the treatment group which received guselkumab 200 mg intravenous induction followed by 200 mg subcutaneous q4w, and 1.4% (0.6% of injections) of patients in the guselkumab 200 mg intravenous induction followed by 100 mg subcutaneous q8w group. Overall injection site reactions were mild; none were serious.

In a Phase III Crohn's disease clinical study through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7% (1.3% of injections) in the treatment group

which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 4.3% (0.7% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Most injection site reactions were mild; none were serious.

Immunogenicity
The immunogenicity of guselkumab was evaluated using a sensitive and drug-tolerant immunoassay.

In pooled Phase II and Phase III analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 8% (n=12) had antibodies that were classified as neutralising, which equates to 0.4% of all patients treated with guselkumab. In pooled Phase III analyses in patients with psoriasis, approximately 15% of patients treated with guselkumab developed antidrug antibodies in up to 264 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising, which equates to 0.76% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

In the Phase III paediatric study, 18% (n=21) of paediatric psoriasis patients treated with guselkumab developed antidrug antibodies in up to Week 44. Of the patients who developed antidrug antibodies, none had antibodies that were classified as neutralising. Antibodies to guselkumab were not associated with changes in pharmacokinetics, clinical efficacy or development of injection site reactions. However, the number of patients who were positive for antibodies to guselkumab is too small for definitive conclusions about the impact on efficacy and safety of guselkumab.

In pooled Phase II and Phase III analyses in patients with ulcerative colitis who were treated with intravenous induction followed by subcutaneous maintenance, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralising, which equates to 2% of all patients treated with guselkumab. In a Phase III analysis up to Week 24 in patients with ulcerative colitis who were treated with subcutaneous induction followed by subcutaneous maintenance, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or the development of injection site reactions.

In pooled Phase II and Phase III analyses up to Week 48 in patients with Crohn's disease who were treated with intravenous induction followed by subcutaneous maintenance dose regimen, approximately 5% (n=30) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 7% (n=2) had antibodies that were classified as neutralising antibodies, which equates to 0.3% of guselkumab treated patients. In a Phase III analysis up to Week 48 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of these patients, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

Paediatric population

Plaque psoriasis
The safety of guselkumab was assessed in a Phase III placebo- and active-controlled study in paediatric patients with moderate to severe plaque psoriasis. This clinical study evaluated safety for up to 52 weeks in 120 patients 6 to 17 years of age. The safety profile for guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe in paediatric patients 6 to 17 years was consistent with the safety profile reported in the adult plaque psoriasis studies (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Guselkumab intravenous doses up to 1 200 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, the patient must be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment must be administered immediately.

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 high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In patients with ulcerative colitis or 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 exerts 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, ulcerative colitis, and Crohn's disease. 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 I 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 patients with plaque psoriasis at Week 12 compared to baseline. In the same Phase I 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 patients in Phase II and Phase III plaque psoriasis studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In psoriatic arthritis patients in Phase III studies, 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 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

In patients with ulcerative colitis or Crohn's disease, guselkumab treatment led to decreases in inflammatory markers including C-reactive protein (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.

Clinical efficacy and safety

Adult plaque psoriasis
The efficacy and safety of guselkumab was assessed in three randomised, double-blind, active controlled Phase III studies in adult patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic therapy.

VOYAGE 1 and VOYAGE 2
Two studies (VOYAGE 1 and VOYAGE 2) evaluated the efficacy and safety of guselkumab versus placebo and adalimumab in 1 829 adult patients. Patients randomised to guselkumab (N=825) received 100 mg at Weeks 0 and 4, and every 8 weeks (q8w) thereafter through Week 48 (VOYAGE 1) and Week 20 (VOYAGE 2). Patients randomised to adalimumab (N=582) received 80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week (q2w) through Week 48 (VOYAGE 1) and Week 23 (VOYAGE 2). In both studies, patients randomised to placebo (N=422) received guselkumab 100 mg at Weeks 16, 20 and q8w thereafter. In VOYAGE 1, all patients, including those randomised to adalimumab at Week 0, started to receive open-label guselkumab q8w at Week 52. In VOYAGE 2, patients randomised to guselkumab at Week 0 who were Psoriasis Area and Severity Index (PASI) 90 responders at Week 28 were re-randomised to either continue treatment with guselkumab q8w (maintenance treatment) or receive placebo (withdrawal treatment). Withdrawal patients re-initiated guselkumab (dosed at time of retreatment, 4 weeks later and q8w thereafter) when they experienced at least a 50% loss of their Week 28 PASI improvement. Patients randomised to adalimumab at Week 0 who were PASI 90 non-responders received guselkumab at Weeks 28, 32 and q8w thereafter. In VOYAGE 2, all patients started to receive open-label guselkumab q8w at Week 76.

Baseline disease characteristics were consistent for the study populations in VOYAGE 1 and 2 with a median body surface area (BSA) of 22% and 24%, a median baseline PASI score of 19 for both studies, a median baseline dermatology quality of life index (DLQI) score of 14 and 14.5, a baseline investigator global assessment (IGA) score of severe for 25% and 23% of patients, and a history of psoriatic arthritis for 19% and 18% of patients, respectively.

Of all patients included in VOYAGE 1 and 2, 32% and 29% were naïve to both conventional systemic and biologic therapy, 54% and 57% had received prior phototherapy, and 62% and 64% had received prior conventional systemic therapy, respectively. In both studies, 21% had received prior biologic therapy, including 11% who had received at least one anti-tumour necrosis factor alpha (TNFα) agent, and approximately 10% who had received an anti-IL-12/IL-23 agent.

The efficacy of guselkumab was evaluated with respect to overall skin disease, regional disease (scalp, hand and foot and nails) and quality of life and patient reported outcomes. The co-primary endpoints in VOYAGE 1 and 2 were the proportion of patients who achieved an IGA score of cleared or minimal (IGA 0/1) and a PASI 90 response at Week 16 versus placebo (see Table 3).

Overall skin disease
Treatment with guselkumab resulted in significant improvements in the measures of disease activity compared to placebo and adalimumab at Week 16 and compared to adalimumab at Weeks 24 and 48. The key efficacy results for the primary and major secondary study endpoints are shown in Table 3 below.

Table 3: 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)
Week 16						
PASI 75	10 (5.7)	300 (91.2)[a]	244 (73.1)[b]	20 (8.1)	428 (86.3)[a]	170 (68.5)[b]
PASI 90	5 (2.9)	241 (73.3)[c]	166 (49.7)[b]	6 (2.4)	347 (70.0)[c]	116 (46.8)[b]
PASI 100	1 (0.6)	123 (37.4)[a]	57 (17.1)[d]	2 (0.8)	169 (34.1)[a]	51 (20.6)[d]
IGA 0/1	12 (6.9)	280 (85.1)[c]	220 (65.9)[b]	21 (8.5)	417 (84.1)[c]	168 (67.7)[b]
IGA 0	2 (1.1)	157 (47.7)[a]	88 (26.3)[d]	2 (0.8)	215 (43.3)[a]	71 (28.6)[d]
Week 24						
PASI 75	-	300 (91.2)	241 (72.2)[e]	-	442 (89.1)	176 (71.0)[e]
PASI 90	-	264 (80.2)	177 (53.0)[b]	-	373 (75.2)	136 (54.8)[b]
PASI 100	-	146 (44.4)	83 (24.9)[e]	-	219 (44.2)	66 (26.6)[e]
IGA 0/1	-	277 (84.2)	206 (61.7)[b]	-	414 (83.5)	161 (64.9)[b]
IGA 0	-	173 (52.6)	98 (29.3)[b]	-	257 (51.8)	78 (31.5)[b]
Week 48						
PASI 75	-	289 (87.8)	209 (62.6)[e]	-	-	-
PASI 90	-	251 (76.3)	160 (47.9)[b]	-	-	-
PASI 100	-	156 (47.4)	78 (23.4)[e]	-	-	-
IGA 0/1	-	265 (80.5)	185 (55.4)[b]	-	-	-
IGA 0	-	166 (50.5)	86 (25.7)[b]	-	-	-

[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.

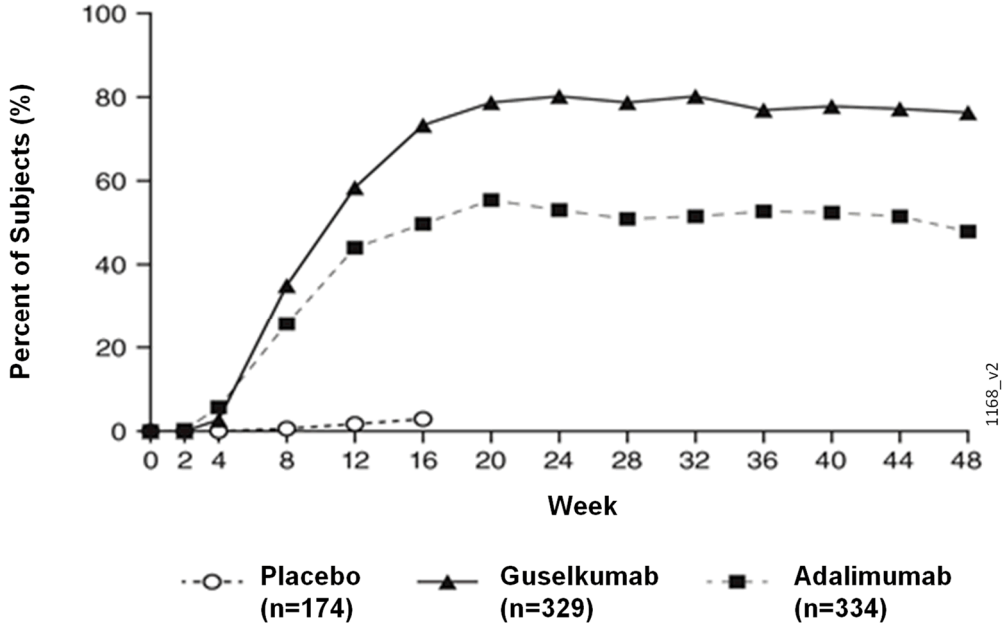
[d] comparisons between guselkumab and adalimumab were not performed.

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

Response over time

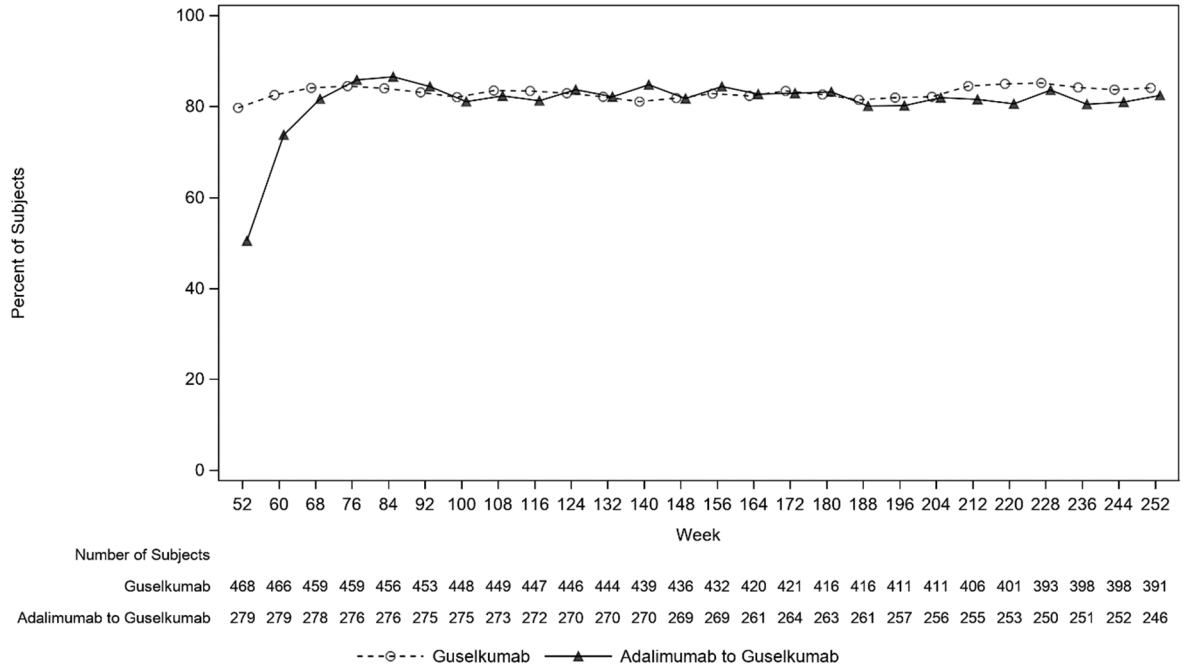
Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 ($p < 0.001$). The percentage of patients achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the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

Figure 1: Percent of patients who achieved a PASI 90 response through week 48 by visit (patients randomised at Week 0) in VOYAGE 1



In VOYAGE 1, for patients receiving continuous guselkumab treatment, the PASI 90 response rate was maintained from Week 52 through Week 252. For patients randomised to adalimumab at Week 0 who crossed over to guselkumab at Week 52, the PASI 90 response rate increased from Week 52 through Week 76 and was then maintained through Week 252 (see Figure 2).

Figure 2: Percent of patients who achieved a PASI 90 response by visit in the open-label phase 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-naïve, biologic-naïve, 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 patients randomised to adalimumab 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. In addition, among 95 patients randomised to guselkumab who failed to achieve a PASI 90 response at Week 28, 36% and 41% achieved a PASI 90 response with an additional 20 and 44 weeks of continued 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 4). 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 4: 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 patients with ss-IGA, f-PGA, hf-PGA score ≥ 2 at baseline or baseline NAPSI score > 0.

[b] Includes only patients 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

Across VOYAGE 1 and 2 significantly greater improvements in health-related quality of life as measured by Dermatology Life Quality Index (DLQI) and in patient-reported psoriasis symptoms (itching, pain, burning, stinging and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) as measured by the Psoriasis Symptoms and Signs Diary (PSSD) were observed in guselkumab patients compared to placebo patients at Week 16 (Table 5). Signs of improvement on patient-reported outcomes were maintained through Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1). In VOYAGE 1, for patients receiving continuous guselkumab treatment, these improvements were maintained in the open-label phase through Week 252 (Table 6).

Table 5: Summary of patient reported outcomes at week 16 in VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	guselkumab	adalimumab	Placebo	guselkumab	adalimumab
DLQI, patients with baseline score	170	322	328	248	495	247
Change from baseline, mean (standard deviation)						
Week 16	-0.6 (6.4)	-11.2 (7.2)[c]	-9.3 (7.8)[b]	-2.6 (6.9)	-11.3 (6.8)[c]	-9.7 (6.8)[b]
PSSD Symptom score, patients with baseline score > 0	129	248	273	198	410	200
Symptom score = 0, n (%)						
Week 16	1 (0.8)	67 (27.0)[a]	45 (16.5)[b]	0	112 (27.3)[a]	30 (15.0)[b]
PSSD Sign score, patients with baseline score > 0	129	248	274	198	411	201
Sign score = 0, n (%)						
Week 16	0	50 (20.2)[a]	32 (11.7)[b]	0	86 (20.9)[a]	21 (10.4)[b]

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

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

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

Table 6: Summary of patient reported outcomes in the open-label phase in VOYAGE 1

	guselkumab			adalimumab-guselkumab		
	Week 76	Week 156	Week 252	Week 76	Week 156	Week 252
DLQI score > 1 at baseline, n	445	420	374	264	255	235
Patients with DLQI 0/1	337 (75.7%)	308 (73.3%)	272 (72.7%)	198 (75.0%)	190 (74.5%)	174 (74.0%)
PSSD Symptom Score, patients with baseline score > 0	347	327	297	227	218	200
Symptom score = 0, n (%)	136 (39.2%)	130 (39.8%)	126 (42.4%)	99 (43.6%)	96 (44.0%)	96 (48.0%)
PSSD Sign score, patients with baseline score > 0	347	327	297	228	219	201
Sign score = 0, n (%)	102 (29.4%)	94 (28.7%)	98 (33.0%)	71 (31.1%)	69 (31.5%)	76 (37.8%)

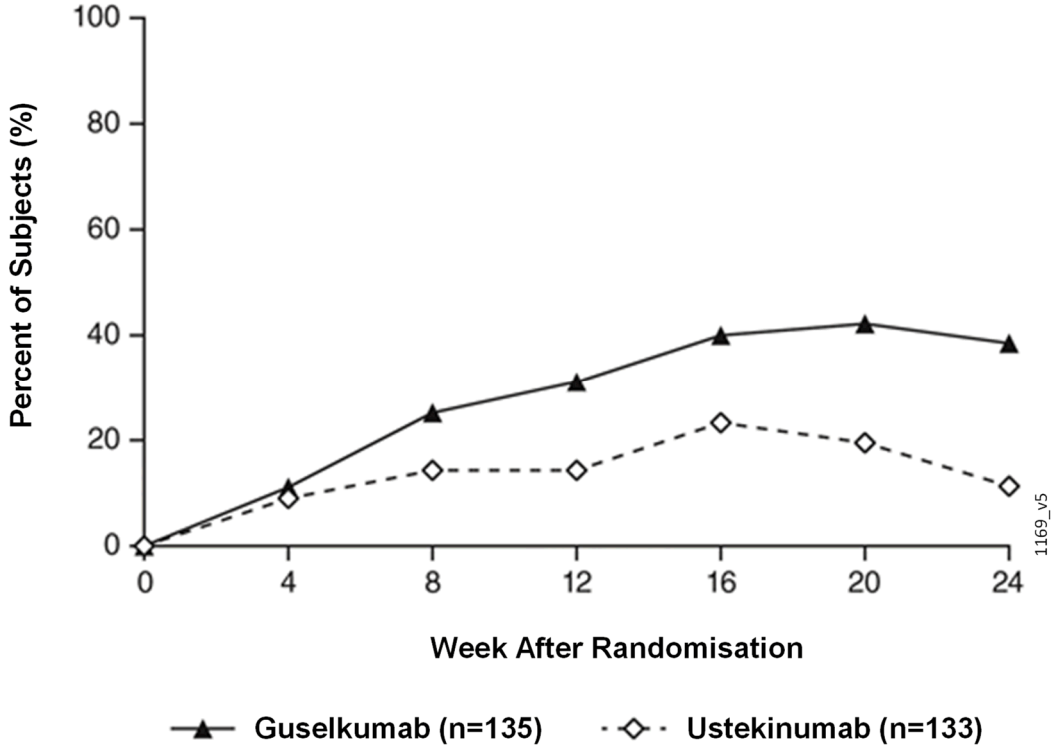
In VOYAGE 2, guselkumab patients had significantly greater improvement from baseline compared to placebo in health-related quality of life, anxiety and depression, and work limitation measures at Week 16, as measured by the 36-item Short Form (SF-36) health survey questionnaire, Hospital Anxiety and Depression Scale (HADS), and Work Limitations Questionnaire (WLQ), respectively. The improvements in SF-36, HADS and WLQ were all maintained through Week 48 and in the open-label phase through Week 252 among patients randomised to maintenance therapy at Week 28.

NAVIGATE

The NAVIGATE study examined the efficacy of guselkumab in patients who had an inadequate response (i.e., who had not achieved a 'cleared' or 'minimal' response defined as IGA ≥ 2) to ustekinumab at Week 16. All patients (N=871) received open-label ustekinumab (45 mg ≤100 kg and 90 mg >100 kg) at Weeks 0 and 4. At Week 16, 268 patients with an IGA ≥ 2 score were randomised to either continue ustekinumab treatment (N=133) q12w, or to initiate guselkumab treatment (N=135) at Weeks 16, 20, and q8w thereafter. Baseline characteristics for randomised patients were similar to those observed in VOYAGE 1 and 2.

After randomisation, the primary endpoint was the number of post-randomisation visits between Weeks 12 and 24 at which patients achieved an IGA score 0/1 and had ≥ 2 grade improvement. Patients were examined at four week intervals for a total of four visits. Among patients who inadequately responded to ustekinumab at the time of randomisation, significantly greater improvement of efficacy was observed in patients who switched to guselkumab treatment compared to patients who continued ustekinumab treatment. Between 12 and 24 weeks after randomisation, guselkumab patients achieved an IGA score 0/1 with ≥ 2 grade improvement twice as often as ustekinumab patients (mean 1.5 vs 0.7 visits, respectively, $p < 0.001$). Additionally, at 12 weeks after randomisation a higher proportion of guselkumab patients compared to ustekinumab patients achieved an IGA score 0/1 and ≥ 2 grade improvement (31.1% vs. 14.3%, respectively; $p = 0.001$) and a PASI 90 response (48% vs 23%, respectively, $p < 0.001$). Differences in response rates between guselkumab and ustekinumab-treated patients were noted as early as 4 weeks after randomisation (11.1% and 9.0%, respectively) and reached a maximum 24 weeks after randomisation (see Figure 3). No new safety findings were observed in patients who switched from ustekinumab to guselkumab.

Figure 3: Percent of patients 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



ECLIPSE
Efficacy and safety of guselkumab were also investigated in a double-blind study compared to secukinumab. Patients were randomised to receive guselkumab (N=534; 100 mg at Week 0, 4 and q8w thereafter), or secukinumab (N=514; 300 mg at Week 0, 1, 2, 3, 4, and q4w thereafter). The last dose was at week 44 for both treatment groups.

Baseline disease characteristics were consistent with a population of moderate to severe plaque psoriasis with a median BSA of 20%, a median PASI score of 18, and an IGA score of severe for 24% of patients.

Guselkumab 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 PASI response rates are presented in Table 7.

Table 7: PASI response rates in ECLIPSE

	Number of patients (%)	
	guselkumab (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%)

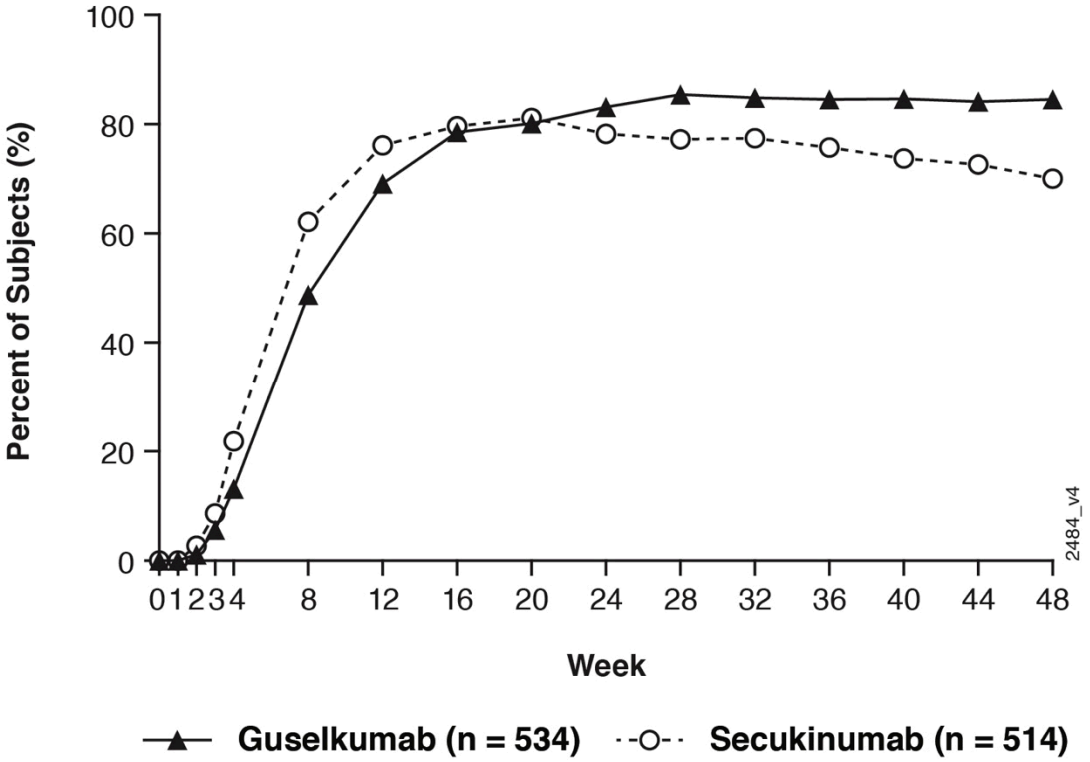
[a] $p < 0.001$ for superiority

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

[c] formal statistical testing was not performed

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

Figure 4: Percent of patients who achieved a PASI 90 response through week 48 by visit (Patients randomised at Week 0) in ECLIPSE



Psoriatic arthritis (PsA)

Guselkumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

DISCOVER 1 and DISCOVER 2

Two randomised, double-blind, placebo-controlled Phase III studies (DISCOVER 1 and DISCOVER 2) evaluated the efficacy and safety of guselkumab versus placebo in adult patients with active PsA (≥ 3 swollen and ≥ 3 tender joints, and a C-reactive protein (CRP) level of ≥ 0.3 mg/dL in DISCOVER 1, and ≥ 5 swollen and ≥ 5 tender joints, and a CRP level of ≥ 0.6 mg/dL in DISCOVER 2), despite conventional synthetic (cs)DMARD, apremilast, or nonsteroidal anti-inflammatory drug (NSAID) therapy. Patients in these studies had a diagnosis of PsA based on the Classification criteria for Psoriatic Arthritis [CASPAR]) for a median duration of 4 years. 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%). Over 65% and 42% of the patients had enthesitis and dactylitis at baseline, respectively, and over 75% of patients had ≥ 3% BSA psoriasis skin involvement. DISCOVER 1 and DISCOVER 2 evaluated 381 and 739 patients, respectively, who received treatment with guselkumab 100 mg administered at Weeks 0 and 4 followed by every 8 weeks (q8w) or guselkumab 100 mg q4w, or placebo. At Week 24, placebo patients in both studies crossed over to receive guselkumab 100 mg q4w. Approximately 58% of patients in both studies continued on stable doses of MTX (≤ 25 mg/week).

In both studies over 90% of patients had prior csDMARD use. In DISCOVER 1, 31% of patients had previously received anti-TNFα treatment. In DISCOVER 2, all patients were naïve to biologic therapy.

Signs and symptoms
Treatment with guselkumab resulted in significant improvements in the measures of disease activity compared to placebo at Week 24. The primary endpoint in both studies was the percentage of patients who achieved American College of Rheumatology (ACR) 20 response at Week 24. The key efficacy results are shown in Table 8.

Table 8: Clinical responses in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
	Placebo (N=126)	guselkumab 100 mg q8w (N=127)	guselkumab 100 mg q4w (N=128)	Placebo (N=246)	guselkumab 100 mg q8w (N=248)	guselkumab 100 mg q4w (N=245)
ACR 20 response						
Week 16	25.4%	52.0% [b]	60.2% [b]	33.7%	55.2% [g]	55.9% [c]
Difference from placebo (95% CI)	-	26.7 (15.3, 38.1)	34.8 (23.5, 46.0)	-	21.5 (13.1, 30.0)	22.2 (13.7, 30.7)
Week 24	22.2%	52.0% [a]	59.4% [a]	32.9%	64.1% [a]	63.7% [a]
Difference from placebo (95% CI)	-	29.8 (18.6, 41.1)	37.1 (26.1, 48.2)	-	31.2 (22.9, 39.5)	30.8 (22.4, 39.1)
ACR 50 response						
Week 16	12.7%	22.8% [d]	26.6% [c]	9.3%	28.6% [g]	20.8% [c]
Difference from placebo (95% CI)	-	10.2 (1.0, 19.3)	13.9 (4.4, 23.4)	-	19.3 (12.6, 25.9)	11.5 (5.2, 17.7)
Week 24	8.7%	29.9% [b]	35.9% [b]	14.2%	31.5% [g]	33.1% [c]
Difference from placebo (95% CI)	-	21.4 (12.1, 30.7)	27.2 (17.6, 36.8)	-	17.2 (10.0, 24.4)	18.8 (11.5, 26.1)
ACR 70 response						
Week 24	5.6%	11.8% [d]	20.3% [b]	4.1%	18.5% [g]	13.1% [c]
Difference from placebo (95% CI)	-	6.4 (-0.3, 13.1)	14.8 (6.9, 22.7)	-	14.5 (9.1, 19.9)	9.0 (4.1, 13.8)
DAS 28 (CRP) LSMean change[i] from baseline						
Week 24[c]	-0.70	-1.43[b]	-1.61[b]	-0.97	-1.59[b]	-1.62[b]
Difference from placebo (95% CI)	-	-0.73 (-0.98, -0.48)	-0.91 (-1.16, -0.66)	-	-0.61 (-0.80, -0.43)	-0.65 (-0.83, -0.47)
Minimal Disease Activity (MDA)						
Week 24	11.1%	22.8% [f]	30.5% [e]	6.1%	25.0% [e]	18.8% [e]
Difference from placebo (95% CI)	-	11.9 (2.9, 20.9)	19.3 (9.7, 28.9)	-	18.9 (12.8, 25.0)	12.7 (7.0, 18.4)
Patients with ≥ 3% BSA and IGA ≥ 2	n=78	n=82	n=89	n=183	n=176	n=184
IGA response [h]						
Week 24	15.4%	57.3% [b]	75.3% [b]	19.1%	70.5% [b]	68.5% [b]
Difference from placebo (95% CI)	-	42.0 (28.9, 55.1)	60.0 (48.3, 71.8)	-	50.9 (42.2, 59.7)	49.8 (41.2, 58.4)
PASI 90 response						
Week 16	10.3%	45.1% [e]	52.8% [e]	8.2%	55.1% [e]	53.8% [e]
Difference from placebo (95% CI)	-	34.9 (22.2, 47.6)	42.6 (30.5, 54.8)	-	46.6 (38.4, 54.8)	45.6 (37.6, 53.6)
Week 24	11.5%	50.0% [e]	62.9% [e]	9.8%	68.8% [e]	60.9% [e]
Difference from placebo (95% CI)	-	38.6 (25.8, 51.4)	51.7 (39.7, 63.7)	-	58.6 (50.6, 66.6)	51.3 (43.2, 59.3)

[a] $p < 0.001$ (primary endpoint)
[b] $p < 0.001$ (major secondary endpoint)
[c] $p = 0.006$ (major secondary endpoint)
[d] not statistically significant p=0.086 (major secondary endpoint)
[e] nominal $p < 0.001$
[f] nominal $p = 0.012$
[g] not formally tested in the hierarchical testing procedure, nominal $p < 0.001$ (major secondary endpoint)
[h] defined as a IGA response of 0 (cleared) or 1 (minimal) and ≥ 2-grade reduction from baseline in the IGA psoriasis score
[i] LSmean change = least squares mean change

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 in DISCOVER 1 and DISCOVER 2 (see Table 9).

Table 9: Clinical responses in DISCOVER 1 and DISCOVER 2 at week 52[a]

	DISCOVER 1		DISCOVER 2	
	guselkumab 100 mg q8w	guselkumab 100 mg q4w	guselkumab 100 mg q8w	guselkumab 100 mg q4w
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%
DAS 28 (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 patients with an observed response status.
[c] Patients have an observed change from baseline.

Clinical response was maintained up to Week 100 as assessed by ACR 20/50/70, DAS 28 (CRP), MDA, IGA and PASI 90 response rates in DISCOVER 2 (see Table 10).

Table 10: Clinical responses in DISCOVER 2 at week 100[a]

	guselkumab 100 mg q8w	guselkumab 100 mg q4w
ACR 20		
N[b]	223	219
% Response	82.1%	84.9%
ACR 50		
N[b]	224	220
% Response	60.7%	62.3%

ACR 70		
N[b]	224	220
% Response	39.3%	38.6%
DAS 28 (CRP) change from baseline		
N[c]	223	219
Mean (SD)	-2.37 (1.215)	-2.36 (1.120)
MDA		
N[b]	224	220
% Response	44.6%	42.7%
Patients with ≥ 3% BSA and IGA ≥ 2 at baseline		
IGA Response		
N[b]	165	170
% Response	76.4%	82.4%
PASI 90		
N[b]	164	170
% Response	75.0%	80.0%

[a] There was no placebo arm beyond Week 24.

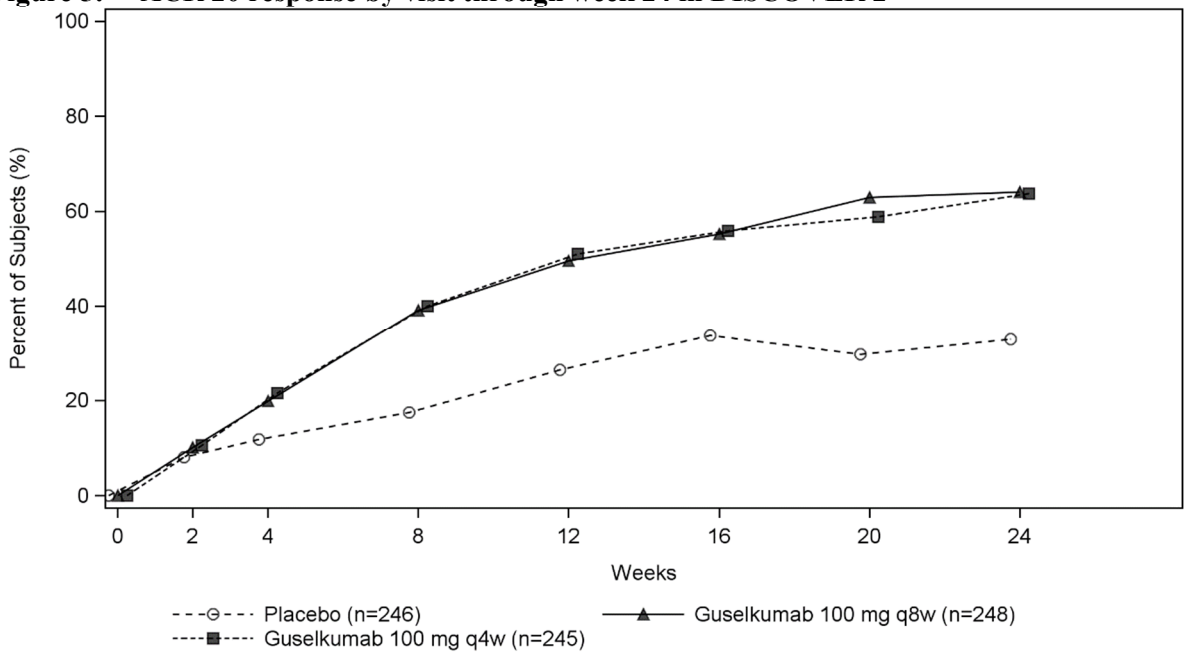
[b] Evaluable patients with an observed response status.

[c] Patients have an observed change from baseline.

Response over time

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

Figure 5: ACR 20 response by visit through week 24 in DISCOVER 2



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

Figure 6: ACR 20 response by visit from week 24 through week 52 in DISCOVER 2

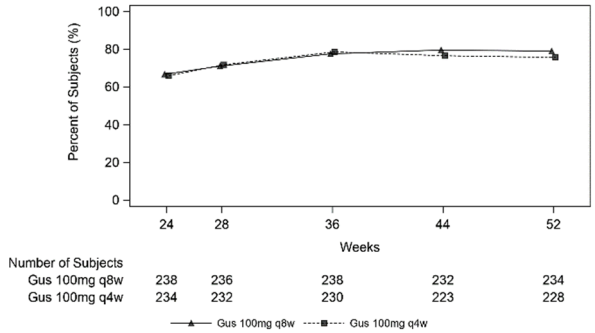
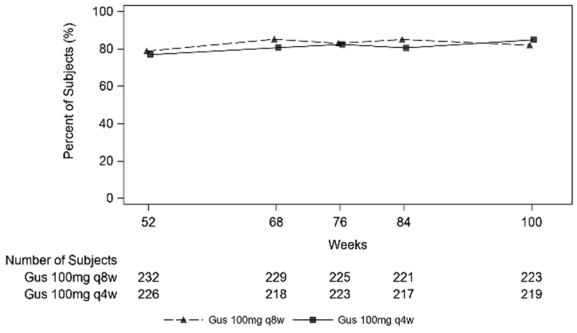


Figure 7: ACR 20 response by visit from week 52 through week 100 in DISCOVER 2



Responses observed in the guselkumab groups were similar regardless of concomitant csDMARD use, including MTX (DISCOVER 1 and 2). Additionally, examination of age, gender, race, body weight, and previous csDMARD use (DISCOVER 1 and 2) and previous anti-TNFα use (DISCOVER 1), did not identify differences in response to guselkumab among these subgroups.

In DISCOVER 1 and 2, improvements were shown in all components of the ACR scores including patient assessment of pain. At Week 24 in both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) response was greater in the guselkumab groups compared to placebo. PsARC responses were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Dactylitis and enthesitis were assessed based on pooled data from DISCOVER 1 and 2. At Week 24, among patients with dactylitis at baseline, the proportion of patients with dactylitis resolution was greater in the guselkumab q8w group (59.4%, nominal $p < 0.001$) and q4w group (63.5%, $p = 0.006$) compared to placebo (42.2%). At Week 24, among patients with enthesitis at baseline, the proportion of patients with enthesitis resolution was greater in the guselkumab q8w group (49.6%, nominal $p < 0.001$) and q4w group (44.9%, $p = 0.006$) compared to placebo (29.4%). At Week 52, the proportions of patients with dactylitis resolution (81.2% in q8w group and 80.4% in q4w group) and enthesitis resolution (62.7% in q8w group and 60.9% in q4w group) were maintained. In DISCOVER 2, among patients with dactylitis and enthesitis at baseline, the proportion of patients with dactylitis resolution (91.1% in q8w group and 82.9% in q4w group) and enthesitis resolution (77.5% in q8w group and 67.7% in q4w group) were maintained at Week 100.

In DISCOVER 1 and 2, patients treated with guselkumab 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.

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, the guselkumab q4w group demonstrated statistically significantly less radiographic progression and the guselkumab q8w group showed numerically less progression than placebo (Table 11). The observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (i.e., smaller mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in patients with both a high C-reactive protein value and high number of joints with erosions at baseline.

Table 11: Change from baseline in total modified vdH-S score at week 24 in DISCOVER 2

	N	LSMean change[c] (95% CI[d]) from baseline in modified vdH-S score at Week 24
Placebo	246	0.95 (0.61, 1.29)
guselkumab 100 mg q8w	248	0.52[a] (0.18, 0.86)
guselkumab 100 mg q4w	245	0.29[b] (-0.05, 0.63)

[a] not statistically significant p = 0.068 (major secondary endpoint).

[b] p = 0.006 (major secondary endpoint).

[c] LSmean change = least squares mean change.

[d] CI = confidence interval.

At Week 52 and Week 100, the mean change from baseline in total modified vdH-S was similar in the guselkumab q8w and q4w groups (Table 12).

Table 12: Change from baseline in total modified vdH-S score at week 52 and week 100 in DISCOVER 2

	N[a]	Mean change (SD[b]) from baseline in total modified vdH-S score
Week 52		
guselkumab 100 mg q8w	235	0.97 (3.623)
guselkumab 100 mg q4w	229	1.07 (3.843)
Week 100		
guselkumab 100 mg q8w	216	1.50 (4.393)
guselkumab 100 mg q4w	211	1.68 (7.018)

[a] Evaluable patients have observed change for the specified time period

[b] SD = standard deviation

Note: no placebo group beyond Week 24

Physical function and health-related quality of life

In DISCOVER 1 and 2, guselkumab treated patients showed significant improvement ($p < 0.001$) in physical function compared to placebo as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

A significantly greater improvement from baseline in the SF-36 Physical Component Summary (PCS) score was observed in guselkumab treated patients compared to placebo at Week 24 in DISCOVER 1 ($p < 0.001$ for both dose groups) and DISCOVER 2 ($p = 0.006$ for q4w group). At Week 24, a greater 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 studies. In DISCOVER 2, greater improvements in health-related quality of life as measured by the Dermatology Life Quality Index (DLQI) were observed in guselkumab treated patients compared to placebo at Week 24. Improvements in SF-36 PCS, FACIT-F and DLQI scores were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Ulcerative colitis

The efficacy and safety of guselkumab were evaluated in three Phase III multicentre, randomised, double-blind, placebo-controlled studies (QUASAR intravenous induction study, QUASAR maintenance study, and ASTRO subcutaneous induction 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 (AZA, 6-MP), biologic therapy (TNF blockers, vedolizumab), a Janus kinase (JAK) inhibitor, and/or sphingosine-1-phosphate receptor modulators (S1PRM) applicable only for ASTRO. In addition, efficacy and safety of guselkumab were evaluated in a randomised, double-blind, placebo-controlled, Phase IIb induction dose-finding study (QUASAR induction dose-ranging study) that enrolled a similar ulcerative colitis patient population as the Phase III induction 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 ≥ 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).

Induction study: QUASAR IS
In the induction study QUASAR IS, patients were randomised in a 3:2 ratio to receive either guselkumab 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 and 1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, MTX, 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, 87.5%, 54.1% and 18% had previously failed a TNF blocker, vedolizumab or a JAK inhibitor, respectively, and 47.4% 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, fatigue response and IBDQ remission (Table 13).

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

Table 13: Proportion of patients meeting efficacy endpoints at Week 12 in QUASAR IS

Endpoint	Placebo %	Guselkumab 200 mg intravenous induction[a] %	Treatment Difference (95% CI)
Clinical remission[b]			
Total population	8% (N=280)	23% (N=421)	15% (10%, 20%)[c]
Biologic and JAK inhibitor naïve[d]	12% (N=137)	32% (N=202)	20% (12%, 28%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 14%)
Symptomatic remission[f]			
Total population	21% (N=280)	50% (N=421)	29% (23%, 36%)[c]
Biologic and JAK inhibitor naïve[d]	26% (N=137)	60% (N=202)	34% (24%, 44%)
Prior biologic and/or JAK inhibitor failure[e]	14% (N=136)	38% (N=208)	24% (16%, 33%)
Endoscopic healing[g]			
Total population	11% (N=280)	27% (N=421)	16% (10%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	17% (N=137)	38% (N=202)	21% (12%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	5% (N=136)	15% (N=208)	10% (4%, 16%)
Clinical response[h]			
Total population	28% (N=280)	62% (N=421)	34% (27%, 41%)[c]

Biologic and JAK inhibitor naïve[d]	35% (N=137)	71% (N=202)	36% (26%, 46%)
Prior biologic and/or JAK inhibitor failure[e]	20% (N=136)	51% (N=208)	32% (22%, 41%)
Histologic endoscopic mucosal healing[i]			
Total Population	8% (N=280)	24% (N=421)	16% (11%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	11% (N=137)	33% (N=202)	22% (13%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 15%)
Fatigue response[j]			
Total population	21% (N=280)	41% (N=421)	20% (13%, 26%)[c]
Biologic and JAK inhibitor naïve[d]	29% (N=137)	42% (N=202)	12% (2%, 23%)
Prior biologic and/or JAK inhibitor failure[e]	13% (N=136)	38% (N=208)	25% (17%, 34%)
IBDQ remission[k]			
Total population	30% (N=280)	51% (N=421)	22% (15%, 29%)[c]
Biologic and JAK inhibitor naïve[d]	34% (N=137)	62% (N=202)	28% (18%, 38%)
Prior biologic and/or JAK inhibitor failure[e]	24% (N=136)	39% (N=208)	15% (5%, 25%)

[a] Guselkumab 200 mg as an intravenous induction 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.

[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 patients in the placebo group and 11 patients in the guselkumab 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.

[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.

[k] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

QUASAR IS and QUASAR induction dose-ranging study also enrolled 48 patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥ 1. In patients with a baseline mMS of 4, guselkumab 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 ulcerative colitis population.

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

Maintenance study: QUASAR MS
The QUASAR MS evaluated 568 patients who achieved clinical response at 12 weeks following the intravenous administration of guselkumab in either QUASAR IS or from the QUASAR induction dose-ranging study. In the QUASAR MS, these patients were randomised to receive a subcutaneous maintenance regimen of either guselkumab 100 mg every 8 weeks, guselkumab 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, fatigue response and IBDQ remission (Table 14).

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

Table 14: Proportion of patients meeting efficacy endpoints at Week 44 in QUASAR MS

Endpoint	Placebo %	Guselkumab 100 mg q8w subcutaneous injection[a] %	Guselkumab 200 mg q4w subcutaneous injection[b] %	Treatment Difference (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[c]					
Total population[d]	19% (N=190)	45% (N=188)	50% (N=190)	25% (16%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	58% (N=96)	24% (12%, 36%)	29% (17%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	40% (N=77)	40% (N=88)	30% (19%, 42%)	32% (21%, 44%)
Symptomatic remission[h]					
Total population[d]	37% (N=190)	70% (N=188)	69% (N=190)	32% (23%, 41%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	46% (N=108)	74% (N=105)	76% (N=96)	28% (15%, 40%)	28% (15%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	24% (N=75)	65% (N=77)	60% (N=88)	39% (26%, 52%)	37% (23%, 50%)
Corticosteroid-free clinical remission[i]					
Total population[d]	18% (N=190)	45% (N=188)	49% (N=190)	26% (17%, 34%)[e]	29% (20%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	56% (N=96)	24% (12%, 36%)	27% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	7% (N=75)	40% (N=77)	40% (N=88)	32% (21%, 43%)	34% (23%, 45%)
Endoscopic healing[j]					
Total population[d]	19% (N=190)	49% (N=188)	52% (N=190)	30% (21%, 38%)[e]	31% (22%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	53% (N=105)	59% (N=96)	27% (15%, 40%)	30% (18%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	45% (N=77)	42% (N=88)	36% (24%, 48%)	35% (23%, 46%)
Histologic endoscopic mucosal healing[k]					
Total population[d]	17% (N=190)	44% (N=188)	48% (N=190)	26% (17%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	23% (N=108)	50% (N=105)	56% (N=96)	26% (14%, 38%)	30% (17%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	38% (N=77)	39% (N=88)	28% (16%, 39%)	31% (20%, 43%)
Clinical response[l]					
Total population[d]	43% (N=190)	78% (N=188)	75% (N=190)	34% (25%, 43%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	54% (N=108)	83% (N=105)	81% (N=96)	29% (17%, 41%)	26% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	28% (N=75)	70% (N=77)	67% (N=88)	41% (27%, 54%)	39% (26%, 53%)

Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population[q]	34% (N=59)	61% (N=66)	72% (N=69)	26% (9%, 43%)[m]	38% (23%, 54%)[e]
Biologic and JAK-inhibitor naïve[r]	34% (N=41)	65% (N=43)	79% (N=48)	31% (9%, 51%)	45% (25%, 62%)
Prior biologic and/or JAK-inhibitor failure[g]	27% (N=15)	60% (N=20)	56% (N=18)	33% (-1%, 62%)	29% (-6%, 59%)
Endoscopic normalisation[n]					
Total population[d]	15% (N=190)	35% (N=188)	34% (N=190)	18% (10%, 27%)[e]	17% (9%, 25%)[e]
Biologic and JAK-inhibitor naïve [f]	20% (N=108)	38% (N=105)	42% (N=96)	17% (6%, 29%)	17% (6%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	31% (N=77)	24% (N=88)	21% (10%, 33%)	16% (6%, 26%)
Fatigue response[o]					
Total population [d]	29% (N=190)	51% (N=188)	43% (N=190)	20% (11%, 29%)[e]	13% (3%, 22%)[m]
Biologic and JAK-inhibitor naïve[f]	36% (N=108)	51% (N=105)	53% (N=96)	15% (2%, 28%)	16% (3%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	47% (N=77)	32% (N=88)	27% (13%, 40%)	13% (1%, 26%)
IBDQ remission[p]					
Total population[d]	37% (N=190)	64% (N=188)	64% (N=190)	26% (17%, 36%)[e]	26% (16%, 35%)[e]
Biologic and JAK-inhibitor naïve [f]	49% (N=108)	68% (N=105)	74% (N=96)	19% (6%, 32%)	24% (11%, 37%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	58% (N=77)	53% (N=88)	38% (26%, 50%)	35% (23%, 48%)

[a] Guselkumab 100 mg as a subcutaneous injection every 8 weeks after the induction regimen.

[b] Guselkumab 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.

[d] Patients who achieved clinical response 12 weeks following the intravenous administration of guselkumab 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 patients in the placebo group, 6 patients in the guselkumab 100 mg group, and 6 patients in the guselkumab 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.

[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.

[p] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

[q] Subjects who achieved clinical remission 12 weeks following intravenous administration of guselkumab in either QUASAR induction study or QUASAR induction dose-ranging study.

[r] An additional 3 patients in the placebo group, 3 patients in the guselkumab 100 mg group, and 3 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic or JAK inhibitor.

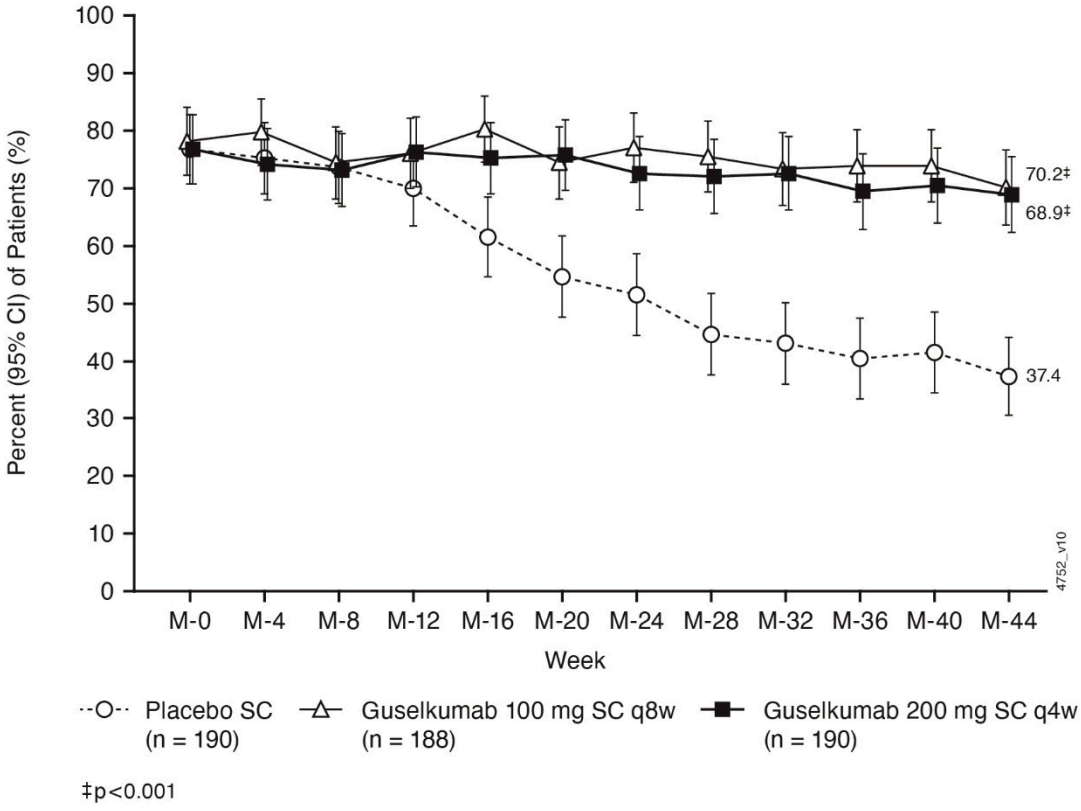
In QUASAR IS and QUASAR MS, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race, body weight, and previous treatment with a biologic therapy or JAK inhibitor.

In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of > 15% were observed between the two guselkumab 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).

QUASAR MS enrolled 31 patients with an induction 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 guselkumab in QUASAR IS or QUASAR induction dose-ranging study. In these patients, guselkumab efficacy relative to placebo as measured by clinical remission, clinical response, and endoscopic healing at Week 44 was consistent with the total population.

Symptomatic remission over time
In QUASAR MS symptomatic remission defined as 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 guselkumab 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 guselkumab extended treatment
Guselkumab treated patients who were not in clinical response at induction Week 12, received guselkumab 200 mg subcutaneous at Weeks 12, 16 and 20. In QUASAR IS, 66/120 (55%) guselkumab treated patients who were not in clinical response at induction Week 12 achieved clinical response at Week 24. Week 24 responders to guselkumab entered QUASAR MS and received

guselkumab 200 mg subcutaneous every 4 weeks. At Week 44 of QUASAR MS, 83/123 (67%) of these patients maintained clinical response and 37/123 (30%) achieved clinical remission.

Recapture of efficacy after loss of response to guselkumab
Nineteen patients receiving guselkumab 100 mg subcutaneous q8w who experienced a first loss of response (10%) between Week 8 and 32 of QUASAR MS received blinded guselkumab dosing with 200 mg guselkumab subcutaneous q4w 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). In QUASAR IS, histologic remission at Week 12 was achieved in 40% of patients treated with guselkumab and 19% of patients in the placebo group. In QUASAR MS, histologic remission at Week 44 was achieved in 59% and 61% of patients treated with guselkumab 100 mg subcutaneous q8w and guselkumab 200 mg subcutaneous q4w and 27% of patients in the placebo group.

Normalisation of the endoscopic appearance of the mucosa was defined as ES of 0. In QUASAR IS, endoscopic normalisation at Week 12 was achieved in 15% of patients treated with guselkumab and 5% of patients in the placebo group.

Composite histologic-endoscopic mucosal outcomes
Combined symptomatic remission, endoscopic normalisation, histologic remission, and faecal calprotectin ≤ 250 mg/kg at Week 44 was achieved by a greater proportion of patients treated with guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (22% and 28% vs 9%, respectively).

Health-related quality of life
At Week 12 of QUASAR IS, patients receiving guselkumab showed greater and clinically meaningful improvements from baseline when compared with placebo in inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score, and all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function). These improvements were maintained in guselkumab treated patients in QUASAR MS through Week 44.

Ulcerative colitis related hospitalisations
Through Week 12 of QUASAR IS, lower proportions of patients in the guselkumab group compared with the placebo group had ulcerative colitis-related hospitalisations (1.9%, 8/421 vs. 5.4%, 15/280).

ASTRO
In ASTRO, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg subcutaneous maintenance every 8 weeks; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg subcutaneous maintenance every 4 weeks; or placebo.

A total of 418 patients were evaluated. The median age of patients was 40 years (ranging from 18 to 80 years); 38.8% were female; and 64.6% identified as White, 28.9% as Asian, and 3.1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, immunomodulators (AZA, 6-MP, MTX), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 77.3% of patients were receiving aminosalicylates, 20.1% of patients were receiving immunomodulators, and 32.8% of patients were receiving corticosteroids. Concomitant biologic therapies, JAK inhibitors, or S1PRMs were not permitted. A total of 40.2% of patients had previously failed treatment with at least one biologic therapy, JAK inhibitor, and/or S1PRM, 58.1% were biologic, JAK inhibitor, and S1PRM naïve, and 1.7% had previously received but had not failed a biologic, JAK inhibitor, or S1PRM.

In ASTRO, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included symptomatic remission, endoscopic healing, clinical response and histologic-endoscopic mucosal healing (see Table 15). Secondary endpoints at Week 24 included clinical remission and endoscopic healing (see Table 16).

Table 15: Proportion of patients meeting efficacy endpoints at Week 12 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg Subcutaneous Induction[a] %	Treatment Difference vs Placebo (95% CI)[b]
Clinical remission[c]			
Total Population	6% (N=139)	28% (N=279)	21% (15%, 28%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	9% (N=79)	36% (N=164)	27% (18%, 37%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	4% (N=56)	16% (N=112)	12% (3%, 20%)
Symptomatic remission[d]			
Total Population	21% (N=139)	51% (N=279)	30% (22%, 39%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	25% (N=79)	59% (N=164)	34% (22%, 46%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	14% (N=56)	41% (N=112)	26% (13%, 39%)
Endoscopic healing[h]			
Total Population	13% (N=139)	37% (N=279)	24% (17%, 32%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	46% (N=164)	28% (17%, 40%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	24% (N=112)	16% (6%, 26%)
Clinical response[i]			
Total Population	35% (N=139)	66% (N=279)	31% (22%, 40%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	42% (N=79)	71% (N=164)	30% (17%, 43%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	25% (N=56)	57% (N=112)	31% (17%, 45%)
Histologic endoscopic mucosal healing[j]			
Total Population	11% (N=139)	30% (N=279)	20% (12%, 27%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	14% (N=79)	38% (N=164)	25% (14%, 35%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	19% (N=112)	11% (1%, 20%)

[a] Guselkumab 400 mg subcutaneous induction at Week 0, Week 4, and Week 8

[b] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[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

[d] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group and 3 patients in the guselkumab group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

[i] Decrease from 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

[j] An endoscopy subscore of 0, or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Table 16: Proportion of patients meeting efficacy endpoints at Week 24 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg SC induction→ 100 mg q8w Subcutaneous Injection[a] %	Guselkumab 400 mg SC induction→ 200 mg q4w Subcutaneous Injection[b] %	Treatment Difference vs Placebo (95% CI)[c]	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[d]					
Total population	9% (N=139)	35% (N=139)	36% (N=140)	26% (17%, 35%)[e]	27% (18%, 36%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	13% (N=79)	49% (N=81)	43% (N=83)	37% (24%, 50%)	31% (18%, 44%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	16% (N=57)	27% (N=55)	10% (-1%, 21%)	21% (9%, 34%)
Endoscopic healing[h]					
Total population	12% (N=139)	40% (N=139)	45% (N=140)	28% (18%, 38%)[e]	33% (23%, 42%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	54% (N=81)	52% (N=83)	37% (23%, 51%)	34% (21%, 48%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	19% (N=57)	36% (N=55)	13% (1%, 25%)	30% (17%, 44%)

[a] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks

[b] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg SC maintenance every 4 weeks

[c] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[d] 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

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group, 1 patient in the guselkumab 100 mg group, and 2 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

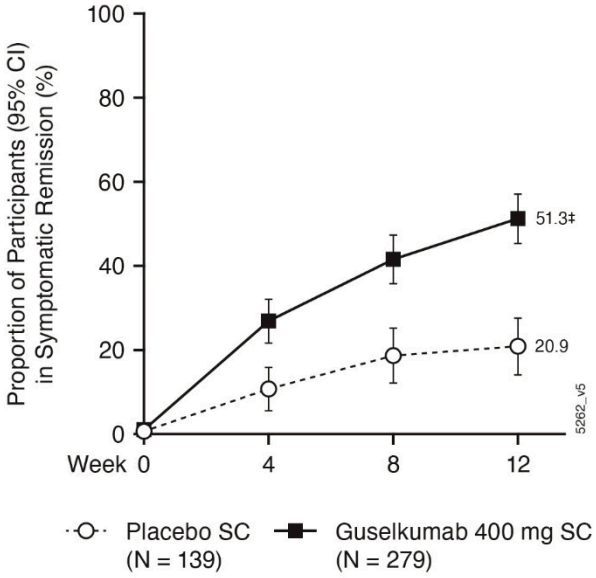
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

Symptomatic remission over time

In ASTRO, symptomatic remission defined as stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0 observed through Week 12, a greater proportion of patients in the guselkumab treatment groups achieved symptomatic remission compared with the placebo group (Figure 9):

Figure 9: Proportion of patients in symptomatic remission through Week 12 in ASTRO



‡p<0.001

Rectal bleeding and stool frequency subscores
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with guselkumab compared to placebo.

Histologic and endoscopic assessment
Histologic remission at Week 12 was achieved in 44% of patients treated with guselkumab 400 mg subcutaneous induction compared to 20% of patients on placebo.

Endoscopic normalisation at Week 24 was achieved in 21% and 26% of patients treated with guselkumab 400 mg subcutaneous induction, followed by guselkumab 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or guselkumab 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter, respectively, compared to 4% of patients on placebo.

Abdominal pain and bowel urgency
A greater proportion of patients treated with guselkumab 400 mg subcutaneous induction compared to placebo had no abdominal pain (56% vs 31%), and no bowel urgency (49% vs 24%) at Week 12.

Health-related quality of life
Disease-specific health-related quality of life was assessed with the IBDQ. A greater proportion of patients in the combined 400 mg SC guselkumab group (61%) achieved IBDQ remission at Week 12 compared with the placebo group (34%).

Crohn's disease
The efficacy and safety of guselkumab were evaluated in three Phase III clinical studies 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 active-controlled (ustekinumab), parallel group studies (GALAXI 2 and GALAXI 3) and one 24-Week multicentre, randomised, double-blind, placebo-controlled, parallel group study (GRAVITI). All three studies had a treat-through study design: patients randomised to guselkumab (or ustekinumab for GALAXI 2 and GALAXI 3) maintained that treatment assignment for the duration of the study.

GALAXI 2 and GALAXI 3
In the Phase III studies GALAXI 2 and GALAXI 3, 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). Additional criteria for GALAXI 2/3 included a mean daily stool frequency (SF) > 3 or mean daily abdominal pain score (AP) > 1.

In GALAXI 2 and GALAXI 3 studies, patients were randomised in a 2:2:2:1 ratio to receive guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg subcutaneous q4w maintenance; or guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8, followed by guselkumab 100 mg subcutaneous q8w maintenance; or ustekinumab approximately 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w maintenance; or placebo. Placebo non-responders received ustekinumab 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), 57.6% were male; and 74.3% identified as White, 21.3% as Asian and 1.5% as Black.

In GALAXI 2, 52.8% of patients had previously failed treatment with at least one biologic therapy (50.6% were intolerant or failed at least 1 prior anti-TNFα therapy, 7.5% were intolerant or failed prior vedolizumab 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 (50.3% were intolerant or failed at least 1 prior anti-TNFα therapy, 9.6% were intolerant or failed prior vedolizumab 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.

The results of the co-primary and major secondary endpoints compared to placebo in GALAXI 2 and GALAXI 3 are presented in Tables 17 (Week 12) and 18 (Week 48). The results of the major secondary endpoints at Week 48 compared to ustekinumab are presented in Tables 19 and 20.

Table 17: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GALAXI 2 and GALAXI 3

	GALAXI 2		GALAXI 3	
	Placebo %	Guselkumab intravenous induction[a] %	Placebo %	Guselkumab intravenous induction[a] %
Co-primary efficacy endpoints				
Clinical remission[b] at Week 12				
Total population	22% (N=76)	47%[i] (N=289)	15% (N=72)	47%[i] (N=293)
Biologic naïve[c]	18% (N=34)	50% (N=121)	15% (N=27)	50% (N=123)
Prior biologic failure[d]	23% (N=39)	45% (N=150)	15% (N=39)	47% (N=150)
Endoscopic response[e] at Week 12				
Total population	11% (N=76)	38%[i] (N=289)	14% (N=72)	36%[i] (N=293)
Biologic naïve[c]	15% (N=34)	51% (N=121)	22% (N=27)	41% (N=123)
Prior biologic failure[d]	5% (N=39)	27% (N=150)	8% (N=39)	31% (N=150)
Major secondary efficacy endpoints				
PRO-2 remission[f] at Week 12				
Total population	21% (N=76)	43%[i] (N=289)	14% (N=72)	42%[i] (N=293)
Biologic naïve[c]	24% (N=34)	43% (N=121)	15% (N=27)	47% (N=123)
Prior biologic failure[d]	13% (N=39)	41% (N=150)	13% (N=39)	39% (N=150)
Fatigue response[g] at Week 12				
Total population	29% (N=76)	45%[j] (N=289)	18% (N=72)	43%[i] (N=293)
Biologic naïve[c]	32% (N=34)	48% (N=121)	19% (N=27)	46% (N=123)
Prior biologic failure[d]	26% (N=39)	41% (N=150)	18% (N=39)	43% (N=150)
Endoscopic remission[h] at Week 12				
Total population	1% (N=76)	15% (N=289)	8% (N=72)	16% (N=293)
Biologic naïve[c]	3% (N=34)	22% (N=121)	19% (N=27)	25% (N=123)
Prior biologic failure[d]	0% (N=39)	9% (N=150)	0% (N=39)	9% (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 – Two guselkumab treatment groups were combined for this column as patients received the same intravenous induction dose regimen prior to Week 12.

[b] Clinical remission is defined as CDAI score < 150.

[c] An additional 9 patients in the placebo group and 38 patients in the guselkumab 200 mg intravenous group were previously exposed to but did not fail a biological therapy.

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

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

[f] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

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

[h] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] $p < 0.001$

[j] $p < 0.05$

Table 18: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus placebo at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Placebo	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]	Placebo (N=72)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]
Corticosteroid-free clinical remission[c] at Week 48[f]						
Total population	12% (N=76)	45%[e] (N=143)	51%[e] (N=146)	14% (N=72)	44%[e] (N=143)	48%[e] (N=150)
Endoscopic response[d] at Week 48[f]						
Total population	7% (N=76)	38%[e] (N=143)	38%[e] (N=146)	6% (N=72)	33%[e] (N=143)	36%[e] (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[c] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

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

[e] $p < 0.001$

[f] Participants who met inadequate response criteria at Week 12 were considered non-responders at Week 48, regardless of treatment arm.

Table 19: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus ustekinumab at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]
Clinical remission at Week 48 and endoscopic response[d] at Week 48						
Total population	39% (N=143)	42% (N=143)	49% (N=146)	28% (N=148)	41%[k] (N=143)	45%[k] (N=150)
Endoscopic response[e] at Week 48[l]						
Total population	42% (N=143)	49% (N=143)	56% (N=146)	32% (N=148)	47% (N=143)	49% (N=150)
Endoscopic remission[f] at Week 48						
Total population	20% (N=143)	27% (N=143)	24% (N=146)	13% (N=148)	24%[k] (N=143)	19% (N=150)
Clinical remission[g] at Week 48						
Total population	65% (N=143)	64% (N=143)	75% (N=146)	61% (N=148)	66% (N=143)	66% (N=150)
Corticosteroid-free clinical remission[h] at Week 48[l]						
Total population	61% (N=143)	63% (N=143)	71% (N=146)	59% (N=148)	64% (N=143)	64% (N=150)
Durable clinical remission[i] at Week 48						
Total population	45% (N=143)	46% (N=143)	52% (N=146)	39% (N=148)	50% (N=143)	49% (N=150)
PRO-2 remission[j] at Week 48						
Total population	59% (N=143)	60% (N=143)	69% (N=146)	53% (N=148)	58% (N=143)	56% (N=150)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

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

[f] Endoscopic remission is defined as SES-CD Score ≤ 2.

[g] Clinical remission is defined as CDAI score < 150.

[h] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

[i] Durable clinical remission is defined as CDAI < 150 for ≥ 80% of all visits between Week 12 and Week 48 (at least 8 of 10 visits), which must include Week 48.

[j] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

[k] $p < 0.05$

[l] Responses at Week 48 were evaluated irrespective of clinical response at Week 12

Table 20: Proportion of patients meeting efficacy endpoints with guselkumab versus ustekinumab at Week 48 in pooled GALAXI 2 and GALAXI 3

	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	**Guselkumab intravenous induction → 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**
Clinical remission at Week 48 and endoscopic response[d] at Week 48			
Total population	34% (N=291)	42% (N=286)	47% (N=296)
Biologic naïve[e]	43% (N=121)	51% (N=116)	55% (N=128)
Prior biologic failure[f]	26% (N=156)	37% (N=153)	41% (N=147)
Endoscopic response[g] at Week 48			
Total population	37% (N=291)	48% (N=286)	53% (N=296)
Biologic naïve[e]	43% (N=121)	59% (N=116)	59% (N=128)
Prior biologic failure[f]	31% (N=156)	43% (N=153)	47% (N=147)
Endoscopic remission[h] at Week 48			
Total population	16% (N=291)	25% (N=286)	21% (N=296)
Biologic naïve[e]	19% (N=121)	34% (N=116)	27% (N=128)
Prior biologic failure[f]	13% (N=156)	21% (N=153)	14% (N=147)
Clinical remission[i] at Week 48			
Total population	63% (N=291)	65% (N=286)	70% (N=296)
Biologic naïve[e]	75% (N=121)	73% (N=116)	77% (N=128)
Prior biologic failure[f]	53% (N=156)	61% (N=153)	64% (N=147)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

[e] An additional 14 patients in the ustekinumab group, 21 patients in the guselkumab 200 mg subcutaneous q4w group, and 17 patients in the guselkumab 100 mg subcutaneous q8w group were previously exposed to but did not fail a biological 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] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] Clinical remission is defined as CDAI score < 150.

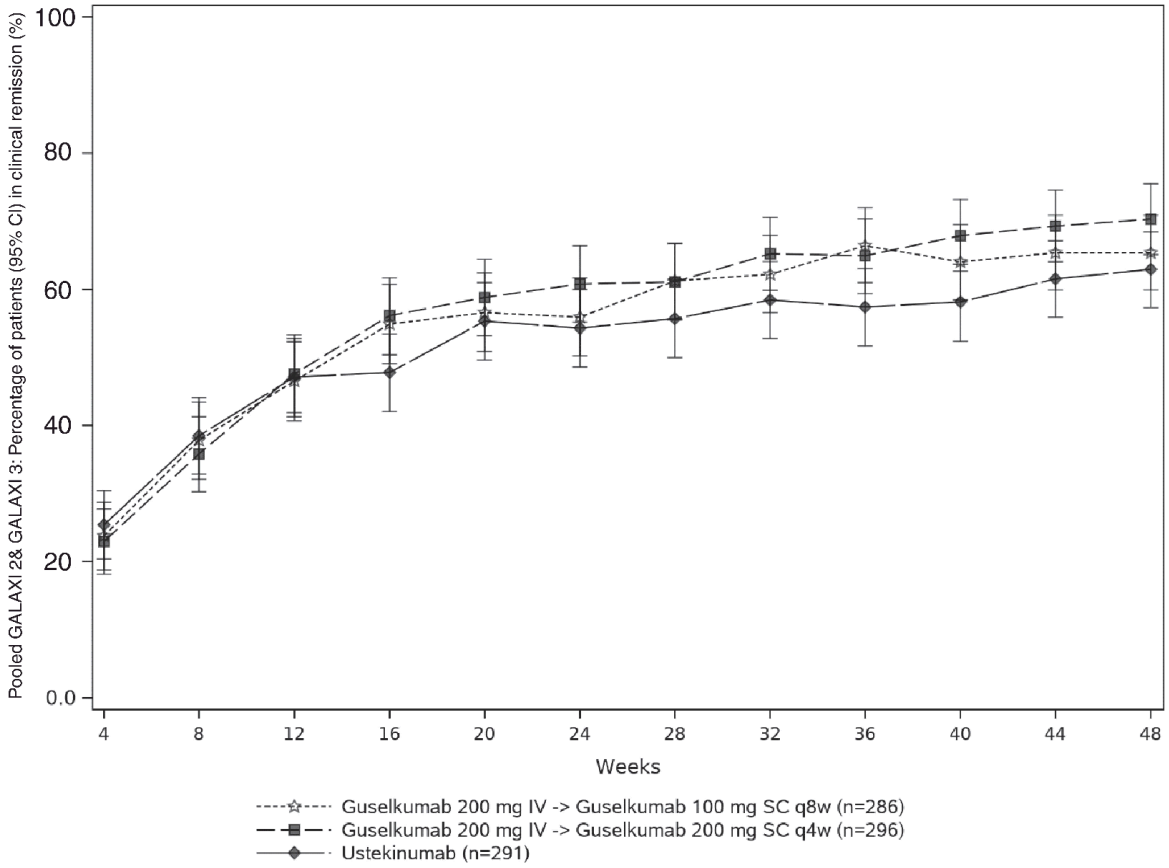
In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight.

In the pooled GALAXI Phase III studies subpopulation analysis, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w maintenance dose regimens. A clinically meaningful difference was observed between the two guselkumab 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: 54.1% vs 200 mg subcutaneous q4w: 71.0%); endoscopic response at Week 48 (100 mg subcutaneous q8w: 36.5% vs 200 mg subcutaneous q4w: 50.5%); and PRO-2 remission at Week 48 (100 mg subcutaneous q8w: 51.8% vs 200 mg subcutaneous q4w: 61.7%).

Clinical remission over time

CDAI scores were recorded at each patient visit. The proportion of patients in clinical remission through Week 48 is presented in Figure 10.

Figure 10: Proportion of patients in clinical remission through Week 48 in pooled GALAXI 2 and GALAXI 3



Health-related quality of life

Greater improvements from baseline were seen at Week 12 in guselkumab treatment groups when compared with placebo for inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score. The improvements were maintained through Week 48 in both studies.

GRAVITI

In the Phase III GRAVITI study, moderately to severely active Crohn's disease was defined as a CDAI score of ≥ 220 and ≤ 450 and a CD (SES-CD) of ≥ 6 (or ≥ 4 for patients with isolated ileal disease) and a mean daily SF ≥ 4 or mean daily AP score ≥ 2.

In GRAVITI, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg q8w subcutaneous maintenance; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg q4w subcutaneous maintenance; or placebo. All patients in the placebo group who met rescue criteria received the induction dosing with guselkumab 400 mg subcutaneous at Weeks 16, 20, and 24 followed by guselkumab 100 mg subcutaneous q8w.

A total of 347 patients were evaluated. The median age of patients was 36 years (ranging from 18 to 83 years), 58.5% were male, and 66% identified as White, 21.9% as Asian and 2.6% as Black.

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.

The results of the co-primary and major secondary efficacy endpoints compared to placebo at Week 12 are presented in Table 21.

Table 21: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GRAVITI

	Placebo	Guselkumab 400 mg subcutaneous injection[a]
Co-primary efficacy endpoints		
Clinical remission[b] at Week 12		
Total population	21% (N=117)	56%[c] (N=230)
Biologic naïve[d]	25% (N=56)	50% (N=105)
Prior biologic failure[e]	17% (N=53)	60% (N=108)
Endoscopic response[f] at Week 12		
Total population	21% (N=117)	41%[c] (N=230)
Biologic naïve[d]	27% (N=56)	49% (N=105)
Prior biologic failure[e]	17% (N=53)	33% (N=108)
Major secondary efficacy endpoints		
Clinical response[g] at Week 12		
Total population	33% (N=117)	73%[c] (N=230)
Biologic naïve[d]	38% (N=56)	68% (N=105)
Prior biologic failure[e]	28% (N=53)	78% (N=108)
PRO-2 remission[h] at Week 12		
Total population	17% (N=117)	49%[c] (N=230)
Biologic naïve[d]	18% (N=56)	44% (N=105)
Prior biologic failure[e]	17% (N=53)	52% (N=108)

[a] Guselkumab 400 mg subcutaneous at Week 0, Week 4 and Week 8

[b] Clinical remission: CDAI score < 150

[c] p< 0.001

[d] An additional 8 patients in the placebo group and 17 patients in the guselkumab 400 mg subcutaneous group, were previously exposed to but did not fail a biological therapy.

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

[f] Endoscopic response: ≥ 50% improvement from baseline in SES-CD score.

[g] Clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score < 150.

[h] PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

Clinical remission at Week 24 was achieved by a significantly greater proportion of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (60.9% and 58.3% vs 21.4% respectively, both p-values < 0.001). Clinical remission at Week 48 was achieved by 60% and 66.1% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Endoscopic response at Week 48 was achieved by 44.3% and 51.3% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Health-related quality of life
In GRAVITI, clinically meaningful improvements were observed in IBD-specific quality of life as assessed with IBDQ total score at Week 12 and Week 24 compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with guselkumab in one or more subsets of the paediatric population in psoriatic arthritis, ulcerative colitis, and Crohn's disease (see section 4.2 for information on paediatric use).

Paediatric plaque psoriasis

The safety and efficacy of guselkumab were assessed in one multicentre, randomised, placebo- and active biological comparator-controlled study (PROTOSTAR) in 120 paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy and were inadequately controlled by phototherapy and/or topical therapies. PROTOSTAR was conducted in two parts. Part 1 consisted of a 16-week randomised, placebo and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. Part 2 consisted of an open-label guselkumab arm through Week 52.

Enrolled patients had an IGA score of ≥3 on a 5-point scale of overall disease severity, a PASI ≥12, and a minimum affected BSA of ≥10%, and at least one of the following: 1) very thick lesions, 2) clinically relevant facial, genital, or hand/foot involvement, 3) PASI ≥20, 4) BSA >20%, or 5) IGA=4. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

In Part 1, 92 patients 6 to 17 years of age were randomised to receive subcutaneous injection of either guselkumab (n=41) or placebo (n=25) at Week 0, 4, and 12, or an active biological comparator (n=26) weekly. In Part 2, 28 additional adolescent patients 12 to 17 years of age were enrolled to receive subcutaneous injection of guselkumab at Week 0, 4, and every 8 weeks thereafter. In the guselkumab group, patients with a body weight less than 70 kg received 1.3 mg/kg administered with the 45 mg/0.45 mL pre-filled pen, and patients with a body weight of 70 kg or more received 100 mg administered with the pre-filled syringe.

The co-primary endpoints were the proportion of patients who achieved a PASI 75 response and the proportion of patients who achieved an IGA score of 0 (“cleared”) or 1 (“minimal”) at Week 16. Secondary endpoints included but were not limited to the proportion of patients who achieved a PASI 90 response, an IGA score of 0 (“cleared”) or a PASI 100 response at Week 16.

Of the 92 patients in the controlled part of the study, baseline demographic characteristics were generally comparable across treatment groups. Overall, over 55% were male, 85% were white, the mean body weight was approximately 57.3 kg, and the mean age was 12.9 years with 33% of the patients less than 12 years.

The baseline disease characteristics were generally comparable across treatment groups with median baseline BSA of 20%, median baseline PASI score of approximately 17, and baseline IGA score of severe for 20% (placebo) and 24% (guselkumab) of patients, and a history of psoriatic arthritis for 3.3% of patients.

Overall skin disease

Treatment with guselkumab resulted in significant improvements in the outcome measures of disease activity compared to placebo at Week 16. The key efficacy results for the study endpoints are shown in Table 22 below.

Table 22: Summary of endpoints at week 16 in PROTOSTAR

	Placebo (N=25)	**Guselkumab (N=41)**	**P-value**
IGA scores of cleared (0) or minimal (1), n (%)	4 (16.0%)	27 (65.9%)	<0.001
IGA scores of cleared (0), n (%)	1 (4.0%)	16 (39.0%)	0.004
PASI 75 responders, n (%)	5 (20.0%)	31 (75.6%)	<0.001
PASI 90 responders, n (%)	4 (16.0%)	23 (56.1%)	0.003
PASI 100 responders, n (%)	0	14 (34.1%)	0.002
Change from baseline in CDLQI, LSMean (95% CI)[a]	-1.88 (-3.81, 0.05)	-7.28 (-8.87, -5.68)	<0.001

CDLQI = Children’s Dermatology Life Quality Index

[a] LSMean = least squares mean

Beyond the 16-week placebo-controlled period in Part 1 of PROTOSTAR, the guselkumab treated patients who achieved PASI 90 at Week 16 were withdrawn from treatment. Loss of PASI 90 response was noted as early as 12 weeks after withdrawal of guselkumab treatment with a median time to loss of PASI 90 response of approximately 24 weeks. Of the guselkumab treated patients who failed to achieve a PASI 90 response at Week 16, 72.2% of patients that received an additional 32 weeks of continued guselkumab treatment were PASI 75 responders at Week 52, and 61.1% achieved a PASI 90 response at Week 52.

In patients randomised to placebo at Week 0 who failed to achieve a PASI 90 response at Week 16 and crossed over to receive guselkumab 95.0% and 65.0% achieved PASI 75 and PASI 90 response, respectively, at Week 52.

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) 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 patients with plaque psoriasis, following subcutaneous administrations of guselkumab 100 mg 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 III studies in patients with plaque psoriasis were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. The pharmacokinetics of guselkumab in patients with psoriatic arthritis was similar to that in patients with psoriasis. Following subcutaneous administration of guselkumab 100 mg at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was also approximately 1.2 mcg/mL. Following subcutaneous administration of guselkumab 100 mg every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3.8 mcg/mL.

The pharmacokinetics of guselkumab were similar in patients with ulcerative colitis and Crohn's disease. Following the recommended intravenous induction dose regimen of guselkumab 200 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was 68.27 mcg/mL in patients with ulcerative colitis, and 70.5 mcg/mL in patients with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of guselkumab 400 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was estimated to be 28.8 mcg/mL in patients with ulcerative colitis, and 27.7 mcg/mL in patients with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimen was similar following subcutaneous and intravenous induction.

Following subcutaneous maintenance dosing of guselkumab 100 mg every 8 weeks or guselkumab 200 mg 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 guselkumab 100 mg every 8 weeks or guselkumab 200 mg every 4 weeks in patients 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 across studies.

Biotransformation

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

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day across studies. Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies, and approximately 17 days in patients with ulcerative colitis or Crohn's disease.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, AZA, 6-MP, oral corticosteroids and csDMARDs such as MTX, did not affect the clearance of guselkumab.

Linearity/non-linearity

The systemic exposure of guselkumab (C_{max} 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 patients with plaque psoriasis. Serum guselkumab concentrations were approximately dose proportional following intravenous administration in patients with ulcerative colitis or Crohn's disease.

Paediatric population

Steady-state serum trough concentrations of guselkumab were achieved by Week 20 in paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis treated with guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe (see section 4.2), and were within the range of those observed in adults.

The recommended dosing regimen results in similar predicted serum guselkumab exposure in paediatric patients with plaque psoriasis as compared to adults across the body weight range.

Elderly patients

No specific studies have been conducted in elderly patients. Of the 1 384 plaque psoriasis patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, 70 patients were 65 years of age or older, including 4 patients who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in Phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. Of the 859 ulcerative colitis patients exposed to guselkumab in Phase II/III clinical studies and included in the population pharmacokinetic analysis, a total of 52 patients were 65 years of age or older, and 9 patients were 75 years of age or older. Of the 1 009 Crohn's disease patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, a total of 39 patients were 65 years of age or older, and 5 patients were 75 years of age or older.

Population pharmacokinetic analyses in plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease patients indicated no apparent changes in CL/F estimate in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Patients with renal or hepatic impairment

No specific study has 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. Based on population pharmacokinetic analyses, creatinine clearance or hepatic function did not have a meaningful impact on guselkumab clearance.

Body weight

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, toxicity to reproduction and pre- and post-natal development.

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well tolerated via intravenous and subcutaneous routes of administration. A weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 23 times the maximum clinical exposures following a dose of 200 mg given intravenously. Additionally, there were no adverse immunotoxicity or cardiovascular safety pharmacology effects noted during the conduct of the repeat-dose toxicity studies or in a targeted cardiovascular safety pharmacology study in cynomolgus monkeys.

There were no preneoplastic changes observed in histopathology evaluations of animals treated up to 24 weeks, or following the 12-week recovery period during which active substance was detectable in the serum.

No mutagenicity or carcinogenicity studies were conducted with guselkumab.

Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper, a fixed needle and a needle shield, assembled in an automatic needle guard.
Tremfya is available in packs containing one pre-filled syringe and in multipacks containing 2 (2 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Prior to use, a visual inspection of the pre-filled syringe is recommended. The solution should be clear, colourless to light yellow, and may contain a few small white or clear particles. Tremfya should not be used if the solution is cloudy or discoloured, or contains large particles.

Each pack is provided with an 'Instructions for use' leaflet that fully describes the preparation and administration of the pre-filled syringe.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1234/001 1 pre-filled syringe
EU/1/17/1234/004 2 pre-filled syringes

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal:15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg OnePress solution for injection in pre-filled pen
Tremfya 100 mg PushPen solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tremfya 100 mg OnePress solution for injection in pre-filled pen

Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution.

Tremfya 100 mg PushPen solution for injection in pre-filled pen

Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

This medicinal product contains 0.5 mg of polysorbate 80 (E433) in each pre-filled pen which is equivalent to 0.5 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear and colourless to light yellow and may contain a few small white or clear particles, with target pH of 5.8 and approximate osmolarity of 367.5 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult plaque psoriasis

Tremfya is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Psoriatic arthritis

Tremfya, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

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, or a biologic treatment.

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 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

Posology

Plaque psoriasis
The recommended dose is 100 mg by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks (q8w).

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

Psoriatic arthritis
The recommended dose is 100 mg by subcutaneous injection at Weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks (q4w) may be considered (see section 5.1).

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

Ulcerative colitis
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion at Week 0, Week 4 and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

or

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 200 mg dose, see SmPC for Tremfya 200 mg solution for injection.

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

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

Crohn's disease
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion at Week 0, Week 4, and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

or

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose regimen of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 200 mg dose, see SmPC for Tremfya 200 mg solution for injection.

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

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is required (see section 5.2).
There is limited information in patients aged ≥ 65 years and very limited information in patients aged ≥ 75 years (see section 5.2).

Renal or hepatic impairment
Tremfya has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies, and no dose adjustments are considered necessary. For further information on elimination of guselkumab, see section 5.2.

Paediatric population
The safety and efficacy of Tremfya in patients less than 18 years with ulcerative colitis, Crohn's disease and psoriatic arthritis and in patients less than 6 years with psoriasis have not been established. No data are available. Tremfya 100 mg solution for injection in pre-filled pens are not recommended for use in children below 18 years due to insufficient data on safety and efficacy. Currently available data with other presentations are described in sections 4.8, 5.1 and 5.2.

Method of administration

Subcutaneous use only. Sites for injection include the abdomen, thigh and back of the upper arm. Tremfya should not be injected into areas where the skin is tender, bruised, red, hard, thick or scaly. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients may inject Tremfya if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow-up of patients. Patients should be instructed to inject the full amount of solution according to the 'Instructions for use' provided in the carton.
For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g., active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Guselkumab may increase the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with guselkumab should be instructed 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, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving guselkumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting (see section 4.8). Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately and appropriate therapy initiated.

Hepatic transaminase elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with guselkumab q4w compared to patients treated with guselkumab q8w or placebo (see section 4.8).

When prescribing guselkumab q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter according to routine patient management. If increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, treatment should be temporarily interrupted until this diagnosis is excluded.

Immunisations

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

Before live viral or live bacterial vaccination, treatment 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 Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Excipients with known effect

Polysorbate 80 content
This medicinal product contains 0.5 mg of polysorbate 80 (E433) in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

In a Phase I study in patients 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, indicating that 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.

Concomitant immunosuppressive therapy or phototherapy

In psoriasis studies, the safety and efficacy of guselkumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of guselkumab.

In ulcerative colitis and Crohn's disease studies, concomitant use of immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP]) or corticosteroids did not appear to influence the safety or efficacy of guselkumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are limited data from the use of guselkumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tremfya during pregnancy.

Breast-feeding

It is unknown whether guselkumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant during this period cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from Tremfya therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. See section 5.3 for information on the excretion of guselkumab in animal (cynomolgus monkey) milk.

Fertility

The effect of guselkumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was respiratory tract infections (approximately 8% of patients in ulcerative colitis studies, 11% of patients in the Crohn's disease studies, and 15% of patients in the psoriasis and psoriatic arthritis clinical studies).

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

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

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

Description of selected adverse reactions

Transaminases increased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia) were reported more frequently in the guselkumab treated groups (8.6% in the 100 mg subcutaneous q4w group and 8.3% in the 100 mg subcutaneous q8w group) than in the placebo group (4.6%). Through 1-year, adverse reactions 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, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the guselkumab q4w group compared with the guselkumab q8w group (Table 2). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 2: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through Week 24[a]			Through 1 year[b]	
	Placebo N=370[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 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 guselkumab are not included.

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

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the guselkumab q8w dose was similar to that observed for the guselkumab q8w dose in the psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled induction period (Week 0-12), adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, and liver function test increased) were reported more frequently in the guselkumab treated groups (1.7% of patients) than in the placebo group (0.6% of patients). In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, adverse reactions 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 guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase II and Phase III Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies. In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled period (Week 12), ALT (< 1% of patients) and AST (< 1% of patients) elevations ≥ 3x ULN were reported in guselkumab treated patients. In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, ALT and/or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.6% of patients in the guselkumab 100 mg subcutaneous 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.

Neutrophil count decreased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, the adverse reaction of decreased neutrophil count was reported more frequently in the guselkumab treated group

(0.9%) than in the placebo group (0%). Through 1 year, the adverse reaction of decreased neutrophil count was reported in 0.9% of patients treated with guselkumab. In most cases, the decrease in blood neutrophil count was mild, transient, not associated with infection and did not lead to discontinuation of treatment.

Gastroenteritis
In two Phase III psoriasis clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the guselkumab treated group (1.1%) than in the placebo group (0.7%). Through Week 264, 5.8% of all guselkumab treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of guselkumab through Week 264. Gastroenteritis rates observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies.

Injection site reactions
In two Phase III psoriasis clinical studies through Week 48, 0.7% of guselkumab injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 264, 0.4% of guselkumab injections were associated with injection site reactions. Injection site reactions were generally mild to moderate in severity; none were serious, and one led to discontinuation of guselkumab.

In two Phase III psoriatic arthritis clinical studies through Week 24, the number of patients that reported 1 or more injection site reactions was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) patients in the guselkumab q8w group, 4 (1.1%) patients in the guselkumab q4w group, and 1 (0.3%) patient in the placebo group. One patient discontinued guselkumab due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Through 1 year, the proportion of patients reporting 1 or more injection site reactions was 1.6% and 2.4% in the guselkumab q8w and q4w groups respectively. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period was similar to rates observed in the psoriasis clinical studies.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group (guselkumab 200 mg was administered as two 100 mg injections in the Phase III ulcerative colitis maintenance clinical study) and no injection site reactions in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and none were serious.

In Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 4.1% (0.8% of injections) in the treatment group which received guselkumab 200 mg intravenous induction followed by 200 mg subcutaneous q4w, and 1.4% (0.6% of injections) of patients in the guselkumab 200 mg intravenous induction followed by 100 mg subcutaneous q8w group. Overall injection site reactions were mild; none were serious.

In a Phase III Crohn's disease clinical study through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7% (1.3% of injections) in the treatment group which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 4.3% (0.7% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Most injection site reactions were mild; none were serious.

Immunogenicity
The immunogenicity of guselkumab was evaluated using a sensitive and drug-tolerant immunoassay.

In pooled Phase II and Phase III analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 8% (n=12) had antibodies that were classified as neutralising, which equates to 0.4% of all patients treated with guselkumab. In pooled

Phase III analyses in patients with psoriasis, approximately 15% of patients treated with guselkumab developed antidrug antibodies in up to 264 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising, which equates to 0.76% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

In pooled Phase II and Phase III analyses in patients with ulcerative colitis who were treated with intravenous induction followed by subcutaneous maintenance, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralising, which equates to 2% of all patients treated with guselkumab. In a Phase III analysis up to Week 24 in patients with ulcerative colitis who were treated with subcutaneous induction followed by subcutaneous maintenance, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or the development of injection site reactions.

In pooled Phase II and Phase III analyses up to Week 48 in patients with Crohn's disease who were treated with intravenous induction followed by subcutaneous maintenance dose regimen, approximately 5% (n=30) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 7% (n=2) had antibodies that were classified as neutralising antibodies, which equates to 0.3% of guselkumab treated patients. In a Phase III analysis up to Week 48 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of these patients, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

Paediatric population

Plaque psoriasis
The safety of guselkumab was assessed in a Phase III placebo- and active-controlled study in paediatric patients with moderate to severe plaque psoriasis. This clinical study evaluated safety for up to 52 weeks in 120 patients 6 to 17 years of age. The safety profile for guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe in paediatric patients 6 to 17 years was consistent with the safety profile reported in the adult plaque psoriasis studies (see section 4.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Guselkumab intravenous doses up to 1 200 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, the patient must be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment must be administered immediately.

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 high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In patients with ulcerative colitis or 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 exerts 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, ulcerative colitis, and Crohn's disease. 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 I 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 patients with plaque psoriasis at Week 12 compared to baseline. In the same Phase I 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 patients in Phase II and Phase III plaque psoriasis studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In psoriatic arthritis patients in Phase III studies, 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 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

In patients with ulcerative colitis or Crohn's disease, guselkumab treatment led to decreases in inflammatory markers including C-reactive protein (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.

Clinical efficacy and safety

Plaque psoriasis
The efficacy and safety of guselkumab was assessed in three randomised, double-blind, active controlled Phase III studies in adult patients with moderate to severe plaque psoriasis, who were candidates for phototherapy or systemic therapy.

VOYAGE 1 and VOYAGE 2
Two studies (VOYAGE 1 and VOYAGE 2) evaluated the efficacy and safety of guselkumab versus placebo and adalimumab in 1 829 adult patients. Patients randomised to guselkumab (N=825) received 100 mg at Weeks 0 and 4, and every 8 weeks (q8w) thereafter through Week 48 (VOYAGE 1) and Week 20 (VOYAGE 2). Patients randomised to adalimumab (N=582) received 80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week (q2w) through Week 48 (VOYAGE 1) and Week 23 (VOYAGE 2). In both studies, patients randomised to placebo (N=422) received guselkumab 100 mg at Weeks 16, 20 and q8w thereafter. In VOYAGE 1, all patients, including those randomised to adalimumab at Week 0, started to receive open-label guselkumab q8w at Week 52. In VOYAGE 2, patients randomised to guselkumab at Week 0 who were Psoriasis Area and Severity Index (PASI) 90 responders at Week 28 were re-randomised to either continue treatment with guselkumab q8w (maintenance treatment) or receive placebo (withdrawal treatment). Withdrawal patients re-initiated guselkumab (dosed at time of retreatment, 4 weeks later and q8w thereafter) when they experienced at least a 50% loss of their Week 28 PASI improvement. Patients randomised to adalimumab at Week 0 who were PASI 90 non-responders received guselkumab at Weeks 28, 32 and q8w thereafter. In VOYAGE 2, all patients started to receive open-label guselkumab q8w at Week 76.

Baseline disease characteristics were consistent for the study populations in VOYAGE 1 and 2 with a median body surface area (BSA) of 22% and 24%, a median baseline PASI score of 19 for both studies, a median baseline dermatology quality of life index (DLQI) score of 14 and 14.5, a baseline investigator global assessment (IGA) score of severe for 25% and 23% of patients, and a history of psoriatic arthritis for 19% and 18% of patients, respectively.

Of all patients included in VOYAGE 1 and 2, 32% and 29% were naïve to both conventional systemic and biologic therapy, 54% and 57% had received prior phototherapy, and 62% and 64% had received prior conventional systemic therapy, respectively. In both studies, 21% had received prior biologic therapy, including 11% who had received at least one anti-tumour necrosis factor alpha (TNFα) agent, and approximately 10% who had received an anti-IL-12/IL-23 agent.

The efficacy of guselkumab was evaluated with respect to overall skin disease, regional disease (scalp, hand and foot and nails) and quality of life and patient reported outcomes. The co-primary endpoints in VOYAGE 1 and 2 were the proportion of patients who achieved an IGA score of cleared or minimal (IGA 0/1) and a PASI 90 response at Week 16 versus placebo (see Table 3).

Overall skin disease
Treatment with guselkumab resulted in significant improvements in the measures of disease activity compared to placebo and adalimumab at Week 16 and compared to adalimumab at Weeks 24 and 48. The key efficacy results for the primary and major secondary study endpoints are shown in Table 3 below.

Table 3: 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)
Week 16						
PASI 75	10 (5.7)	300 (91.2)[a]	244 (73.1)[b]	20 (8.1)	428 (86.3)[a]	170 (68.5)[b]
PASI 90	5 (2.9)	241 (73.3)[c]	166 (49.7)[b]	6 (2.4)	347 (70.0)[c]	116 (46.8)[b]
PASI 100	1 (0.6)	123 (37.4)[a]	57 (17.1)[d]	2 (0.8)	169 (34.1)[a]	51 (20.6)[d]
IGA 0/1	12 (6.9)	280 (85.1)[c]	220 (65.9)[b]	21 (8.5)	417 (84.1)[c]	168 (67.7)[b]
IGA 0	2 (1.1)	157 (47.7)[a]	88 (26.3)[d]	2 (0.8)	215 (43.3)[a]	71 (28.6)[d]
Week 24						
PASI 75	-	300 (91.2)	241 (72.2)[e]	-	442 (89.1)	176 (71.0)[e]
PASI 90	-	264 (80.2)	177 (53.0)[b]	-	373 (75.2)	136 (54.8)[b]
PASI 100	-	146 (44.4)	83 (24.9)[e]	-	219 (44.2)	66 (26.6)[e]
IGA 0/1	-	277 (84.2)	206 (61.7)[b]	-	414 (83.5)	161 (64.9)[b]
IGA 0	-	173 (52.6)	98 (29.3)[b]	-	257 (51.8)	78 (31.5)[b]

Week 48						
PASI 75	-	289 (87.8)	209 (62.6)[e]	-	-	-
PASI 90	-	251 (76.3)	160 (47.9)[b]	-	-	-
PASI 100	-	156 (47.4)	78 (23.4)[e]	-	-	-
IGA 0/1	-	265 (80.5)	185 (55.4)[b]	-	-	-
IGA 0	-	166 (50.5)	86 (25.7)[b]	-	-	-

[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.

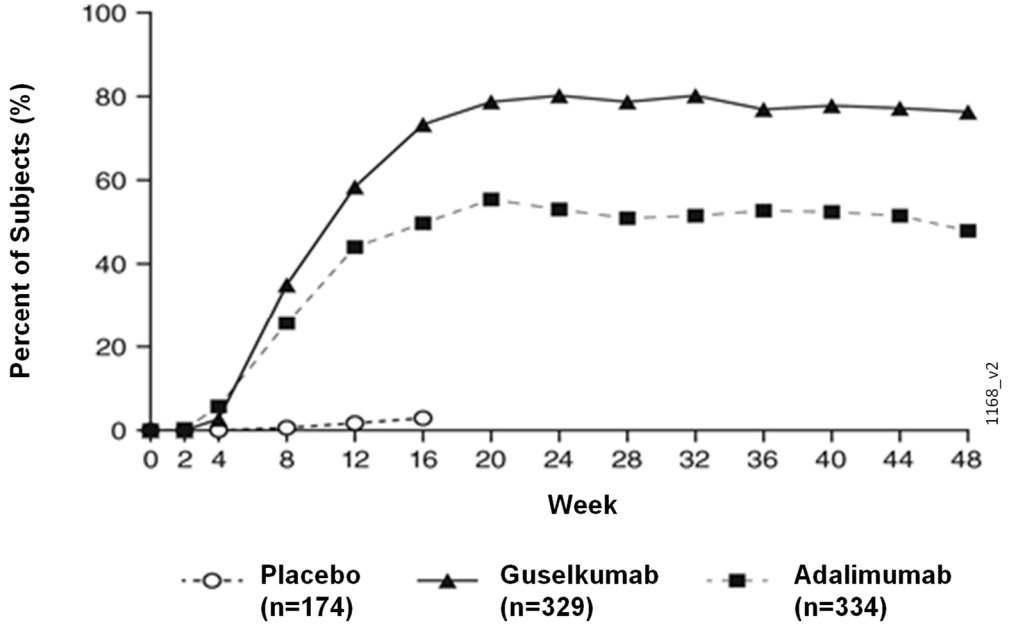
[d] comparisons between guselkumab and adalimumab were not performed.

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

Response over time

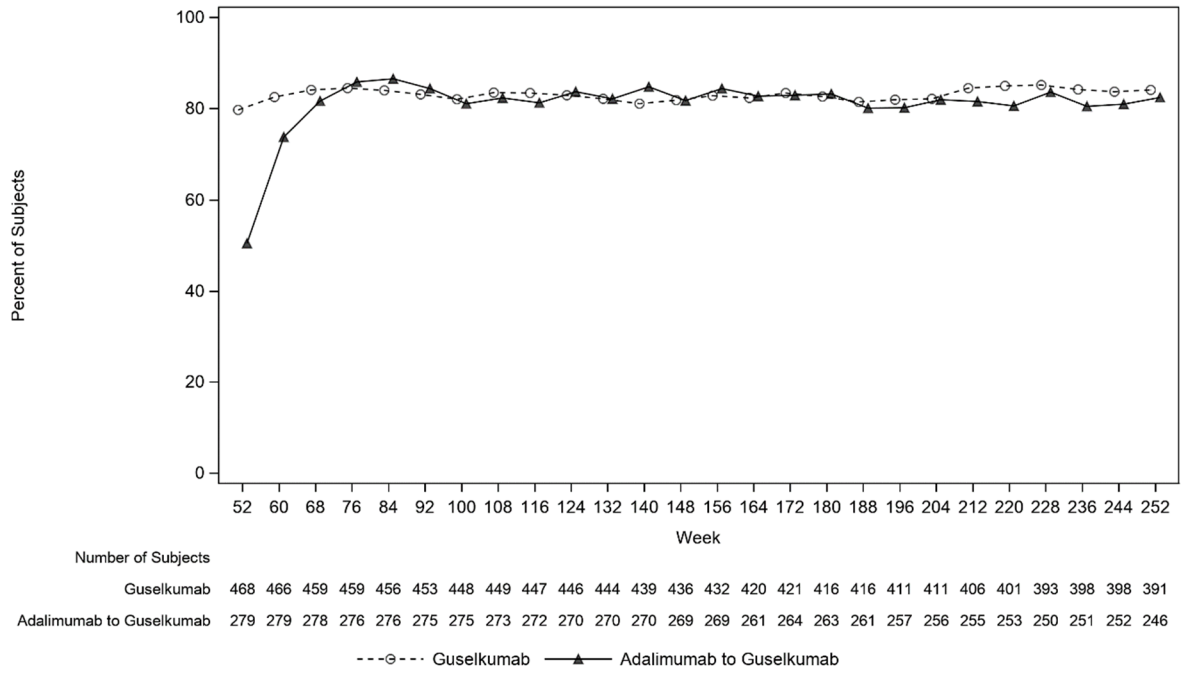
Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 ($p < 0.001$). The percentage of patients achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the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

Figure 1: Percent of patients who achieved a PASI 90 response through week 48 by visit (patients randomised at Week 0) in VOYAGE 1



In VOYAGE 1, for patients receiving continuous guselkumab treatment, the PASI 90 response rate was maintained from Week 52 through Week 252. For patients randomised to adalimumab at Week 0 who crossed over to guselkumab at Week 52, the PASI 90 response rate increased from Week 52 through Week 76 and was then maintained through Week 252 (see Figure 2).

Figure 2: Percent of patients who achieved a PASI 90 response by visit in the open-label phase 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-naïve, biologic-naïve, 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 patients randomised to adalimumab 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. In addition, among 95 patients randomised to guselkumab who failed to achieve a PASI 90 response at Week 28, 36% and 41% achieved a PASI 90 response with an additional 20 and 44 weeks of continued 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 4). 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 4: 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 patients with ss-IGA, f-PGA, hf-PGA score ≥ 2 at baseline or baseline NAPSI score > 0.

[b] Includes only patients 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

Across VOYAGE 1 and 2 significantly greater improvements in health-related quality of life as measured by Dermatology Life Quality Index (DLQI) and in patient-reported psoriasis symptoms (itching, pain, burning, stinging and skin tightness) and signs (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) as measured by the Psoriasis Symptoms and Signs Diary (PSSD) were observed in guselkumab patients compared to placebo patients at Week 16 (Table 5). Signs of improvement on patient-reported outcomes were maintained through Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1). In VOYAGE 1, for patients receiving continuous guselkumab treatment, these improvements were maintained in the open-label phase through Week 252 (Table 6).

Table 5: Summary of patient reported outcomes at week 16 in VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	guselkumab	adalimumab	Placebo	guselkumab	adalimumab
DLQI, patients with baseline score	170	322	328	248	495	247
Change from baseline, mean (standard deviation)						
Week 16	-0.6 (6.4)	-11.2 (7.2)[c]	-9.3 (7.8)[b]	-2.6 (6.9)	-11.3 (6.8)[c]	-9.7 (6.8)[b]
PSSD Symptom score, patients with baseline score > 0	129	248	273	198	410	200
Symptom score = 0, n (%)						
Week 16	1 (0.8)	67 (27.0)[a]	45 (16.5)[b]	0	112 (27.3)[a]	30 (15.0)[b]
PSSD Sign score, patients with baseline score > 0	129	248	274	198	411	201
Sign score = 0, n (%)						
Week 16	0	50 (20.2)[a]	32 (11.7)[b]	0	86 (20.9)[a]	21 (10.4)[b]

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

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

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

Table 6: Summary of patient reported outcomes in the open-label phase in VOYAGE 1

	guselkumab			adalimumab-guselkumab		
	Week 76	Week 156	Week 252	Week 76	Week 156	Week 252
DLQI score > 1 at baseline, n	445	420	374	264	255	235
Patients with DLQI 0/1	337 (75.7%)	308 (73.3%)	272 (72.7%)	198 (75.0%)	190 (74.5%)	174 (74.0%)

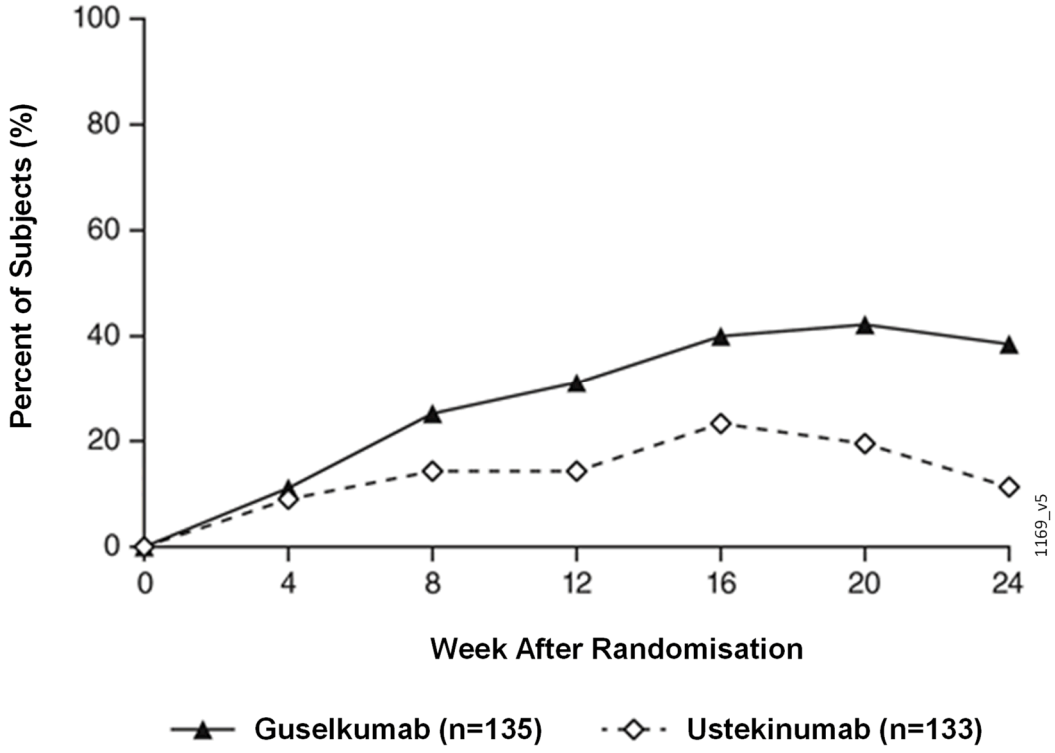
PSSD Symptom Score, patients with baseline score > 0	347	327	297	227	218	200
Symptom score = 0, n (%)	136 (39.2%)	130 (39.8%)	126 (42.4%)	99 (43.6%)	96 (44.0%)	96 (48.0%)
PSSD Sign score, patients with baseline score > 0	347	327	297	228	219	201
Sign score = 0, n (%)	102 (29.4%)	94 (28.7%)	98 (33.0%)	71 (31.1%)	69 (31.5%)	76 (37.8%)

In VOYAGE 2, guselkumab patients had significantly greater improvement from baseline compared to placebo in health-related quality of life, anxiety and depression, and work limitation measures at Week 16, as measured by the 36-item Short Form (SF-36) health survey questionnaire, Hospital Anxiety and Depression Scale (HADS), and Work Limitations Questionnaire (WLQ), respectively. The improvements in SF-36, HADS and WLQ were all maintained through Week 48 and in the open-label phase through Week 252 among patients randomised to maintenance therapy at Week 28.

NAVIGATE
The NAVIGATE study examined the efficacy of guselkumab in patients who had an inadequate response (i.e., who had not achieved a 'cleared' or 'minimal' response defined as IGA ≥ 2) to ustekinumab at Week 16. All patients (N=871) received open-label ustekinumab (45 mg ≤100 kg and 90 mg >100 kg) at Weeks 0 and 4. At Week 16, 268 patients with an IGA ≥ 2 score were randomised to either continue ustekinumab treatment (N=133) q12w, or to initiate guselkumab treatment (N=135) at Weeks 16, 20, and q8w thereafter. Baseline characteristics for randomised patients were similar to those observed in VOYAGE 1 and 2.

After randomisation, the primary endpoint was the number of post-randomisation visits between Weeks 12 and 24 at which patients achieved an IGA score 0/1 and had ≥ 2 grade improvement. Patients were examined at four week intervals for a total of four visits. Among patients who inadequately responded to ustekinumab at the time of randomisation, significantly greater improvement of efficacy was observed in patients who switched to guselkumab treatment compared to patients who continued ustekinumab treatment. Between 12 and 24 weeks after randomisation, guselkumab patients achieved an IGA score 0/1 with ≥ 2 grade improvement twice as often as ustekinumab patients (mean 1.5 vs 0.7 visits, respectively, $p < 0.001$). Additionally, at 12 weeks after randomisation a higher proportion of guselkumab patients compared to ustekinumab patients achieved an IGA score 0/1 and ≥ 2 grade improvement (31.1% vs. 14.3%, respectively; $p = 0.001$) and a PASI 90 response (48% vs 23%, respectively, $p < 0.001$). Differences in response rates between guselkumab and ustekinumab-treated patients were noted as early as 4 weeks after randomisation (11.1% and 9.0%, respectively) and reached a maximum 24 weeks after randomisation (see Figure 3). No new safety findings were observed in patients who switched from ustekinumab to guselkumab.

Figure 3: Percent of patients 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



ECLIPSE
Efficacy and safety of guselkumab were also investigated in a double-blind study compared to secukinumab. Patients were randomised to receive guselkumab (N=534; 100 mg at Week 0, 4 and q8w thereafter), or secukinumab (N=514; 300 mg at Week 0, 1, 2, 3, 4, and q4w thereafter). The last dose was at week 44 for both treatment groups.

Baseline disease characteristics were consistent with a population of moderate to severe plaque psoriasis with a median BSA of 20%, a median PASI score of 18, and an IGA score of severe for 24% of patients.

Guselkumab 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 PASI response rates are presented in Table 7.

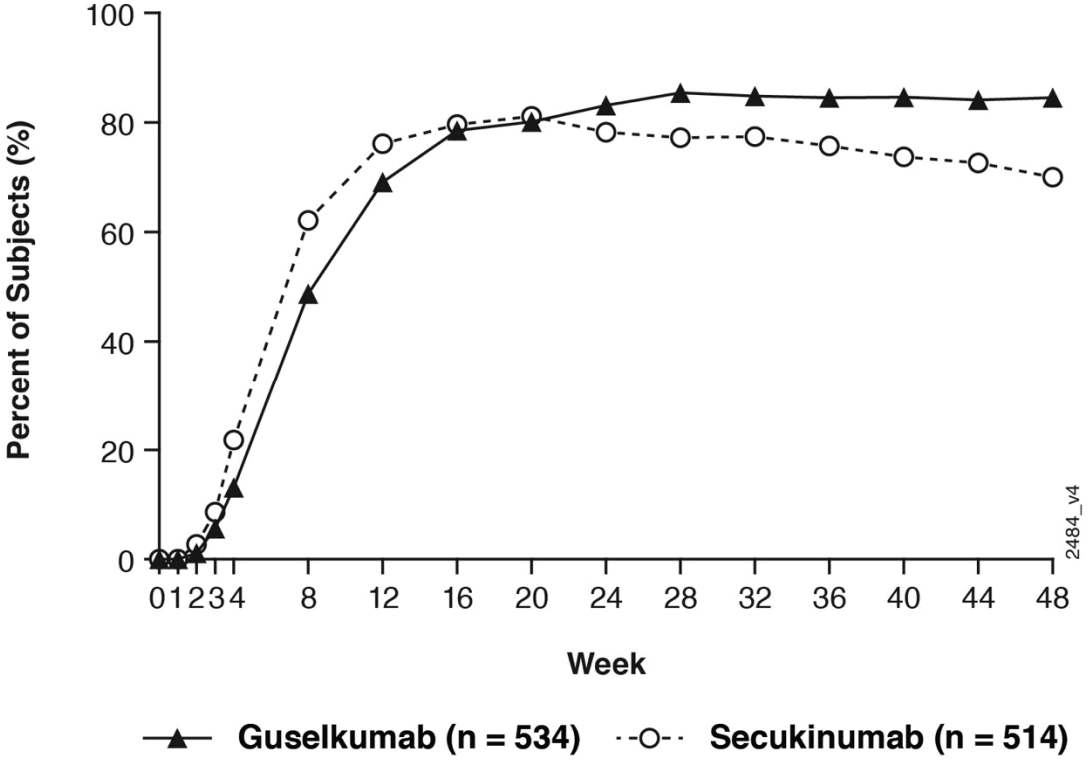
Table 7: PASI response rates in ECLIPSE

	Number of patients (%)	
	guselkumab (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%)

[a] $p < 0.001$ for superiority
[b] $p < 0.001$ for non-inferiority, $p=0.062$ for superiority
[c] formal statistical testing was not performed

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

Figure 4: Percent of patients who achieved a PASI 90 response through week 48 by visit (Patients randomised at Week 0) in ECLIPSE



Psoriatic arthritis (PsA)
Guselkumab has been shown to improve signs and symptoms, physical function and health-related quality of life, and reduce the rate of progression of peripheral joint damage in adult patients with active PsA.

DISCOVER 1 and DISCOVER 2
Two randomised, double-blind, placebo-controlled Phase III studies (DISCOVER 1 and DISCOVER 2) evaluated the efficacy and safety of guselkumab versus placebo in adult patients with active PsA (≥ 3 swollen and ≥ 3 tender joints, and a C-reactive protein (CRP) level of ≥ 0.3 mg/dL in DISCOVER 1, and ≥ 5 swollen and ≥ 5 tender joints, and a CRP level of ≥ 0.6 mg/dL in DISCOVER 2), despite conventional synthetic (cs)DMARD, apremilast, or nonsteroidal anti-inflammatory drug (NSAID) therapy. Patients in these studies had a diagnosis of PsA based on the Classification criteria for Psoriatic Arthritis [CASPAR]) for a median duration of 4 years. 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%). Over 65% and 42% of the patients had enthesitis and dactylitis at baseline, respectively, and over 75% of patients had ≥ 3% BSA psoriasis skin involvement. DISCOVER 1 and DISCOVER 2 evaluated 381 and 739 patients, respectively, who received treatment with guselkumab 100 mg administered at Weeks 0 and 4 followed by every 8 weeks (q8w) or guselkumab 100 mg q4w, or placebo. At Week 24, placebo patients in both studies crossed over to receive guselkumab 100 mg q4w. Approximately 58% of patients in both studies continued on stable doses of MTX (≤ 25 mg/week).

In both studies over 90% of patients had prior csDMARD use. In DISCOVER 1, 31% of patients had previously received anti-TNFα treatment. In DISCOVER 2, all patients were naïve to biologic therapy.

Signs and symptoms
Treatment with guselkumab resulted in significant improvements in the measures of disease activity compared to placebo at Week 24. The primary endpoint in both studies was the percentage of patients

who achieved American College of Rheumatology (ACR) 20 response at Week 24. The key efficacy results are shown in Table 8.

Table 8: Clinical responses in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
	Placebo (N=126)	guselkumab 100 mg q8w (N=127)	guselkumab 100 mg q4w (N=128)	Placebo (N=246)	guselkumab 100 mg q8w (N=248)	guselkumab 100 mg q4w (N=245)
ACR 20 response						
Week 16	25.4%	52.0% [b]	60.2% [b]	33.7%	55.2% [g]	55.9% [c]
Difference from placebo (95% CI)	-	26.7 (15.3, 38.1)	34.8 (23.5, 46.0)	-	21.5 (13.1, 30.0)	22.2 (13.7, 30.7)
Week 24	22.2%	52.0% [a]	59.4% [a]	32.9%	64.1% [a]	63.7% [a]
Difference from placebo (95% CI)	-	29.8 (18.6, 41.1)	37.1 (26.1, 48.2)	-	31.2 (22.9, 39.5)	30.8 (22.4, 39.1)
ACR 50 response						
Week 16	12.7%	22.8% [d]	26.6% [c]	9.3%	28.6% [g]	20.8% [c]
Difference from placebo (95% CI)	-	10.2 (1.0, 19.3)	13.9 (4.4, 23.4)	-	19.3 (12.6, 25.9)	11.5 (5.2, 17.7)
Week 24	8.7%	29.9% [b]	35.9% [b]	14.2%	31.5% [g]	33.1% [c]
Difference from placebo (95% CI)	-	21.4 (12.1, 30.7)	27.2 (17.6, 36.8)	-	17.2 (10.0, 24.4)	18.8 (11.5, 26.1)
ACR 70 response						
Week 24	5.6%	11.8% [d]	20.3% [b]	4.1%	18.5% [g]	13.1% [c]
Difference from placebo (95% CI)	-	6.4 (-0.3, 13.1)	14.8 (6.9, 22.7)	-	14.5 (9.1, 19.9)	9.0 (4.1, 13.8)
DAS 28 (CRP) LSMean change[i] from baseline						
Week 24[c]	-0.70	-1.43[b]	-1.61[b]	-0.97	-1.59[b]	-1.62[b]
Difference from placebo (95% CI)	-	-0.73 (-0.98, -0.48)	-0.91 (-1.16, -0.66)	-	-0.61 (-0.80, -0.43)	-0.65 (-0.83, -0.47)
Minimal Disease Activity (MDA)						
Week 24	11.1%	22.8% [f]	30.5% [e]	6.1%	25.0% [e]	18.8% [e]
Difference from placebo (95% CI)	-	11.9 (2.9, 20.9)	19.3 (9.7, 28.9)	-	18.9 (12.8, 25.0)	12.7 (7.0, 18.4)
Patients with ≥ 3% BSA and IGA ≥ 2	n=78	n=82	n=89	n=183	n=176	n=184
IGA response [h]						
Week 24	15.4%	57.3% [b]	75.3% [b]	19.1%	70.5% [b]	68.5% [b]
Difference from placebo (95% CI)	-	42.0 (28.9, 55.1)	60.0 (48.3, 71.8)	-	50.9 (42.2, 59.7)	49.8 (41.2, 58.4)
PASI 90 response						
Week 16	10.3%	45.1% [e]	52.8% [e]	8.2%	55.1% [e]	53.8% [e]
Difference from placebo (95% CI)	-	34.9 (22.2, 47.6)	42.6 (30.5, 54.8)	-	46.6 (38.4, 54.8)	45.6 (37.6, 53.6)
Week 24	11.5%	50.0% [e]	62.9% [e]	9.8%	68.8% [e]	60.9% [e]
Difference from placebo (95% CI)	-	38.6 (25.8, 51.4)	51.7 (39.7, 63.7)	-	58.6 (50.6, 66.6)	51.3 (43.2, 59.3)

[a] $p < 0.001$ (primary endpoint)

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

[c] $p = 0.006$ (major secondary endpoint)

[d] not statistically significant p=0.086 (major secondary endpoint)

[e] nominal $p < 0.001$

[f] nominal $p = 0.012$

[g] not formally tested in the hierarchical testing procedure, nominal $p < 0.001$ (major secondary endpoint)

[h] defined as a IGA response of 0 (cleared) or 1 (minimal) and ≥ 2-grade reduction from baseline in the IGA psoriasis score

[i] LSmean change = least squares mean change

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 in DISCOVER 1 and DISCOVER 2 (see Table 9).

Table 9: Clinical responses in DISCOVER 1 and DISCOVER 2 at week 52[a]

	DISCOVER 1		DISCOVER 2	
	guselkumab 100 mg q8w	guselkumab 100 mg q4w	guselkumab 100 mg q8w	guselkumab 100 mg q4w
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%
DAS 28 (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 patients with an observed response status.

[c] Patients have an observed change from baseline.

Clinical response was maintained up to Week 100 as assessed by ACR 20/50/70, DAS 28 (CRP), MDA, IGA and PASI 90 response rates in DISCOVER 2 (see Table 10).

Table 10: Clinical responses in DISCOVER 2 at week 100[a]

	guselkumab 100 mg q8w	guselkumab 100 mg q4w
ACR 20		
N[b]	223	219
% Response	82.1%	84.9%
ACR 50		
N[b]	224	220
% Response	60.7%	62.3%

ACR 70		
N[b]	224	220
% Response	39.3%	38.6%
DAS 28 (CRP) change from baseline		
N[c]	223	219
Mean (SD)	-2.37 (1.215)	-2.36 (1.120)
MDA		
N[b]	224	220
% Response	44.6%	42.7%
Patients with ≥ 3% BSA and IGA ≥ 2 at baseline		
IGA Response		
N[b]	165	170
% Response	76.4%	82.4%
PASI 90		
N[b]	164	170
% Response	75.0%	80.0%

[a] There was no placebo arm beyond Week 24.

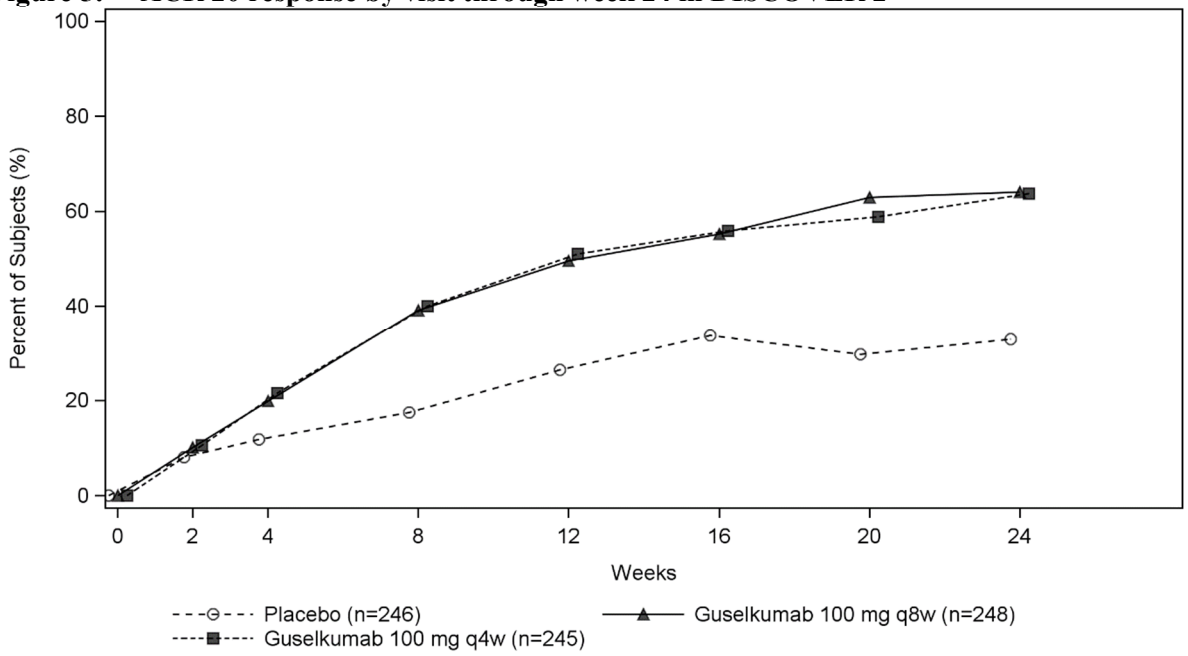
[b] Evaluable patients with an observed response status.

[c] Patients have an observed change from baseline.

Response over time

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

Figure 5: ACR 20 response by visit through week 24 in DISCOVER 2



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

Figure 6: ACR 20 response by visit from week 24 through week 52 in DISCOVER 2

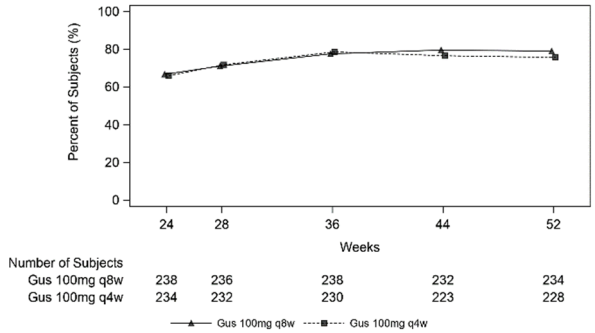
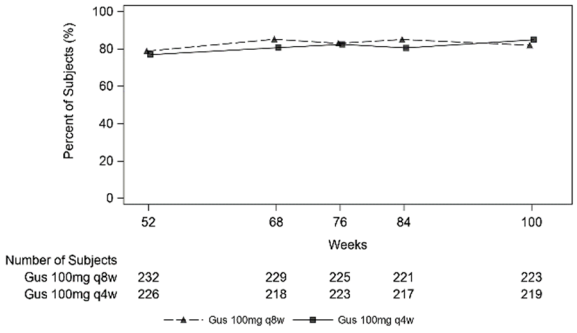


Figure 7: ACR 20 response by visit from week 52 through week 100 in DISCOVER 2



Responses observed in the guselkumab groups were similar regardless of concomitant csDMARD use, including MTX (DISCOVER 1 and 2). Additionally, examination of age, gender, race, body weight, and previous csDMARD use (DISCOVER 1 and 2) and previous anti-TNFα use (DISCOVER 1), did not identify differences in response to guselkumab among these subgroups.

In DISCOVER 1 and 2, improvements were shown in all components of the ACR scores including patient assessment of pain. At Week 24 in both studies, the proportion of patients achieving a modified PsA response criteria (PsARC) response was greater in the guselkumab groups compared to placebo. PsARC responses were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Dactylitis and enthesitis were assessed based on pooled data from DISCOVER 1 and 2. At Week 24, among patients with dactylitis at baseline, the proportion of patients with dactylitis resolution was greater in the guselkumab q8w group (59.4%, nominal $p < 0.001$) and q4w group (63.5%, $p = 0.006$) compared to placebo (42.2%). At Week 24, among patients with enthesitis at baseline, the proportion of patients with enthesitis resolution was greater in the guselkumab q8w group (49.6%, nominal $p < 0.001$) and q4w group (44.9%, $p = 0.006$) compared to placebo (29.4%). At Week 52, the proportions of patients with dactylitis resolution (81.2% in q8w group and 80.4% in q4w group) and enthesitis resolution (62.7% in q8w group and 60.9% in q4w group) were maintained. In DISCOVER 2, among patients with dactylitis and enthesitis at baseline, the proportion of patients with dactylitis resolution (91.1% in q8w group and 82.9% in q4w group) and enthesitis resolution (77.5% in q8w group and 67.7% in q4w group) were maintained at Week 100.

In DISCOVER 1 and 2, patients treated with guselkumab 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.

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, the guselkumab q4w group demonstrated statistically significantly less radiographic progression and the guselkumab q8w group showed numerically less progression than placebo (Table 11). The observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (i.e., smaller mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in patients with both a high C-reactive protein value and high number of joints with erosions at baseline.

Table 11: Change from baseline in total modified vdH-S score at week 24 in DISCOVER 2

	N	LSMean change[c] (95% CI[d]) from baseline in modified vdH-S score at Week 24
Placebo	246	0.95 (0.61, 1.29)
guselkumab 100 mg q8w	248	0.52[a] (0.18, 0.86)
guselkumab 100 mg q4w	245	0.29[b] (-0.05, 0.63)

[a] not statistically significant p = 0.068 (major secondary endpoint).

[b] p = 0.006 (major secondary endpoint).

[c] LSmean change = least squares mean change.

[d] CI = confidence interval.

At Week 52 and Week 100, the mean change from baseline in total modified vdH-S was similar in the guselkumab q8w and q4w groups (Table 12).

Table 12: Change from baseline in total modified vdH-S score at week 52 and week 100 in DISCOVER 2

	N[a]	Mean change (SD[b]) from baseline in total modified vdH-S score
Week 52		
guselkumab 100 mg q8w	235	0.97 (3.623)
guselkumab 100 mg q4w	229	1.07 (3.843)
Week 100		
guselkumab 100 mg q8w	216	1.50 (4.393)
guselkumab 100 mg q4w	211	1.68 (7.018)

[a] Evaluable patients have observed change for the specified time period

[b] SD = standard deviation

Note: no placebo group beyond Week 24

Physical function and health-related quality of life

In DISCOVER 1 and 2, guselkumab treated patients showed significant improvement ($p < 0.001$) in physical function compared to placebo as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

A significantly greater improvement from baseline in the SF-36 Physical Component Summary (PCS) score was observed in guselkumab treated patients compared to placebo at Week 24 in DISCOVER 1 ($p < 0.001$ for both dose groups) and DISCOVER 2 ($p = 0.006$ for q4w group). At Week 24, a greater 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 studies. In DISCOVER 2, greater improvements in health-related quality of life as measured by the Dermatology Life Quality Index (DLQI) were observed in guselkumab treated patients compared to placebo at Week 24. Improvements in SF-36 PCS, FACIT-F and DLQI scores were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

Ulcerative colitis

The efficacy and safety of guselkumab were evaluated in three Phase III multicentre, randomised, double-blind, placebo-controlled studies (QUASAR intravenous induction study, QUASAR maintenance study, and ASTRO subcutaneous induction 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 (AZA, 6-MP), biologic therapy (TNF blockers, vedolizumab), a Janus kinase (JAK) inhibitor, and/or sphingosine-1-phosphate receptor modulators (S1PRM) applicable only for ASTRO. In addition, efficacy and safety of guselkumab were evaluated in a randomised, double-blind, placebo-controlled, Phase IIb induction dose-finding study (QUASAR induction dose-ranging study) that enrolled a similar ulcerative colitis patient population as the Phase III induction 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 ≥ 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).

Induction study: QUASAR IS
In the induction study QUASAR IS, patients were randomised in a 3:2 ratio to receive either guselkumab 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 and 1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, MTX, 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, 87.5%, 54.1% and 18% had previously failed a TNF blocker, vedolizumab or a JAK inhibitor, respectively, and 47.4% 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, fatigue response and IBDQ remission (Table 13).

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

Table 13: Proportion of patients meeting efficacy endpoints at Week 12 in QUASAR IS

Endpoint	Placebo %	Guselkumab 200 mg intravenous induction[a] %	Treatment Difference (95% CI)
Clinical remission[b]			
Total population	8% (N=280)	23% (N=421)	15% (10%, 20%)[c]
Biologic and JAK inhibitor naïve[d]	12% (N=137)	32% (N=202)	20% (12%, 28%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 14%)
Symptomatic remission[f]			
Total population	21% (N=280)	50% (N=421)	29% (23%, 36%)[c]
Biologic and JAK inhibitor naïve[d]	26% (N=137)	60% (N=202)	34% (24%, 44%)
Prior biologic and/or JAK inhibitor failure[e]	14% (N=136)	38% (N=208)	24% (16%, 33%)
Endoscopic healing[g]			
Total population	11% (N=280)	27% (N=421)	16% (10%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	17% (N=137)	38% (N=202)	21% (12%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	5% (N=136)	15% (N=208)	10% (4%, 16%)
Clinical response[h]			
Total population	28% (N=280)	62% (N=421)	34% (27%, 41%)[c]

Biologic and JAK inhibitor naïve[d]	35% (N=137)	71% (N=202)	36% (26%, 46%)
Prior biologic and/or JAK inhibitor failure[e]	20% (N=136)	51% (N=208)	32% (22%, 41%)
Histologic endoscopic mucosal healing[i]			
Total Population	8% (N=280)	24% (N=421)	16% (11%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	11% (N=137)	33% (N=202)	22% (13%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 15%)
Fatigue response[j]			
Total population	21% (N=280)	41% (N=421)	20% (13%, 26%)[c]
Biologic and JAK inhibitor naïve[d]	29% (N=137)	42% (N=202)	12% (2%, 23%)
Prior biologic and/or JAK inhibitor failure[e]	13% (N=136)	38% (N=208)	25% (17%, 34%)
IBDQ remission[k]			
Total population	30% (N=280)	51% (N=421)	22% (15%, 29%)[c]
Biologic and JAK inhibitor naïve[d]	34% (N=137)	62% (N=202)	28% (18%, 38%)
Prior biologic and/or JAK inhibitor failure[e]	24% (N=136)	39% (N=208)	15% (5%, 25%)

[a] Guselkumab 200 mg as an intravenous induction 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.

[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 patients in the placebo group and 11 patients in the guselkumab 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.

[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.

[k] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

QUASAR IS and QUASAR induction dose-ranging study also enrolled 48 patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥ 1. In patients with a baseline mMS of 4, guselkumab 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 ulcerative colitis population.

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

Maintenance study: QUASAR MS
The QUASAR MS evaluated 568 patients who achieved clinical response at 12 weeks following the intravenous administration of guselkumab in either QUASAR IS or from the QUASAR induction dose-ranging study. In the QUASAR MS, these patients were randomised to receive a subcutaneous maintenance regimen of either guselkumab 100 mg every 8 weeks, guselkumab 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, fatigue response and IBDQ remission (Table 14).

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

Table 14: Proportion of patients meeting efficacy endpoints at Week 44 in QUASAR MS

Endpoint	Placebo %	Guselkumab 100 mg q8w subcutaneous injection[a] %	Guselkumab 200 mg q4w subcutaneous injection[b] %	Treatment Difference (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[c]					
Total population[d]	19% (N=190)	45% (N=188)	50% (N=190)	25% (16%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	58% (N=96)	24% (12%, 36%)	29% (17%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	40% (N=77)	40% (N=88)	30% (19%, 42%)	32% (21%, 44%)
Symptomatic remission[h]					
Total population[d]	37% (N=190)	70% (N=188)	69% (N=190)	32% (23%, 41%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	46% (N=108)	74% (N=105)	76% (N=96)	28% (15%, 40%)	28% (15%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	24% (N=75)	65% (N=77)	60% (N=88)	39% (26%, 52%)	37% (23%, 50%)
Corticosteroid-free clinical remission[i]					
Total population[d]	18% (N=190)	45% (N=188)	49% (N=190)	26% (17%, 34%)[e]	29% (20%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	56% (N=96)	24% (12%, 36%)	27% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	7% (N=75)	40% (N=77)	40% (N=88)	32% (21%, 43%)	34% (23%, 45%)
Endoscopic healing[j]					
Total population[d]	19% (N=190)	49% (N=188)	52% (N=190)	30% (21%, 38%)[e]	31% (22%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	53% (N=105)	59% (N=96)	27% (15%, 40%)	30% (18%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	45% (N=77)	42% (N=88)	36% (24%, 48%)	35% (23%, 46%)
Histologic endoscopic mucosal healing[k]					
Total population[d]	17% (N=190)	44% (N=188)	48% (N=190)	26% (17%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	23% (N=108)	50% (N=105)	56% (N=96)	26% (14%, 38%)	30% (17%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	38% (N=77)	39% (N=88)	28% (16%, 39%)	31% (20%, 43%)
Clinical response[l]					
Total population[d]	43% (N=190)	78% (N=188)	75% (N=190)	34% (25%, 43%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	54% (N=108)	83% (N=105)	81% (N=96)	29% (17%, 41%)	26% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	28% (N=75)	70% (N=77)	67% (N=88)	41% (27%, 54%)	39% (26%, 53%)

Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population[q]	34% (N=59)	61% (N=66)	72% (N=69)	26% (9%, 43%)[m]	38% (23%, 54%)[e]
Biologic and JAK-inhibitor naïve[r]	34% (N=41)	65% (N=43)	79% (N=48)	31% (9%, 51%)	45% (25%, 62%)
Prior biologic and/or JAK-inhibitor failure[g]	27% (N=15)	60% (N=20)	56% (N=18)	33% (-1%, 62%)	29% (-6%, 59%)
Endoscopic normalisation[n]					
Total population[d]	15% (N=190)	35% (N=188)	34% (N=190)	18% (10%, 27%)[e]	17% (9%, 25%)[e]
Biologic and JAK-inhibitor naïve [f]	20% (N=108)	38% (N=105)	42% (N=96)	17% (6%, 29%)	17% (6%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	31% (N=77)	24% (N=88)	21% (10%, 33%)	16% (6%, 26%)
Fatigue response[o]					
Total population [d]	29% (N=190)	51% (N=188)	43% (N=190)	20% (11%, 29%)[e]	13% (3%, 22%)[m]
Biologic and JAK-inhibitor naïve[f]	36% (N=108)	51% (N=105)	53% (N=96)	15% (2%, 28%)	16% (3%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	47% (N=77)	32% (N=88)	27% (13%, 40%)	13% (1%, 26%)
IBDQ remission[p]					
Total population[d]	37% (N=190)	64% (N=188)	64% (N=190)	26% (17%, 36%)[e]	26% (16%, 35%)[e]
Biologic and JAK-inhibitor naïve [f]	49% (N=108)	68% (N=105)	74% (N=96)	19% (6%, 32%)	24% (11%, 37%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	58% (N=77)	53% (N=88)	38% (26%, 50%)	35% (23%, 48%)

[a] Guselkumab 100 mg as a subcutaneous injection every 8 weeks after the induction regimen.

[b] Guselkumab 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.

[d] Patients who achieved clinical response 12 weeks following the intravenous administration of guselkumab 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 patients in the placebo group, 6 patients in the guselkumab 100 mg group, and 6 patients in the guselkumab 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.

[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.

[p] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

[q] Subjects who achieved clinical remission 12 weeks following intravenous administration of guselkumab in either QUASAR induction study or QUASAR induction dose-ranging study.

[r] An additional 3 patients in the placebo group, 3 patients in the guselkumab 100 mg group, and 3 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic or JAK inhibitor.

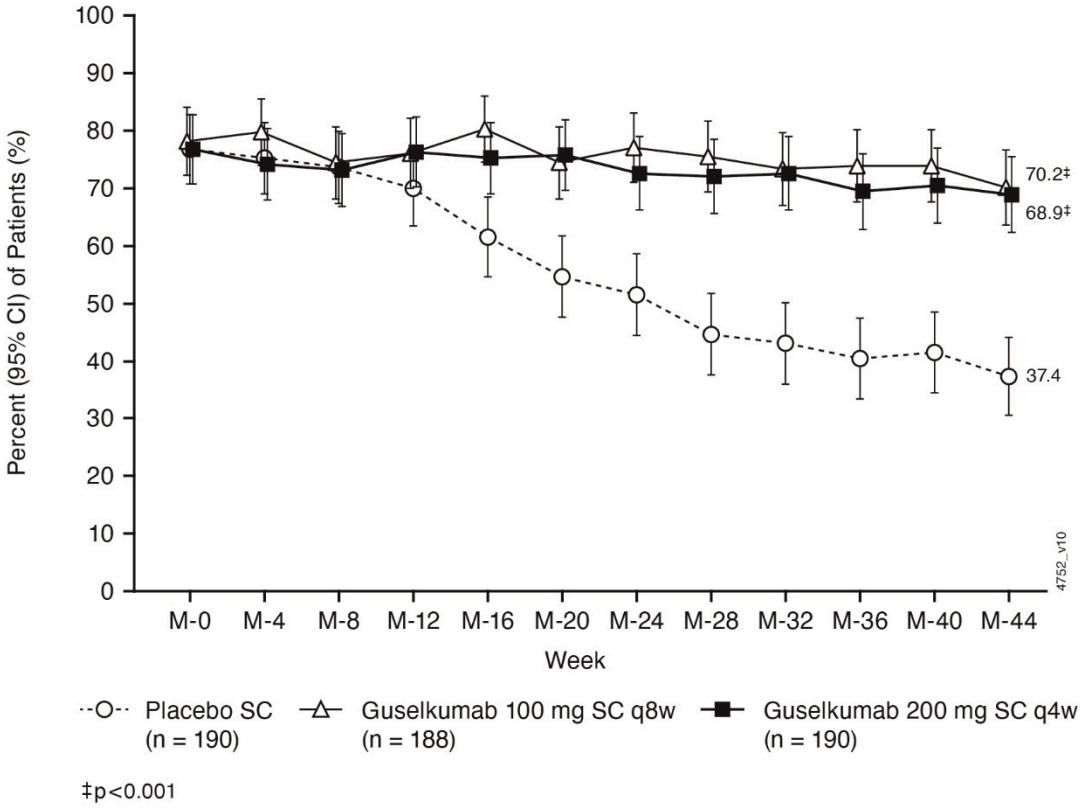
In QUASAR IS and QUASAR MS, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race, body weight, and previous treatment with a biologic therapy or JAK inhibitor.

In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of > 15% were observed between the two guselkumab 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).

QUASAR MS enrolled 31 patients with an induction 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 guselkumab in QUASAR IS or QUASAR induction dose-ranging study. In these patients, guselkumab efficacy relative to placebo as measured by clinical remission, clinical response, and endoscopic healing at Week 44 was consistent with the total population.

Symptomatic remission over time
In QUASAR MS symptomatic remission defined as 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 guselkumab 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 guselkumab extended treatment
Guselkumab treated patients who were not in clinical response at induction Week 12, received guselkumab 200 mg subcutaneous at Weeks 12, 16 and 20. In QUASAR IS, 66/120 (55%) guselkumab treated patients who were not in clinical response at induction Week 12 achieved clinical response at Week 24. Week 24 responders to guselkumab entered QUASAR MS and received

guselkumab 200 mg subcutaneous every 4 weeks. At Week 44 of QUASAR MS, 83/123 (67%) of these patients maintained clinical response and 37/123 (30%) achieved clinical remission.

Recapture of efficacy after loss of response to guselkumab
Nineteen patients receiving guselkumab 100 mg subcutaneous q8w who experienced a first loss of response (10%) between Week 8 and 32 of QUASAR MS received blinded guselkumab dosing with 200 mg guselkumab subcutaneous q4w 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). In QUASAR IS, histologic remission at Week 12 was achieved in 40% of patients treated with guselkumab and 19% of patients in the placebo group. In QUASAR MS, histologic remission at Week 44 was achieved in 59% and 61% of patients treated with guselkumab 100 mg subcutaneous q8w and guselkumab 200 mg subcutaneous q4w and 27% of patients in the placebo group.

Normalisation of the endoscopic appearance of the mucosa was defined as ES of 0. In QUASAR IS, endoscopic normalisation at Week 12 was achieved in 15% of patients treated with guselkumab and 5% of patients in the placebo group.

Composite histologic-endoscopic mucosal outcomes
Combined symptomatic remission, endoscopic normalisation, histologic remission, and faecal calprotectin ≤ 250 mg/kg at Week 44 was achieved by a greater proportion of patients treated with guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (22% and 28% vs 9%, respectively).

Health-related quality of life
At Week 12 of QUASAR IS, patients receiving guselkumab showed greater and clinically meaningful improvements from baseline when compared with placebo in inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score, and all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function). These improvements were maintained in guselkumab treated patients in QUASAR MS through Week 44.

Ulcerative colitis related hospitalisations
Through Week 12 of QUASAR IS, lower proportions of patients in the guselkumab group compared with the placebo group had ulcerative colitis-related hospitalisations (1.9%, 8/421 vs. 5.4%, 15/280).

ASTRO
In ASTRO, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg subcutaneous maintenance every 8 weeks; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg subcutaneous maintenance every 4 weeks; or placebo.

A total of 418 patients were evaluated. The median age of patients was 40 years (ranging from 18 to 80 years); 38.8% were female; and 64.6% identified as White, 28.9% as Asian, and 3.1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, immunomodulators (AZA, 6-MP, MTX), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 77.3% of patients were receiving aminosalicylates, 20.1% of patients were receiving immunomodulators, and 32.8% of patients were receiving corticosteroids. Concomitant biologic therapies, JAK inhibitors, or S1PRMs were not permitted. A total of 40.2% of patients had previously failed treatment with at least one biologic therapy, JAK inhibitor, and/or S1PRM, 58.1% were biologic, JAK inhibitor, and S1PRM naïve, and 1.7% had previously received but had not failed a biologic, JAK inhibitor, or S1PRM.

In ASTRO, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included symptomatic remission, endoscopic healing, clinical response and histologic-endoscopic mucosal healing (see Table 15). Secondary endpoints at Week 24 included clinical remission and endoscopic healing (see Table 16).

Table 15: Proportion of patients meeting efficacy endpoints at Week 12 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg Subcutaneous Induction[a] %	Treatment Difference vs Placebo (95% CI)[b]
Clinical remission[c]			
Total Population	6% (N=139)	28% (N=279)	21% (15%, 28%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	9% (N=79)	36% (N=164)	27% (18%, 37%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	4% (N=56)	16% (N=112)	12% (3%, 20%)
Symptomatic remission[d]			
Total Population	21% (N=139)	51% (N=279)	30% (22%, 39%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	25% (N=79)	59% (N=164)	34% (22%, 46%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	14% (N=56)	41% (N=112)	26% (13%, 39%)
Endoscopic healing[h]			
Total Population	13% (N=139)	37% (N=279)	24% (17%, 32%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	46% (N=164)	28% (17%, 40%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	24% (N=112)	16% (6%, 26%)
Clinical response[i]			
Total Population	35% (N=139)	66% (N=279)	31% (22%, 40%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	42% (N=79)	71% (N=164)	30% (17%, 43%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	25% (N=56)	57% (N=112)	31% (17%, 45%)
Histologic endoscopic mucosal healing[j]			
Total Population	11% (N=139)	30% (N=279)	20% (12%, 27%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	14% (N=79)	38% (N=164)	25% (14%, 35%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	19% (N=112)	11% (1%, 20%)

[a] Guselkumab 400 mg subcutaneous induction at Week 0, Week 4, and Week 8

[b] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[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

[d] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group and 3 patients in the guselkumab group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

[i] Decrease from 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

[j] An endoscopy subscore of 0, or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Table 16: Proportion of patients meeting efficacy endpoints at Week 24 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg SC induction→ 100 mg q8w Subcutaneous Injection[a] %	Guselkumab 400 mg SC induction→ 200 mg q4w Subcutaneous Injection[b] %	Treatment Difference vs Placebo (95% CI)[c]	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[d]					
Total population	9% (N=139)	35% (N=139)	36% (N=140)	26% (17%, 35%)[e]	27% (18%, 36%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	13% (N=79)	49% (N=81)	43% (N=83)	37% (24%, 50%)	31% (18%, 44%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	16% (N=57)	27% (N=55)	10% (-1%, 21%)	21% (9%, 34%)
Endoscopic healing[h]					
Total population	12% (N=139)	40% (N=139)	45% (N=140)	28% (18%, 38%)[e]	33% (23%, 42%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	54% (N=81)	52% (N=83)	37% (23%, 51%)	34% (21%, 48%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	19% (N=57)	36% (N=55)	13% (1%, 25%)	30% (17%, 44%)

[a] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks

[b] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg SC maintenance every 4 weeks

[c] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[d] 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

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group, 1 patient in the guselkumab 100 mg group, and 2 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

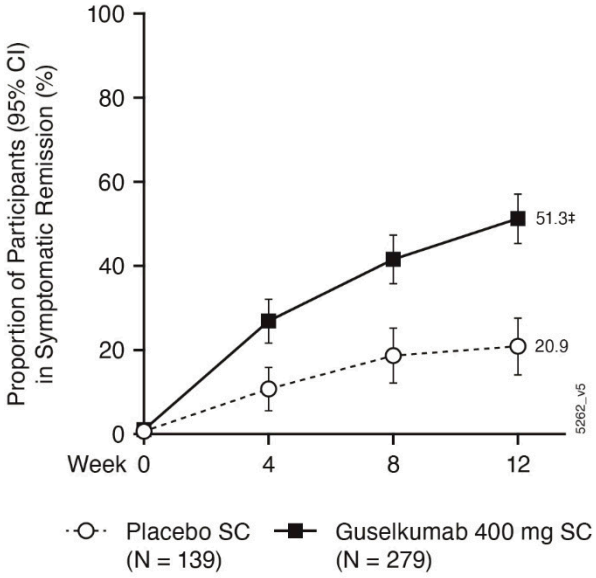
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

Symptomatic remission over time

In ASTRO, symptomatic remission defined as stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0 observed through Week 12, a greater proportion of patients in the guselkumab treatment groups achieved symptomatic remission compared with the placebo group (Figure 9):

Figure 9: Proportion of patients in symptomatic remission through Week 12 in ASTRO



‡p<0.001

Rectal bleeding and stool frequency subscores
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with guselkumab compared to placebo.

Histologic and endoscopic assessment
Histologic remission at Week 12 was achieved in 44% of patients treated with guselkumab 400 mg subcutaneous induction compared to 20% of patients on placebo.

Endoscopic normalisation at Week 24 was achieved in 21% and 26% of patients treated with guselkumab 400 mg subcutaneous induction, followed by guselkumab 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or guselkumab 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter, respectively, compared to 4% of patients on placebo.

Abdominal pain and bowel urgency
A greater proportion of patients treated with guselkumab 400 mg subcutaneous induction compared to placebo had no abdominal pain (56% vs 31%), and no bowel urgency (49% vs 24%) at Week 12.

Health-related quality of life
Disease-specific health-related quality of life was assessed with the IBDQ. A greater proportion of patients in the combined 400 mg SC guselkumab group (61%) achieved IBDQ remission at Week 12 compared with the placebo group (34%).

Crohn's disease
The efficacy and safety of guselkumab were evaluated in three Phase III clinical studies 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 active-controlled (ustekinumab), parallel group studies (GALAXI 2 and GALAXI 3) and one 24-Week multicentre, randomised, double-blind, placebo-controlled, parallel group study (GRAVITI). All three studies had a treat-through study design: patients randomised to guselkumab (or ustekinumab for GALAXI 2 and GALAXI 3) maintained that treatment assignment for the duration of the study.

GALAXI 2 and GALAXI 3
In the Phase III studies GALAXI 2 and GALAXI 3, 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). Additional criteria for GALAXI 2/3 included a mean daily stool frequency (SF) > 3 or mean daily abdominal pain score (AP) > 1.

In GALAXI 2 and GALAXI 3 studies, patients were randomised in a 2:2:2:1 ratio to receive guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg subcutaneous q4w maintenance; or guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8, followed by guselkumab 100 mg subcutaneous q8w maintenance; or ustekinumab approximately 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w maintenance; or placebo. Placebo non-responders received ustekinumab 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), 57.6% were male; and 74.3% identified as White, 21.3% as Asian and 1.5% as Black.

In GALAXI 2, 52.8% of patients had previously failed treatment with at least one biologic therapy (50.6% were intolerant or failed at least 1 prior anti-TNFα therapy, 7.5% were intolerant or failed prior vedolizumab 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 (50.3% were intolerant or failed at least 1 prior anti-TNFα therapy, 9.6% were intolerant or failed prior vedolizumab 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.

The results of the co-primary and major secondary endpoints compared to placebo in GALAXI 2 and GALAXI 3 are presented in Tables 17 (Week 12) and 18 (Week 48). The results of the major secondary endpoints at Week 48 compared to ustekinumab are presented in Tables 19 and 20.

Table 17: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GALAXI 2 and GALAXI 3

	GALAXI 2		GALAXI 3	
	Placebo %	Guselkumab intravenous induction[a] %	Placebo %	Guselkumab intravenous induction[a] %
Co-primary efficacy endpoints				
Clinical remission[b] at Week 12				
Total population	22% (N=76)	47%[i] (N=289)	15% (N=72)	47%[i] (N=293)
Biologic naïve[c]	18% (N=34)	50% (N=121)	15% (N=27)	50% (N=123)
Prior biologic failure[d]	23% (N=39)	45% (N=150)	15% (N=39)	47% (N=150)
Endoscopic response[e] at Week 12				
Total population	11% (N=76)	38%[i] (N=289)	14% (N=72)	36%[i] (N=293)
Biologic naïve[c]	15% (N=34)	51% (N=121)	22% (N=27)	41% (N=123)
Prior biologic failure[d]	5% (N=39)	27% (N=150)	8% (N=39)	31% (N=150)
Major secondary efficacy endpoints				
PRO-2 remission[f] at Week 12				
Total population	21% (N=76)	43%[i] (N=289)	14% (N=72)	42%[i] (N=293)
Biologic naïve[c]	24% (N=34)	43% (N=121)	15% (N=27)	47% (N=123)
Prior biologic failure[d]	13% (N=39)	41% (N=150)	13% (N=39)	39% (N=150)
Fatigue response[g] at Week 12				
Total population	29% (N=76)	45%[j] (N=289)	18% (N=72)	43%[i] (N=293)
Biologic naïve[c]	32% (N=34)	48% (N=121)	19% (N=27)	46% (N=123)
Prior biologic failure[d]	26% (N=39)	41% (N=150)	18% (N=39)	43% (N=150)
Endoscopic remission[h] at Week 12				
Total population	1% (N=76)	15% (N=289)	8% (N=72)	16% (N=293)
Biologic naïve[c]	3% (N=34)	22% (N=121)	19% (N=27)	25% (N=123)
Prior biologic failure[d]	0% (N=39)	9% (N=150)	0% (N=39)	9% (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 – Two guselkumab treatment groups were combined for this column as patients received the same intravenous induction dose regimen prior to Week 12.

[b] Clinical remission is defined as CDAI score < 150.

[c] An additional 9 patients in the placebo group and 38 patients in the guselkumab 200 mg intravenous group were previously exposed to but did not fail a biological therapy.

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

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

[f] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

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

[h] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] $p < 0.001$

[j] $p < 0.05$

Table 18: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus placebo at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Placebo	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]	Placebo (N=72)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]
Corticosteroid-free clinical remission[c] at Week 48[f]						
Total population	12% (N=76)	45%[e] (N=143)	51%[e] (N=146)	14% (N=72)	44%[e] (N=143)	48%[e] (N=150)
Endoscopic response[d] at Week 48[f]						
Total population	7% (N=76)	38%[e] (N=143)	38%[e] (N=146)	6% (N=72)	33%[e] (N=143)	36%[e] (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[c] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

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

[e] $p < 0.001$

[f] Participants who met inadequate response criteria at Week 12 were considered non-responders at Week 48, regardless of treatment arm.

Table 19: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus ustekinumab at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]
Clinical remission at Week 48 and endoscopic response[d] at Week 48						
Total population	39% (N=143)	42% (N=143)	49% (N=146)	28% (N=148)	41%[k] (N=143)	45%[k] (N=150)
Endoscopic response[e] at Week 48[l]						
Total population	42% (N=143)	49% (N=143)	56% (N=146)	32% (N=148)	47% (N=143)	49% (N=150)
Endoscopic remission[f] at Week 48						
Total population	20% (N=143)	27% (N=143)	24% (N=146)	13% (N=148)	24%[k] (N=143)	19% (N=150)
Clinical remission[g] at Week 48						
Total population	65% (N=143)	64% (N=143)	75% (N=146)	61% (N=148)	66% (N=143)	66% (N=150)
Corticosteroid-free clinical remission[h] at Week 48[l]						
Total population	61% (N=143)	63% (N=143)	71% (N=146)	59% (N=148)	64% (N=143)	64% (N=150)
Durable clinical remission[i] at Week 48						
Total population	45% (N=143)	46% (N=143)	52% (N=146)	39% (N=148)	50% (N=143)	49% (N=150)
PRO-2 remission[j] at Week 48						
Total population	59% (N=143)	60% (N=143)	69% (N=146)	53% (N=148)	58% (N=143)	56% (N=150)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

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

[f] Endoscopic remission is defined as SES-CD Score ≤ 2.

[g] Clinical remission is defined as CDAI score < 150.

[h] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

[i] Durable clinical remission is defined as CDAI < 150 for ≥ 80% of all visits between Week 12 and Week 48 (at least 8 of 10 visits), which must include Week 48.

[j] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

[k] $p < 0.05$

[l] Responses at Week 48 were evaluated irrespective of clinical response at Week 12

Table 20: Proportion of patients meeting efficacy endpoints with guselkumab versus ustekinumab at Week 48 in pooled GALAXI 2 and GALAXI 3

	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	**Guselkumab intravenous induction → 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**
Clinical remission at Week 48 and endoscopic response[d] at Week 48			
Total population	34% (N=291)	42% (N=286)	47% (N=296)
Biologic naïve[e]	43% (N=121)	51% (N=116)	55% (N=128)
Prior biologic failure[f]	26% (N=156)	37% (N=153)	41% (N=147)
Endoscopic response[g] at Week 48			
Total population	37% (N=291)	48% (N=286)	53% (N=296)
Biologic naïve[e]	43% (N=121)	59% (N=116)	59% (N=128)
Prior biologic failure[f]	31% (N=156)	43% (N=153)	47% (N=147)
Endoscopic remission[h] at Week 48			
Total population	16% (N=291)	25% (N=286)	21% (N=296)
Biologic naïve[e]	19% (N=121)	34% (N=116)	27% (N=128)
Prior biologic failure[f]	13% (N=156)	21% (N=153)	14% (N=147)
Clinical remission[i] at Week 48			
Total population	63% (N=291)	65% (N=286)	70% (N=296)
Biologic naïve[e]	75% (N=121)	73% (N=116)	77% (N=128)
Prior biologic failure[f]	53% (N=156)	61% (N=153)	64% (N=147)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

[e] An additional 14 patients in the ustekinumab group, 21 patients in the guselkumab 200 mg subcutaneous q4w group, and 17 patients in the guselkumab 100 mg subcutaneous q8w group were previously exposed to but did not fail a biological 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] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] Clinical remission is defined as CDAI score < 150.

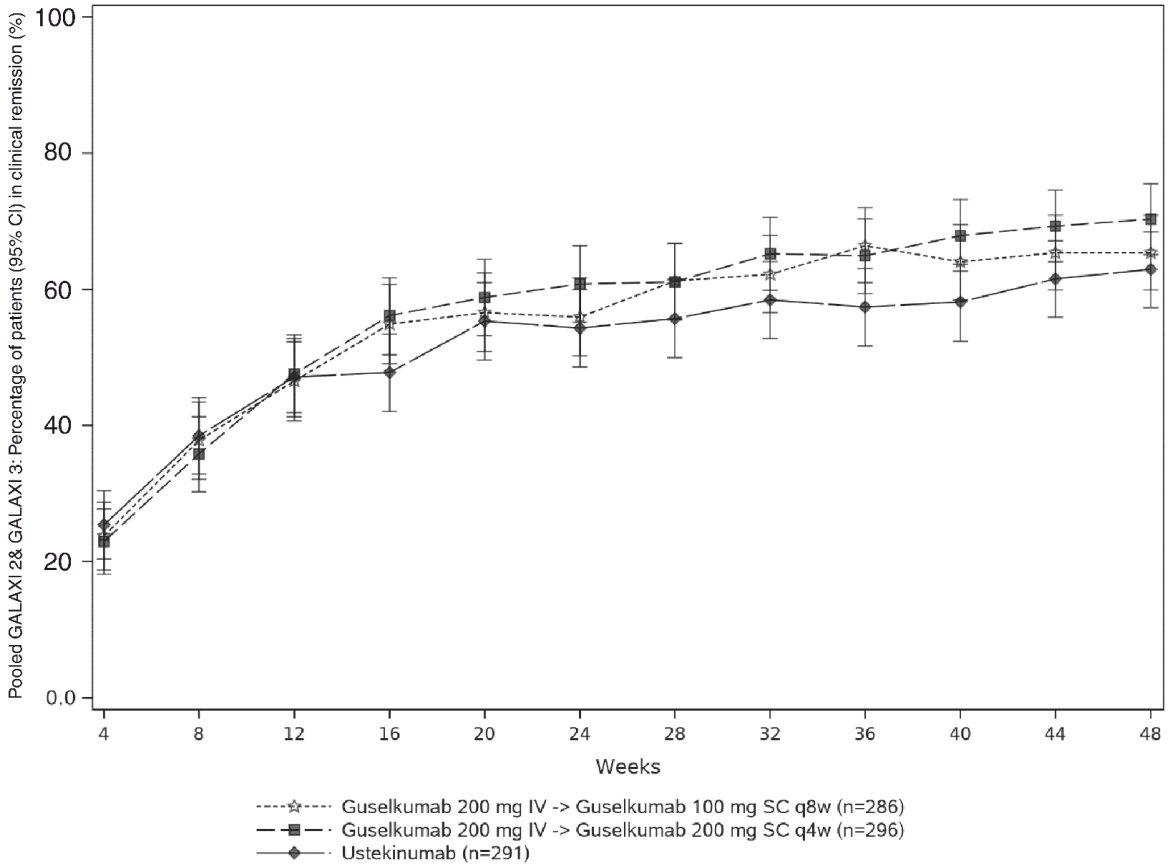
In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight.

In the pooled GALAXI Phase III studies subpopulation analysis, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w maintenance dose regimens. A clinically meaningful difference was observed between the two guselkumab 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: 54.1% vs 200 mg subcutaneous q4w: 71.0%); endoscopic response at Week 48 (100 mg subcutaneous q8w: 36.5% vs 200 mg subcutaneous q4w: 50.5%); and PRO-2 remission at Week 48 (100 mg subcutaneous q8w: 51.8% vs 200 mg subcutaneous q4w: 61.7%).

Clinical remission over time

CDAI scores were recorded at each patient visit. The proportion of patients in clinical remission through Week 48 is presented in Figure 10.

Figure 10: Proportion of patients in clinical remission through Week 48 in pooled GALAXI 2 and GALAXI 3



Health-related quality of life

Greater improvements from baseline were seen at Week 12 in guselkumab treatment groups when compared with placebo for inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score. The improvements were maintained through Week 48 in both studies.

GRAVITI

In the Phase III GRAVITI study, moderately to severely active Crohn's disease was defined as a CDAI score of ≥ 220 and ≤ 450 and a CD (SES-CD) of ≥ 6 (or ≥ 4 for patients with isolated ileal disease) and a mean daily SF ≥ 4 or mean daily AP score ≥ 2.

In GRAVITI, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg q8w subcutaneous maintenance; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg q4w subcutaneous maintenance; or placebo. All patients in the placebo group who met rescue criteria received the induction dosing with guselkumab 400 mg subcutaneous at Weeks 16, 20, and 24 followed by guselkumab 100 mg subcutaneous q8w.

A total of 347 patients were evaluated. The median age of patients was 36 years (ranging from 18 to 83 years), 58.5% were male, and 66% identified as White, 21.9% as Asian and 2.6% as Black.

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.

The results of the co-primary and major secondary efficacy endpoints compared to placebo at Week 12 are presented in Table 21.

Table 21: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GRAVITI

	Placebo	Guselkumab 400 mg subcutaneous injection[a]
Co-primary efficacy endpoints		
Clinical remission[b] at Week 12		
Total population	21% (N=117)	56%[c] (N=230)
Biologic naïve[d]	25% (N=56)	50% (N=105)
Prior biologic failure[e]	17% (N=53)	60% (N=108)
Endoscopic response[f] at Week 12		
Total population	21% (N=117)	41%[c] (N=230)
Biologic naïve[d]	27% (N=56)	49% (N=105)
Prior biologic failure[e]	17% (N=53)	33% (N=108)
Major secondary efficacy endpoints		
Clinical response[g] at Week 12		
Total population	33% (N=117)	73%[c] (N=230)
Biologic naïve[d]	38% (N=56)	68% (N=105)
Prior biologic failure[e]	28% (N=53)	78% (N=108)
PRO-2 remission[h] at Week 12		
Total population	17% (N=117)	49%[c] (N=230)
Biologic naïve[d]	18% (N=56)	44% (N=105)
Prior biologic failure[e]	17% (N=53)	52% (N=108)

[a] Guselkumab 400 mg subcutaneous at Week 0, Week 4 and Week 8

[b] Clinical remission: CDAI score < 150

[c] p< 0.001

[d] An additional 8 patients in the placebo group and 17 patients in the guselkumab 400 mg subcutaneous group, were previously exposed to but did not fail a biological therapy.

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

[f] Endoscopic response: ≥ 50% improvement from baseline in SES-CD score.

[g] Clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score < 150.

[h] PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

Clinical remission at Week 24 was achieved by a significantly greater proportion of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (60.9% and 58.3% vs 21.4% respectively, both p-values < 0.001). Clinical remission at Week 48 was achieved by 60% and 66.1% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Endoscopic response at Week 48 was achieved by 44.3% and 51.3% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Health-related quality of life
In GRAVITI, clinically meaningful improvements were observed in IBD-specific quality of life as assessed with IBDQ total score at Week 12 and Week 24 compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with guselkumab in one or more subsets of the paediatric population in psoriatic arthritis, ulcerative colitis, and Crohn's disease. The 100 mg pre-filled pens (PushPen and OnePress) have not been studied in the paediatric population and are not recommended for use in paediatric patients (see section 4.2 for information on paediatric use).

Paediatric plaque psoriasis
The safety and efficacy of guselkumab were assessed in one multicentre, randomised, placebo- and active biological comparator-controlled study (PROTOSTAR) in 120 paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy and were inadequately controlled by phototherapy and/or topical therapies. PROTOSTAR was conducted in two parts. Part 1 consisted of a 16-week randomised, placebo and active comparator-controlled period followed by an uncontrolled period of withdrawal and retreatment or initiation of treatment with guselkumab through Week 52. Part 2 consisted of an open-label guselkumab arm through Week 52.

Enrolled patients had an IGA score of ≥3 on a 5-point scale of overall disease severity, a PASI ≥12, and a minimum affected BSA of ≥10%, and at least one of the following: 1) very thick lesions, 2) clinically relevant facial, genital, or hand/foot involvement, 3) PASI ≥20, 4) BSA >20%, or 5) IGA=4. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

In Part 1, 92 patients 6 to 17 years of age were randomised to receive subcutaneous injection of either guselkumab (n=41) or placebo (n=25) at Week 0, 4, and 12, or an active biological comparator (n=26) weekly. In Part 2, 28 additional adolescent patients 12 to 17 years of age were enrolled to receive subcutaneous injection of guselkumab at Week 0, 4, and every 8 weeks thereafter. In the guselkumab group, patients with a body weight less than 70 kg received 1.3 mg/kg administered with the 45 mg/0.45 mL pre-filled pen, and patients with a body weight of 70 kg or more received 100 mg administered with the pre-filled syringe.

The co-primary endpoints were the proportion of patients who achieved a PASI 75 response and the proportion of patients who achieved an IGA score of 0 (“cleared”) or 1 (“minimal”) at Week 16. Secondary endpoints included but were not limited to the proportion of patients who achieved a PASI 90 response, an IGA score of 0 (“cleared”) or a PASI 100 response at Week 16.

Of the 92 patients in the controlled part of the study, baseline demographic characteristics were generally comparable across treatment groups. Overall, over 55% were male, 85% were white, the mean body weight was approximately 57.3 kg, and the mean age was 12.9 years with 33% of the patients less than 12 years.

The baseline disease characteristics were generally comparable across treatment groups with median baseline BSA of 20%, median baseline PASI score of approximately 17, and baseline IGA score of severe for 20% (placebo) and 24% (guselkumab) of patients, and a history of psoriatic arthritis for 3.3% of patients.

Overall skin disease
Treatment with guselkumab resulted in significant improvements in the outcome measures of disease activity compared to placebo at Week 16. The key efficacy results for the study endpoints are shown in Table 22 below.

Table 22: Summary of endpoints at week 16 in PROTOSTAR

	Placebo (N=25)	**Guselkumab (N=41)**	**P-value**
IGA scores of cleared (0) or minimal (1), n (%)	4 (16.0%)	27 (65.9%)	<0.001
IGA scores of cleared (0), n (%)	1 (4.0%)	16 (39.0%)	0.004
PASI 75 responders, n (%)	5 (20.0%)	31 (75.6%)	<0.001
PASI 90 responders, n (%)	4 (16.0%)	23 (56.1%)	0.003
PASI 100 responders, n (%)	0	14 (34.1%)	0.002
Change from baseline in CDLQI, LSMean (95% CI)[a]	-1.88 (-3.81, 0.05)	-7.28 (-8.87, -5.68)	<0.001

CDLQI = Children’s Dermatology Life Quality Index

[a] LSMean = least squares mean

Beyond the 16-week placebo-controlled period in Part 1 of PROTOSTAR, the guselkumab treated patients who achieved PASI 90 at Week 16 were withdrawn from treatment. Loss of PASI 90 response was noted as early as 12 weeks after withdrawal of guselkumab treatment with a median time to loss of PASI 90 response of approximately 24 weeks. Of the guselkumab treated patients who failed to achieve a PASI 90 response at Week 16, 72.2% of patients that received an additional 32 weeks of continued guselkumab treatment were PASI 75 responders at Week 52, and 61.1% achieved a PASI 90 response at Week 52.

In patients randomised to placebo at Week 0 who failed to achieve a PASI 90 response at Week 16 and crossed over to receive guselkumab 95.0% and 65.0% achieved PASI 75 and PASI 90 response, respectively, at Week 52.

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) 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 patients with plaque psoriasis, following subcutaneous administrations of guselkumab 100 mg 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 III studies in patients with plaque psoriasis were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. The pharmacokinetics of guselkumab in patients with psoriatic arthritis was similar to that in patients with psoriasis. Following subcutaneous administration of guselkumab 100 mg at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was also approximately 1.2 mcg/mL. Following subcutaneous administration of guselkumab 100 mg every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3.8 mcg/mL.

The pharmacokinetics of guselkumab were similar in patients with ulcerative colitis and Crohn's disease. Following the recommended intravenous induction dose regimen of guselkumab 200 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was 68.27 mcg/mL in patients with ulcerative colitis, and 70.5 mcg/mL in patients with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of guselkumab 400 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was estimated to be 28.8 mcg/mL in patients with ulcerative colitis, and 27.7 mcg/mL in patients with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimen was similar following subcutaneous and intravenous induction.

Following subcutaneous maintenance dosing of guselkumab 100 mg every 8 weeks or guselkumab 200 mg 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 guselkumab 100 mg every 8 weeks or guselkumab 200 mg every 4 weeks in patients 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 across studies.

Biotransformation

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

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day across studies. Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies, and approximately 17 days in patients with ulcerative colitis or Crohn's disease.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, AZA, 6-MP, oral corticosteroids and csDMARDs such as MTX, did not affect the clearance of guselkumab.

Linearity/non-linearity

The systemic exposure of guselkumab (C_{max} 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 patients with plaque psoriasis. Serum guselkumab concentrations were approximately dose proportional following intravenous administration in patients with ulcerative colitis or Crohn's disease.

Paediatric population

Steady-state serum trough concentrations of guselkumab were achieved by Week 20 in paediatric patients 6 to 17 years of age with moderate to severe plaque psoriasis treated with guselkumab subcutaneous injection using the 45 mg/0.45 mL pre-filled pen or the 100 mg pre-filled syringe (see section 4.2), and were within the range of those observed in adults.

The recommended dosing regimen results in similar predicted serum guselkumab exposure in paediatric patients with plaque psoriasis as compared to adults across the body weight range.

Elderly patients

No specific studies have been conducted in elderly patients. Of the 1 384 plaque psoriasis patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, 70 patients were 65 years of age or older, including 4 patients who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in Phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. Of the 859 ulcerative colitis patients exposed to guselkumab in Phase II/III clinical studies and included in the population pharmacokinetic analysis, a total of 52 patients were 65 years of age or older, and 9 patients were 75 years of age or older. Of the 1 009 Crohn's disease patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, a total of 39 patients were 65 years of age or older, and 5 patients were 75 years of age or older.

Population pharmacokinetic analyses in plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease patients indicated no apparent changes in CL/F estimate in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Patients with renal or hepatic impairment

No specific study has 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. Based on population pharmacokinetic analyses, creatinine clearance or hepatic function did not have a meaningful impact on guselkumab clearance.

Body weight

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, toxicity to reproduction and pre- and post-natal development.

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well tolerated via intravenous and subcutaneous routes of administration. A weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 23 times the maximum clinical exposures following a dose of 200 mg given intravenously. Additionally, there were no adverse immunotoxicity or cardiovascular safety pharmacology effects noted during the conduct of the repeat-dose toxicity studies or in a targeted cardiovascular safety pharmacology study in cynomolgus monkeys.

There were no preneoplastic changes observed in histopathology evaluations of animals treated up to 24 weeks, or following the 12-week recovery period during which active substance was detectable in the serum.

No mutagenicity or carcinogenicity studies were conducted with guselkumab.

Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

Tremfya 100 mg OnePress solution for injection in pre-filled pen

1 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper, assembled in a pre-filled pen with an automatic needle guard.
Tremfya is available in a pack containing one pre-filled pen and in a multipack containing 2 (2 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

Tremfya 100 mg PushPen solution for injection in pre-filled pen

1 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper assembled in a pre-filled pen with an automatic needle guard.
Tremfya is available in a pack containing one pre-filled pen and in a multipack containing 2 (2 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After removing the OnePress pre-filled pen or the PushPen pre-filled pen from the refrigerator, keep the pre-filled pen inside the carton and allow to reach room temperature by waiting for 30 minutes before injecting Tremfya. The pre-filled pens should not be shaken.

Prior to use, a visual inspection of the pre-filled pens is recommended. The solution should be clear, colourless to light yellow, and may contain a few small white or clear particles. Tremfya should not be used if the solution is cloudy or discoloured, or contains large particles.

Each pack is provided with an 'Instructions for use' leaflet that fully describes the preparation and administration of the pre-filled pens.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBERS

Tremfya 100 mg OnePress solution for injection in pre-filled pen

EU/1/17/1234/002 1 pre-filled pen
EU/1/17/1234/003 2 pre-filled pens

Tremfya 100 mg PushPen solution for injection in pre-filled pen

EU/1/17/1234/010 1 pre-filled pen
EU/1/17/1234/011 2 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal:15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled syringe
Tremfya 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tremfya 200 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 200 mg of guselkumab in 2 mL solution.

Tremfya 200 mg solution for injection in pre-filled pen

Each pre-filled pen contains 200 mg of guselkumab in 2 mL solution.

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

This medicinal product contains 1 mg of polysorbate 80 (E433) in each pre-filled syringe/pre-filled pen which is equivalent to 0.5 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)
Solution for injection (injection) in pre-filled pen (PushPen)

The solution is clear and colourless to light yellow and may contain a few small white or clear particles, with target pH of 5.8 and approximate osmolarity of 367.5 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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, or a biologic treatment.

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 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

Posology

Ulcerative colitis
Either of the following two induction dose regimens are recommended:
- 200 mg administered by intravenous infusion at Week 0, Week 4 and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 100 mg dose, see SmPC for Tremfya 100 mg solution for injection.

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

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

Crohn's disease
Either of the following two induction dose regimens are recommended:
- 200 mg administered by intravenous infusion at Week 0, Week 4, and Week 8. See SmPC for Tremfya 200 mg concentrate for solution for infusion.

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

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose regimen of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). For the 100 mg dose, see SmPC for Tremfya 100 mg solution for injection.

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

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is required (see section 5.2).
There is limited information in patients aged ≥ 65 years and very limited information in patients aged ≥ 75 years (see section 5.2).

Renal or hepatic impairment
Tremfya has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies, and no dose adjustments are considered necessary. For further information on elimination of guselkumab, see section 5.2.

Paediatric population
The safety and efficacy of Tremfya in children and adolescents with ulcerative colitis and Crohn's disease below the age of 18 years have not been established. No data are available.

Method of administration

Subcutaneous use only. Sites for injection include the abdomen, thigh and back of the upper arm. Tremfya should not be injected into areas where the skin is tender, bruised, red, hard, thick or scaly.

After proper training in subcutaneous injection technique, patients may inject Tremfya if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow-up of patients. Patients should be instructed to inject the full amount of solution according to the 'Instructions for use' provided in the carton.

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g., active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Guselkumab may increase the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with guselkumab should be instructed 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, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving guselkumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting (see section 4.8). Some serious hypersensitivity reactions occurred several days after treatment

with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately and appropriate therapy initiated.

Hepatic transaminase elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with guselkumab q4w compared to patients treated with guselkumab q8w or placebo (see section 4.8).

When prescribing guselkumab q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter according to routine patient management. If increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, treatment should be temporarily interrupted until this diagnosis is excluded.

Immunisations

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

Before live viral or live bacterial vaccination, treatment 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 Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Excipients with known effect

Polysorbate 80 content
This medicinal product contains 1 mg of polysorbate 80 (E433) in each pre-filled syringe/pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

In a Phase I study in patients 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, indicating that 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.

Concomitant immunosuppressive therapy or phototherapy

In psoriasis studies, the safety and efficacy of guselkumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant methotrexate (MTX) use did not appear to influence the safety or efficacy of guselkumab.

In ulcerative colitis and Crohn's disease studies, concomitant use of immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP]) or corticosteroids did not appear to influence the safety or efficacy of guselkumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are limited data from the use of guselkumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Tremfya during pregnancy.

Breast-feeding

It is unknown whether guselkumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant during this period cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from Tremfya therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. See section 5.3 for information on the excretion of guselkumab in animal (cynomolgus monkey) milk.

Fertility

The effect of guselkumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was respiratory tract infections (approximately 8% of patients in ulcerative colitis studies, 11% of patients in the Crohn's disease studies, and 15% of patients in the psoriasis and psoriatic arthritis clinical studies).

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

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

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

Description of selected adverse reactions

Transaminases increased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia) were reported more frequently in the guselkumab treated groups (8.6% in the 100 mg subcutaneous q4w group and 8.3% in the 100 mg subcutaneous q8w group) than in the placebo group (4.6%). Through 1 year, adverse reactions 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, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the guselkumab q4w group compared with the guselkumab q8w group (Table 2). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 2: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through week 24[a]			Through 1 year[b]	
	Placebo N=370[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 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 guselkumab are not included.

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

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the guselkumab q8w dose was similar to that observed for the guselkumab q8w dose in the

psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled induction period (Week 0-12), adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, and liver function test increased) were reported more frequently in the guselkumab treated groups (1.7% of patients) than in the placebo group (0.6% of patients). In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, adverse reactions 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 guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase II and Phase III Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies. In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled period (Week 12), ALT (< 1% of patients) and AST (< 1% of patients) elevations ≥ 3x ULN were reported in guselkumab treated patients. In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, ALT and/or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.6% of patients in the guselkumab 100 mg subcutaneous 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.

Neutrophil count decreased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, the adverse reaction of decreased neutrophil count was reported more frequently in the guselkumab treated group (0.9%) than in the placebo group (0%). Through 1 year, the adverse reaction of decreased neutrophil count was reported in 0.9% of patients treated with guselkumab. In most cases, the decrease in blood neutrophil count was mild, transient, not associated with infection and did not lead to discontinuation of treatment.

Gastroenteritis
In two Phase III psoriasis clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the guselkumab treated group (1.1%) than in the placebo group (0.7%). Through Week 264, 5.8% of all guselkumab treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of guselkumab through Week 264. Gastroenteritis rates observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies.

Injection site reactions
In two Phase III psoriasis clinical studies through Week 48, 0.7% of guselkumab injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 264, 0.4% of guselkumab injections were associated with injection site reactions. Injection site reactions were generally mild to moderate in severity; none were serious, and one led to discontinuation of guselkumab.

In two Phase III psoriatic arthritis clinical studies through Week 24, the number of patients that reported 1 or more injection site reactions was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) patients in the guselkumab q8w group, 4 (1.1%) patients in the guselkumab q4w group, and 1 (0.3%) patient in the placebo group. One patient discontinued guselkumab due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Through 1 year, the proportion of patients reporting 1 or more injection site

reactions was 1.6% and 2.4% in the guselkumab q8w and q4w groups respectively. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period was similar to rates observed in the psoriasis clinical studies.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group (guselkumab 200 mg was administered as two 100 mg injections in the Phase III ulcerative colitis maintenance clinical study) and no injection site reactions in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and none were serious.

In Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 4.1% (0.8% of injections) in the treatment group which received guselkumab 200 mg intravenous induction followed by 200 mg subcutaneous q4w, and 1.4% (0.6% of injections) of patients in the guselkumab 200 mg intravenous induction followed by 100 mg subcutaneous q8w group. Overall injection site reactions were mild; none were serious.

In a Phase III Crohn's disease clinical study through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7% (1.3% of injections) in the treatment group which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 4.3% (0.7% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Most injection site reactions were mild; none were serious.

Immunogenicity
The immunogenicity of guselkumab was evaluated using a sensitive and drug-tolerant immunoassay.

In pooled Phase II and Phase III analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 8% (n=12) had antibodies that were classified as neutralising, which equates to 0.4% of all patients treated with guselkumab. In pooled Phase III analyses in patients with psoriasis, approximately 15% of patients treated with guselkumab developed antidrug antibodies in up to 264 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising, which equates to 0.76% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

In pooled Phase II and Phase III analyses in patients with ulcerative colitis who were treated with intravenous induction followed by subcutaneous maintenance, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralising, which equates to 2% of all patients treated with guselkumab. In a Phase III analysis up to Week 24 in patients with ulcerative colitis who were treated with subcutaneous induction followed by subcutaneous maintenance, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or the development of injection site reactions.

In pooled Phase II and Phase III analyses up to Week 48 in patients with Crohn's disease who were treated with intravenous induction followed by subcutaneous maintenance dose regimen, approximately 5% (n=30) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 7% (n=2) had antibodies that were classified as neutralising antibodies, which equates to 0.3% of guselkumab treated patients.
In a Phase III analysis up to Week 48 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of these patients, 13%

(n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Guselkumab intravenous doses up to 1 200 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, the patient must be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment must be administered immediately.

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 high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In patients with ulcerative colitis or 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 exerts 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, ulcerative colitis, and Crohn's disease. 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 I 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 patients with plaque psoriasis at Week 12 compared to baseline. In the same Phase I 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 patients in Phase II and Phase III plaque psoriasis studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In psoriatic arthritis patients in Phase III studies, 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 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

In patients with ulcerative colitis or Crohn's disease, guselkumab treatment led to decreases in inflammatory markers including C-reactive protein (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.

Clinical efficacy and safety

Ulcerative colitis
The efficacy and safety of guselkumab were evaluated in three Phase III multicentre, randomised, double-blind, placebo-controlled studies (QUASAR intravenous induction study, QUASAR maintenance study, and ASTRO subcutaneous induction 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 (AZA, 6-MP), biologic therapy (TNF blockers, vedolizumab), a Janus kinase (JAK) inhibitor, and/or sphingosine-1-phosphate receptor modulators (S1PRM) applicable only for ASTRO. In addition, efficacy and safety of guselkumab were evaluated in a randomised, double-blind, placebo-controlled, Phase IIb induction dose-finding study (QUASAR induction dose-ranging study) that enrolled a similar ulcerative colitis patient population as the Phase III induction 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 ≥ 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).

Induction study: QUASAR IS
In the induction study QUASAR IS, patients were randomised in a 3:2 ratio to receive either guselkumab 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 and 1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, MTX, 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, 87.5%, 54.1% and 18% had previously failed a TNF blocker, vedolizumab or a JAK inhibitor, respectively, and 47.4% 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, fatigue response and IBDQ remission (Table 3).

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

Table 3: Proportion of patients meeting efficacy endpoints at Week 12 in QUASAR IS

Endpoint	Placebo %	Guselkumab 200 mg intravenous induction[a] %	Treatment Difference (95% CI)
Clinical remission[b]			
Total population	8% (N=280)	23% (N=421)	15% (10%, 20%)[c]
Biologic and JAK inhibitor naïve[d]	12% (N=137)	32% (N=202)	20% (12%, 28%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 14%)
Symptomatic remission[f]			
Total population	21% (N=280)	50% (N=421)	29% (23%, 36%)[c]
Biologic and JAK inhibitor naïve[d]	26% (N=137)	60% (N=202)	34% (24%, 44%)
Prior biologic and/or JAK inhibitor failure[e]	14% (N=136)	38% (N=208)	24% (16%, 33%)
Endoscopic healing[g]			
Total population	11% (N=280)	27% (N=421)	16% (10%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	17% (N=137)	38% (N=202)	21% (12%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	5% (N=136)	15% (N=208)	10% (4%, 16%)
Clinical response[h]			
Total population	28% (N=280)	62% (N=421)	34% (27%, 41%)[c]
Biologic and JAK inhibitor naïve[d]	35% (N=137)	71% (N=202)	36% (26%, 46%)
Prior biologic and/or JAK inhibitor failure[e]	20% (N=136)	51% (N=208)	32% (22%, 41%)
Histologic endoscopic mucosal healing[i]			
Total Population	8% (N=280)	24% (N=421)	16% (11%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	11% (N=137)	33% (N=202)	22% (13%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 15%)
Fatigue response[j]			
Total population	21% (N=280)	41% (N=421)	20% (13%, 26%)[c]
Biologic and JAK inhibitor naïve[d]	29% (N=137)	42% (N=202)	12% (2%, 23%)
Prior biologic and/or JAK inhibitor failure[e]	13% (N=136)	38% (N=208)	25% (17%, 34%)
IBDQ remission[k]			
Total population	30% (N=280)	51% (N=421)	22% (15%, 29%)[c]
Biologic and JAK inhibitor naïve[d]	34% (N=137)	62% (N=202)	28% (18%, 38%)
Prior biologic and/or JAK inhibitor failure[e]	24% (N=136)	39% (N=208)	15% (5%, 25%)

[a] Guselkumab 200 mg as an intravenous induction 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.

[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 patients in the placebo group and 11 patients in the guselkumab 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.

[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.

[k] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

QUASAR IS and QUASAR induction dose-ranging study also enrolled 48 patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥ 1. In patients with a baseline mMS of 4, guselkumab 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 ulcerative colitis population.

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

Maintenance study: QUASAR MS
The QUASAR MS evaluated 568 patients who achieved clinical response at 12 weeks following the intravenous administration of guselkumab in either QUASAR IS or from the QUASAR induction dose-ranging study. In the QUASAR MS, these patients were randomised to receive a subcutaneous maintenance regimen of either guselkumab 100 mg every 8 weeks, guselkumab 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, fatigue response and IBDQ remission (Table 4).

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

Table 4: Proportion of patients meeting efficacy endpoints at Week 44 in QUASAR MS

Endpoint	Placebo %	Guselkumab 100 mg q8w subcutaneous injection[a] %	Guselkumab 200 mg q4w subcutaneous injection[b] %	Treatment Difference (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[c]					
Total population[d]	19% (N=190)	45% (N=188)	50% (N=190)	25% (16%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	58% (N=96)	24% (12%, 36%)	29% (17%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	40% (N=77)	40% (N=88)	30% (19%, 42%)	32% (21%, 44%)
Symptomatic remission[h]					
Total population[d]	37% (N=190)	70% (N=188)	69% (N=190)	32% (23%, 41%)[e]	31% (21%, 40%)[e]

Biologic and JAK-inhibitor naïve[f]	46% (N=108)	74% (N=105)	76% (N=96)	28% (15%, 40%)	28% (15%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	24% (N=75)	65% (N=77)	60% (N=88)	39% (26%, 52%)	37% (23%, 50%)
Corticosteroid-free clinical remission[i]					
Total population[d]	18% (N=190)	45% (N=188)	49% (N=190)	26% (17%, 34%)[e]	29% (20%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	56% (N=96)	24% (12%, 36%)	27% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	7% (N=75)	40% (N=77)	40% (N=88)	32% (21%, 43%)	34% (23%, 45%)
Endoscopic healing[j]					
Total population[d]	19% (N=190)	49% (N=188)	52% (N=190)	30% (21%, 38%)[e]	31% (22%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	53% (N=105)	59% (N=96)	27% (15%, 40%)	30% (18%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	45% (N=77)	42% (N=88)	36% (24%, 48%)	35% (23%, 46%)
Histologic endoscopic mucosal healing[k]					
Total population[d]	17% (N=190)	44% (N=188)	48% (N=190)	26% (17%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	23% (N=108)	50% (N=105)	56% (N=96)	26% (14%, 38%)	30% (17%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	38% (N=77)	39% (N=88)	28% (16%, 39%)	31% (20%, 43%)
Clinical response[l]					
Total population[d]	43% (N=190)	78% (N=188)	75% (N=190)	34% (25%, 43%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	54% (N=108)	83% (N=105)	81% (N=96)	29% (17%, 41%)	26% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	28% (N=75)	70% (N=77)	67% (N=88)	41% (27%, 54%)	39% (26%, 53%)
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population[q]	34% (N=59)	61% (N=66)	72% (N=69)	26% (9%, 43%)[m]	38% (23%, 54%)[e]
Biologic and JAK-inhibitor naïve[r]	34% (N=41)	65% (N=43)	79% (N=48)	31% (9%, 51%)	45% (25%, 62%)
Prior biologic and/or JAK-inhibitor failure[g]	27% (N=15)	60% (N=20)	56% (N=18)	33% (-1%, 62%)	29% (-6%, 59%)
Endoscopic normalisation[n]					
Total population[d]	15% (N=190)	35% (N=188)	34% (N=190)	18% (10%, 27%)[e]	17% (9%, 25%)[e]
Biologic and JAK-inhibitor naïve [f]	20% (N=108)	38% (N=105)	42% (N=96)	17% (6%, 29%)	17% (6%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	31% (N=77)	24% (N=88)	21% (10%, 33%)	16% (6%, 26%)
Fatigue response[o]					
Total population [d]	29% (N=190)	51% (N=188)	43% (N=190)	20% (11%, 29%)[e]	13% (3%, 22%)[m]
Biologic and JAK-inhibitor naïve[f]	36% (N=108)	51% (N=105)	53% (N=96)	15% (2%, 28%)	16% (3%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	47% (N=77)	32% (N=88)	27% (13%, 40%)	13% (1%, 26%)

IBDQ remission[p]					
Total population[d]	37% (N=190)	64% (N=188)	64% (N=190)	26% (17%, 36%)[e]	26% (16%, 35%)[e]
Biologic and JAK-inhibitor naïve [f]	49% (N=108)	68% (N=105)	74% (N=96)	19% (6%, 32%)	24% (11%, 37%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	58% (N=77)	53% (N=88)	38% (26%, 50%)	35% (23%, 48%)

[a] Guselkumab 100 mg as a subcutaneous injection every 8 weeks after the induction regimen.

[b] Guselkumab 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.

[d] Patients who achieved clinical response 12 weeks following the intravenous administration of guselkumab 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 patients in the placebo group, 6 patients in the guselkumab 100 mg group, and 6 patients in the guselkumab 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.

[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.

[p] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

[q] Subjects who achieved clinical remission 12 weeks following intravenous administration of guselkumab in either QUASAR induction study or QUASAR induction dose-ranging study.

[r] An additional 3 patients in the placebo group, 3 patients in the guselkumab 100 mg group, and 3 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic or JAK inhibitor.

In QUASAR IS and QUASAR MS, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race, body weight, and previous treatment with a biologic therapy or JAK inhibitor.

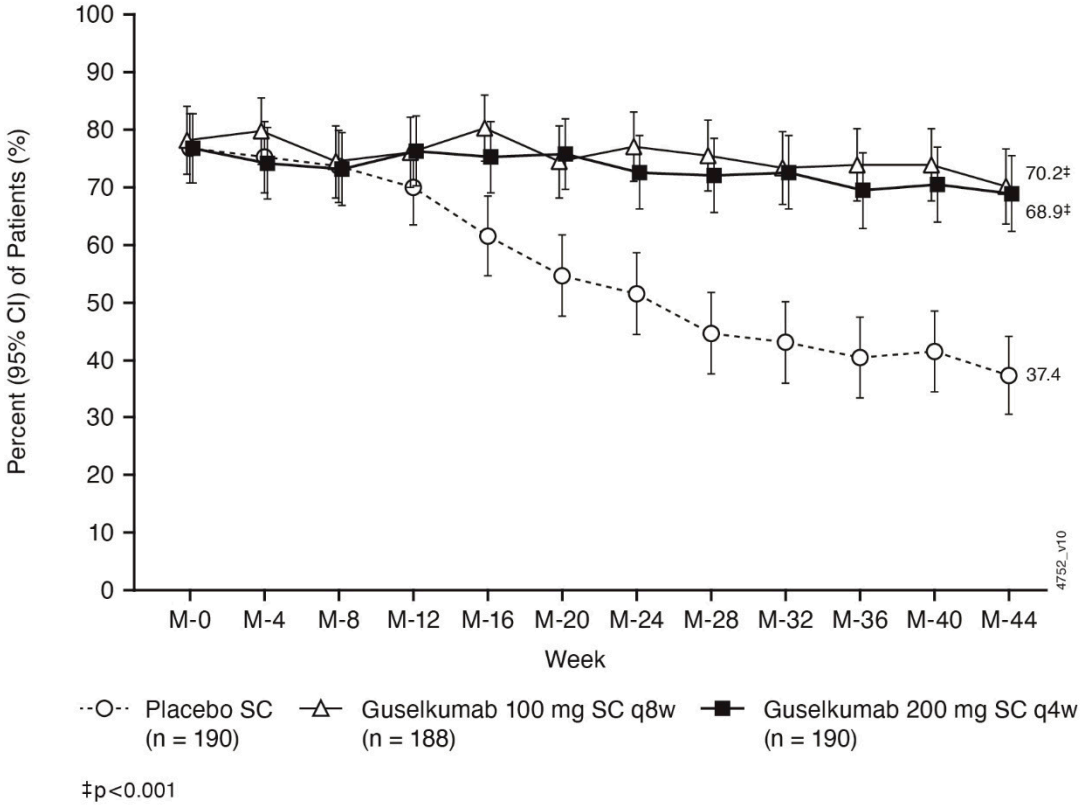
In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of > 15% were observed between the two guselkumab dose groups 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).

QUASAR MS enrolled 31 patients with an induction 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 guselkumab in QUASAR IS or QUASAR induction dose-ranging study. In these patients, guselkumab efficacy relative to placebo as measured by clinical remission, clinical response, and endoscopic healing at Week 44 was consistent with the total population.

Symptomatic remission over time

In QUASAR MS symptomatic remission defined as 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 guselkumab treatment groups, while a decline was observed in the placebo group (Figure 1):

Figure 1: Proportion of patients in symptomatic remission through Week 44 in QUASAR MS



Week 24 responders to guselkumab extended treatment
Guselkumab treated patients who were not in clinical response at induction Week 12, received guselkumab 200 mg subcutaneous at Weeks 12, 16 and 20. In QUASAR IS, 66/120 (55%) guselkumab treated patients who were not in clinical response at induction Week 12 achieved clinical response at Week 24. Week 24 responders to guselkumab entered QUASAR MS and received guselkumab 200 mg subcutaneous every 4 weeks. At Week 44 of QUASAR MS, 83/123 (67%) of these patients maintained clinical response and 37/123 (30%) achieved clinical remission.

Recapture of efficacy after loss of response to guselkumab
Nineteen patients receiving guselkumab 100 mg subcutaneous q8w who experienced a first loss of response (10%) between Week 8 and 32 of QUASAR MS received blinded guselkumab dosing with 200 mg guselkumab subcutaneous q4w 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). In QUASAR IS, histologic remission at Week 12 was achieved in 40% of patients treated with guselkumab and 19% of patients in the placebo group. In QUASAR MS, histologic remission at Week 44 was achieved in 59% and 61% of patients treated with guselkumab 100 mg subcutaneous q8w and guselkumab 200 mg subcutaneous q4w and 27% of patients in the placebo group.

Normalisation of the endoscopic appearance of the mucosa was defined as ES of 0. In QUASAR IS, endoscopic normalisation at Week 12 was achieved in 15% of patients treated with guselkumab and 5% of patients in the placebo group.

Composite histologic-endoscopic mucosal outcomes
Combined symptomatic remission, endoscopic normalisation, histologic remission, and faecal calprotectin ≤ 250 mg/kg at Week 44 was achieved by a greater proportion of patients treated with guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (22% and 28% vs 9%, respectively).

Health-related quality of life
At Week 12 of QUASAR IS, patients receiving guselkumab showed greater and clinically meaningful improvements from baseline when compared with placebo in inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score, and all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function). These improvements were maintained in guselkumab treated patients in QUASAR MS through Week 44.

Ulcerative colitis related hospitalisations
Through Week 12 of QUASAR IS, lower proportions of patients in the guselkumab group compared with the placebo group had ulcerative colitis-related hospitalisations (1.9%, 8/421 vs. 5.4%, 15/280).

ASTRO
In ASTRO, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg subcutaneous maintenance every 8 weeks; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg subcutaneous maintenance every 4 weeks; or placebo.

A total of 418 patients were evaluated. The median age of patients was 40 years (ranging from 18 to 80 years); 38.8% were female; and 64.6% identified as White, 28.9% as Asian, and 3.1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, immunomodulators (AZA, 6-MP, MTX), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 77.3% of patients were receiving aminosalicylates, 20.1% of patients were receiving immunomodulators, and 32.8% of patients were receiving corticosteroids. Concomitant biologic therapies, JAK inhibitors, or S1PRMs were not permitted. A total of 40.2% of patients had previously failed treatment with at least one biologic therapy, JAK inhibitor, and/or S1PRM, 58.1% were biologic, JAK inhibitor, and S1PRM naïve, and 1.7% had previously received but had not failed a biologic, JAK inhibitor, or S1PRM.

In ASTRO, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included symptomatic remission, endoscopic healing, clinical response and histologic-endoscopic mucosal healing (see Table 5). Secondary endpoints at Week 24 included clinical remission and endoscopic healing (see Table 6).

Table 5: Proportion of patients meeting efficacy endpoints at Week 12 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg Subcutaneous Induction[a] %	Treatment Difference vs Placebo (95% CI)[b]
Clinical remission[c]			
Total Population	6% (N=139)	28% (N=279)	21% (15%, 28%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	9% (N=79)	36% (N=164)	27% (18%, 37%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	4% (N=56)	16% (N=112)	12% (3%, 20%)
Symptomatic remission[d]			
Total Population	21% (N=139)	51% (N=279)	30% (22%, 39%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	25% (N=79)	59% (N=164)	34% (22%, 46%)

Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	14% (N=56)	41% (N=112)	26% (13%, 39%)
Endoscopic healing[h]			
Total Population	13% (N=139)	37% (N=279)	24% (17%, 32%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	46% (N=164)	28% (17%, 40%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	24% (N=112)	16% (6%, 26%)
Clinical response[i]			
Total Population	35% (N=139)	66% (N=279)	31% (22%, 40%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	42% (N=79)	71% (N=164)	30% (17%, 43%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	25% (N=56)	57% (N=112)	31% (17%, 45%)
Histologic endoscopic mucosal healing[j]			
Total Population	11% (N=139)	30% (N=279)	20% (12%, 27%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	14% (N=79)	38% (N=164)	25% (14%, 35%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	19% (N=112)	11% (1%, 20%)

[a] Guselkumab 400 mg subcutaneous induction at Week 0, Week 4, and Week 8

[b] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[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

[d] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group and 3 patients in the guselkumab group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

[i] Decrease from 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

[j] An endoscopy subscore of 0, or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Table 6: Proportion of patients meeting efficacy endpoints at Week 24 in ASTRO

Endpoint	**Placebo %**	**Guselkumab 400 mg SC induction→ 100 mg q8w Subcutaneous Injection[a] %**	**Guselkumab 400 mg SC induction→ 200 mg q4w Subcutaneous Injection[b] %**	**Treatment Difference vs Placebo (95% CI)[c]**	
				Guselkumab 100 mg	**Guselkumab 200 mg**
Clinical remission[d]					
Total population	9% (N=139)	35% (N=139)	36% (N=140)	26% (17%, 35%)[e]	27% (18%, 36%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	13% (N=79)	49% (N=81)	43% (N=83)	37% (24%, 50%)	31% (18%, 44%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	16% (N=57)	27% (N=55)	10% (-1%, 21%)	21% (9%, 34%)
Endoscopic healing[h]					
Total population	12% (N=139)	40% (N=139)	45% (N=140)	28% (18%, 38%)[e]	33% (23%, 42%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	54% (N=81)	52% (N=83)	37% (23%, 51%)	34% (21%, 48%)

Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	19% (N=57)	36% (N=55)	13% (1%, 25%)	30% (17%, 44%)

[a] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks

[b] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg SC maintenance every 4 weeks

[c] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[d] 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

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group, 1 patient in the guselkumab 100 mg group, and 2 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

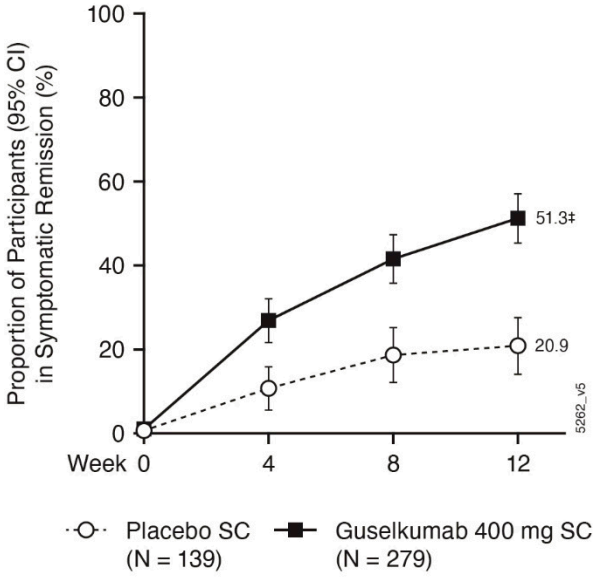
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

Symptomatic remission over time

In ASTRO, symptomatic remission defined as stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0 observed through Week 12, a greater proportion of patients in the guselkumab treatment groups achieved symptomatic remission compared with the placebo group (Figure 2):

Figure 2: Proportion of patients in symptomatic remission through Week 12 in ASTRO



‡p<0.001

Rectal bleeding and stool frequency subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with guselkumab compared to placebo.

Histologic and endoscopic assessment

Histologic remission at Week 12 was achieved in 44% of patients treated with guselkumab 400 mg subcutaneous induction compared to 20% of patients on placebo.

Endoscopic normalisation at Week 24 was achieved in 21% and 26% of patients treated with guselkumab 400 mg subcutaneous induction, followed by guselkumab 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or guselkumab 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter, respectively, compared to 4% of patients on placebo.

Abdominal pain and bowel urgency
A greater proportion of patients treated with guselkumab 400 mg subcutaneous induction compared to placebo had no abdominal pain (56% vs 31%), and no bowel urgency (49% vs 24%) at Week 12.

Health-related quality of life
Disease-specific health-related quality of life was assessed with the IBDQ. A greater proportion of patients in the combined 400 mg SC guselkumab group (61%) achieved IBDQ remission at Week 12 compared with the placebo group (34%).

Crohn's disease
The efficacy and safety of guselkumab were evaluated in three Phase III clinical studies 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 active-controlled (ustekinumab), parallel group studies (GALAXI 2 and GALAXI 3) and one 24-Week multicentre, randomised, double-blind, placebo-controlled, parallel group study (GRAVITI). All three studies had a treat-through study design: patients randomised to guselkumab (or ustekinumab for GALAXI 2 and GALAXI 3) maintained that treatment assignment for the duration of the study.

GALAXI 2 and GALAXI 3
In the Phase III studies GALAXI 2 and GALAXI 3, 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). Additional criteria for GALAXI 2/3 included a mean daily stool frequency (SF) > 3 or mean daily abdominal pain score (AP) > 1.

In GALAXI 2 and GALAXI 3 studies, patients were randomised in a 2:2:2:1 ratio to receive guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg subcutaneous q4w maintenance; or guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8, followed by guselkumab 100 mg subcutaneous q8w maintenance; or ustekinumab approximately 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w maintenance; or placebo. Placebo non-responders received ustekinumab 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), 57.6% were male; and 74.3% identified as White, 21.3% as Asian and 1.5% as Black.

In GALAXI 2, 52.8% of patients had previously failed treatment with at least one biologic therapy (50.6% were intolerant or failed at least 1 prior anti-TNFα therapy, 7.5% were intolerant or failed prior vedolizumab 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 (50.3% were intolerant or failed at least 1 prior anti-TNFα therapy, 9.6% were intolerant or failed prior vedolizumab 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.

The results of the co-primary and major secondary endpoints compared to placebo in GALAXI 2 and GALAXI 3 are presented in Tables 7 (Week 12) and 8 (Week 48). The results of the major secondary endpoints at Week 48 compared to ustekinumab are presented in Tables 9 and 10.

Table 7: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GALAXI 2 and GALAXI 3

	GALAXI 2		GALAXI 3	
	Placebo %	Guselkumab intravenous induction[a] %	Placebo %	Guselkumab intravenous induction[a] %
Co-primary efficacy endpoints				
Clinical remission[b] at Week 12				
Total population	22% (N=76)	47%[i] (N=289)	15% (N=72)	47%[i] (N=293)
Biologic naïve[c]	18% (N=34)	50% (N=121)	15% (N=27)	50% (N=123)
Prior biologic failure[d]	23% (N=39)	45% (N=150)	15% (N=39)	47% (N=150)
Endoscopic response[e] at Week 12				
Total population	11% (N=76)	38%[i] (N=289)	14% (N=72)	36%[i] (N=293)
Biologic naïve[c]	15% (N=34)	51% (N=121)	22% (N=27)	41% (N=123)
Prior biologic failure[d]	5% (N=39)	27% (N=150)	8% (N=39)	31% (N=150)
Major secondary efficacy endpoints				
PRO-2 remission[f] at Week 12				
Total population	21% (N=76)	43%[i] (N=289)	14% (N=72)	42%[i] (N=293)
Biologic naïve[c]	24% (N=34)	43% (N=121)	15% (N=27)	47% (N=123)
Prior biologic failure[d]	13% (N=39)	41% (N=150)	13% (N=39)	39% (N=150)
Fatigue response[g] at Week 12				
Total population	29% (N=76)	45%[j] (N=289)	18% (N=72)	43%[i] (N=293)
Biologic naïve[c]	32% (N=34)	48% (N=121)	19% (N=27)	46% (N=123)
Prior biologic failure[d]	26% (N=39)	41% (N=150)	18% (N=39)	43% (N=150)
Endoscopic remission[h] at Week 12				
Total population	1% (N=76)	15% (N=289)	8% (N=72)	16% (N=293)
Biologic naïve[c]	3% (N=34)	22% (N=121)	19% (N=27)	25% (N=123)
Prior biologic failure[d]	0% (N=39)	9% (N=150)	0% (N=39)	9% (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 – Two guselkumab treatment groups were combined for this column as patients received the same intravenous induction dose regimen prior to Week 12.

[b] Clinical remission is defined as CDAI score < 150.

[c] An additional 9 patients in the placebo group and 38 patients in the guselkumab 200 mg intravenous group were previously exposed to but did not fail a biological therapy.

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

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

[f] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

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

[h] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] $p < 0.001$

[j] $p < 0.05$

Table 8: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus placebo at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Placebo	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]	Placebo (N=72)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]
Corticosteroid-free clinical remission[c] at Week 48[f]						
Total population	12% (N=76)	45%[e] (N=143)	51%[e] (N=146)	14% (N=72)	44%[e] (N=143)	48%[e] (N=150)

Endoscopic response[d] at Week 48[f]						
Total population	7% (N=76)	38%[e] (N=143)	38%[e] (N=146)	6% (N=72)	33%[e] (N=143)	36%[e] (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[c] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

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

[e] $p < 0.001$

[f] Participants who met inadequate response criteria at Week 12 were considered non-responders at Week 48, regardless of treatment arm.

Table 9: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus ustekinumab at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			**GALAXI 3**		
	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	**Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**	**Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]**	**Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**
Clinical remission at Week 48 and endoscopic response[d] at Week 48						
Total population	39% (N=143)	42% (N=143)	49% (N=146)	28% (N=148)	41%[k] (N=143)	45%[k] (N=150)
Endoscopic response[e] at Week 48[l]						
Total population	42% (N=143)	49% (N=143)	56% (N=146)	32% (N=148)	47% (N=143)	49% (N=150)
Endoscopic remission[f] at Week 48						
Total population	20% (N=143)	27% (N=143)	24% (N=146)	13% (N=148)	24%[k] (N=143)	19% N=150)
Clinical remission[g] at Week 48						
Total population	65% (N=143)	64% (N=143)	75% (N=146)	61% (N=148)	66% (N=143)	66% (N=150)
Corticosteroid-free clinical remission[h] at Week 48[l]						
Total population	61% (N=143)	63% (N=143)	71% (N=146)	59% (N=148)	64% (N=143)	64% (N=150)
Durable clinical remission[i] at Week 48						
Total population	45% (N=143)	46% (N=143)	52% (N=146)	39% (N=148)	50% (N=143)	49% (N=150)
PRO-2 remission[j] at Week 48						
Total population	59% (N=143)	60% (N=143)	69% (N=146)	53% (N=148)	58% (N=143)	56% (N=150)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

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

[f] Endoscopic remission is defined as SES-CD Score ≤ 2.

[g] Clinical remission is defined as CDAI score < 150.

[h] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

[i] Durable clinical remission is defined as CDAI < 150 for ≥ 80% of all visits between Week 12 and Week 48 (at least 8 of 10 visits), which must include Week 48.

[j] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

[k] $p < 0.05$

[l] Responses at Week 48 were evaluated irrespective of clinical response at Week 12

Table 10: Proportion of patients meeting efficacy endpoints with guselkumab versus ustekinumab at Week 48 in pooled GALAXI 2 and GALAXI 3

	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	**Guselkumab intravenous induction → 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**
Clinical remission at Week 48 and endoscopic response[d] at Week 48			
Total population	34% (N=291)	42% (N=286)	47% (N=296)
Biologic naïve[e]	43% (N=121)	51% (N=116)	55% (N=128)
Prior biologic failure[f]	26% (N=156)	37% (N=153)	41% (N=147)
Endoscopic response[g] at Week 48			
Total population	37% (N=291)	48% (N=286)	53% (N=296)
Biologic naïve[e]	43% (N=121)	59% (N=116)	59% (N=128)
Prior biologic failure[f]	31% (N=156)	43% (N=153)	47% (N=147)
Endoscopic remission[h] at Week 48			
Total population	16% (N=291)	25% (N=286)	21% (N=296)
Biologic naïve[e]	19% (N=121)	34% (N=116)	27% (N=128)
Prior biologic failure[f]	13% (N=156)	21% (N=153)	14% (N=147)
Clinical remission[i] at Week 48			
Total population	63% (N=291)	65% (N=286)	70% (N=296)
Biologic naïve[e]	75% (N=121)	73% (N=116)	77% (N=128)
Prior biologic failure[f]	53% (N=156)	61% (N=153)	64% (N=147)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

[e] An additional 14 patients in the ustekinumab group, 21 patients in the guselkumab 200 mg subcutaneous q4w group, and 17 patients in the guselkumab 100 mg subcutaneous q8w group were previously exposed to but did not fail a biological 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] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] Clinical remission is defined as CDAI score < 150.

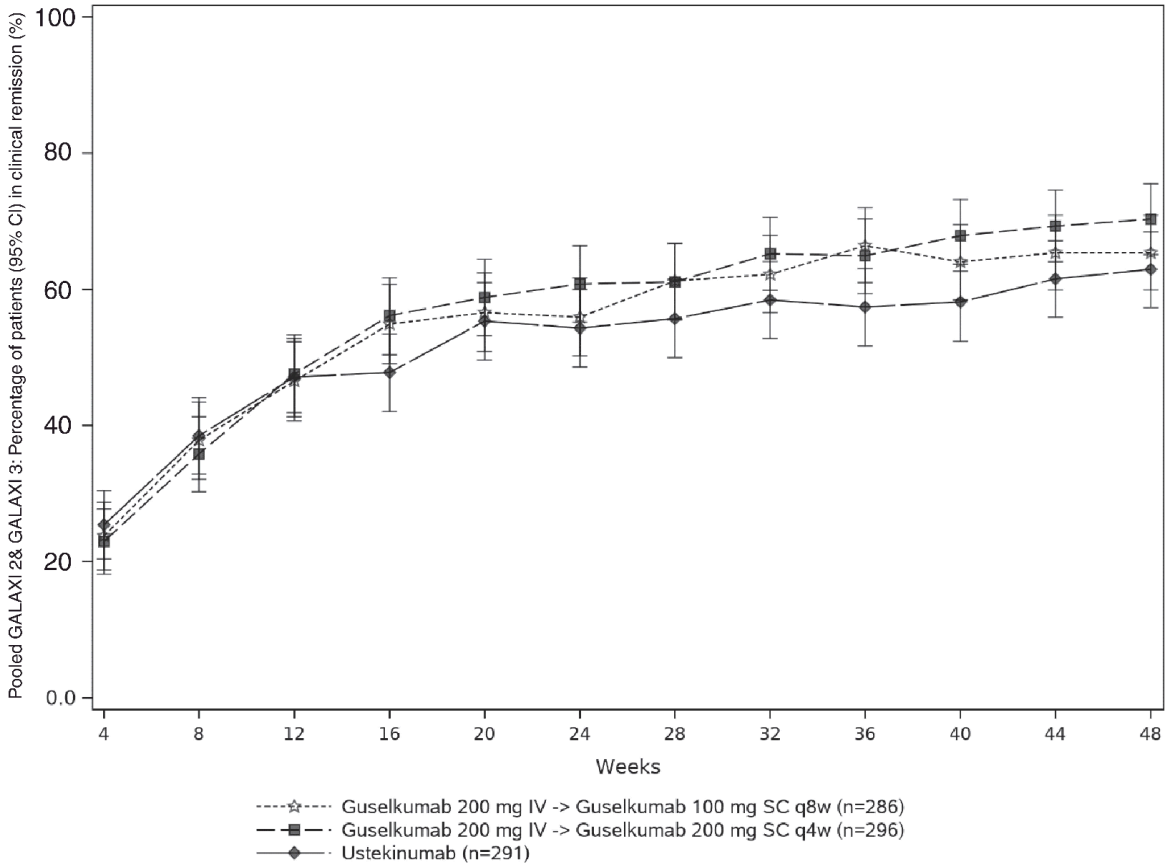
In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight.

In the pooled GALAXI Phase III studies subpopulation analysis, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w maintenance dose regimens. A clinically meaningful difference was observed between the two guselkumab 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: 54.1% vs 200 mg subcutaneous q4w: 71.0%); endoscopic response at Week 48 (100 mg subcutaneous q8w: 36.5% vs 200 mg subcutaneous q4w: 50.5%); and PRO-2 remission at Week 48 (100 mg subcutaneous q8w: 51.8% vs 200 mg subcutaneous q4w: 61.7%).

Clinical remission over time

CDAI scores were recorded at each patient visit. The proportion of patients in clinical remission through Week 48 is presented in Figure 3.

Figure 3: Proportion of patients in clinical remission through Week 48 in pooled GALAXI 2 and GALAXI 3



Health-related quality of life

Greater improvements from baseline were seen at Week 12 in guselkumab treatment groups when compared with placebo for inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score. The improvements were maintained through Week 48 in both studies.

GRAVITI

In the Phase III GRAVITI study, moderately to severely active Crohn's disease was defined as a CDAI score of ≥ 220 and ≤ 450 and a CD (SES-CD) of ≥ 6 (or ≥ 4 for patients with isolated ileal disease) and a mean daily SF ≥ 4 or mean daily AP score ≥ 2.

In GRAVITI, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg q8w subcutaneous maintenance; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg q4w subcutaneous maintenance; or placebo. All patients in the placebo group who met rescue criteria received the induction dosing with guselkumab 400 mg subcutaneous at Weeks 16, 20, and 24 followed by guselkumab 100 mg subcutaneous q8w.

A total of 347 patients were evaluated. The median age of patients was 36 years (ranging from 18 to 83 years), 58.5% were male, and 66% identified as White, 21.9% as Asian and 2.6% as Black.

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.

The results of the co-primary and major secondary efficacy endpoints compared to placebo at Week 12 are presented in Table 11.

Table 11: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GRAVITI

	Placebo	Guselkumab 400 mg subcutaneous injection[a]
Co-primary efficacy endpoints		
Clinical remission[b] at Week 12		
Total population	21% (N=117)	56%[c] (N=230)
Biologic naïve[d]	25% (N=56)	50% (N=105)
Prior biologic failure[e]	17% (N=53)	60% (N=108)
Endoscopic response[f] at Week 12		
Total population	21% (N=117)	41%[c] (N=230)
Biologic naïve[d]	27% (N=56)	49% (N=105)
Prior biologic failure[e]	17% (N=53)	33% (N=108)
Major secondary efficacy endpoints		
Clinical response[g] at Week 12		
Total population	33% (N=117)	73%[c] (N=230)
Biologic naïve[d]	38% (N=56)	68% (N=105)
Prior biologic failure[e]	28% (N=53)	78% (N=108)
PRO-2 remission[h] at Week 12		
Total population	17% (N=117)	49%[c] (N=230)
Biologic naïve[d]	18% (N=56)	44% (N=105)
Prior biologic failure[e]	17% (N=53)	52% (N=108)

[a] Guselkumab 400 mg subcutaneous at Week 0, Week 4 and Week 8

[b] Clinical remission: CDAI score < 150

[c] p< 0.001

[d] An additional 8 patients in the placebo group and 17 patients in the guselkumab 400 mg subcutaneous group, were previously exposed to but did not fail a biological therapy.

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

[f] Endoscopic response: ≥ 50% improvement from baseline in SES-CD score.

[g] Clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score < 150.

[h] PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

Clinical remission at Week 24 was achieved by a significantly greater proportion of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (60.9% and 58.3% vs 21.4% respectively, both p-values < 0.001). Clinical remission at Week 48 was achieved by 60% and 66.1% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Endoscopic response at Week 48 was achieved by 44.3% and 51.3% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Health-related quality of life

In GRAVITI, clinically meaningful improvements were observed in IBD-specific quality of life as assessed with IBDQ total score at Week 12 and Week 24 compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with guselkumab in one or more subsets of the paediatric population in ulcerative colitis and Crohn's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) 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 patients with plaque psoriasis, following subcutaneous administrations of guselkumab 100 mg 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 III studies in patients with plaque psoriasis were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. The pharmacokinetics of guselkumab in patients with psoriatic arthritis was similar to that in patients with psoriasis. Following subcutaneous administration of guselkumab 100 mg at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was also approximately 1.2 mcg/mL. Following subcutaneous administration of guselkumab 100 mg every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3.8 mcg/mL.

The pharmacokinetics of guselkumab were similar in patients with ulcerative colitis and Crohn's disease. Following the recommended intravenous induction dose regimen of guselkumab 200 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was 68.27 mcg/mL in patients with ulcerative colitis, and 70.5 mcg/mL in patients with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of guselkumab 400 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was estimated to be 28.8 mcg/mL in patients with ulcerative colitis and 27.7 mcg/mL in patients with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimen was similar following subcutaneous and intravenous induction.

Following subcutaneous maintenance dosing of guselkumab 100 mg every 8 weeks or guselkumab 200 mg 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 guselkumab 100 mg every 8 weeks or guselkumab 200 mg every 4 weeks in patients 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 across studies.

Biotransformation

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

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day across studies. Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies, and approximately 17 days in patients with ulcerative colitis or Crohn's disease.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, AZA, 6-MP, oral corticosteroids and csDMARDs such as MTX, did not affect the clearance of guselkumab.

Linearity/non-linearity

The systemic exposure of guselkumab (C_{max} 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 patients with plaque psoriasis. Serum guselkumab concentrations were approximately dose proportional following intravenous administration in patients with ulcerative colitis or Crohn's disease.

Paediatric population

The pharmacokinetics of guselkumab in paediatric patients with ulcerative colitis and Crohn's disease have not been established.

Elderly patients

No specific studies have been conducted in elderly patients. Of the 1 384 plaque psoriasis patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, 70 patients were 65 years of age or older, including 4 patients who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in Phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. Of the 859 ulcerative colitis patients exposed to guselkumab in Phase II/III clinical studies and included in the population pharmacokinetic analysis, a total of 52 patients were 65 years of age or older, and 9 patients were 75 years of age or older. Of the 1 009 Crohn's disease patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, a total of 39 patients were 65 years of age or older, and 5 patients were 75 years of age or older.

Population pharmacokinetic analyses in plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease patients indicated no apparent changes in CL/F estimate in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Patients with renal or hepatic impairment

No specific study has 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. Based on population pharmacokinetic analyses, creatinine clearance or hepatic function did not have a meaningful impact on guselkumab clearance.

Body weight

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, toxicity to reproduction and pre- and post-natal development.

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well tolerated via intravenous and subcutaneous routes of administration. A weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 23 times the maximum clinical exposures following a dose of 200 mg given intravenously. Additionally, there were no adverse immunotoxicity or cardiovascular safety pharmacology effects noted during the conduct of the

repeat-dose toxicity studies or in a targeted cardiovascular safety pharmacology study in cynomolgus monkeys.

There were no preneoplastic changes observed in histopathology evaluations of animals treated up to 24 weeks, or following the 12-week recovery period during which active substance was detectable in the serum.

No mutagenicity or carcinogenicity studies were conducted with guselkumab.

Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride monohydrate
Polysorbate 80 (E433)
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

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the pre-filled syringe or pre-filled pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

Tremfya 200 mg solution for injection in pre-filled syringe

2 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper with a fixed needle and a needle shield, assembled in an automatic needle guard.
Tremfya is available in packs containing one pre-filled syringe and in multipacks containing 2 (2 packs of 1) pre-filled syringes.

Not all pack sizes may be marketed.

Tremfya 200 mg solution for injection in pre-filled pen

2 mL solution in a pre-filled glass syringe with a bromobutyl rubber stopper, assembled in a pre-filled pen with an automatic needle guard.
Tremfya is available in a pack containing one pre-filled pen and in a multipack containing 2 (2 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After removing the pre-filled syringe or pre-filled pen from the refrigerator, keep the pre-filled syringe or pre-filled 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.

Prior to use, a visual inspection of the pre-filled syringe or pre-filled pen is recommended. The solution should be clear, colourless to light yellow, and may contain a few small white or clear particles. Tremfya should not be used if the solution is cloudy or discoloured, or contains large particles.

Each pack is provided with an 'Instructions for use' leaflet that fully describes the preparation and administration of the pre-filled syringe or pre-filled pen.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBERS

Tremfya 200 mg solution for injection in pre-filled syringe

EU/1/17/1234/006 1 pre-filled syringe
EU/1/17/1234/007 2 pre-filled syringes

Tremfya 200 mg solution for injection in pre-filled pen

EU/1/17/1234/008 1 pre-filled pen
EU/1/17/1234/009 2 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal:15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg of guselkumab in 20 mL solution (10 mg/mL). After dilution, each mL contains 0.8 mg of guselkumab

Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Excipient(s) with known effect

This medicinal product contains 10 mg of polysorbate 80 (E433) in each vial which is equivalent to 0.5 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is clear and colourless to light yellow, with target pH of 5.8 and approximate osmolarity of 302.7 mOsm/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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, or a biologic treatment.

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 Posology and method of administration

This medicinal product is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which it is indicated.

Guselkumab 200 mg concentrate for solution for infusion should only be used for induction dose.

Posology

Ulcerative colitis
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion 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. See SmPC for Tremfya 200 mg solution for injection.

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). See SmPC for Tremfya 100 mg solution for injection and 200 mg solution for injection.

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

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

Crohn's disease
Either of the following two induction dose regimens are recommended:

- 200 mg administered by intravenous infusion 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. See SmPC for Tremfya 200 mg solution for injection.

After completion of the induction dose regimen, the recommended maintenance dose starting at Week 16 is 100 mg administered by subcutaneous injection every 8 weeks (q8w). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose regimen of 200 mg administered by subcutaneous injection starting at Week 12 and every 4 weeks (q4w) thereafter, may be considered (see section 5.1). See SmPC for Tremfya 100 mg solution for injection and 200 mg solution for injection.

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

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is required (see section 5.2).
There is limited information in patients aged ≥ 65 years and very limited information in patients aged ≥ 75 years (see section 5.2).

Renal or hepatic impairment
Tremfya has not been studied in these patient populations. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies, and no dose adjustments are considered necessary. For further information on elimination of guselkumab, see section 5.2.

Paediatric population
The safety and efficacy of Tremfya in children and adolescents with ulcerative colitis and Crohn's disease below the age of 18 years have not been established. No data are available.

Method of administration

Tremfya 200 mg concentrate for solution for infusion is for intravenous use only. It should be administered over a period of at least one hour. Each vial is for single use only. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Serious hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically important active infections (e.g., active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Infections

Guselkumab may increase the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

Patients treated with guselkumab should be instructed 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, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving guselkumab should be monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting (see section 4.8). Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately and appropriate therapy initiated.

Hepatic transaminase elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with guselkumab q4w compared to patients treated with guselkumab q8w or placebo (see section 4.8).

When prescribing guselkumab q4w in psoriatic arthritis, it is recommended to evaluate liver enzymes at baseline and thereafter according to routine patient management. If increases in alanine

aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, treatment should be temporarily interrupted until this diagnosis is excluded.

Immunisations

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

Before live viral or live bacterial vaccination, treatment 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 Summary of Product Characteristics of the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

Excipients with known effect

Polysorbate 80 content
This medicinal product contains 10 mg of polysorbate 80 (E433) in each vial which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

In a Phase I study in patients 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, indicating that 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.

Concomitant immunosuppressive therapy or phototherapy

In psoriasis studies, the safety and efficacy of guselkumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant methotrexate (MTX) use did not appear to influence the safety or efficacy of guselkumab.

In ulcerative colitis and Crohn's disease studies, concomitant use of immunomodulators (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP]) or corticosteroids did not appear to influence the safety or efficacy of guselkumab.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 12 weeks after treatment.

Pregnancy

There are limited data from the use of guselkumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the

use of Tremfya during pregnancy.

Breast-feeding

It is unknown whether guselkumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, and decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant during this period cannot be excluded. A decision should be made whether to discontinue breast-feeding or to abstain from Tremfya therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. See section 5.3 for information on the excretion of guselkumab in animal (cynomolgus monkey) milk.

Fertility

The effect of guselkumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction was respiratory tract infections (approximately 8% of patients in ulcerative colitis studies, 11% of patients in the Crohn's disease studies, and 15% of patients in the psoriasis and psoriatic arthritis clinical studies).

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

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease clinical studies as well as adverse reactions reported from post-marketing experience. The adverse reactions are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

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

Description of selected adverse reactions

Transaminases increased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, liver function test abnormal, hypertransaminasaemia) were reported more frequently in the guselkumab treated groups (8.6% in the 100 mg subcutaneous q4w group and 8.3% in the 100 mg subcutaneous q8w group) than in the placebo group (4.6%). Through 1 year, adverse reactions 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, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the guselkumab q4w group compared with the guselkumab q8w group (Table 2). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 2: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through week 24[a]			Through 1 year[b]	
	Placebo N=370[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373[c]	guselkumab 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 guselkumab are not included.

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

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the guselkumab q8w dose was similar to that observed for the guselkumab q8w dose in the

psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled induction period (Week 0-12), adverse reactions of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased, and liver function test increased) were reported more frequently in the guselkumab treated groups (1.7% of patients) than in the placebo group (0.6% of patients). In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, adverse reactions 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 guselkumab 200 mg subcutaneous q4w treatment group and 4.1% of patients in the guselkumab 100 mg subcutaneous q8w treatment group compared to 2.4% in the placebo group.

Based on laboratory assessments in pooled Phase II and Phase III Crohn's disease clinical studies, the frequency of ALT or AST elevations were lower than those observed in psoriatic arthritis Phase III clinical studies. In pooled Phase II and Phase III Crohn's disease clinical studies, through the placebo-controlled period (Week 12), ALT (< 1% of patients) and AST (< 1% of patients) elevations ≥ 3x ULN were reported in guselkumab treated patients. In pooled Phase II and Phase III Crohn's disease clinical studies, through the reporting period of approximately one year, ALT and/or AST elevations ≥ 3x ULN were reported in 2.7% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.6% of patients in the guselkumab 100 mg subcutaneous 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.

Neutrophil count decreased
In two Phase III psoriatic arthritis clinical studies, through the placebo-controlled period, the adverse reaction of decreased neutrophil count was reported more frequently in the guselkumab treated group (0.9%) than in the placebo group (0%). Through 1 year, the adverse reaction of decreased neutrophil count was reported in 0.9% of patients treated with guselkumab. In most cases, the decrease in blood neutrophil count was mild, transient, not associated with infection and did not lead to discontinuation of treatment.

Gastroenteritis
In two Phase III psoriasis clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the guselkumab treated group (1.1%) than in the placebo group (0.7%). Through Week 264, 5.8% of all guselkumab treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of guselkumab through Week 264. Gastroenteritis rates observed in psoriatic arthritis clinical studies through the placebo-controlled period were similar to those observed in the psoriasis clinical studies.

Injection site reactions
In two Phase III psoriasis clinical studies through Week 48, 0.7% of guselkumab injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 264, 0.4% of guselkumab injections were associated with injection site reactions. Injection site reactions were generally mild to moderate in severity; none were serious, and one led to discontinuation of guselkumab.

In two Phase III psoriatic arthritis clinical studies through Week 24, the number of patients that reported 1 or more injection site reactions was low and slightly higher in the guselkumab groups than in the placebo group; 5 (1.3%) patients in the guselkumab q8w group, 4 (1.1%) patients in the guselkumab q4w group, and 1 (0.3%) patient in the placebo group. One patient discontinued guselkumab due to an injection site reaction during the placebo-controlled period of the psoriatic arthritis clinical studies. Through 1 year, the proportion of patients reporting 1 or more injection site

reactions was 1.6% and 2.4% in the guselkumab q8w and q4w groups respectively. Overall, the rate of injections associated with injection site reactions observed in psoriatic arthritis clinical studies through the placebo-controlled period was similar to rates observed in the psoriasis clinical studies.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group (guselkumab 200 mg was administered as two 100 mg injections in the Phase III ulcerative colitis maintenance clinical study) and no injection site reactions in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and none were serious.

In Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 4.1% (0.8% of injections) in the treatment group which received guselkumab 200 mg intravenous induction followed by 200 mg subcutaneous q4w, and 1.4% (0.6% of injections) of patients in the guselkumab 200 mg intravenous induction followed by 100 mg subcutaneous q8w group. Overall injection site reactions were mild; none were serious.

In a Phase III Crohn's disease clinical study through Week 48, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 7% (1.3% of injections) in the treatment group which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 4.3% (0.7% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Most injection site reactions were mild; none were serious.

Immunogenicity
The immunogenicity of guselkumab was evaluated using a sensitive and drug-tolerant immunoassay.

In pooled Phase II and Phase III analyses in patients with psoriasis and psoriatic arthritis, 5% (n=145) of patients treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 8% (n=12) had antibodies that were classified as neutralising, which equates to 0.4% of all patients treated with guselkumab. In pooled Phase III analyses in patients with psoriasis, approximately 15% of patients treated with guselkumab developed antidrug antibodies in up to 264 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralising, which equates to 0.76% of all patients treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

In pooled Phase II and Phase III analyses in patients with ulcerative colitis who were treated with intravenous induction followed by subcutaneous maintenance, approximately 12% (n=58) of patients treated with guselkumab for up to 56 weeks developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 16% (n=9) had antibodies that were classified as neutralising, which equates to 2% of all patients treated with guselkumab. In a Phase III analysis up to Week 24 in patients with ulcerative colitis who were treated with subcutaneous induction followed by subcutaneous maintenance, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, 13% (n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or the development of injection site reactions.

In pooled Phase II and Phase III analyses up to Week 48 in patients with Crohn's disease who were treated with intravenous induction followed by subcutaneous maintenance dose regimen, approximately 5% (n=30) of patients treated with guselkumab developed antidrug antibodies. Of the patients who developed antidrug antibodies, approximately 7% (n=2) had antibodies that were classified as neutralising antibodies, which equates to 0.3% of guselkumab treated patients.
In a Phase III analysis up to Week 48 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 9% (n=24) of patients treated with guselkumab developed antidrug antibodies. Of these patients, 13%

(n=3) had antibodies that were classified as neutralising antibodies, which equates to 1% of guselkumab treated patients. Antidrug antibodies were not associated with lower efficacy or development of injection site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Guselkumab intravenous doses up to 1 200 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, the patient must be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment must be administered immediately.

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 high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In patients with ulcerative colitis or 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 exerts 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, ulcerative colitis, and Crohn's disease. 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 I 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 patients with plaque psoriasis at Week 12 compared to baseline. In the same Phase I 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 patients in Phase II and Phase III plaque psoriasis studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

In psoriatic arthritis patients in Phase III studies, 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 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

In patients with ulcerative colitis or Crohn's disease, guselkumab treatment led to decreases in inflammatory markers including C-reactive protein (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.

Clinical efficacy and safety

Ulcerative colitis
The efficacy and safety of guselkumab were evaluated in three Phase III multicentre, randomised, double-blind, placebo-controlled studies (QUASAR intravenous induction study, QUASAR maintenance study, and ASTRO subcutaneous induction 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 (AZA, 6-MP), biologic therapy (TNF blockers, vedolizumab), a Janus kinase (JAK) inhibitor, and/or sphingosine-1-phosphate receptor modulators (S1PRM) applicable only for ASTRO. In addition, efficacy and safety of guselkumab were evaluated in a randomised, double-blind, placebo-controlled, Phase IIb induction dose-finding study (QUASAR induction dose-ranging study) that enrolled a similar ulcerative colitis patient population as the Phase III induction 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 ≥ 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).

Induction study: QUASAR IS
In the induction study QUASAR IS, patients were randomised in a 3:2 ratio to receive either guselkumab 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 and 1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, MTX, 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, 87.5%, 54.1% and 18% had previously failed a TNF blocker, vedolizumab or a JAK inhibitor, respectively, and 47.4% 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, fatigue response and IBDQ remission (Table 3).

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

Table 3: Proportion of patients meeting efficacy endpoints at Week 12 in QUASAR IS

Endpoint	Placebo %	Guselkumab 200 mg intravenous induction[a] %	Treatment Difference (95% CI)
Clinical remission[b]			
Total population	8% (N=280)	23% (N=421)	15% (10%, 20%)[c]
Biologic and JAK inhibitor naïve[d]	12% (N=137)	32% (N=202)	20% (12%, 28%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 14%)
Symptomatic remission[f]			
Total population	21% (N=280)	50% (N=421)	29% (23%, 36%)[c]
Biologic and JAK inhibitor naïve[d]	26% (N=137)	60% (N=202)	34% (24%, 44%)
Prior biologic and/or JAK inhibitor failure[e]	14% (N=136)	38% (N=208)	24% (16%, 33%)
Endoscopic healing[g]			
Total population	11% (N=280)	27% (N=421)	16% (10%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	17% (N=137)	38% (N=202)	21% (12%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	5% (N=136)	15% (N=208)	10% (4%, 16%)
Clinical response[h]			
Total population	28% (N=280)	62% (N=421)	34% (27%, 41%)[c]
Biologic and JAK inhibitor naïve[d]	35% (N=137)	71% (N=202)	36% (26%, 46%)
Prior biologic and/or JAK inhibitor failure[e]	20% (N=136)	51% (N=208)	32% (22%, 41%)
Histologic endoscopic mucosal healing[i]			
Total Population	8% (N=280)	24% (N=421)	16% (11%, 21%)[c]
Biologic and JAK inhibitor naïve[d]	11% (N=137)	33% (N=202)	22% (13%, 30%)
Prior biologic and/or JAK inhibitor failure[e]	4% (N=136)	13% (N=208)	9% (3%, 15%)
Fatigue response[j]			
Total population	21% (N=280)	41% (N=421)	20% (13%, 26%)[c]
Biologic and JAK inhibitor naïve[d]	29% (N=137)	42% (N=202)	12% (2%, 23%)
Prior biologic and/or JAK inhibitor failure[e]	13% (N=136)	38% (N=208)	25% (17%, 34%)
IBDQ remission[k]			
Total population	30% (N=280)	51% (N=421)	22% (15%, 29%)[c]
Biologic and JAK inhibitor naïve[d]	34% (N=137)	62% (N=202)	28% (18%, 38%)
Prior biologic and/or JAK inhibitor failure[e]	24% (N=136)	39% (N=208)	15% (5%, 25%)

[a] Guselkumab 200 mg as an intravenous induction 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.

[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 patients in the placebo group and 11 patients in the guselkumab 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.

[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.

[k] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

QUASAR IS and QUASAR induction dose-ranging study also enrolled 48 patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS ≥ 1. In patients with a baseline mMS of 4, guselkumab 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 ulcerative colitis population.

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

Maintenance study: QUASAR MS
The QUASAR MS evaluated 568 patients who achieved clinical response at 12 weeks following the intravenous administration of guselkumab in either QUASAR IS or from the QUASAR induction dose-ranging study. In the QUASAR MS, these patients were randomised to receive a subcutaneous maintenance regimen of either guselkumab 100 mg every 8 weeks, guselkumab 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, fatigue response and IBDQ remission (Table 4).

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

Table 4: Proportion of patients meeting efficacy endpoints at Week 44 in QUASAR MS

Endpoint	Placebo %	Guselkumab 100 mg q8w subcutaneous injection[a] %	Guselkumab 200 mg q4w subcutaneous injection[b] %	Treatment Difference (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission[c]					
Total population[d]	19% (N=190)	45% (N=188)	50% (N=190)	25% (16%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	58% (N=96)	24% (12%, 36%)	29% (17%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	40% (N=77)	40% (N=88)	30% (19%, 42%)	32% (21%, 44%)
Symptomatic remission[h]					
Total population[d]	37% (N=190)	70% (N=188)	69% (N=190)	32% (23%, 41%)[e]	31% (21%, 40%)[e]

Biologic and JAK-inhibitor naïve[f]	46% (N=108)	74% (N=105)	76% (N=96)	28% (15%, 40%)	28% (15%, 41%)
Prior biologic and/or JAK-inhibitor failure[g]	24% (N=75)	65% (N=77)	60% (N=88)	39% (26%, 52%)	37% (23%, 50%)
Corticosteroid-free clinical remission[i]					
Total population[d]	18% (N=190)	45% (N=188)	49% (N=190)	26% (17%, 34%)[e]	29% (20%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	50% (N=105)	56% (N=96)	24% (12%, 36%)	27% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	7% (N=75)	40% (N=77)	40% (N=88)	32% (21%, 43%)	34% (23%, 45%)
Endoscopic healing[j]					
Total population[d]	19% (N=190)	49% (N=188)	52% (N=190)	30% (21%, 38%)[e]	31% (22%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	26% (N=108)	53% (N=105)	59% (N=96)	27% (15%, 40%)	30% (18%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	45% (N=77)	42% (N=88)	36% (24%, 48%)	35% (23%, 46%)
Histologic endoscopic mucosal healing[k]					
Total population[d]	17% (N=190)	44% (N=188)	48% (N=190)	26% (17%, 34%)[e]	30% (21%, 38%)[e]
Biologic and JAK-inhibitor naïve[f]	23% (N=108)	50% (N=105)	56% (N=96)	26% (14%, 38%)	30% (17%, 42%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	38% (N=77)	39% (N=88)	28% (16%, 39%)	31% (20%, 43%)
Clinical response[l]					
Total population[d]	43% (N=190)	78% (N=188)	75% (N=190)	34% (25%, 43%)[e]	31% (21%, 40%)[e]
Biologic and JAK-inhibitor naïve[f]	54% (N=108)	83% (N=105)	81% (N=96)	29% (17%, 41%)	26% (14%, 39%)
Prior biologic and/or JAK-inhibitor failure[g]	28% (N=75)	70% (N=77)	67% (N=88)	41% (27%, 54%)	39% (26%, 53%)
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population[q]	34% (N=59)	61% (N=66)	72% (N=69)	26% (9%, 43%)[m]	38% (23%, 54%)[e]
Biologic and JAK-inhibitor naïve[r]	34% (N=41)	65% (N=43)	79% (N=48)	31% (9%, 51%)	45% (25%, 62%)
Prior biologic and/or JAK-inhibitor failure[g]	27% (N=15)	60% (N=20)	56% (N=18)	33% (-1%, 62%)	29% (-6%, 59%)
Endoscopic normalisation[n]					
Total population[d]	15% (N=190)	35% (N=188)	34% (N=190)	18% (10%, 27%)[e]	17% (9%, 25%)[e]
Biologic and JAK-inhibitor naïve [f]	20% (N=108)	38% (N=105)	42% (N=96)	17% (6%, 29%)	17% (6%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	8% (N=75)	31% (N=77)	24% (N=88)	21% (10%, 33%)	16% (6%, 26%)
Fatigue response[o]					
Total population [d]	29% (N=190)	51% (N=188)	43% (N=190)	20% (11%, 29%)[e]	13% (3%, 22%)[m]
Biologic and JAK-inhibitor naïve[f]	36% (N=108)	51% (N=105)	53% (N=96)	15% (2%, 28%)	16% (3%, 29%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	47% (N=77)	32% (N=88)	27% (13%, 40%)	13% (1%, 26%)

IBDQ remission[p]					
Total population[d]	37% (N=190)	64% (N=188)	64% (N=190)	26% (17%, 36%)[e]	26% (16%, 35%)[e]
Biologic and JAK-inhibitor naïve [f]	49% (N=108)	68% (N=105)	74% (N=96)	19% (6%, 32%)	24% (11%, 37%)
Prior biologic and/or JAK-inhibitor failure[g]	19% (N=75)	58% (N=77)	53% (N=88)	38% (26%, 50%)	35% (23%, 48%)

[a] Guselkumab 100 mg as a subcutaneous injection every 8 weeks after the induction regimen.

[b] Guselkumab 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.

[d] Patients who achieved clinical response 12 weeks following the intravenous administration of guselkumab 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 patients in the placebo group, 6 patients in the guselkumab 100 mg group, and 6 patients in the guselkumab 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.

[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.

[p] Total Inflammatory Bowel Disease Questionnaire score ≥ 170.

[q] Subjects who achieved clinical remission 12 weeks following intravenous administration of guselkumab in either QUASAR induction study or QUASAR induction dose-ranging study.

[r] An additional 3 patients in the placebo group, 3 patients in the guselkumab 100 mg group, and 3 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic or JAK inhibitor.

In QUASAR IS and QUASAR MS, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race, body weight, and previous treatment with a biologic therapy or JAK inhibitor.

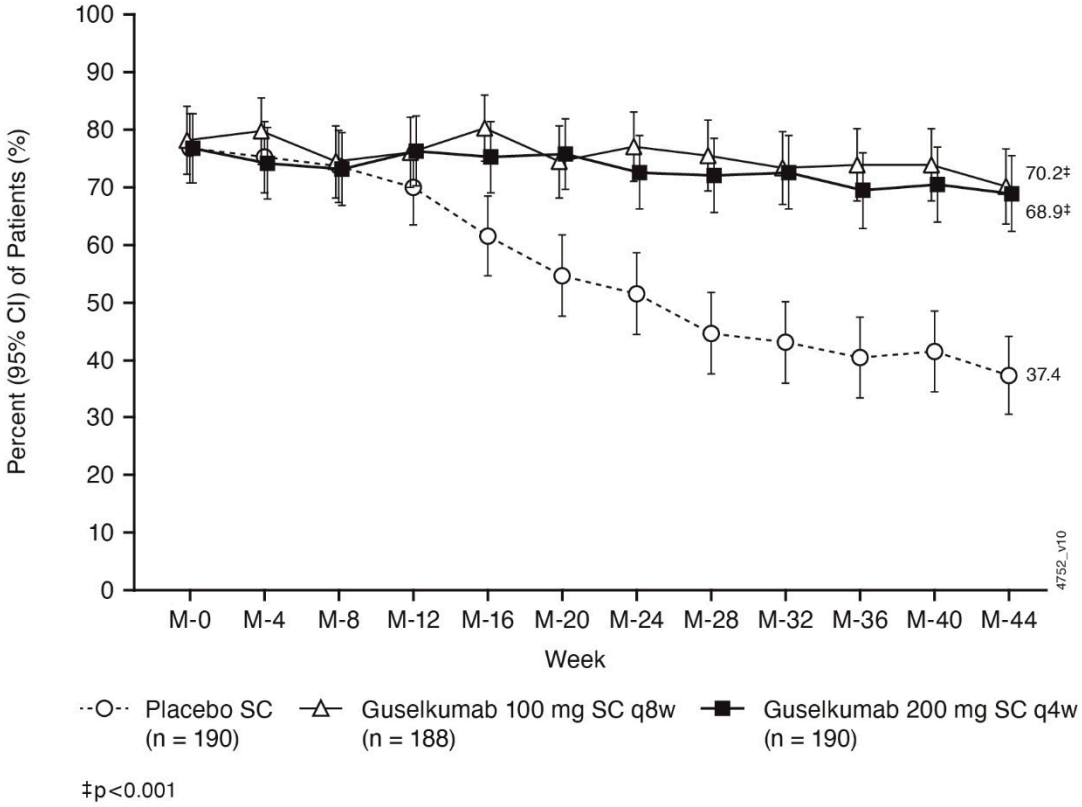
In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of > 15% were observed between the two guselkumab dose groups 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).

QUASAR MS enrolled 31 patients with an induction 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 guselkumab in QUASAR IS or QUASAR induction dose-ranging study. In these patients, guselkumab efficacy relative to placebo as measured by clinical remission, clinical response, and endoscopic healing at Week 44 was consistent with the total population.

Symptomatic remission over time

In QUASAR MS symptomatic remission defined as 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 guselkumab treatment groups, while a decline was observed in the placebo group (Figure 1):

Figure 1: Proportion of patients in symptomatic remission through Week 44 in QUASAR MS



Week 24 responders to guselkumab extended treatment
Guselkumab treated patients who were not in clinical response at induction Week 12, received guselkumab 200 mg subcutaneous at Weeks 12, 16 and 20. In QUASAR IS, 66/120 (55%) guselkumab treated patients who were not in clinical response at induction Week 12 achieved clinical response at Week 24. Week 24 responders to guselkumab entered QUASAR MS and received guselkumab 200 mg subcutaneous every 4 weeks. At Week 44 of QUASAR MS, 83/123 (67%) of these patients maintained clinical response and 37/123 (30%) achieved clinical remission.

Recapture of efficacy after loss of response to guselkumab
Nineteen patients receiving guselkumab 100 mg subcutaneous q8w who experienced a first loss of response (10%) between Week 8 and 32 of QUASAR MS received blinded guselkumab dosing with 200 mg guselkumab subcutaneous q4w 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). In QUASAR IS, histologic remission at Week 12 was achieved in 40% of patients treated with guselkumab and 19% of patients in the placebo group. In QUASAR MS, histologic remission at Week 44 was achieved in 59% and 61% of patients treated with guselkumab 100 mg subcutaneous q8w and guselkumab 200 mg subcutaneous q4w and 27% of patients in the placebo group.

Normalisation of the endoscopic appearance of the mucosa was defined as ES of 0. In QUASAR IS, endoscopic normalisation at Week 12 was achieved in 15% of patients treated with guselkumab and 5% of patients in the placebo group.

Composite histologic-endoscopic mucosal outcomes
Combined symptomatic remission, endoscopic normalisation, histologic remission, and faecal calprotectin ≤ 250 mg/kg at Week 44 was achieved by a greater proportion of patients treated with guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (22% and 28% vs 9%, respectively).

Health-related quality of life
At Week 12 of QUASAR IS, patients receiving guselkumab showed greater and clinically meaningful improvements from baseline when compared with placebo in inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score, and all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function). These improvements were maintained in guselkumab treated patients in QUASAR MS through Week 44.

Ulcerative colitis related hospitalisations
Through Week 12 of QUASAR IS, lower proportions of patients in the guselkumab group compared with the placebo group had ulcerative colitis-related hospitalisations (1.9%, 8/421 vs. 5.4%, 15/280).

ASTRO
In ASTRO, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg subcutaneous maintenance every 8 weeks; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg subcutaneous maintenance every 4 weeks; or placebo.

A total of 418 patients were evaluated. The median age of patients was 40 years (ranging from 18 to 80 years); 38.8% were female; and 64.6% identified as White, 28.9% as Asian, and 3.1% as Black.

Enrolled patients were permitted to use stable doses of oral aminosalicylates, immunomodulators (AZA, 6-MP, MTX), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 77.3% of patients were receiving aminosalicylates, 20.1% of patients were receiving immunomodulators, and 32.8% of patients were receiving corticosteroids. Concomitant biologic therapies, JAK inhibitors, or S1PRMs were not permitted. A total of 40.2% of patients had previously failed treatment with at least one biologic therapy, JAK inhibitor, and/or S1PRM, 58.1% were biologic, JAK inhibitor, and S1PRM naïve, and 1.7% had previously received but had not failed a biologic, JAK inhibitor, or S1PRM.

In ASTRO, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included symptomatic remission, endoscopic healing, clinical response and histologic-endoscopic mucosal healing (see Table 5). Secondary endpoints at Week 24 included clinical remission and endoscopic healing (see Table 6).

Table 5: Proportion of patients meeting efficacy endpoints at Week 12 in ASTRO

Endpoint	Placebo %	Guselkumab 400 mg Subcutaneous Induction[a] %	Treatment Difference vs Placebo (95% CI)[b]
Clinical remission[c]			
Total Population	6% (N=139)	28% (N=279)	21% (15%, 28%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	9% (N=79)	36% (N=164)	27% (18%, 37%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	4% (N=56)	16% (N=112)	12% (3%, 20%)
Symptomatic remission[d]			
Total Population	21% (N=139)	51% (N=279)	30% (22%, 39%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	25% (N=79)	59% (N=164)	34% (22%, 46%)

Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	14% (N=56)	41% (N=112)	26% (13%, 39%)
Endoscopic healing[h]			
Total Population	13% (N=139)	37% (N=279)	24% (17%, 32%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	46% (N=164)	28% (17%, 40%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	24% (N=112)	16% (6%, 26%)
Clinical response[i]			
Total Population	35% (N=139)	66% (N=279)	31% (22%, 40%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	42% (N=79)	71% (N=164)	30% (17%, 43%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	25% (N=56)	57% (N=112)	31% (17%, 45%)
Histologic endoscopic mucosal healing[j]			
Total Population	11% (N=139)	30% (N=279)	20% (12%, 27%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	14% (N=79)	38% (N=164)	25% (14%, 35%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	7% (N=56)	19% (N=112)	11% (1%, 20%)

[a] Guselkumab 400 mg subcutaneous induction at Week 0, Week 4, and Week 8

[b] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[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

[d] A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group and 3 patients in the guselkumab group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

[i] Decrease from 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

[j] An endoscopy subscore of 0, or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Table 6: Proportion of patients meeting efficacy endpoints at Week 24 in ASTRO

Endpoint	**Placebo %**	**Guselkumab 400 mg SC induction→ 100 mg q8w Subcutaneous Injection[a] %**	**Guselkumab 400 mg SC induction→ 200 mg q4w Subcutaneous Injection[b] %**	**Treatment Difference vs Placebo (95% CI)[c]**	
				Guselkumab 100 mg	**Guselkumab 200 mg**
Clinical remission[d]					
Total population	9% (N=139)	35% (N=139)	36% (N=140)	26% (17%, 35%)[e]	27% (18%, 36%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	13% (N=79)	49% (N=81)	43% (N=83)	37% (24%, 50%)	31% (18%, 44%)
Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	16% (N=57)	27% (N=55)	10% (-1%, 21%)	21% (9%, 34%)
Endoscopic healing[h]					
Total population	12% (N=139)	40% (N=139)	45% (N=140)	28% (18%, 38%)[e]	33% (23%, 42%)[e]
Biologic, JAK-inhibitor, and S1PRM naïve[f]	18% (N=79)	54% (N=81)	52% (N=83)	37% (23%, 51%)	34% (21%, 48%)

Prior biologic, JAK-inhibitor, and/or S1PRM failure[g]	5% (N=56)	19% (N=57)	36% (N=55)	13% (1%, 25%)	30% (17%, 44%)

[a] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg SC maintenance every 8 weeks

[b] Guselkumab 400 mg SC induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg SC maintenance every 4 weeks

[c] The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and Sato variance estimator. The stratification variables used were prior biologic, JAK inhibitor, and/or S1PRM failure status (Yes or No), and Mayo endoscopy subscore at baseline (moderate [2] or severe [3]).

[d] 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

[e] $p < 0.001$

[f] An additional 4 patients in the placebo group, 1 patient in the guselkumab 100 mg group, and 2 patients in the guselkumab 200 mg group were previously exposed to but did not fail a biologic, JAK inhibitor or S1PRM

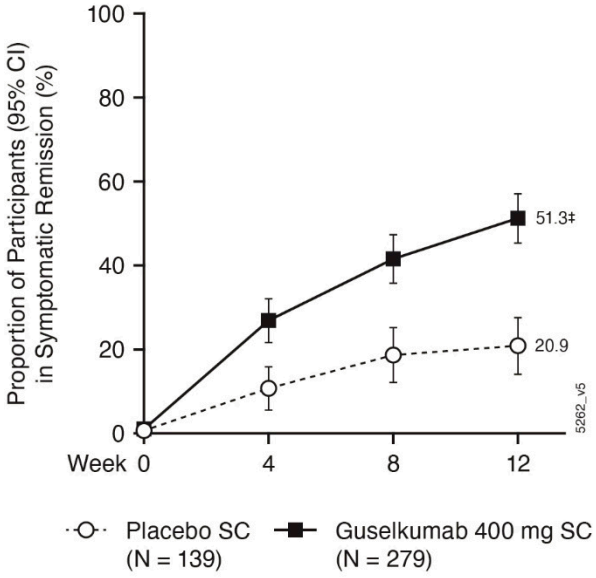
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[h] An endoscopy subscore of 0, or 1 with no friability

Symptomatic remission over time

In ASTRO, symptomatic remission defined as stool frequency subscore of 0 or 1 and not increased from baseline, and a rectal bleeding subscore of 0 observed through Week 12, a greater proportion of patients in the guselkumab treatment groups achieved symptomatic remission compared with the placebo group (Figure 2):

Figure 2: Proportion of patients in symptomatic remission through Week 12 in ASTRO



‡p<0.001

Rectal bleeding and stool frequency subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with guselkumab compared to placebo.

Histologic and endoscopic assessment

Histologic remission at Week 12 was achieved in 44% of patients treated with guselkumab 400 mg subcutaneous induction compared to 20% of patients on placebo.

Endoscopic normalisation at Week 24 was achieved in 21% and 26% of patients treated with guselkumab 400 mg subcutaneous induction, followed by guselkumab 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or guselkumab 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter, respectively, compared to 4% of patients on placebo.

Abdominal pain and bowel urgency
A greater proportion of patients treated with guselkumab 400 mg subcutaneous induction compared to placebo had no abdominal pain (56% vs 31%), and no bowel urgency (49% vs 24%) at Week 12.

Health-related quality of life
Disease-specific health-related quality of life was assessed with the IBDQ. A greater proportion of patients in the combined 400 mg SC guselkumab group (61%) achieved IBDQ remission at Week 12 compared with the placebo group (34%).

Crohn's disease
The efficacy and safety of guselkumab were evaluated in three Phase III clinical studies 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 active-controlled (ustekinumab), parallel group studies (GALAXI 2 and GALAXI 3) and one 24-Week multicentre, randomised, double-blind, placebo-controlled, parallel group study (GRAVITI). All three studies had a treat-through study design: patients randomised to guselkumab (or ustekinumab for GALAXI 2 and GALAXI 3) maintained that treatment assignment for the duration of the study.

GALAXI 2 and GALAXI 3
In the Phase III studies GALAXI 2 and GALAXI 3, 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). Additional criteria for GALAXI 2/3 included a mean daily stool frequency (SF) > 3 or mean daily abdominal pain score (AP) > 1.

In GALAXI 2 and GALAXI 3 studies, patients were randomised in a 2:2:2:1 ratio to receive guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8 followed by guselkumab 200 mg subcutaneous q4w maintenance; or guselkumab 200 mg intravenous induction at Weeks 0, 4 and 8, followed by guselkumab 100 mg subcutaneous q8w maintenance; or ustekinumab approximately 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w maintenance; or placebo. Placebo non-responders received ustekinumab 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), 57.6% were male; and 74.3% identified as White, 21.3% as Asian and 1.5% as Black.

In GALAXI 2, 52.8% of patients had previously failed treatment with at least one biologic therapy (50.6% were intolerant or failed at least 1 prior anti-TNFα therapy, 7.5% were intolerant or failed prior vedolizumab 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 (50.3% were intolerant or failed at least 1 prior anti-TNFα therapy, 9.6% were intolerant or failed prior vedolizumab 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.

The results of the co-primary and major secondary endpoints compared to placebo in GALAXI 2 and GALAXI 3 are presented in Tables 7 (Week 12) and 8 (Week 48). The results of the major secondary endpoints at Week 48 compared to ustekinumab are presented in Tables 9 and 10.

Table 7: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GALAXI 2 and GALAXI 3

	GALAXI 2		GALAXI 3	
	Placebo %	**Guselkumab intravenous induction[a] %**	**Placebo %**	**Guselkumab intravenous induction[a] %**
Co-primary efficacy endpoints				
Clinical remission[b] at Week 12				
Total population	22% (N=76)	47%[i] (N=289)	15% (N=72)	47%[i] (N=293)
Biologic naïve[c]	18% (N=34)	50% (N=121)	15% (N=27)	50% (N=123)
Prior biologic failure[d]	23% (N=39)	45% (N=150)	15% (N=39)	47% (N=150)
Endoscopic response[e] at Week 12				
Total population	11% (N=76)	38%[i] (N=289)	14% (N=72)	36%[i] (N=293)
Biologic naïve[c]	15% (N=34)	51% (N=121)	22% (N=27)	41% (N=123)
Prior biologic failure[d]	5% (N=39)	27% (N=150)	8% (N=39)	31% (N=150)
Major secondary efficacy endpoints				
PRO-2 remission[f] at Week 12				
Total population	21% (N=76)	43%[i] (N=289)	14% (N=72)	42%[i](N=293)
Biologic naïve[c]	24% (N=34)	43% (N=121)	15% (N=27)	47% (N=123)
Prior biologic failure[d]	13% (N=39)	41% (N=150)	13% (N=39)	39% (N=150)
Fatigue response[g] at Week 12				
Total population	29% (N=76)	45%[j] (N=289)	18% (N=72)	43%[i](N=293)
Biologic naïve[c]	32% (N=34)	48% (N=121)	19% (N=27)	46% (N=123)
Prior biologic failure[d]	26% (N=39)	41% (N=150)	18% (N=39)	43% (N=150)
Endoscopic remission[h] at Week 12				
Total population	1% (N=76)	15% (N=289)	8% (N=72)	16% (N=293)
Biologic naïve[c]	3% (N=34)	22% (N=121)	19% (N=27)	25% (N=123)
Prior biologic failure[d]	0% (N=39)	9% (N=150)	0% (N=39)	9% (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 – Two guselkumab treatment groups were combined for this column as patients received the same intravenous induction dose regimen prior to Week 12.

[b] Clinical remission is defined as CDAI score < 150.

[c] An additional 9 patients in the placebo group and 38 patients in the guselkumab 200 mg intravenous group were previously exposed to but did not fail a biological therapy.

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

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

[f] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

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

[h] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] $p < 0.001$

[j] $p < 0.05$

Table 8: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus placebo at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Placebo	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]	Placebo (N=72)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection[b]
Corticosteroid-free clinical remission[c] at Week 48[f]						
Total population	12% (N=76)	45%[e] (N=143)	51%[e] (N=146)	14% (N=72)	44%[e] (N=143)	48%[e] (N=150)
Endoscopic response[d] at Week 48[f]						
Total population	7% (N=76)	38%[e] (N=143)	38%[e] (N=146)	6% (N=72)	33%[e] (N=143)	36%[e] (N=150)

[a] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[c] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

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

[e] $p < 0.001$

[f] Participants who met inadequate response criteria at Week 12 were considered non-responders at Week 48, regardless of treatment arm.

Table 9: Proportion of patients meeting major secondary efficacy endpoints with guselkumab versus ustekinumab at Week 48 in GALAXI 2 and GALAXI 3

	GALAXI 2			GALAXI 3		
	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection[b]	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]
Clinical remission at Week 48 and endoscopic response[d] at Week 48						
Total population	39% (N=143)	42% (N=143)	49% (N=146)	28% (N=148)	41%[k] (N=143)	45%[k] (N=150)
Endoscopic response[e] at Week 48[l]						
Total population	42% (N=143)	49% (N=143)	56% (N=146)	32% (N=148)	47% (N=143)	49% (N=150)
Endoscopic remission[f] at Week 48						
Total population	20% (N=143)	27% (N=143)	24% (N=146)	13% (N=148)	24%[k] (N=143)	19% (N=150)
Clinical remission[g] at Week 48						
Total population	65% (N=143)	64% (N=143)	75% (N=146)	61% (N=148)	66% (N=143)	66% (N=150)
Corticosteroid-free clinical remission[h] at Week 48[l]						
Total population	61% (N=143)	63% (N=143)	71% (N=146)	59% (N=148)	64% (N=143)	64% (N=150)
Durable clinical remission[i] at Week 48						
Total population	45% (N=143)	46% (N=143)	52% (N=146)	39% (N=148)	50% (N=143)	49% (N=150)
PRO-2 remission[j] at Week 48						
Total population	59% (N=143)	60% (N=143)	69% (N=146)	53% (N=148)	58% (N=143)	56% (N=150)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

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

[f] Endoscopic remission is defined as SES-CD Score ≤ 2.

[g] Clinical remission is defined as CDAI score < 150.

[h] Corticosteroid-free clinical remission is defined as CDAI score < 150 at Week 48 and not receiving corticosteroids at Week 48.

[i] Durable clinical remission is defined as CDAI < 150 for ≥ 80% of all visits between Week 12 and Week 48 (at least 8 of 10 visits), which must include Week 48.

[j] PRO-2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

[k] $p < 0.05$

[l] Responses at Week 48 were evaluated irrespective of clinical response at Week 12

Table 10: Proportion of patients meeting efficacy endpoints with guselkumab versus ustekinumab at Week 48 in pooled GALAXI 2 and GALAXI 3

	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection[a]	**Guselkumab intravenous induction → 100 mg q8w subcutaneous injection[b]**	**Guselkumab intravenous induction → 200 mg q4w subcutaneous injection[c]**
Clinical remission at Week 48 and endoscopic response[d] at Week 48			
Total population	34% (N=291)	42% (N=286)	47% (N=296)
Biologic naïve[e]	43% (N=121)	51% (N=116)	55% (N=128)
Prior biologic failure[f]	26% (N=156)	37% (N=153)	41% (N=147)
Endoscopic response[g] at Week 48			
Total population	37% (N=291)	48% (N=286)	53% (N=296)
Biologic naïve[e]	43% (N=121)	59% (N=116)	59% (N=128)
Prior biologic failure[f]	31% (N=156)	43% (N=153)	47% (N=147)
Endoscopic remission[h] at Week 48			
Total population	16% (N=291)	25% (N=286)	21% (N=296)
Biologic naïve[e]	19% (N=121)	34% (N=116)	27% (N=128)
Prior biologic failure[f]	13% (N=156)	21% (N=153)	14% (N=147)
Clinical remission[i] at Week 48			
Total population	63% (N=291)	65% (N=286)	70% (N=296)
Biologic naïve[e]	75% (N=121)	73% (N=116)	77% (N=128)
Prior biologic failure[f]	53% (N=156)	61% (N=153)	64% (N=147)

[a] Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.

[b] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 100 mg subcutaneous q8w thereafter for up to 48 weeks.

[c] Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 followed by guselkumab 200 mg subcutaneous q4w thereafter for up to 48 weeks.

[d] A combination of clinical remission and endoscopic response as defined below.

[e] An additional 14 patients in the ustekinumab group, 21 patients in the guselkumab 200 mg subcutaneous q4w group, and 17 patients in the guselkumab 100 mg subcutaneous q8w group were previously exposed to but did not fail a biological 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] Endoscopic remission is defined as SES-CD Score ≤ 2.

[i] Clinical remission is defined as CDAI score < 150.

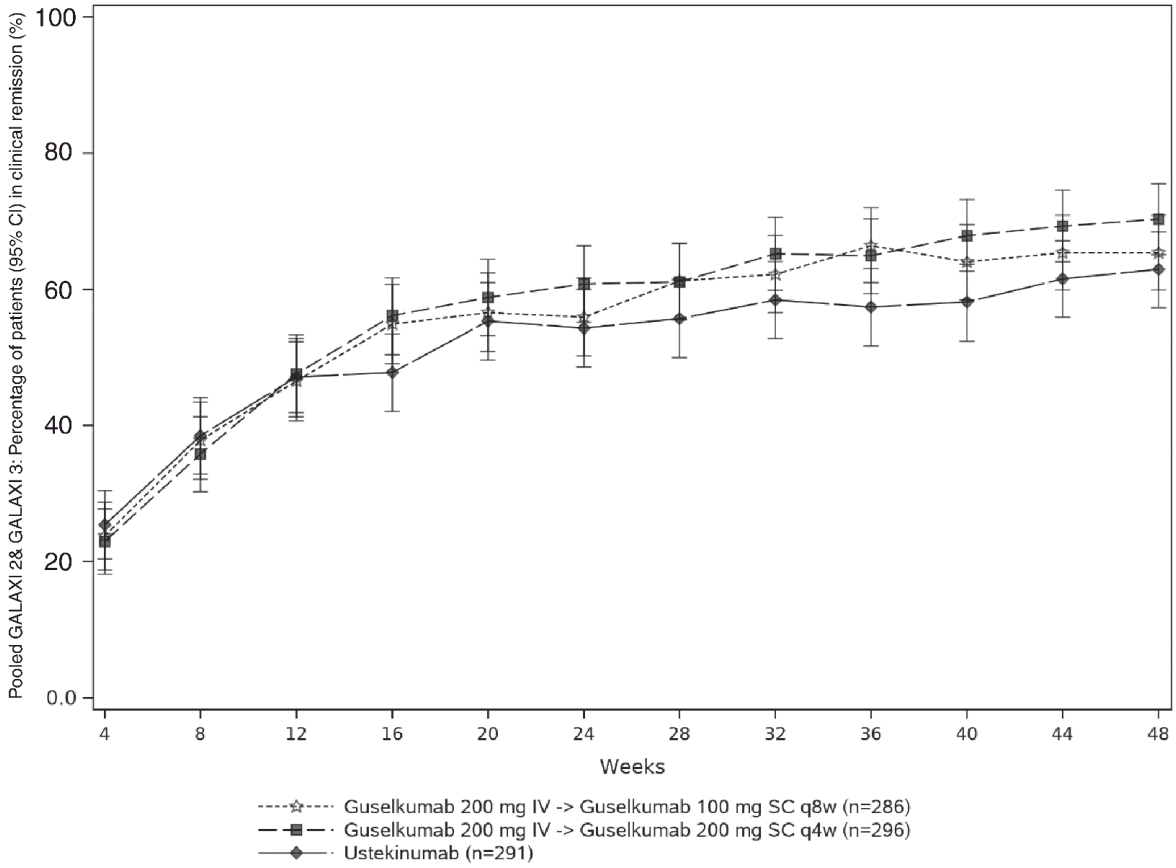
In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight.

In the pooled GALAXI Phase III studies subpopulation analysis, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to the 100 mg subcutaneous q8w maintenance dose regimens. A clinically meaningful difference was observed between the two guselkumab 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: 54.1% vs 200 mg subcutaneous q4w: 71.0%); endoscopic response at Week 48 (100 mg subcutaneous q8w: 36.5% vs 200 mg subcutaneous q4w: 50.5%); and PRO-2 remission at Week 48 (100 mg subcutaneous q8w: 51.8% vs 200 mg subcutaneous q4w: 61.7%).

Clinical remission over time

CDAI scores were recorded at each patient visit. The proportion of patients in clinical remission through Week 48 is presented in Figure 3.

Figure 3: Proportion of patients in clinical remission through Week 48 in pooled GALAXI 2 and GALAXI 3



Health-related quality of life

Greater improvements from baseline were seen at Week 12 in guselkumab treatment groups when compared with placebo for inflammatory bowel disease (IBD)-specific quality of life assessed by IBDQ total score. The improvements were maintained through Week 48 in both studies.

GRAVITI

In the Phase III GRAVITI study, moderately to severely active Crohn's disease was defined as a CDAI score of ≥ 220 and ≤ 450 and a CD (SES-CD) of ≥ 6 (or ≥ 4 for patients with isolated ileal disease) and a mean daily SF ≥ 4 or mean daily AP score ≥ 2.

In GRAVITI, patients were randomised in a 1:1:1 ratio to receive guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8 followed by guselkumab 100 mg q8w subcutaneous maintenance; or guselkumab 400 mg subcutaneous induction at Weeks 0, 4 and 8, followed by guselkumab 200 mg q4w subcutaneous maintenance; or placebo. All patients in the placebo group who met rescue criteria received the induction dosing with guselkumab 400 mg subcutaneous at Weeks 16, 20, and 24 followed by guselkumab 100 mg subcutaneous q8w.

A total of 347 patients were evaluated. The median age of patients was 36 years (ranging from 18 to 83 years), 58.5% were male, and 66% identified as White, 21.9% as Asian and 2.6% as Black.

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.

The results of the co-primary and major secondary efficacy endpoints compared to placebo at Week 12 are presented in Table 11.

Table 11: Proportion of patients meeting co-primary and major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GRAVITI

	Placebo	Guselkumab 400 mg subcutaneous injection[a]
Co-primary efficacy endpoints		
Clinical remission[b] at Week 12		
Total population	21% (N=117)	56%[c] (N=230)
Biologic naïve[d]	25% (N=56)	50% (N=105)
Prior biologic failure[e]	17% (N=53)	60% (N=108)
Endoscopic response[f] at Week 12		
Total population	21% (N=117)	41%[c] (N=230)
Biologic naïve[d]	27% (N=56)	49% (N=105)
Prior biologic failure[e]	17% (N=53)	33% (N=108)
Major secondary efficacy endpoints		
Clinical response[g] at Week 12		
Total population	33% (N=117)	73%[c] (N=230)
Biologic naïve[d]	38% (N=56)	68% (N=105)
Prior biologic failure[e]	28% (N=53)	78% (N=108)
PRO-2 remission[h] at Week 12		
Total population	17% (N=117)	49%[c] (N=230)
Biologic naïve[d]	18% (N=56)	44% (N=105)
Prior biologic failure[e]	17% (N=53)	52% (N=108)

[a] Guselkumab 400 mg subcutaneous at Week 0, Week 4 and Week 8

[b] Clinical remission: CDAI score < 150

[c] p< 0.001

[d] An additional 8 patients in the placebo group and 17 patients in the guselkumab 400 mg subcutaneous group, were previously exposed to but did not fail a biological therapy.

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

[f] Endoscopic response: ≥ 50% improvement from baseline in SES-CD score.

[g] Clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score < 150.

[h] PRO-2 remission: AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline.

Clinical remission at Week 24 was achieved by a significantly greater proportion of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab100 mg subcutaneous q8w or 200 mg subcutaneous q4w compared to placebo (60.9% and 58.3% vs 21.4% respectively, both p-values < 0.001). Clinical remission at Week 48 was achieved by 60% and 66.1% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Endoscopic response at Week 48 was achieved by 44.3% and 51.3% of patients treated with guselkumab 400 mg subcutaneous induction followed by guselkumab 100 mg subcutaneous q8w or 200 mg subcutaneous q4w, respectively (both p-values < 0.001 compared to placebo).

Health-related quality of life
In GRAVITI, clinically meaningful improvements were observed in IBD-specific quality of life as assessed with IBDQ total score at Week 12 and Week 24 compared to placebo.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with guselkumab in one or more subsets of the paediatric population in ulcerative colitis and Crohn's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) 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 patients with plaque psoriasis, following subcutaneous administrations of guselkumab 100 mg 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 III studies in patients with plaque psoriasis were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. The pharmacokinetics of guselkumab in patients with psoriatic arthritis was similar to that in patients with psoriasis. Following subcutaneous administration of guselkumab 100 mg at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was also approximately 1.2 mcg/mL. Following subcutaneous administration of guselkumab 100 mg every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3.8 mcg/mL.

The pharmacokinetics of guselkumab were similar in patients with ulcerative colitis and Crohn's disease. Following the recommended intravenous induction dose regimen of guselkumab 200 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was 68.27 mcg/mL in patients with ulcerative colitis, and 70.5 mcg/mL in patients with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of guselkumab 400 mg at Weeks 0, 4, and 8, mean peak serum guselkumab concentration at Week 8 was estimated to be 28.8 mcg/mL in patients with ulcerative colitis and 27.7 mcg/mL in patients with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimen was similar following subcutaneous and intravenous induction.

Following subcutaneous maintenance dosing of guselkumab 100 mg every 8 weeks or guselkumab 200 mg 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 guselkumab 100 mg every 8 weeks or guselkumab 200 mg every 4 weeks in patients 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 across studies.

Biotransformation

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

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0.288 to 0.479 L/day across studies. Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in patients with plaque psoriasis across studies, and approximately 17 days in patients with ulcerative colitis or Crohn's disease.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, AZA, 6-MP, oral corticosteroids and csDMARDs such as MTX, did not affect the clearance of guselkumab.

Linearity/non-linearity

The systemic exposure of guselkumab (C_{max} 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 patients with plaque psoriasis. Serum guselkumab concentrations were approximately dose proportional following intravenous administration in patients with ulcerative colitis or Crohn's disease.

Paediatric population

The pharmacokinetics of guselkumab in paediatric patients with ulcerative colitis, and Crohn's disease have not been established.

Elderly patients

No specific studies have been conducted in elderly patients. Of the 1 384 plaque psoriasis patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, 70 patients were 65 years of age or older, including 4 patients who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in Phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older. Of the 859 ulcerative colitis patients exposed to guselkumab in Phase II/III clinical studies and included in the population pharmacokinetic analysis, a total of 52 patients were 65 years of age or older, and 9 patients were 75 years of age or older. Of the 1 009 Crohn's disease patients exposed to guselkumab in Phase III clinical studies and included in the population pharmacokinetic analysis, a total of 39 patients were 65 years of age or older, and 5 patients were 75 years of age or older.

Population pharmacokinetic analyses in plaque psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease patients indicated no apparent changes in CL/F estimate in patients ≥ 65 years of age compared to patients < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Patients with renal or hepatic impairment

No specific study has 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. Based on population pharmacokinetic analyses, creatinine clearance or hepatic function did not have a meaningful impact on guselkumab clearance.

Body weight

Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, toxicity to reproduction and pre- and post-natal development.

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well tolerated via intravenous and subcutaneous routes of administration. A weekly subcutaneous dose of 50 mg/kg to monkeys resulted in exposure (AUC) values that were at least 23 times the maximum clinical exposures following a dose of 200 mg given intravenously. Additionally, there were no adverse immunotoxicity or cardiovascular safety pharmacology effects noted during the conduct of the

repeat-dose toxicity studies or in a targeted cardiovascular safety pharmacology study in cynomolgus monkeys.

There were no preneoplastic changes observed in histopathology evaluations of animals treated up to 24 weeks, or following the 12-week recovery period during which active substance was detectable in the serum.

No mutagenicity or carcinogenicity studies were conducted with guselkumab.

Guselkumab could not be detected in breast milk from cynomolgus monkeys as measured at post-natal day 28.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EDTA disodium dihydrate
Histidine
Histidine monohydrochloride monohydrate
Methionine
Polysorbate 80 (E433)
Sucrose
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Tremfya should only be diluted with 0.9% sodium chloride 9 mg/mL (0.9%) solution. Tremfya should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

2 years.

Diluted solution for infusion

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.

6.4 Special precautions for storage

Unopened vial
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

200 mg concentrate solution for infusion in a type I clear glass vial closed with a butyl rubber stopper, an aluminium seal and polypropylene flip top.

Tremfya is available in a 1 vial pack.

6.6 Special precautions for disposal and other handling

Tremfya solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique. 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.

Instructions for Dilution and Administration
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.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017
Date of latest renewal:15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen Inc. (BIIB)
5000 Davis Drive
Research Triangle Park
NC27709
USA

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Co. Cork
Ireland

Name and address of the manufacturers responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
2333CB Leiden
The Netherlands

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 45 mg/0.45 mL solution for injection in pre-filled pen
guselkumab
For children aged 6 years and older with a body weight less than 40 kg

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 45 mg of guselkumab in 0.45 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen (VarioJect)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1234/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 45 mg/0.45 mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN FOR PAEDIATRIC USE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tremfya 45 mg/0.45 mL injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.45 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 2 (2 packs of 1) pre-filled syringes

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/004 (2 packs, each containing 1 pre-filled syringe)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Excipients: sucrose, histidine, histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tremfya 100 mg injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg OnePress solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake

Read Instructions for Use in full before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg OnePress solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 2 (2 packs of 1) pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/003 (2 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg OnePress solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake

Read Instructions for Use in full before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tremfya 100 mg injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg PushPen solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg PushPen solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 2 (2 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/011 (2 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg PushPen solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 100 mg of guselkumab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 100 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tremfya 100 mg injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 2 (2 packs of 1) pre-filled syringes

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/007 (2 packs, each containing 1 pre-filled syringe)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled syringe
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tremfya 200 mg injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
PushPen
1 pre-filled pen

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
PushPen
Multipack: 2 (2 packs of 1) pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/009 (2 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg solution for injection in pre-filled pen
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg of guselkumab in 2 mL.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
PushPen
1 pre-filled pen
Component of a multipack, cannot be sold separately

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tremfya 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tremfya 200 mg injection
guselkumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Tremfya 200 mg concentrate for solution for infusion
guselkumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 200 mg guselkumab in 20 mL.

3. LIST OF EXCIPIENTS

Excipients: EDTA disodium dihydrate, histidine, histidine monohydrochloride monohydrate, methionine, polysorbate 80, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
200 mg/20 mL
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

For IV use after dilution.
Read the package leaflet before use.
Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1234/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Tremfya 200 mg sterile concentrate
guselkumab

2. METHOD OF ADMINISTRATION

For IV use after dilution.
Do not shake.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg/20 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tremfya 45 mg/0.45 mL solution for injection in pre-filled pen
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you. This leaflet has been written for the person taking the medicine. If you are the parent or caregiver who will give Tremfya to a child, please read this information carefully.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with psoriasis.

Plaque psoriasis in children
Tremfya is used to treat children 6 years of age and older with moderate to severe “plaque psoriasis”, an inflammatory condition affecting the skin.

Tremfya can improve the condition of the skin and reduce signs and symptoms, such as scaling and redness.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;

- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya. Children need to be brought up to date with age-appropriate vaccines prior to beginning Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu-like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body which are different from your psoriasis.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children
Do not give this medicine to children less than 6 years of age because it has not been studied in this age group.

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 0.3 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Plaque psoriasis in children from the age of 6 years
Children weighing less than 40 kg:
- The recommended dose of Tremfya for children weighing less than 40 kg depends on their body weight. Your doctor will tell you the correct dose to use.
- A pre-filled pen containing 45 mg/0.45 mL of Tremfya is used to give your dose by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

Children weighing 40 kg or more:
- For children weighing 40 kg or more a 100 mg pre-filled syringe is available.

At the start, your doctor or nurse will inject Tremfya. Your doctor may decide that your caregiver may be able to give Tremfya after receiving appropriate training from your doctor on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about your injection.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g. athlete's foot)
- stomach flu (gastroenteritis)
- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled pen in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled pen inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled pen contains 45 mg of guselkumab in 0.45 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 "Tremfya contains polysorbate 80").

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled pen.

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Turnhoutseweg 30
B-2340 Beerse
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Manufacturer
Janssen Biologics B.V.
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The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

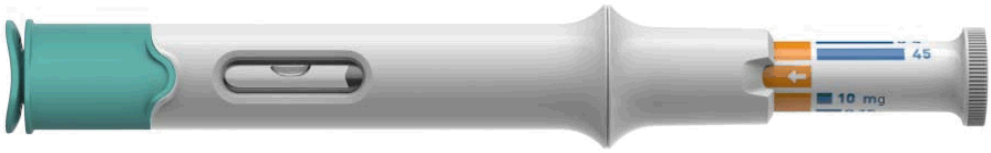
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site https://www.ema.europa.eu.

Instructions for use
Tremfya 45 mg/0.45 mL solution for injection in pre-filled pen
For paediatric patients less than 40 kg

SINGLE-USE DEVICE

This Instructions for Use contains information on how to inject Tremfya.



Know your dose.

Important information you need to know before injecting Tremfya

Tremfya comes in a single-use pre-filled pen that allows you to manually set a specific, prescribed dose.
If unsure of the correct dose, contact the prescribing doctor before injecting.

If your doctor decides that a caregiver may be able to give your injections of Tremfya at home, **they should receive training on the correct way to prepare and inject Tremfya before using the pre-filled pen**. If your caregiver has not been trained, or has any questions, please call your doctor.

Read this Instructions for Use before using the Tremfya pre-filled pen and each time you get a refill. There may be new information.
This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment.
Please also read the Package Leaflet carefully before starting the injection and discuss any questions you may have with your doctor or nurse.

Each pre-filled pen can only be used one time. Throw away the used pre-filled pen after one dose, even if there is medicine left in it.
Do not re-use the pre-filled pen.

Storage information
Store in refrigerator at 2°C to 8°C.
Do not freeze the pre-filled pen.
Do not shake the pre-filled pen.
Keep the pre-filled pen in the original carton to protect from light and physical damage.
Keep the Tremfya pre-filled pen and all medicines out of reach of children.

Need help?
Call your doctor to talk about any questions you may have. For additional assistance refer to the Package Leaflet for your local representative contact information.

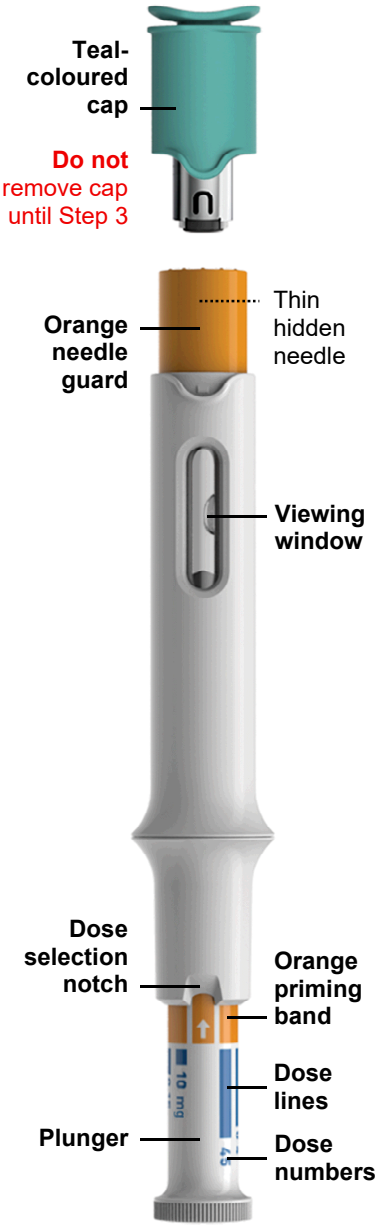
You will need these supplies:

- **1 Pre-filled pen**

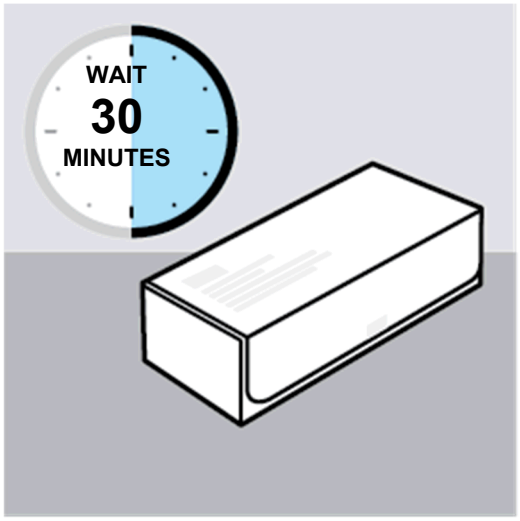
Not provided in the pre-filled pen carton:

- **Alcohol swab**
- **Cotton ball or gauze pad**
- **Adhesive bandage**
- **Sharps container**

Pre-filled pen parts

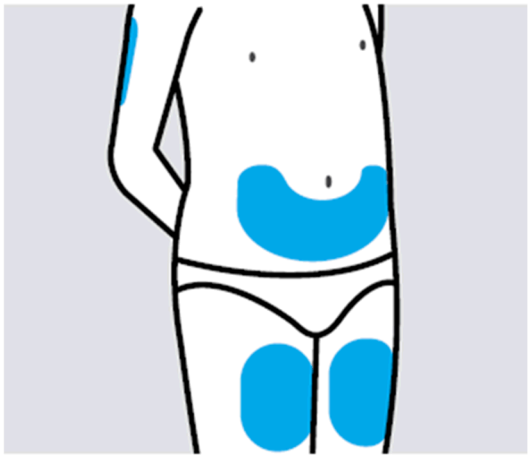


1. Get ready



Allow Tremfya to come to room temperature and inspect carton
Remove the carton from the refrigerator and let the carton sit on a flat surface at room temperature for approximately **30 minutes** before use.
Do not warm the pre-filled pen any other way.
Check the expiry date (‘EXP’) on the carton.
Do not use the pre-filled pen if the expiry date has passed or if the seal on the carton is broken. Call your doctor or pharmacist for a new pre-filled pen.

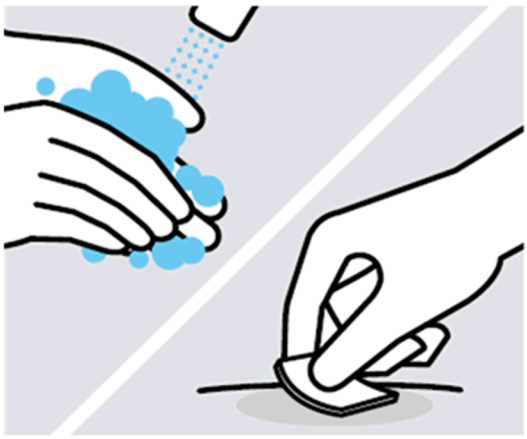
2. Prepare to inject Tremfya



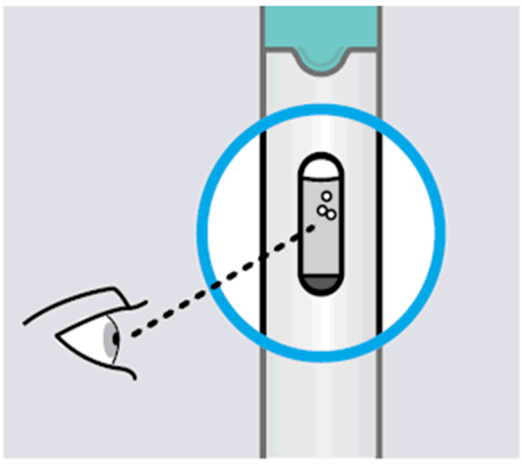
Choose injection site

Select a site from the following areas for the injection:
- Front of thighs
- Lower stomach area (lower abdomen), avoiding the 5-centimetre area around the navel (belly-button)
- Back of upper arms

Do not inject into skin that is tender, bruised, red, scaly, hard, thick, has scars, or is affected by psoriasis.



Wash hands and
Clean injection site
Wash your hands well with soap and warm water.
Wipe the chosen injection site with an alcohol swab and allow it to dry by air.
Do not touch, fan, or blow on the injection site after you have cleaned it.



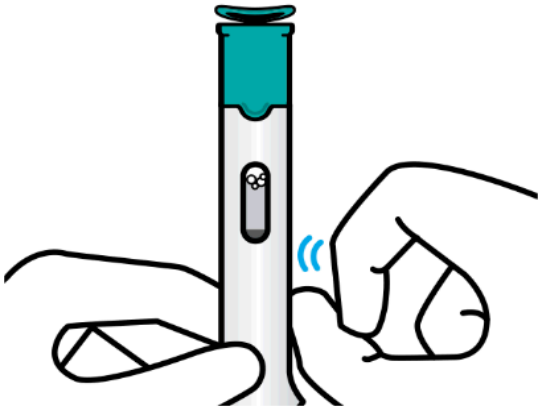
Inspect liquid in viewing window
Take the pre-filled pen out of the carton.
Check the liquid in the viewing window. It should be clear and colourless to slightly yellow and may contain tiny white or clear particles.
.
You may also see air bubbles.
This is normal.
Do not inject if the liquid is:

- cloudy or
- discoloured or
- has large particles

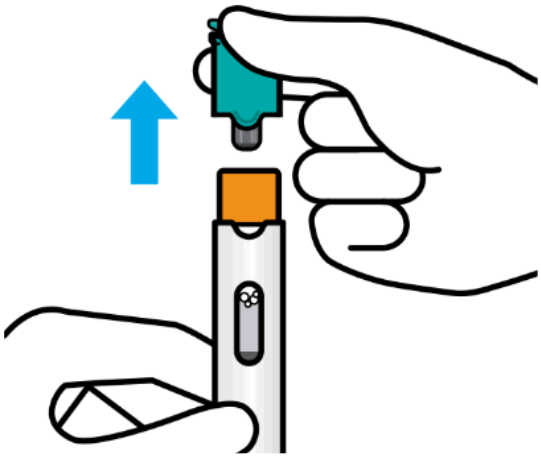
Call your doctor or pharmacist for a new pre-filled pen.

3. Remove air bubbles

Keep the pre-filled pen pointing up during this step



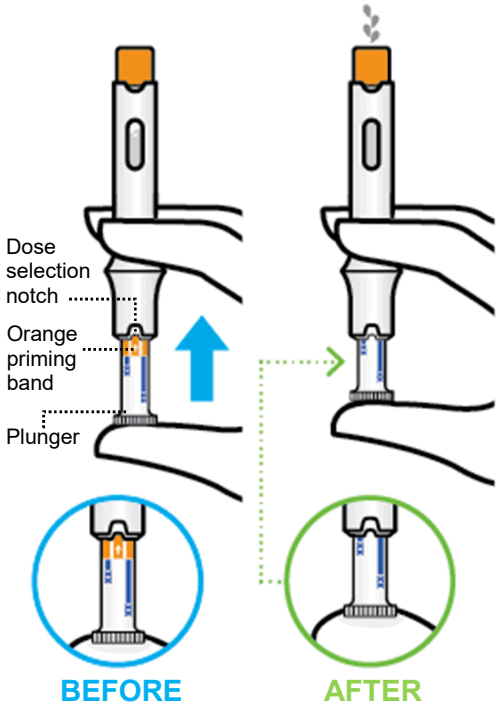
Tap pre-filled pen to move air bubbles to the top even if you do not see any air bubbles
Hold the pre-filled pen with the **teal-coloured cap pointing up**.
Tap gently near the viewing window. This will cause any air bubbles to rise to the top.
Do not set the pre-filled pen down until air bubbles are removed.



Remove cap
Keep holding the pre-filled pen with the teal cap pointing up, then **pull** the cap to remove.

Keep hands away from the orange needle guard after the cap is removed.
Pushing the needle guard too soon may lock the pre-filled pen and you will not be able to give the dose.

Do not put the cap back on as this may damage the needle.
Do not use the pre-filled pen if it is dropped after removing the cap. Call your doctor or pharmacist for a new pre-filled pen.

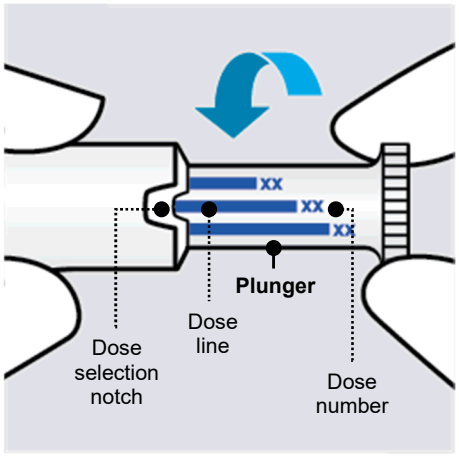


Press the plunger until it stops to push out air bubbles

Keep holding the pre-filled pen with the orange needle guard pointing up.

Confirm air bubbles are removed by checking that the orange priming band is no longer visible in the dose selection notch.
Liquid may squirt out. This is normal.

4. Set the dose

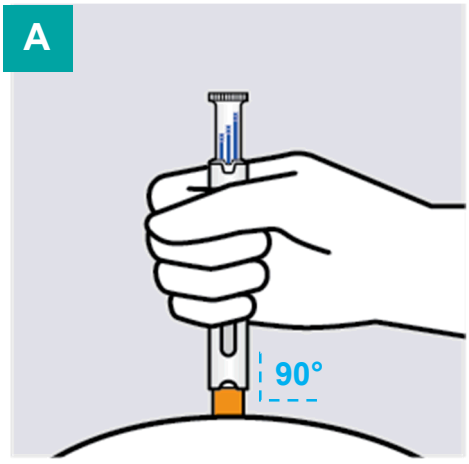


Turn the plunger to set the dose
Turn the plunger until the dose line and dose number that corresponds to the prescribed dose (see table below) is in the dose selection notch as shown in the image above.

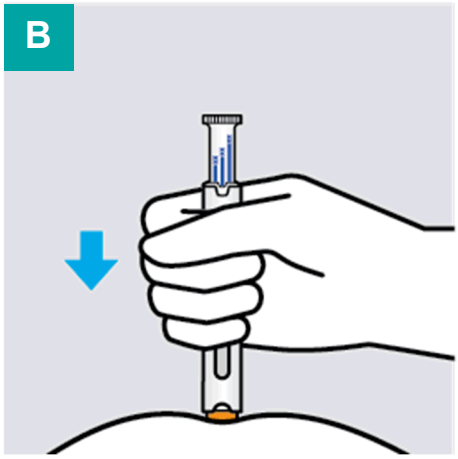
Prescribed dose	Turn plunger to:
20 mg =	20 mg
25 mg =	25
30 mg =	30
35 mg =	35
40 mg =	40
45 mg =	45

5. Inject Tremfya

Read all sub-steps from A to D before injecting



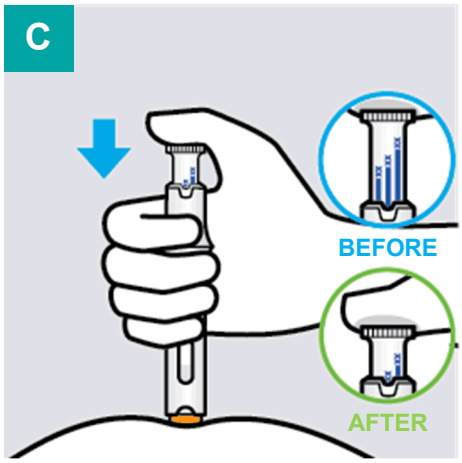
Position pre-filled pen straight onto the injection site
Position the pre-filled pen straight onto the injection site with the orange needle guard against the skin and the viewing window facing you.
Continue to hold the pre-filled pen against the skin.



Push pre-filled pen down to insert the needle into the skin and hold in place

Do not press the plunger yet. **Do not** lift the pre-filled pen from the skin.

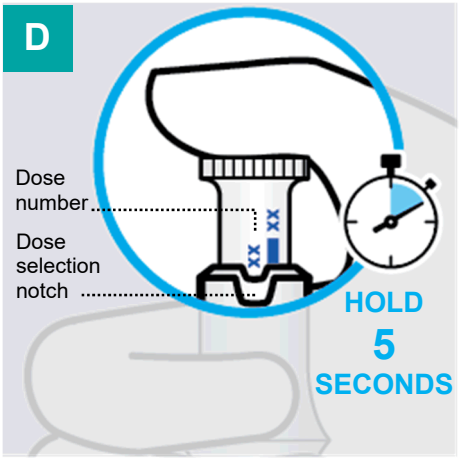
Push the pre-filled pen into the skin until the orange needle guard stops to insert the needle into the skin. Some orange will still be showing.



Slowly press the plunger all the way down until it stops to inject Tremfya

Do not lift the pre-filled pen from the skin during the injection.
Otherwise, the orange needle guard will lock, and you will not be able to give the full dose.

You will feel some resistance as you press the plunger. This is normal.
If a small dose is set, the plunger will only move a short distance.

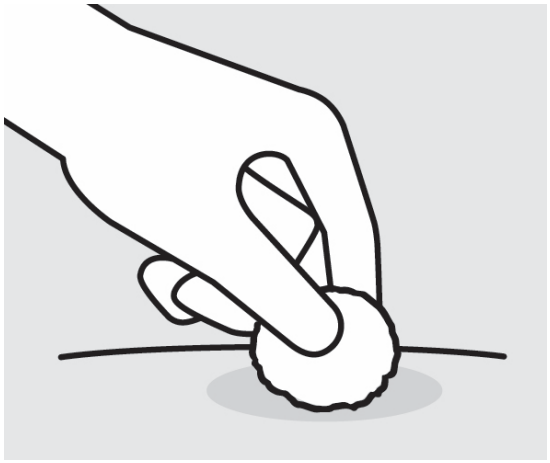


Hold and confirm injection is complete
Hold the pre-filled pen in place and keep pushing against the skin for **5 seconds**.
Confirm injection is complete by checking that:

- **you cannot press the plunger down any more**
- **the selected blue dose line is no longer visible**
- **only the selected dose number is visible in the dose selection notch**

After confirming, lift the pre-filled pen from the skin.
The orange needle guard will extend and lock.
It is normal to see some liquid left in the viewing window.

6. After injection



Check injection site

There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage.



Dispose of the pre-filled pen
Put the used pre-filled pen in a sharps disposal container right away after use.
Do not throw away (dispose of) the pre-filled pen in your household waste.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.
Do not recycle the used sharps disposal container.

Package leaflet: Information for the user

Tremfya 100 mg solution for injection in pre-filled syringe
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.

Plaque psoriasis
Adults
Tremfya is used to treat adults with moderate to severe "plaque psoriasis", an inflammatory condition affecting the skin and nails.

Tremfya can improve the condition of the skin and appearance of nails and reduce symptoms, such as scaling, shedding, flaking, itching, pain and burning.

Children
Tremfya is used to treat children 6 years of age and older with moderate to severe "plaque psoriasis", an inflammatory condition affecting the skin.

Tremfya can improve the condition of the skin and reduce signs and symptoms, such as scaling and redness.

Psoriatic arthritis
Tremfya is used to treat a condition called "psoriatic arthritis", an inflammatory disease of the joints, often accompanied by plaque psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines or in case of intolerance, you will be given Tremfya to reduce the signs and symptoms of the disease. Tremfya can be used alone or with another medicine named methotrexate.

Using Tremfya in psoriatic arthritis will benefit you by reducing the signs and symptoms of the disease, slowing down the damage to the cartilage and bone of the joints and improving your ability to do normal daily activities.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya. Children need to be brought up to date with age-appropriate vaccines prior to beginning Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your

phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body which are different from your psoriasis.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children under 6 years of age with plaque psoriasis or in children under 18 years of age with psoriatic arthritis, ulcerative colitis, and Crohn's disease because it has not been studied in these age groups.

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 0.5 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

<u>Plaque psoriasis</u>
Adults:
- The dose is 100 mg (the content of 1 pre-filled syringe) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

Children:
- For children weighing 40 kg or more, the dose is 100 mg (the content of 1 pre-filled syringe) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.

- For children weighing less than 40 kg a 45 mg/0.45 mL pre-filled pen is available.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

Psoriatic arthritis
- The dose is 100 mg (the content of 1 pre-filled syringe) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will receive the next dose 4 weeks later, and then every 8 weeks. For some patients, after the first dose, Tremfya may be given every 4 weeks. Your doctor will decide how often you may receive Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn's disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

You may decide together with your doctor to give Tremfya yourself in which case you will get the appropriate training on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about giving yourself an injection. It is important not to try to inject yourself until you have been trained by your doctor or nurse.

Children below the age of 18 years should not self-inject Tremfya. Your doctor may decide that your caregiver may be able to give Tremfya after receiving appropriate training on how to inject Tremfya.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete’s foot)
- stomach flu (gastroenteritis)
- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting

system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled syringe in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled syringe inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled syringe contains 100 mg of guselkumab in 1 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 "Tremfya contains polysorbate 80").

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled syringe and in multipacks comprising 2 cartons, each containing 1 pre-filled syringe. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Tremfya
100 mg pre-filled syringe



SINGLE-USE DEVICE

Important
If your doctor decides that you or a caregiver may be able to give your injections of Tremfya at home, you should receive training on the right way to prepare and inject Tremfya using the pre-filled syringe before attempting to inject. Do not try to inject yourself until you have been shown the right way to give the injections by your doctor.
For paediatric patients, Tremfya should be administered by a doctor or nurse or a caregiver who has been shown the right way to give the injections by your doctor.
Please read these Instructions for use before using the Tremfya pre-filled syringe and each time you get a refill. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment. Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.
The Tremfya pre-filled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the body of the device and lock into place.

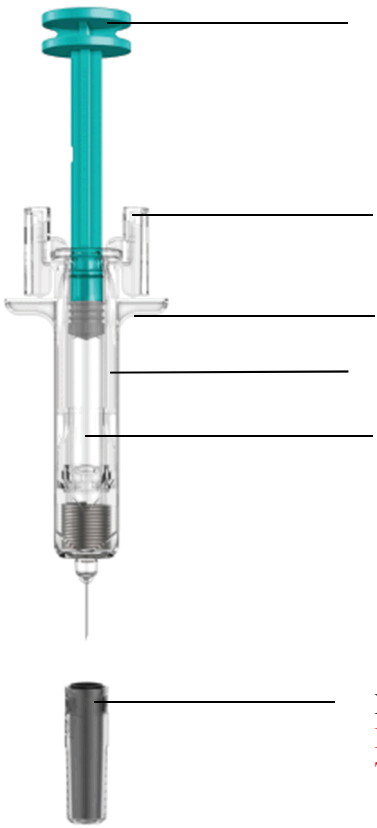
Storage information
Store in refrigerator at 2° to 8°C. **Do not** freeze.

Keep your pre-filled syringe in the original carton to protect from light and physical damage.
Keep Tremfya and all medicines out of reach of children.
Do not shake the pre-filled syringe at any time.

Need help?
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Pre-filled syringe at-a-glance

Before injection



Plunger
Do not hold or pull plunger at any time.

Safety guard

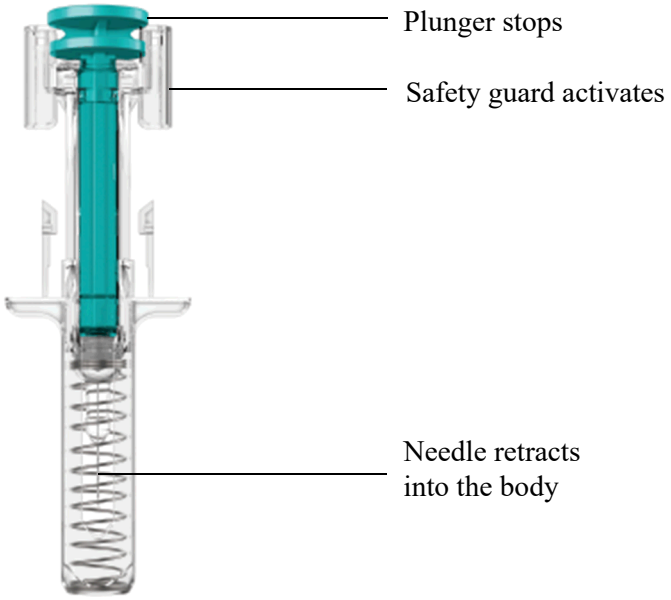
Finger flange

Body
Hold syringe body **below** finger flange.

Viewing window

Needle cover
Do not remove until you are ready to inject Tremfya (See step 2).

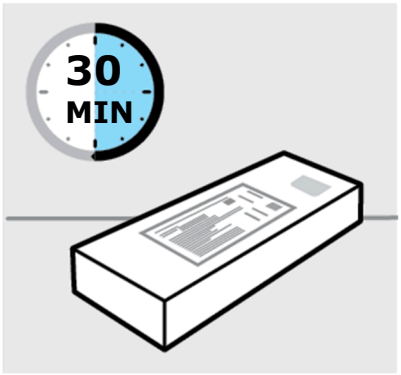
After injection



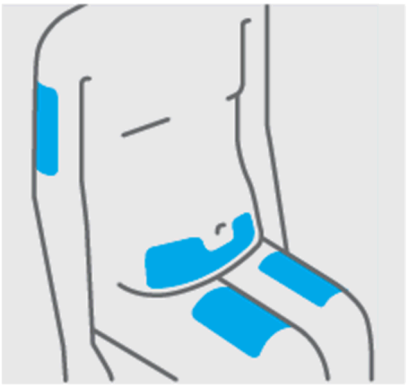
You will need these supplies:

- **1 Alcohol swab**
- **1 Cotton ball** or **gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container** (See step 3)

1. Prepare for your injection



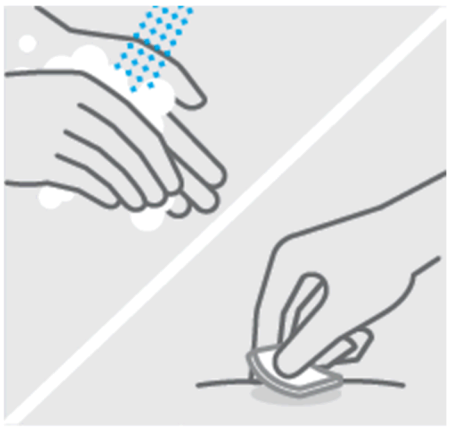
Inspect carton
Remove carton with the pre-filled syringe from the refrigerator.
Keep the pre-filled syringe in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.
Do not warm any other way.
Check the expiry date ('EXP') on the back panel of the carton.
Do not use if the expiry date has passed.
Do not inject if the perforations on the carton are broken.
Call your doctor or pharmacist for a refill.



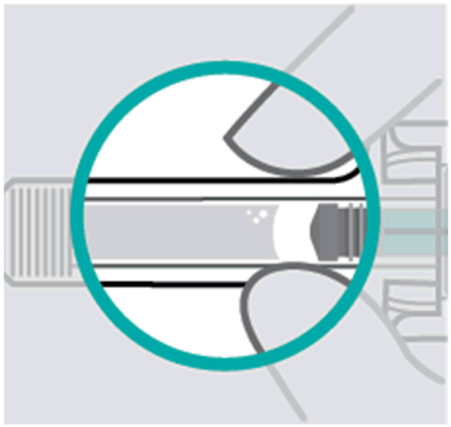
Choose injection site
Select from the following areas for your injection:

- **Front of thighs** (recommended)
- Lower abdomen
  Do not use the 5-centimetre area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly or hard.
Do not inject into areas with scars or stretch marks.

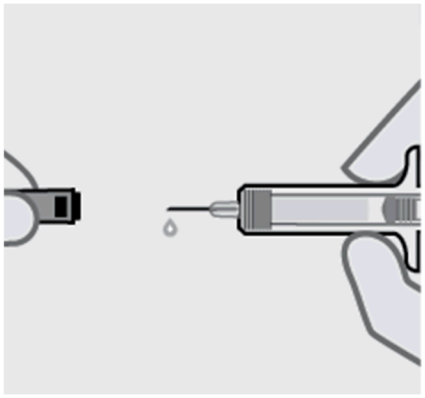


Clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan or blow on the injection site after you have cleaned it.

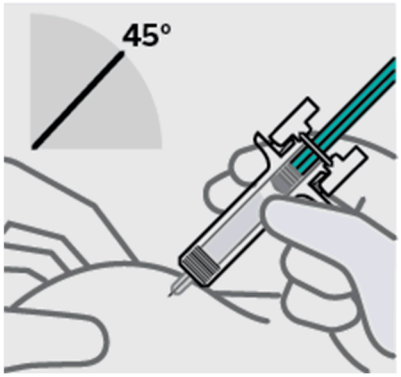


Inspect liquid
Take the pre-filled syringe out of the carton.
Check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see one or more air bubbles.
This is normal.
Do not inject if the liquid is cloudy or discoloured, or has large particles. If you are uncertain, call your doctor or pharmacist for a refill.

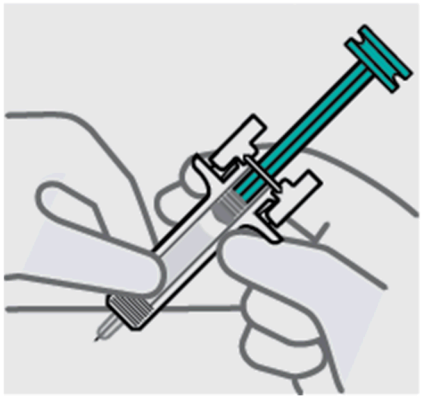
2. Inject Tremfya using the pre-filled syringe



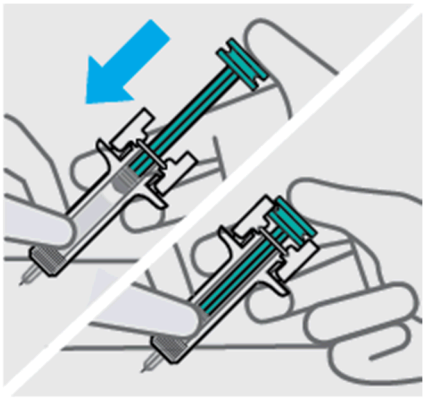
Remove needle cover
Hold syringe by the body and pull needle cover straight off.
It is normal to see a drop of liquid.
Inject within 5 minutes of removing the needle cover.
Do not put needle cover back on, as this may damage the needle.
Do not touch needle or let it touch any surface.
Do not use the Tremfya pre-filled syringe if it is dropped. Call your doctor or pharmacist for a refill.



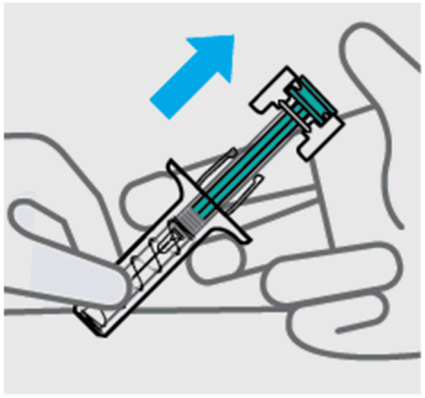
Position fingers and insert needle
Place your thumb, index and middle fingers **directly under the finger flange**, as shown.
Do not touch plunger or area above finger flange as this may cause the needle safety device to activate.
Use your other hand to pinch skin at the injection site. Position syringe at about a 45 degree angle to the skin.
It is important to pinch enough skin to **inject under the skin** and not into the muscle.
Insert needle with a quick, dart-like motion.



Release pinch and reposition hand
Use your free hand to grasp the body of the syringe.



Press plunger
Place thumb from the opposite hand on the plunger and press the plunger **all the way down until it stops**.

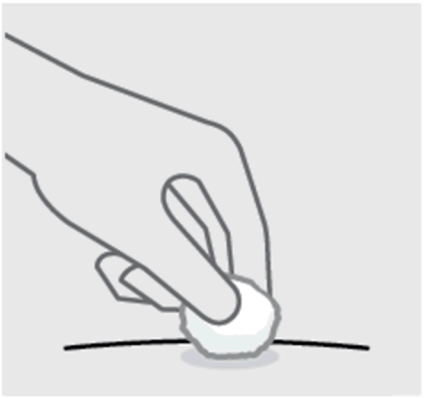


Release pressure from plunger
The safety guard will cover the needle and lock into place, removing the needle from your skin.

3. After your injection



Throw the used pre-filled syringe away
Put your used syringe in a sharps disposal container right away after use.
Do not throw away (dispose of) your pre-filled syringe in your household waste.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.



Check injection site
There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage.
Your injection is now complete!

Package leaflet: Information for the user

Tremfya 100 mg OnePress solution for injection in pre-filled pen
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.

Plaque psoriasis
Tremfya is used to treat adults with moderate to severe "plaque psoriasis", an inflammatory condition affecting the skin and nails.

Tremfya can improve the condition of the skin and appearance of nails and reduce symptoms, such as scaling, shedding, flaking, itching, pain and burning.

Psoriatic arthritis
Tremfya is used to treat a condition called "psoriatic arthritis", an inflammatory disease of the joints, often accompanied by plaque psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines or in case of intolerance, you will be given Tremfya to reduce the signs and symptoms of the disease. Tremfya can be used alone or with another medicine named methotrexate.

Using Tremfya in psoriatic arthritis will benefit you by reducing the signs and symptoms of the disease, slowing down the damage to the cartilage and bone of the joints and improving your ability to do normal daily activities.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body which are different from your psoriasis.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group..

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 0.5 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Plaque psoriasis
- The dose is 100 mg (the content of 1 pre-filled pen) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

Psoriatic arthritis
- The dose is 100 mg (the content of 1 pre-filled pen) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will receive the next dose 4 weeks later, and then every 8 weeks. For some patients, after the first dose, Tremfya may be given every 4 weeks. Your doctor will decide how often you may receive Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn's disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

You may decide together with your doctor to give Tremfya yourself in which case you will get the appropriate training on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about giving yourself an injection. It is important not to try to inject yourself until you have been trained by your doctor or nurse.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete's foot)
- stomach flu (gastroenteritis)
- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled pen in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled pen inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 “Tremfya contains polysorbate 80”).

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled pen and in multipacks comprising 2 cartons, each containing 1 pre-filled pen. Not all pack sizes may be marketed.

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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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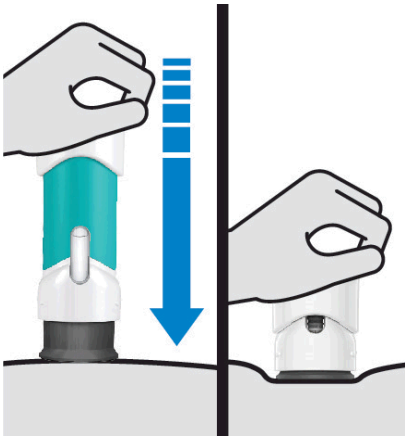
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Tremfya
100 mg OnePress pre-filled pen



SINGLE-USE DEVICE

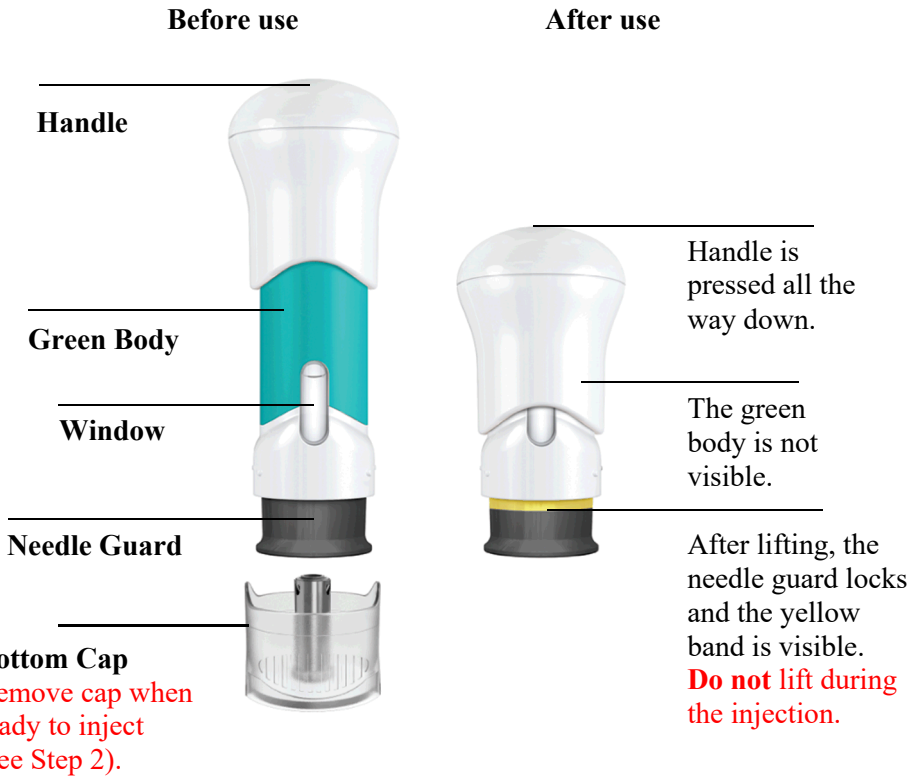
Important
If your doctor decides that you or a caregiver may be able to give your injections of Tremfya at home, you should receive training on the right way to prepare and inject Tremfya using the pre-filled pen.
Please read these Instructions for use before using the Tremfya pre-filled pen and each time you get a new pre-filled pen. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment.
Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.

During injection, push handle all the way down until green body is not visible to inject the full dose.
DO NOT LIFT THE PRE-FILLED PEN during injection. If you do, the pre-filled pen will lock and you will not get the full dose.

Storage information
Store in refrigerator at 2° to 8°C.
Do not freeze.
Do not shake your pre-filled pen at any time.
Keep your pre-filled pen in the original carton to protect from light and physical damage.
Keep Tremfya and all medicines out of reach of children.

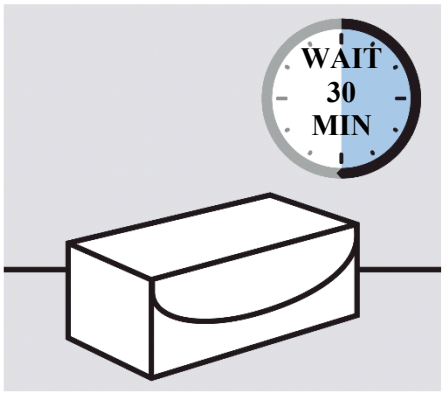
Need help?
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Pre-filled pen at-a-glance

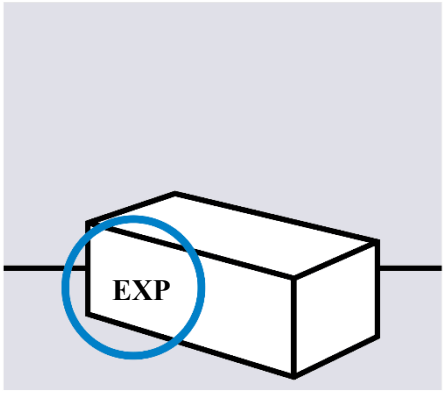


You will need these supplies:
- **1 Alcohol swab**
- **1 Cotton ball** or **gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container** (See step 3)

1. Prepare for your injection



Inspect carton and allow Tremfya to come to room temperature
Remove carton with the pre-filled pen from the refrigerator.
Keep pre-filled pen in the carton and let it sit on a flat surface at room temperature for **approximately 30 minutes** before use.
Do not warm any other way.



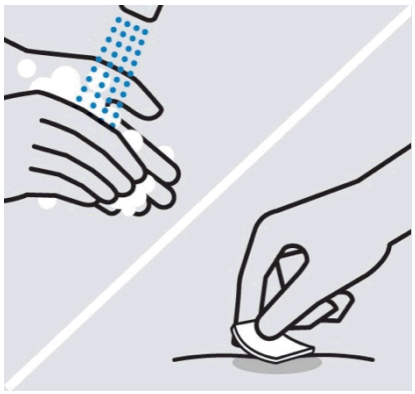
Check the expiry date ('EXP') on the carton.
Do not use if the expiry date has passed.
Do not inject if the seal on the carton is broken.
Call your doctor or pharmacist for a new pre-filled pen.



Choose injection site
Select from the following areas for your injection:

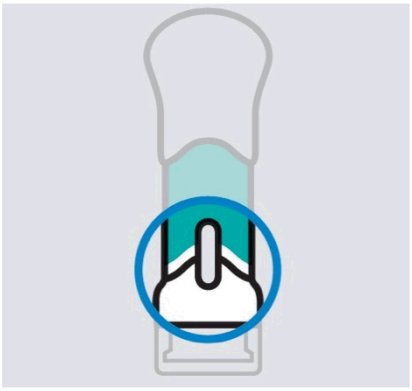
- **Front of thighs** (recommended)
- Lower abdomen
  Do not use the 5-centimetre area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly, hard or has scars or stretch marks.



Wash hands
Wash your hands well with soap and warm water.

Clean injection site
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan or blow on the injection site after you have cleaned it.

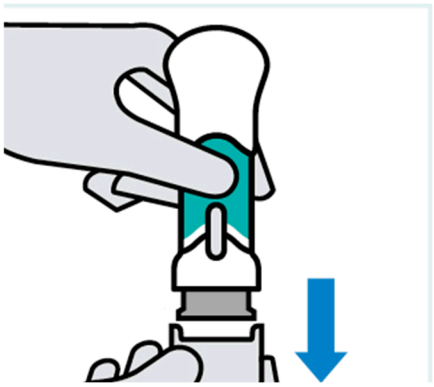


Inspect liquid in window
Take the pre-filled pen out of the carton.
Check the liquid in the window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see one or more air bubbles.
This is normal.
Do not inject if the liquid is:

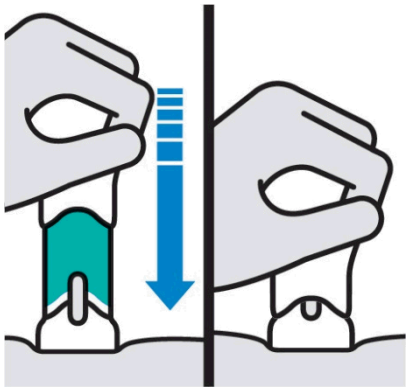
- cloudy, or
- discoloured, or
- has large particles.

If you are uncertain, call your doctor or pharmacist for a new pre-filled pen.

2. Inject Tremfya using the pre-filled pen



Pull off bottom cap when you are ready to inject
Keep hands away from the needle guard after the cap is removed. It is normal to see a few drops of liquid.
Inject within 5 minutes of removing the cap.
Do not put the cap back on. This could damage the needle.
Do not use the pre-filled pen if it is dropped after removing the cap.
Call your doctor or pharmacist for a new pre-filled pen.



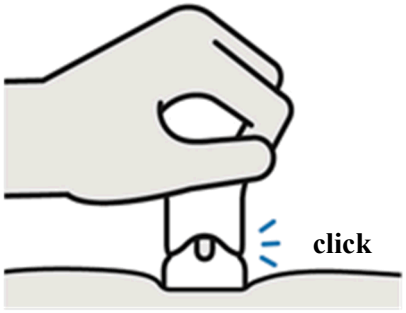
Place straight on skin

Push handle all the way down until green body is not visible

DO NOT LIFT THE PRE-FILLED PEN DURING THE INJECTION!
If you do, the needle guard will lock, showing a yellow band, and you will not get the full dose.

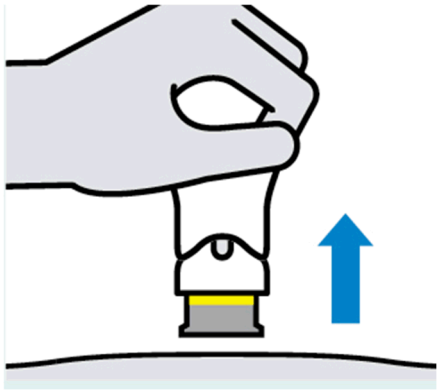
You may hear a click when the injection begins. Keep pushing.
If you feel resistance, keep pushing. This is normal.

The medication injects as you push. Do this at a speed that is comfortable for you.



Confirm injection is complete
Injection is complete when:

- **The green body is no longer visible**
- You cannot press the handle down anymore
- You may hear a click

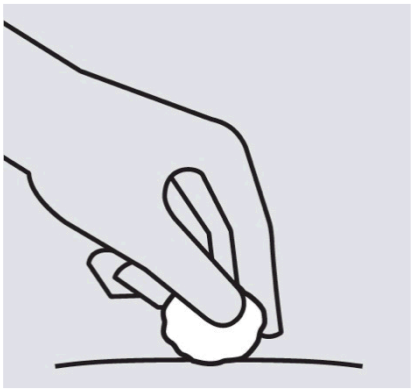


Lift straight up
The yellow band indicates that the needle guard is locked.

3. After your injection



Throw the used pre-filled pen away
Put your used pre-filled pen in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.
Do not throw away (dispose of) your pre-filled pen in your household waste.
Do not recycle your used sharps disposal container.



Check injection site
There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage.
Your injection is now complete!

Package leaflet: Information for the user

Tremfya 100 mg PushPen solution for injection in pre-filled pen
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with psoriasis, psoriatic arthritis, ulcerative colitis, and Crohn's disease.

Plaque psoriasis
Tremfya is used to treat adults with moderate to severe "plaque psoriasis", an inflammatory condition affecting the skin and nails.

Tremfya can improve the condition of the skin and appearance of nails and reduce symptoms, such as scaling, shedding, flaking, itching, pain and burning.

Psoriatic arthritis
Tremfya is used to treat a condition called "psoriatic arthritis", an inflammatory disease of the joints, often accompanied by plaque psoriasis. If you have psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines or in case of intolerance, you will be given Tremfya to reduce the signs and symptoms of the disease. Tremfya can be used alone or with another medicine named methotrexate.

Using Tremfya in psoriatic arthritis will benefit you by reducing the signs and symptoms of the disease, slowing down the damage to the cartilage and bone of the joints and improving your ability to do normal daily activities.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body which are different from your psoriasis.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group..

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 0.5 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Plaque psoriasis
- The dose is 100 mg (the content of 1 pre-filled pen) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

Psoriatic arthritis
- The dose is 100 mg (the content of 1 pre-filled pen) given by injection under the skin (subcutaneous injection). This may be given by your doctor or nurse.
- After the first dose, you will receive the next dose 4 weeks later, and then every 8 weeks. For some patients, after the first dose, Tremfya may be given every 4 weeks. Your doctor will decide how often you may receive Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn's disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

You may decide together with your doctor to give Tremfya yourself in which case you will get the appropriate training on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about giving yourself an injection. It is important not to try to inject yourself until you have been trained by your doctor or nurse.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete's foot)
- stomach flu (gastroenteritis)
- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled pen in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled pen inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 “Tremfya contains polysorbate 80”).

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled pen and in multipacks comprising 2 cartons, each containing 1 pre-filled pen. Not all pack sizes may be marketed.

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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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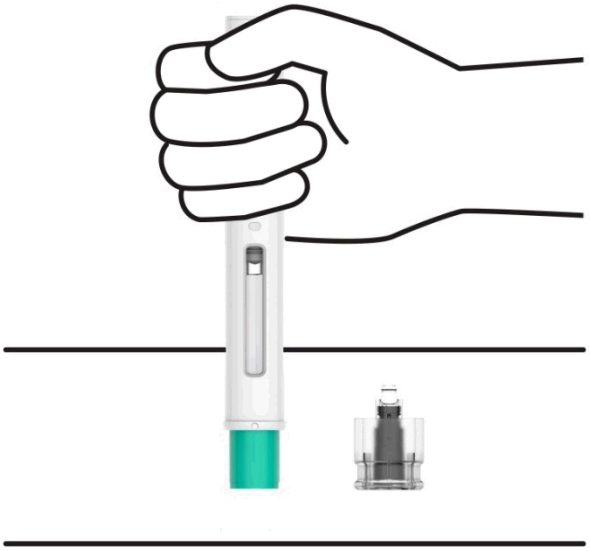
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Tremfya
100 mg PushPen pre-filled pen



SINGLE-USE DEVICE

Important
Tremfya comes in a single-use pre-filled pen containing one 100 mg dose.
If your doctor decides that you or a caregiver may be able to give your injections of Tremfya at home, you should receive training on the right way to prepare and inject Tremfya using the pre-filled pen.

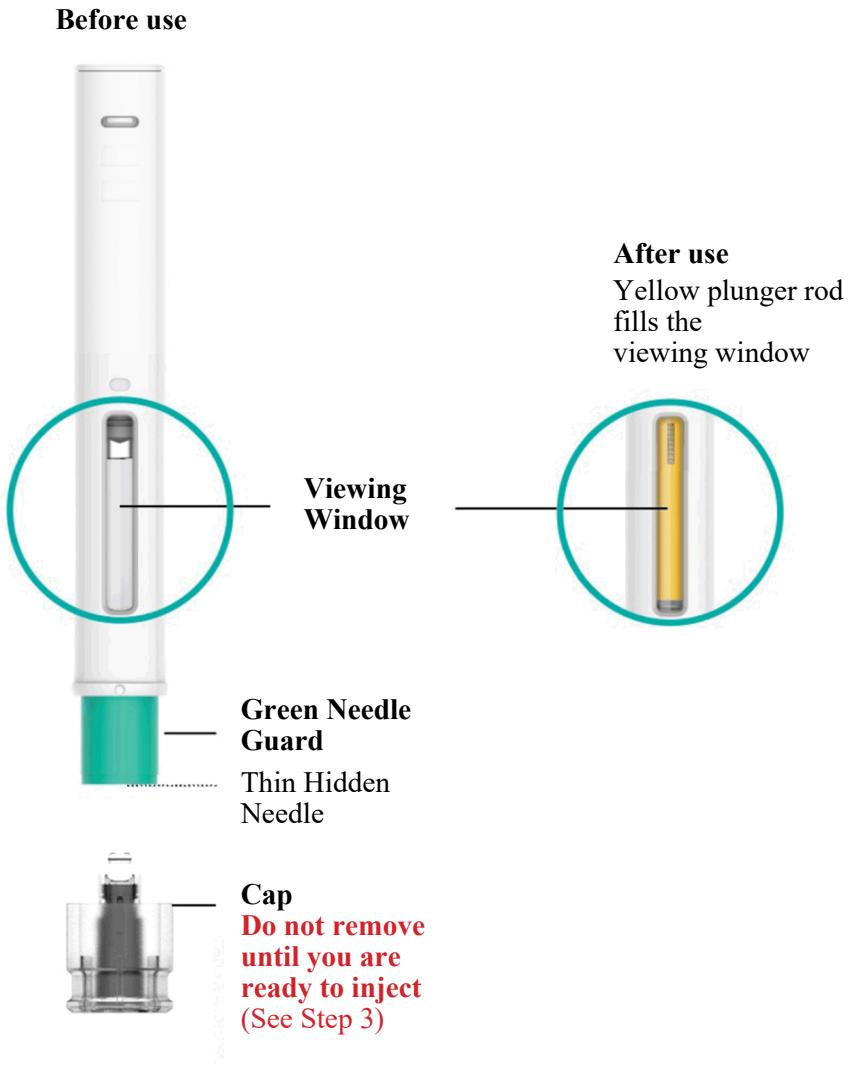
Please read these Instructions for Use before using the Tremfya pre-filled pen and each time you get a new pre-filled pen. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment. Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.

Each Tremfya pre-filled pen can only be used one time. Throw the used pre-filled pen away (see Step 4) after one dose, even if there is still medicine left in it. Do not reuse your pre-filled pen.

**Storage information**
Store in refrigerator at 2° to 8°C.
Do not freeze.
Do not shake your pre-filled pen.
Keep your pre-filled pen in the original carton to protect from light and physical damage.
Keep Tremfya and all medicines out of reach of children.

**Need help?**
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

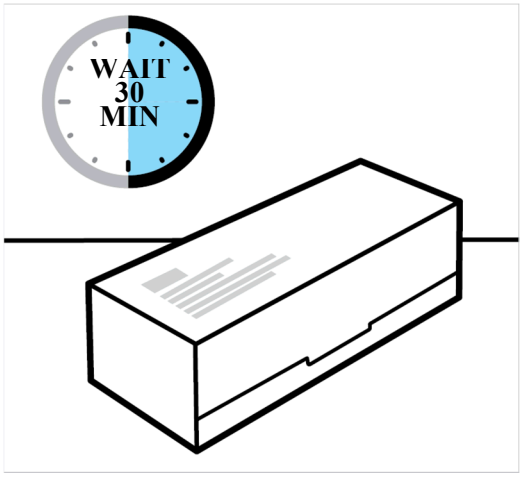
Pre-filled pen at-a-glance



You will need:
- **1 pre-filled pen**

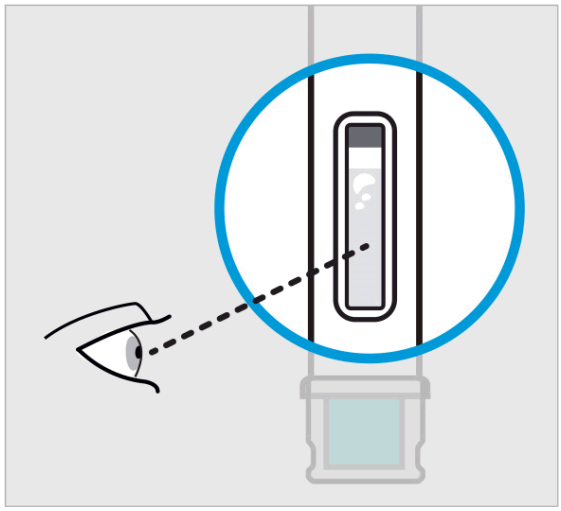
Not provided in the carton:
- **Alcohol swabs**
- **Cotton balls** or **gauze pads**
- **Adhesive bandages**
- **Sharps container** (See Step 4)

1. Get ready



Allow Tremfya to come to room temperature
Remove the carton from the refrigerator and let the carton sit on a flat surface at room temperature for approximately **30 minutes** before use.
Do not warm the pre-filled pen any other way.
Check the expiry ('EXP') date on the carton.
Do not use the pre-filled pen if the expiry date has passed or if the seal on the carton is broken.
Call your doctor or pharmacist for a new pre-filled pen.

2. Prepare for your injection



Inspect liquid in window to see that it is clear to slightly yellow
Take the pre-filled pen out of the carton.
Check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see air bubbles.
This is normal.

Do not inject if the liquid is:
- cloudy or
- discoloured or
- has large particles

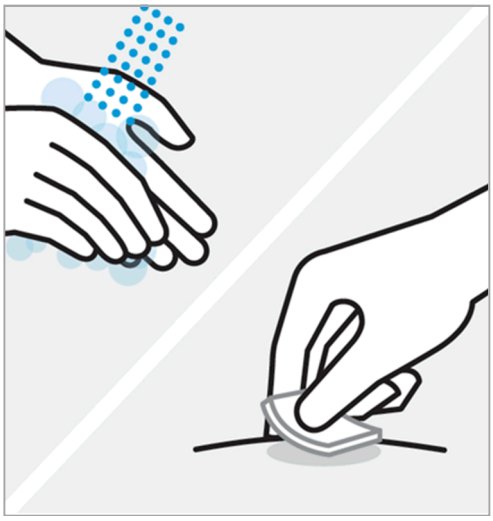
If you are uncertain, call your doctor or pharmacist for a new pre-filled pen.



Choose injection site
Select from the following areas for your injection:

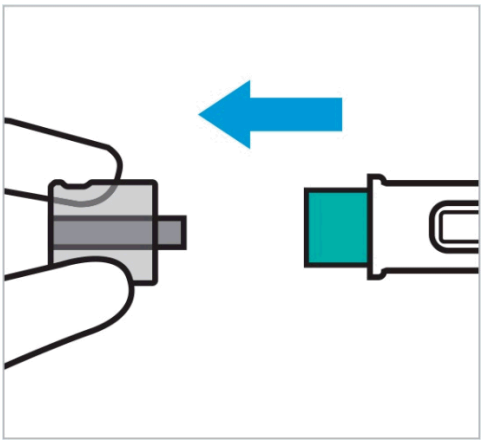
- Front of thighs
- Lower stomach area (lower abdomen)
  Do not use the 5-centimetre area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.



Wash hands and clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

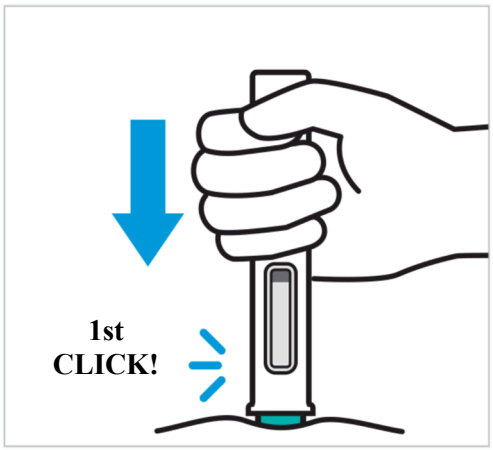
3. Inject Tremfya using the pre-filled pen



Remove cap when you are ready to inject

Do Not Touch Green Needle Guard!
This may start the injection and you will not receive the dose.

Pull the cap straight off. It is normal to see a few drops of liquid.
Inject Tremfya within 5 minutes of removing cap.
Do not put the cap back on as this may damage the needle.
Do not use the pre-filled pen if it is dropped after removing the cap.
Call your doctor or pharmacist for a new pre-filled pen.

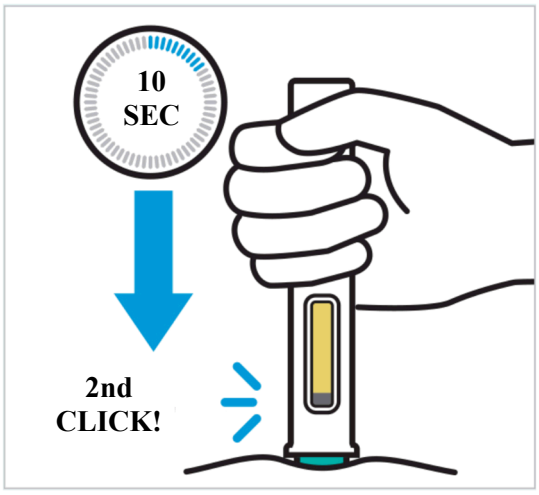


Position pre-filled pen straight onto the injection site then push and hold pre-filled pen

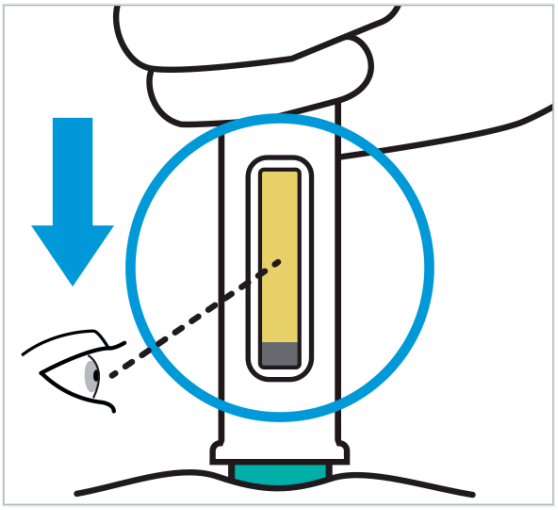
Do Not Lift The Pre-Filled Pen During Injection!
If you do, the green needle guard will lock and the full dose will not be delivered.

Position the pre-filled pen straight onto the injection site with the green needle guard against the skin and the viewing window facing you.
Press down on the pre-filled pen and keep holding it down against the skin.

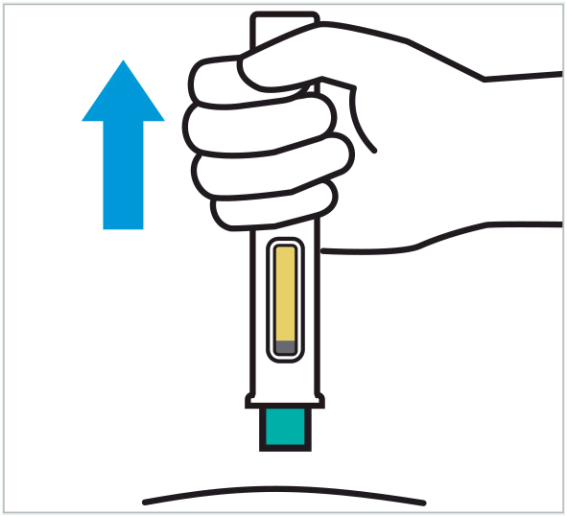
You will hear the first click.



Keep holding the pre-filled pen firmly against the skin for about 10 seconds to hear a second click
You are almost done.



Keep holding firmly against the skin and confirm the injection is complete
The injection is complete when the yellow plunger rod stops moving and fills the viewing window.



Lift straight up

4. After your injection



Check injection site
There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site. If needed, cover the injection site with a bandage.
Your injection is now complete!



Throw away the used pre-filled pen and cap
Put your used pre-filled pen and cap in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.
Do not throw away (dispose of) your pre-filled pen in your household waste.
Do not recycle your used sharps disposal container.

Package leaflet: Information for the user

Tremfya 200 mg solution for injection in pre-filled syringe
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with ulcerative colitis and Crohn's disease.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks

after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 1 mg of polysorbate 80 in each pre-filled syringe which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn’s disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

You may decide together with your doctor to give Tremfya yourself in which case you will get the appropriate training on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about giving yourself an injection. It is important not to try to inject yourself until you have been trained by your doctor or nurse.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete's foot)
- stomach flu (gastroenteritis)

- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled syringe in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled syringe inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled syringe contains 200 mg of guselkumab in 2 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 "Tremfya contains polysorbate 80").

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled syringe and in multipacks comprising 2 cartons, each containing 1 pre-filled syringe. Not all pack sizes may be marketed.

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Manufacturer
Janssen Biologics B.V.
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Tremfya
200 mg pre-filled syringe



SINGLE-USE DEVICE

Important
Tremfya comes in a single-use pre-filled syringe containing one 200 mg dose.

Your doctor will tell you if you will need to use 1 or 2 pre-filled syringes.

If your doctor decides that you or a caregiver may be able to give your injections of Tremfya at home, you should receive training on the right way to prepare and inject Tremfya using the pre-filled syringe. Please read these Instructions for Use before using the Tremfya pre-filled syringe and each time you get a refill. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment. Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.

Each Tremfya pre-filled syringe can only be used one time. Throw the used pre-filled syringe away (see Step 4) after one dose, even if there is still medicine left in it. Do not reuse your Tremfya pre-filled syringe.

The Tremfya pre-filled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the device and lock into place.



Storage information
Store in refrigerator at 2° to 8°C.
Do not freeze.
Do not shake your pre-filled syringe**.**
Keep your pre-filled syringe in the original carton to protect from light and physical damage.
Keep Tremfya and all medicines out of reach of children.



Need help?
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Pre-filled syringe at-a-glance

Before use



Plunger
Do not hold or pull plunger at any time.

Safety guard

Finger flange

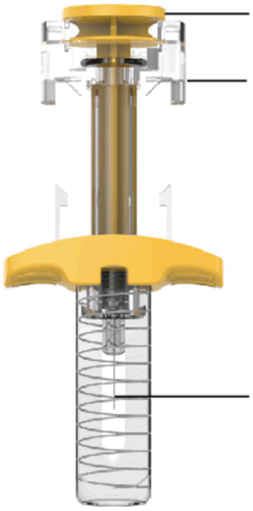
Viewing window

Body

Needle

Needle cover
Do not remove until you are ready to inject (See Step 3)

After use



Plunger stops

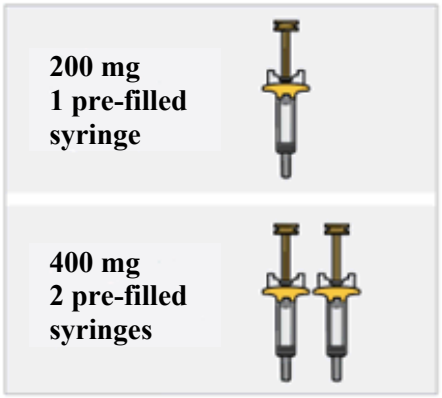
Safety guard activates

Needle retracts into the body

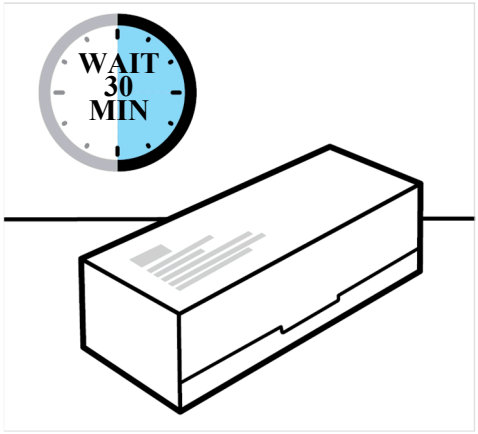
You will need:
- **1 or 2 pre-filled syringes based on the dose prescribed by your doctor**

Not provided in the carton:
- **Alcohol swabs**
- **Cotton balls** or **gauze pads**
- **Adhesive bandages**
- **Sharps container** (See Step 4)

1. Get ready

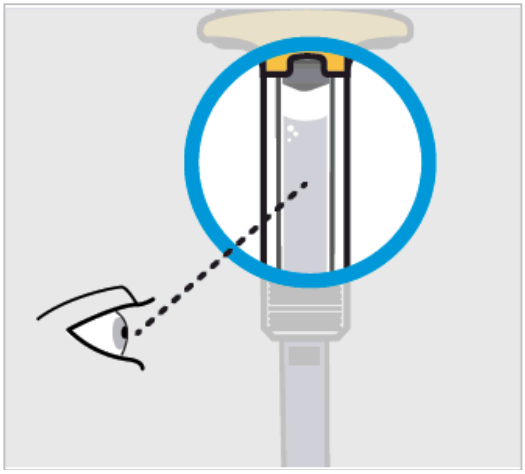


Check your dose to see if you will need to use 1 or 2 pre-filled syringes and inspect carton(s)
Remove the carton(s) with the pre-filled syringe from the refrigerator.
Check the expiry ('EXP') date.
Do not use the pre-filled syringe if the expiry date has passed or if the seal on the carton is broken.
Call your doctor or pharmacist for a new pre-filled syringe.



Allow Tremfya to come to room temperature
Let the carton(s) sit on a flat surface at room temperature for approximately **30 minutes** before use.
Do not warm the pre-filled syringe(s) any other way.

2. Prepare for your injection



Inspect liquid to see that it is clear to slightly yellow
Take the pre-filled syringe out of the carton.
Check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see air bubbles. This is normal.

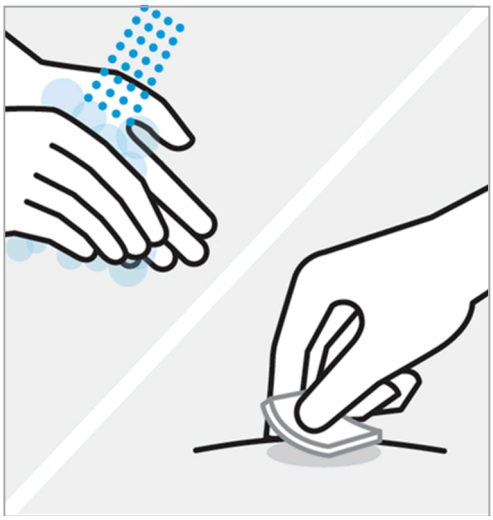
Do not inject if the liquid is:
- cloudy or
- discoloured or
- has large particles

Do not use the pre-filled syringe if it is dropped.
If you are uncertain, call your doctor or pharmacist for a new pre-filled syringe.



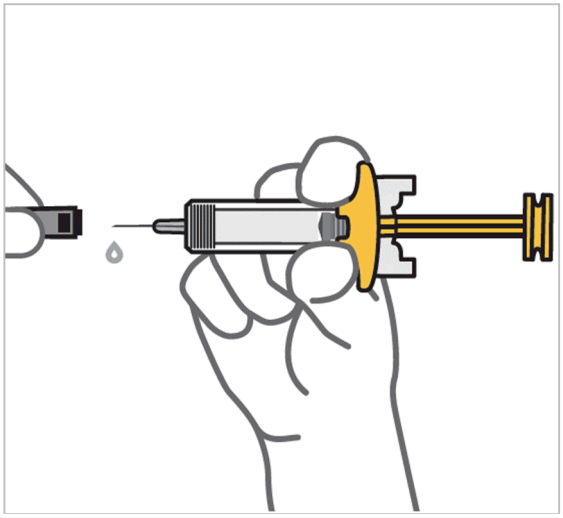
Choose injection site
Select a site from the following areas for your injection:
- Front of thighs
- Lower stomach area (lower abdomen)
  Do not use the 5-centimetre area around your belly-button
- Back of upper arms (if a caregiver is giving you the injection)

If you need to give 2 injections to complete your dose, choose different areas or leave at least 5-centimetres between injection sites.
Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.

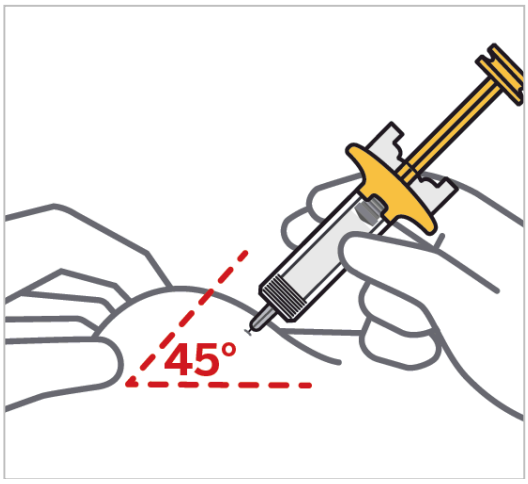


Wash hands and clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

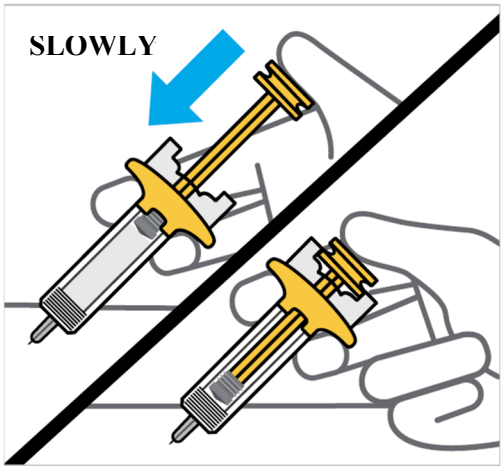
3. Inject Tremfya using the pre-filled syringe



Remove needle cover when you are ready to inject
Hold the pre-filled syringe by the body and pull needle cover straight off.
It is normal to see a few drops of liquid.
Inject Tremfya within 5 minutes of removing the needle cover.
Do not put needle cover back on, as this may damage the needle or cause a needle stick injury.
Do not touch needle or let it touch any surface.
Do not use the pre-filled syringe if it is dropped. Call your doctor or pharmacist for a new pre-filled syringe.
Do not hold or pull the plunger at any time.



Pinch injection site and insert needle at about a 45-degree angle
It is important to pinch enough skin to inject under the skin and not into muscle.
Insert needle with a quick dart-like motion.



Slowly press plunger all the way down until it stops to inject all of the liquid
You will feel some resistance as you press the plunger, this is normal.



Release pressure from plunger to remove the needle from the skin
The needle will retract into the device and lock into place.
If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second pre-filled syringe.

4. After your injection



Check injection site
There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site. If needed, cover the injection site with a bandage.
Your injection is now complete!



Throw away the used pre-filled syringe
Put the used pre-filled syringe in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.
Do not throw away (dispose of) your pre-filled syringe in your household waste.
Do not recycle your used sharps disposal container.

Package leaflet: Information for the user

Tremfya 200 mg solution for injection in pre-filled pen
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with ulcerative colitis and Crohn's disease.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks

after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 1 mg of polysorbate 80 in each pre-filled pen which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Tremfya

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn’s disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

You may decide together with your doctor to give Tremfya yourself in which case you will get the appropriate training on how to inject Tremfya. Talk to your doctor or nurse if you have any questions about giving yourself an injection. It is important not to try to inject yourself until you have been trained by your doctor or nurse.

For detailed instructions on how to use Tremfya, carefully read the 'Instructions for use' leaflet before use, which is included in the carton.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete's foot)
- stomach flu (gastroenteritis)

- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the pre-filled pen in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles. Before use, remove the carton from the refrigerator and keep the pre-filled pen inside the carton and allow to reach room temperature by waiting for 30 minutes.

This medicine is for single use only. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each pre-filled pen contains 200 mg of guselkumab in 2 mL solution.
- The other ingredients are histidine, histidine monohydrochloride monohydrate, polysorbate 80 (E433), sucrose and water for injections (see section 2 "Tremfya contains polysorbate 80").

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for injection (injection). It is available in packs containing one pre-filled pen and in multipacks comprising 2 cartons, each containing 1 pre-filled pen. Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
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Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333CB Leiden

The Netherlands

Janssen Pharmaceutica NV
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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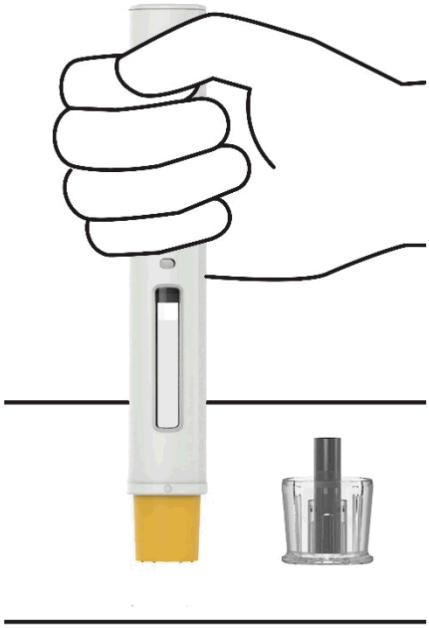
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

Instructions for use
Tremfya
200 mg pre-filled pen



SINGLE-USE DEVICE

Important
Tremfya comes in a single-use pre-filled pen containing one 200 mg dose.

Your doctor will tell you if you will need to use 1 or 2 pre-filled pens.

If your doctor decides that you or a caregiver may be able to give your injections of Tremfya at home, you should receive training on the right way to prepare and inject Tremfya using the pre-filled pen. Please read these Instructions for Use before using the Tremfya pre-filled pen and each time you get a new pre-filled pen. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment. Please also read the Package Leaflet carefully before starting your injection and discuss any questions you may have with your doctor or nurse.

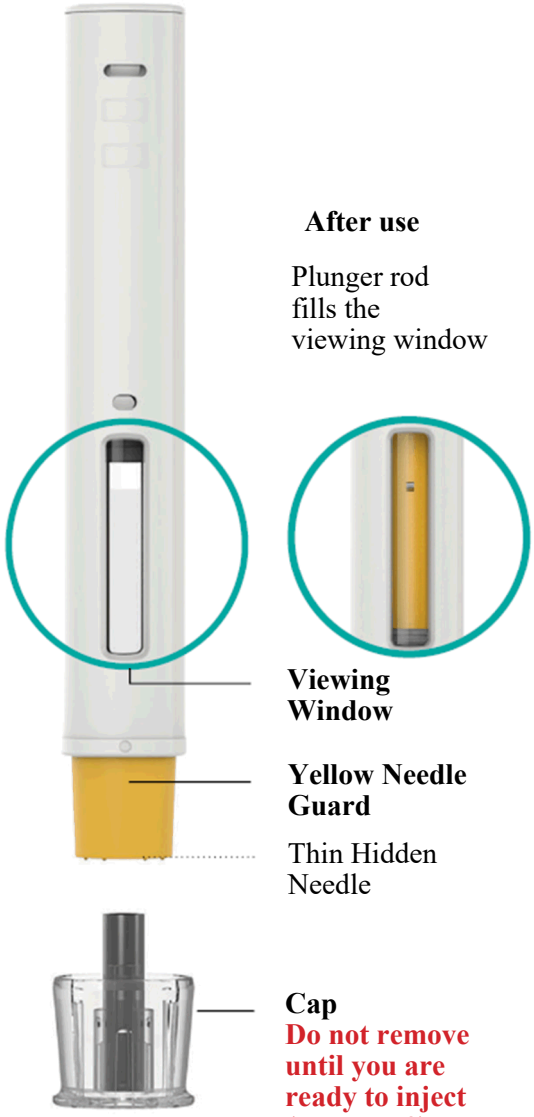
Each Tremfya pre-filled pen can only be used one time. Throw the used pre-filled pen away (see Step 4) after one dose, even if there is still medicine left in it. Do not reuse your pre-filled pen.

**Storage information**
Store in refrigerator at 2° to 8°C.
Do not freeze.
Do not shake your pre-filled pen.
Keep your pre-filled pen in the original carton to protect from light and physical damage.
Keep Tremfya and all medicines out of reach of children.

**Need help?**
Call your doctor to talk about any questions you may have. For additional assistance or to share your feedback refer to the Package Leaflet for your local representative contact information.

Pre-filled pen at-a-glance

Before use



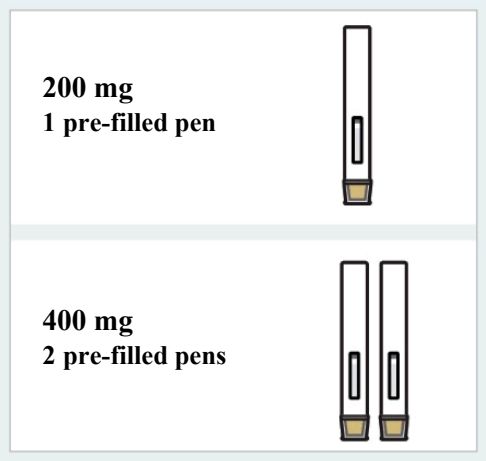
You will need:

- **1 or 2 pre-filled pens based on the dose prescribed by your doctor**

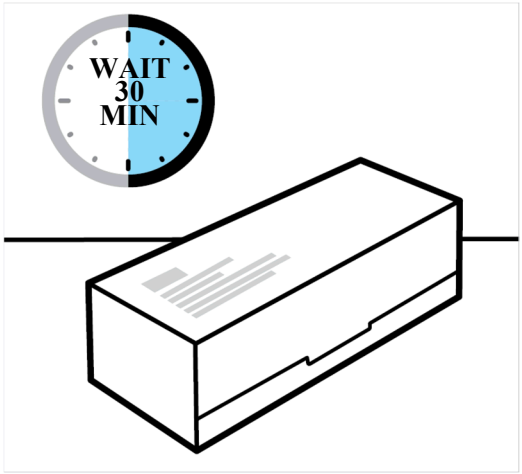
Not provided in the carton:

- **Alcohol swabs**
- **Cotton balls** or **gauze pads**
- **Adhesive bandages**
- **Sharps container** (See Step 4)

1. Get ready

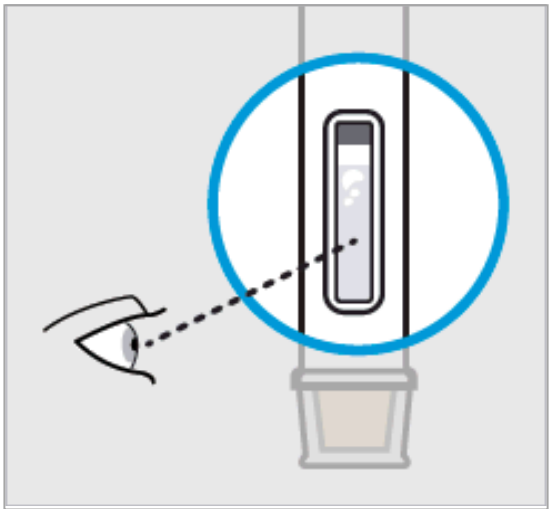


Check your prescribed dose to see if you will need to use 1 or 2 pre-filled pens and inspect carton(s)
Remove the carton(s) with the pre-filled pen from the refrigerator.
Check the expiry ('EXP') date on the carton.
Do not use the pre-filled pen if the expiry date has passed or if the seal on the carton is broken.
Call your doctor or pharmacist for a new pre-filled pen.



Allow Tremfya to come to room temperature
Let the carton(s) sit on a flat surface at room temperature for approximately **30 minutes** before use.
Do not warm the pre-filled pen(s) any other way.

2. Prepare for your injection



Inspect liquid in window to see that it is clear to slightly yellow
Take the pre-filled pen out of the carton.
Check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see air bubbles.
This is normal.

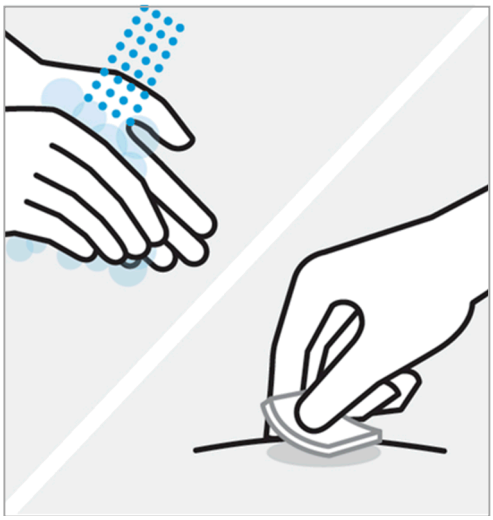
Do not inject if the liquid is:
- cloudy or
- discoloured or
- has large particles

If you are uncertain, call your doctor or pharmacist for a new pre-filled pen.



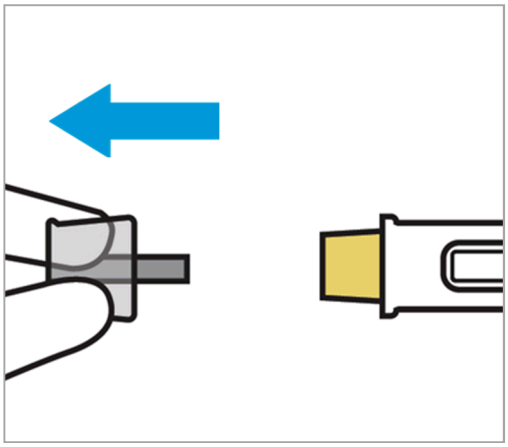
Choose injection site
Select from the following areas for your injection:
- Front of thighs
- Lower stomach area (lower abdomen)
  Do not use the 5-centimetre area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

If you need to give 2 injections to complete your dose, choose different areas or leave at least 5-centimetres between injection sites.
Do not inject into skin that is tender, bruised, red, scaly, thick or hard. Avoid areas with scars or stretch marks.



Wash hands and clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

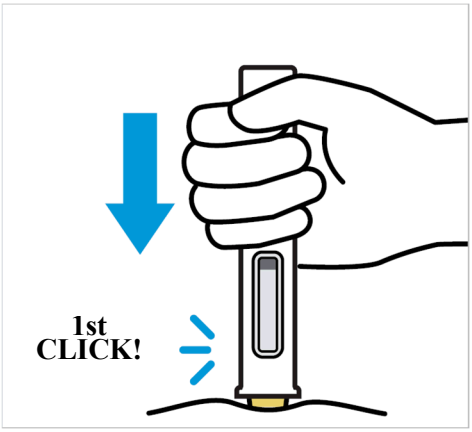
3. Inject Tremfya using the pre-filled pen



Remove cap when you are ready to inject

Do Not Touch Yellow Needle Guard!
This may start the injection and you will not receive the dose.

Pull the cap straight off. It is normal to see a few drops of liquid.
Inject Tremfya within 5 minutes of removing cap.
Do not put the cap back on as this may damage the needle.
Do not use the pre-filled pen if it is dropped after removing the cap.
Call your doctor or pharmacist for a new pre-filled pen.

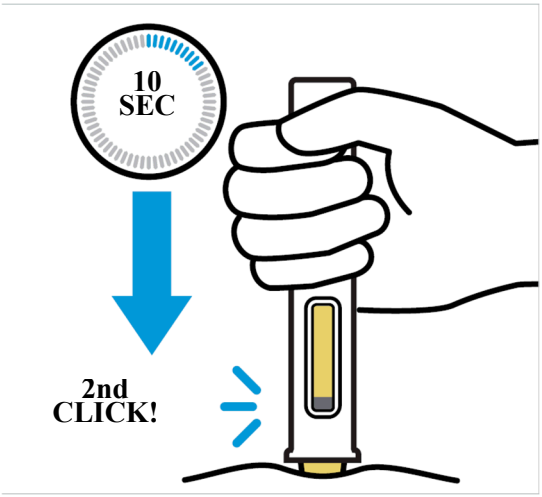


Position pre-filled pen straight onto the injection site then push and hold pre-filled pen

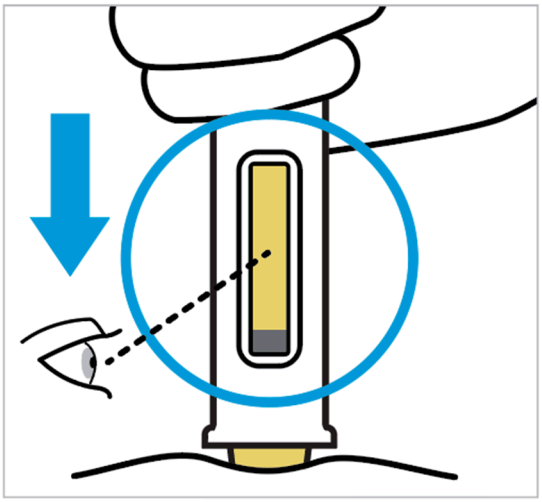
Do Not Lift The Pre-Filled Pen During Injection!
If you do, the yellow needle guard will lock and the full dose will not be delivered.

Position the pre-filled pen straight onto the injection site with the yellow needle guard against the skin and the viewing window facing you.
Press down on the pre-filled pen and keep holding it down against the skin.

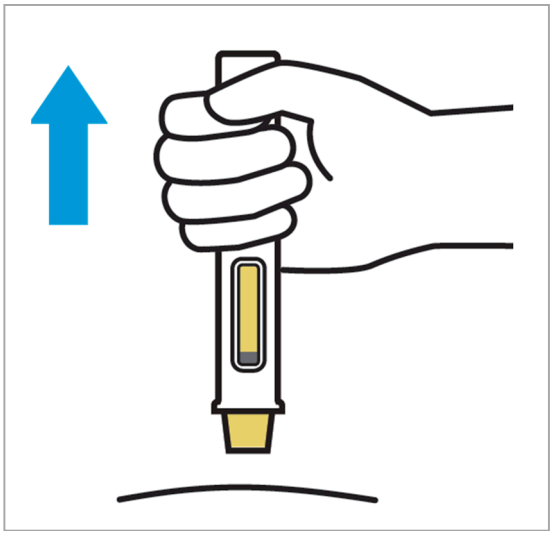
You will hear the first click.



Keep holding the pre-filled pen firmly against the skin for about 10 seconds to hear a second click
You are almost done.



Keep holding firmly against the skin and confirm the injection is complete
The injection is complete when the plunger rod stops moving and fills the viewing window.



Lift straight up

If your prescribed dose requires two injections, repeat Steps 2 to 4 with the second pre-filled pen.

4. After your injection



Check injection site
There may be a small amount of blood or liquid at the injection site. Gently hold pressure over the injection site with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site. If needed, cover the injection site with a bandage.
Your injection is now complete!



Throw away the used pre-filled pen and cap
Put your used pre-filled pen and cap in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.
Do not throw away (dispose of) your pre-filled pen in your household waste.
Do not recycle your used sharps disposal container.

Package leaflet: Information for the user

Tremfya 200 mg concentrate for solution for infusion
guselkumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tremfya is and what it is used for
2. What you need to know before you use Tremfya
3. How to use Tremfya
4. Possible side effects
5. How to store Tremfya
6. Contents of the pack and other information

1. What Tremfya is and what it is used for

Tremfya contains the active substance guselkumab which is a type of protein called a monoclonal antibody.

This medicine works by blocking the activity of a protein called IL-23, which is present at increased levels in people with ulcerative colitis or Crohn's disease.

Ulcerative colitis
Tremfya is used to treat adults with moderate to severe ulcerative colitis, an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in ulcerative colitis can benefit you by reducing the signs and symptoms of the disease including bloody stools, the need to rush to and the number of times you go to the toilet, abdominal pain and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

Crohn's disease
Tremfya is used to treat adults with moderate to severe Crohn's disease, an inflammatory disease of the bowel. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, you may be given Tremfya.

Using Tremfya in Crohn's disease can benefit you by reducing the signs and symptoms of the disease such as diarrhoea, abdominal pain, and the inflammation of your intestinal lining. These effects can improve your ability to do normal daily activities and reduce fatigue.

2. What you need to know before you use Tremfya

Do not use Tremfya
- if you are allergic to guselkumab or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice before using Tremfya.
- if you have an active infection, including active tuberculosis.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tremfya:
- if you are being treated for an infection;
- if you have an infection that does not go away or that keeps coming back;
- if you have tuberculosis or have been in close contact with someone with tuberculosis;
- if you think you have an infection or have symptoms of an infection (see below under 'Look out for infections and allergic reactions');
- if you have recently had a vaccination or if you are due to have a vaccination during treatment with Tremfya.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Tremfya.

As directed by your doctor, you may need blood tests to check if you have high levels of liver enzymes before you start taking Tremfya and when using it. Increases in liver enzymes may occur more frequently in patients receiving Tremfya every 4 weeks than in patients receiving Tremfya every 8 weeks (see "How to use Tremfya" in section 3).

Look out for infections and allergic reactions
Tremfya can potentially cause serious side effects, including allergic reactions and infections. You must look out for signs of these conditions while you are taking Tremfya.

Signs or symptoms of infections may include fever or flu like symptoms; muscle aches; cough; shortness of breath; burning when you urinate or urinating more often than usual; blood in your phlegm (mucus); weight loss; diarrhoea or stomach pain; warm, red, or painful skin or sores on your body.

Serious allergic reactions have occurred with Tremfya. Symptoms may include, swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing, lightheadedness or dizziness, or hives (see "Serious side effects" in section 4).

Stop using Tremfya and tell your doctor or seek medical help **immediately** if you notice any signs indicating a possible serious allergic reaction or an infection.

Children and adolescents
Do not give this medicine to children and adolescents less than 18 years of age because it has not been studied in this age group.

Other medicines and Tremfya
Tell your doctor or pharmacist:
- if you are using, have recently used or might use any other medicines.
- if you recently had or are due to have a vaccination. You should not be given certain types of vaccines (live vaccines) while using Tremfya.

Pregnancy and breast-feeding
- Tremfya should not be used in pregnancy as the effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using Tremfya and for at least 12 weeks

after the last Tremfya dose. Talk to your doctor if you are pregnant, think you may be pregnant or are planning to have a baby.
- Talk to your doctor if you are breast-feeding or are planning to breast-feed. You and your doctor should decide if you will breast-feed or use Tremfya.

Driving and using machines
Tremfya is unlikely to influence your ability to drive and use machines.

Tremfya contains polysorbate 80
This medicine contains 10 mg of polysorbate 80 in each vial which is equivalent to 0.5 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

Tremfya contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

However, before Tremfya is given to you, it is mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

3. How to use Tremfya

Tremfya is intended for use under the guidance and supervision of a doctor experienced in the diagnosis and treatment of ulcerative colitis and Crohn's disease.

How much Tremfya is given and for how long
Your doctor will decide for how long you need to use Tremfya.

Ulcerative colitis
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:
- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

Crohn's disease
Treatment start:
Treatment start can be given either by intravenous infusion or by subcutaneous administration:
- Intravenous infusion: The first dose of Tremfya is 200 mg and will be given by your doctor or nurse by intravenous infusion (drip in a vein in your arm). After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.
- Subcutaneous administration: The first dose of Tremfya is 400 mg and will be given under the skin (subcutaneous injection) at different locations of the body. After the first dose, you will receive a second dose 4 weeks later and then a third dose after an additional 4 weeks.

Maintenance therapy:
A maintenance dose of Tremfya will be given by injection under the skin (subcutaneous injection) either with 100 mg or 200 mg. Your doctor will decide which maintenance dose you will receive:

- A dose of 100 mg will be given 8 weeks after the third treatment start dose, and then every 8 weeks.
- A dose of 200 mg will be given 4 weeks after the third treatment start dose and then every 4 weeks.

If you use more Tremfya than you should
If you have received more Tremfya than you should or the dose has been given sooner than prescribed, inform your doctor.

If you forget to use Tremfya
If you have forgotten to inject a dose of Tremfya, inform your doctor.

If you stop using Tremfya
You should not stop using Tremfya without speaking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Stop using Tremfya and tell your doctor or seek medical help immediately if you get any of the following side effects:

Possible serious allergic reaction (may affect up to 1 in 1 000 people) - the signs or symptoms may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps
- lightheadedness, low blood pressure, or dizziness

Other side effects
The following side effects are all mild to moderate. If any of these side effects becomes severe, tell your doctor, pharmacist or nurse immediately.

Very common (may affect more than 1 in 10 people)
- respiratory tract infections

Common (may affect up to 1 in 10 people)
- headache
- joint pain (arthralgia)
- diarrhoea
- increased level of liver enzymes in the blood
- skin rash
- redness, irritation or pain at the injection site

Uncommon (may affect up to 1 in 100 people)
- decreased number of a type of white blood cell called neutrophils
- herpes simplex infections
- fungal infection of the skin, for instance between the toes (e.g., athlete’s foot)
- stomach flu (gastroenteritis)
- hives

Rare (may affect up to 1 in 1 000 people)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tremfya

Tremfya 200 mg concentrate for solution for infusion is given in a hospital or clinic and patients should not need to store or handle it.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and on the outer carton after "EXP". The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect from light.

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

Do not shake.

Do not use this medicine if you notice that the medicine is cloudy or discoloured, or contains large particles.

This medicine is for single use only.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Tremfya contains
- The active substance is guselkumab. Each vial contains 200 mg of guselkumab in 20 mL solution.
- The other ingredients are EDTA disodium dihydrate, histidine, histidine monohydrochloride monohydrate, methionine, polysorbate 80 (E433), sucrose and water for injections (see section 2 "Tremfya contains polysorbate 80").

What Tremfya looks like and contents of the pack
Tremfya is a clear, colourless to light yellow solution for infusion.

Each pack contains 1 vial.

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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

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Tremfya 200 mg concentrate for solution for infusion
guselkumab

The following information is intended for healthcare professionals only.

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

Tremfya 200 mg/20 mL (10 mg/mL) Vial for Intravenous Infusion
Tremfya solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.. 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.

Instructions for Dilution and Administration
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.