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

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

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.

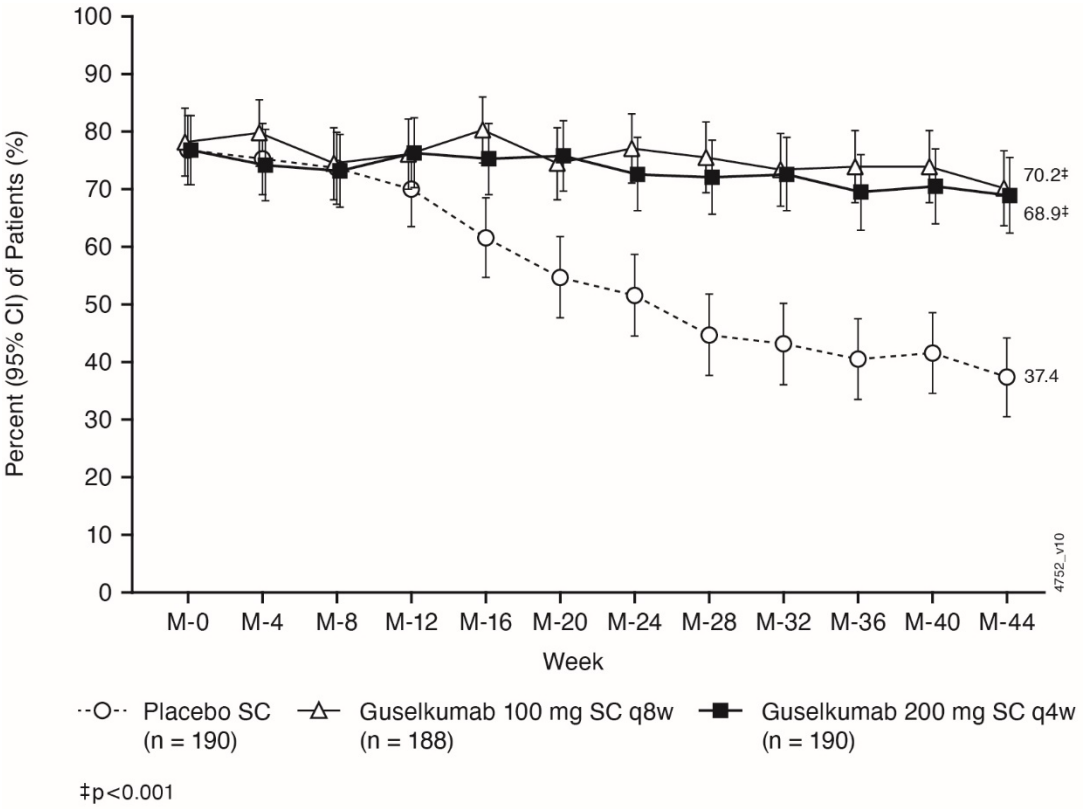
In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of > 15% were observed between the two guselkumab dose groups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

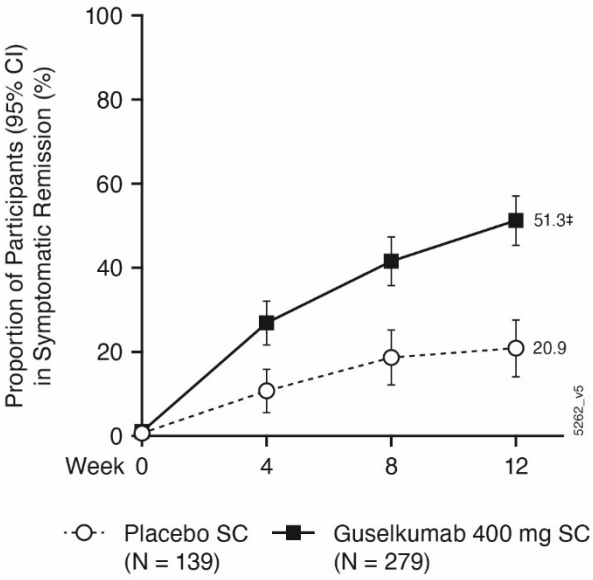
[g] Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab), JAK inhibitor, and/or S1PRM for ulcerative colitis

[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.

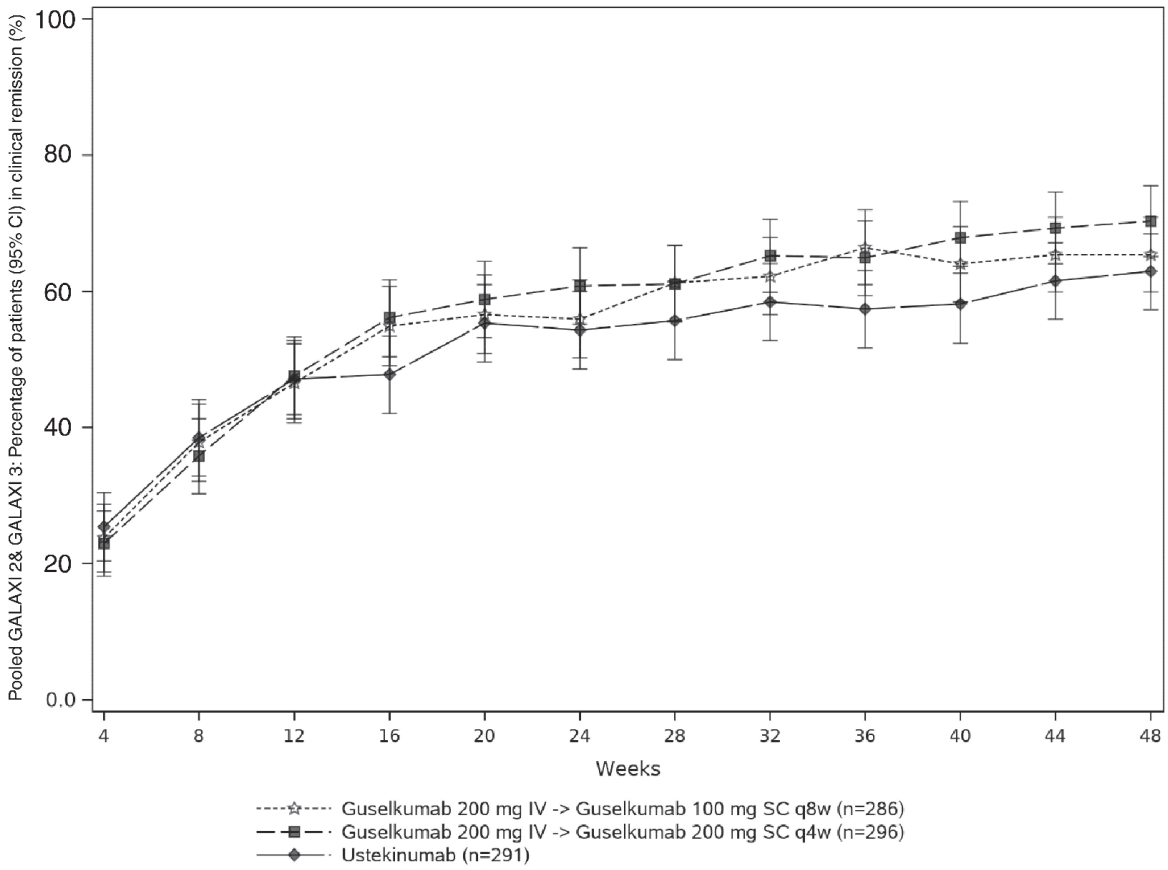
In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight.

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

<u>Tremfya 200 mg solution for injection in pre-filled syringe</u>

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.

<u>Tremfya 200 mg solution for injection in pre-filled pen</u>

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

23 March 2026

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