

## **ANNEX I**

### **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Tremfya 200 mg concentrate for solution for infusion

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains 200 mg 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 (IgG1 $\lambda$ ) monoclonal antibody (mAb) produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

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.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

#### 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.

#### Ulcerative colitis

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

### **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

##### *Crohn's disease*

##### Induction:

The recommended induction dose is:

- 200 mg administered by intravenous infusion at week 0, week 4, and week 8.
- or
- 400 mg administered by subcutaneous injection at week 0, week 4 and week 8.

*For the posology of the subsequent subcutaneous Maintenance dosing regimen, see section 4.2 of the Tremfya 100 mg solution for injection in pre-filled syringe, 100 mg solution for injection in pre-filled pen, 200 mg solution for injection in pre-filled syringe, 200 mg PushPen solution for injection in pre-filled pen Summary of Product Characteristics.*

#### Maintenance:

The recommended maintenance dose is 100 mg administered by subcutaneous injection at week 16 and every 8 weeks (q8w) thereafter after completion of induction dosing.

A dose of 200 mg administered by subcutaneous injection at week 12 and every 4 weeks (q4w) thereafter may be considered for patients who do not show adequate therapeutic benefit, according to clinical judgement (see section 5.1), after completion of induction dosing.

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.

#### Ulcerative colitis

##### Induction

The recommended dose is 200 mg administered by intravenous infusion at week 0, week 4 and week 8.

##### Maintenance

The recommended maintenance dose is 100 mg administered by subcutaneous injection at week 16 and every 8 weeks (q8w) thereafter after completion of induction dosing.

A dose of 200 mg administered by subcutaneous injection at week 12 and every 4 weeks (q4w) thereafter may be considered for patients who do not show adequate therapeutic benefit, according to clinical judgement (see section 5.1), after completion of induction dosing.

*For the posology of the subsequent subcutaneous Maintenance dosing regimen, see section 4.2 of the Tremfya 100 mg solution for injection in pre-filled syringe, 100 mg solution for injection in pre-filled pen, 200 mg solution for injection in pre-filled syringe, 200 mg PushPen solution for injection in pre-filled pen Summary of Product Characteristics.*

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  $\geq 65$  years and very limited information in patients aged  $\geq 75$  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 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.

### **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 Crohn's disease and ulcerative colitis studies, concomitant use of immunomodulators (eg, azathioprine [AZA]) 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 no 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 (from 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, Crohn's disease and ulcerative colitis.

##### Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis 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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

**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	Uncommon	Urticaria
	Common	Rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Uncommon	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 events 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 events of increased transaminases (as above) were reported in 12.9% of patients in the q4w group and 11.7% of patients in the q8w group.

Based on laboratory assessments, most transaminase increases (ALT and AST) were  $\leq 3$  x upper limit of normal (ULN). Transaminase increases from  $> 3$  to  $\leq 5$  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 <sup>a</sup>			Through 1 year <sup>b</sup>	
	Placebo N=370 <sup>c</sup>	guselkumab 100 mg q8w N=373 <sup>c</sup>	guselkumab 100 mg q4w N=371 <sup>c</sup>	guselkumab 100 mg q8w N=373 <sup>c</sup>	guselkumab 100 mg q4w N=371 <sup>c</sup>
<b>ALT</b>					
>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%
<b>AST</b>					
>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%

<sup>a</sup> placebo-controlled period.

<sup>b</sup> patients randomised to placebo at baseline and crossed over to guselkumab are not included.

<sup>c</sup> 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 period (Week 12), adverse events of increased transaminases (includes ALT increased, AST increased, hepatic enzyme increased, transaminases increased) were reported more frequently in the guselkumab treated groups (1.6% of patients) than in the placebo group (0.6% of patients). Through the reporting period of approximately one year, adverse events of increased transaminases were reported in 2.9% of patients in the guselkumab 200 mg subcutaneous q4w treatment group and 2.8% of patients in the guselkumab 100 mg subcutaneous q8w treatment 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. Through the reporting period of approximately one year, ALT (<2% of patients) and AST (<1.5% of patients) elevations ≥3x ULN were reported in guselkumab treated patients. 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 event 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 event 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 Phase II and Phase III Crohn's disease clinical studies through Week 48, the proportion of patients that reported 1 or more subcutaneous 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 24, the proportion of patients that reported 1 or more injection site reactions to guselkumab was 5.2% (0.9% of injections) in the treatment group which received 400 mg subcutaneous induction followed by 200 mg subcutaneous q4w and 2.6% (0.5% of injections) of patients in the 400 mg guselkumab subcutaneous induction followed by 100 mg subcutaneous q8w group. Injection site reactions were mild; none were serious.

In the Phase III ulcerative colitis maintenance clinical study through Week 44, the proportion of patients that reported 1 or more subcutaneous injection site reactions to guselkumab was 7.9% (2.5% of injections) in the guselkumab 200 mg subcutaneous q4w group and no injections in the guselkumab 100 mg subcutaneous q8w group. Most injection site reactions were mild and 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 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 24 in patients with Crohn's disease who were treated with subcutaneous induction followed by subcutaneous maintenance dose regimen, approximately 3% (n=8) of patients treated with guselkumab developed antidrug antibodies. Of the patients, none had antibodies that were classified as neutralising antibodies. 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, 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.

#### 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.

#### **To Report any side effect (s):**

##### **• Saudi Arabia**

The National Pharmacovigilance Centre (NPC):

- SFDA Call Center: 19999
- E-mail: [npc.drug@sfd.gov.sa](mailto:npc.drug@sfd.gov.sa)
- Website: <https://ade.sfda.gov.sa/>

##### **• Other GCC states:**

– Please contact the relevant competent authority

## **4.9 Overdose**

Single intravenous doses of guselkumab up to 987 mg (10 mg/kg) have been administered in healthy volunteers and single subcutaneous doses of guselkumab up to 300 mg have been administered in patients with plaque psoriasis 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 IgG1 $\lambda$  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 Crohn's disease and ulcerative colitis, 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, Crohn's disease and ulcerative colitis through blockade of the IL-23 cytokine pathway.

Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, Crohn's disease and ulcerative colitis. Guselkumab has demonstrated *in vitro* blocking of IL-23 and binding to CD64. These results indicate that guselkumab is able to neutralize 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 Crohn's disease and ulcerative colitis, guselkumab treatment led to decreases in inflammatory markers including C-reactive protein (CRP) and fecal calprotectin through induction Week 12, which were sustained through one year of maintenance treatment. Serum protein levels of IL-17A, IL-22 and IFN $\gamma$  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 IFN $\gamma$  at Week 12.

## Clinical efficacy and safety

### 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  $\geq 220$  and  $\leq 450$  and a Simple Endoscopic Score for CD (SES-CD) of  $\geq 6$  (or  $\geq 4$  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, 41.9% were biologic naïve, and 5.3% had previously received but had not failed a biologic. At baseline, 37.4% of the patients were receiving oral corticosteroids and 29.9% of the patients were receiving conventional immunomodulators.

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

In GALAXI 2 and GALAXI 3, a significantly greater proportion of patients achieved the co-primary efficacy endpoints of clinical remission at Week 12 and endoscopic response at Week 12 in the guselkumab treated group compared to placebo (Table 3). A significantly greater proportion of patients in the guselkumab treated group achieved PRO-2 remission and fatigue response, and a greater proportion of patients achieved endoscopic remission, all at Week 12, compared with the placebo treatment group (Table 4).

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

	GALAXI 2		GALAXI 3	
	Placebo (N=76)	Guselkumab intravenous induction <sup>a</sup> (N=289)	Placebo (N=72)	Guselkumab intravenous induction <sup>a</sup> (N=293)
<b>Clinical remission at Week 12<sup>b</sup></b>				
Total population	17 (22%)	136 (47%) <sup>f</sup>	11 (15%)	138 (47%) <sup>f</sup>
Biologic naïve <sup>c</sup>	6/34 (18%)	60/121 (50%)	4/27 (15%)	61/123 (50%)
Prior biologic failure <sup>d</sup>	9/39 (23%)	67/150 (45%)	6/39 (15%)	71/150 (47%)
<b>Endoscopic response at Week 12<sup>e</sup></b>				
Total population	8 (11%)	109 (38%) <sup>f</sup>	10 (14%)	106 (36%) <sup>f</sup>
Biologic naïve <sup>c</sup>	5/34 (15%)	62/121 (51%)	6/27 (22%)	51/123 (41%)
Prior biologic failure <sup>d</sup>	2/39 (5%)	40/150 (27%)	3/39 (8%)	47/150 (31%)

<sup>a</sup> 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 dose regimen prior to Week 12.

<sup>b</sup> Clinical remission is defined as CDAI score <150.

<sup>c</sup> 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.

<sup>d</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers or vedolizumab) for Crohn's disease.

<sup>e</sup> Endoscopic response is defined as  $\geq 50\%$  improvement from baseline in SES-CD score or SES-CD Score  $\leq 2$ .

<sup>f</sup>  $p < 0.001$

**Table 4: Proportion of patients meeting short-term major secondary efficacy endpoints with guselkumab versus placebo at Week 12 in GALAXI 2 and GALAXI 3**

	GALAXI 2		GALAXI 3	
	Placebo (N=76)	Guselkumab intravenous induction <sup>a</sup> (N=289)	Placebo (N=72)	Guselkumab intravenous induction <sup>a</sup> (N=293)
<b>PRO-2 remission<sup>b</sup> at Week 12</b>				
Total population	16 (21%)	124 (43%) <sup>g</sup>	10 (14%)	122 (42%) <sup>g</sup>
Biologic naïve <sup>c</sup>	8/34 (24%)	52/121 (43%)	4/27 (15%)	58/123 (47%)
Prior biologic failure <sup>d</sup>	5/39 (13%)	61/150 (41%)	5/39 (13%)	59/150 (39%)
<b>Fatigue response<sup>e</sup> at Week 12</b>				
Total population	22 (29%)	131 (45%) <sup>h</sup>	13 (18%)	127 (43%) <sup>g</sup>
Biologic naïve <sup>c</sup>	11/34 (32%)	58/121 (48%)	5/27 (19%)	56/123 (46%)
Prior biologic failure <sup>d</sup>	10/39 (26%)	62/150 (41%)	7/39 (18%)	64/150 (43%)
<b>Endoscopic remission<sup>f</sup> at Week 12</b>				
Total population	1 (1%)	43 (15%)	6 (8%)	47 (16%)
Biologic naïve <sup>c</sup>	1/34 (3%)	27/121 (22%)	5/27 (19%)	31/123 (25%)
Prior biologic failure <sup>d</sup>	0/39	13/150 (9%)	0/39	14/150 (9%)

- <sup>a</sup> Guselkumab 200 mg intravenous induction at Week 0, Week 4 and Week 8 – Two guselkumab treatment groups were combined for this column as they received the same intravenous dose regimen.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers or vedolizumab) for Crohn's disease.
- <sup>e</sup> Fatigue response is defined as improvement of  $\geq 7$  points in PROMIS Fatigue Short Form 7a.
- <sup>f</sup> Endoscopic remission is defined as SES-CD Score  $\leq 2$ .
- <sup>g</sup>  $p < 0.001$
- <sup>h</sup>  $p < 0.05$

In GALAXI 2 and GALAXI 3, a significantly greater proportion of patients were in corticosteroid-free clinical remission at Week 48 and endoscopic response at Week 48 in the guselkumab treated group compared to placebo (Table 5).

**Table 5: Proportion of patients meeting long-term efficacy endpoints with guselkumab versus placebo at Week 48 in GALAXI 2 and GALAXI 3**

	GALAXI 2			GALAXI 3		
	Placebo (N=76)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection <sup>a</sup> (N=143)	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection <sup>b</sup> (N=146)	Placebo (N=72)	Guselkumab intravenous induction→ 100 mg q8w subcutaneous injection <sup>a</sup> (N=143)	Guselkumab intravenous induction→ 200 mg q4w subcutaneous injection <sup>b</sup> (N=150)
<b>Corticosteroid-free clinical remission<sup>c</sup> at Week 48</b>						
Total population	9 (12%)	65 (45%) <sup>g</sup>	75 (51%) <sup>g</sup>	10 (14%)	63 (44%) <sup>g</sup>	72 (48%) <sup>g</sup>
Biologic naïve <sup>d</sup>	2/34 (6%)	32/58 (55%)	33/63 (52%)	5/27 (19%)	25/58 (43%)	32/65 (49%)
Prior biologic failure <sup>e</sup>	5/39 (13%)	28/77 (36%)	37/73 (51%)	5/39 (13%)	37/76 (49%)	36/74 (49%)
<b>Endoscopic response<sup>f</sup> at Week 48</b>						
Total population	5 (7%)	55 (38%) <sup>g</sup>	56 (38%) <sup>g</sup>	4 (6%)	47 (33%) <sup>g</sup>	54 (36%) <sup>g</sup>
Biologic naïve <sup>d</sup>	2/34 (6%)	26/58 (45%)	30/63 (48%)	2/27 (7%)	22/58 (38%)	25/65 (38%)
Prior biologic failure <sup>e</sup>	3/39 (8%)	27/77 (35%)	20/73 (27%)	2/39 (5%)	25/76 (33%)	27/74 (36%)

- <sup>a</sup> 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.
- <sup>b</sup> 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.
- <sup>c</sup> Corticosteroid-free clinical remission is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48.
- <sup>d</sup> An additional 9 patients in the placebo group and 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.
- <sup>e</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers or vedolizumab) for Crohn's disease.
- <sup>f</sup> Endoscopic response is defined as  $\geq 50\%$  improvement from baseline in SES-CD score or SES-CD Score  $\leq 2$ .
- <sup>g</sup>  $p < 0.001$

Results of the long-term efficacy endpoints with both guselkumab maintenance dose regimens compared to ustekinumab at Week 48 are presented below (Table 6). The results were consistent across GALAXI 2 and GALAXI 3.

**Table 6: Proportion of patients meeting long term 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 <sup>a</sup> (N=143)	Guselkumab intravenous induction → 100 mg q8w subcutaneous injection <sup>b</sup> (N=143)	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection <sup>c</sup> (N=146)	Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection <sup>a</sup> (N=148)	Guselkumab intravenous induction → 100 mg q8w subcutaneous injection <sup>b</sup> (N=143)	Guselkumab intravenous induction → 200 mg q4w subcutaneous injection <sup>c</sup> (N=150)
<b>Clinical remission at Week 48 and endoscopic response<sup>d</sup> at Week 48</b>						
Total population	56 (39%)	60 (42%)	72 (49%)	42 (28%)	59 (41%) <sup>k</sup>	68 (45%) <sup>k</sup>
<b>Endoscopic response<sup>e</sup> at Week 48</b>						
Total population	60 (42%)	70 (49%)	82 (56%)	48 (32%)	67 (47%)	74 (49%)
<b>Endoscopic remission<sup>f</sup> at Week 48</b>						
Total population	29 (20%)	38 (27%)	35 (24%)	19 (13%)	34 (24%) <sup>k</sup>	28 (19%)
<b>Clinical remission<sup>g</sup> at Week 48</b>						
Total population	93 (65%)	92 (64%)	109 (75%)	90 (61%)	95 (66%)	99 (66%)
<b>Corticosteroid-free clinical remission<sup>h</sup> at Week 48</b>						
Total population	87 (61%)	90 (63%)	104 (71%)	87 (59%)	92 (64%)	96 (64%)
<b>Durable clinical remission<sup>i</sup> at Week 48</b>						
Total population	64 (45%)	66 (46%)	76 (52%)	58 (39%)	72 (50%)	73 (49%)
<b>PRO-2 remission<sup>j</sup> at Week 48</b>						
Total population	85 (59%)	86 (60%)	101 (69%)	78 (53%)	83 (58%)	84 (56%)

- <sup>a</sup> Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.
- <sup>b</sup> 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.
- <sup>c</sup> 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.
- <sup>d</sup> A combination of clinical remission and endoscopic response as defined below.
- <sup>e</sup> Endoscopic response is defined as  $\geq 50\%$  improvement from baseline in SES-CD score or SES-CD Score  $\leq 2$ .
- <sup>f</sup> Endoscopic remission is defined as SES-CD Score  $\leq 2$ .
- <sup>g</sup> Clinical remission is defined as CDAI score  $<150$ .
- <sup>h</sup> Corticosteroid-free clinical remission is defined as CDAI score  $<150$  at Week 48 and not receiving corticosteroids at Week 48.
- <sup>i</sup> Durable clinical remission is defined as CDAI  $< 150$  for  $\geq 80\%$  of all visits between Week 12 and Week 48 (at least 8 of 10 visits), which must include Week 48.
- <sup>j</sup> 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.
- <sup>k</sup>  $p < 0.05^{12}$

Results of the long-term efficacy endpoints with both guselkumab maintenance dose regimens compared to ustekinumab at Week 48 in the pooled GALAXI 2 and GALAXI 3 studies including biologic naïve and prior biologic failure subpopulations are presented below in Table 7

**Table 7: Proportion of patients meeting long term efficacy endpoints with guselkumab versus ustekinumab at Week 48 in pooled GALAXI 2 and GALAXI 3**

<b>Pooled GALAXI 2 &amp; GALAXI 3</b>			
	<b>Ustekinumab 6 mg/kg intravenous induction → 90 mg q8w subcutaneous injection<sup>a</sup> (N=291)</b>	<b>Guselkumab intravenous induction → 100 mg q8w subcutaneous injection<sup>b</sup> (N=286)</b>	<b>Guselkumab intravenous induction → 200 mg q4w subcutaneous injection<sup>c</sup> (N=296)</b>
<b>Clinical remission at Week 48 and endoscopic response<sup>d</sup> at Week 48</b>			
Total population	98 (34%)	119 (42%)	140 (47%)
Biologic naïve <sup>e</sup>	52/121 (43%)	59/116 (51%)	70/128 (55%)
Prior biologic failure <sup>f</sup>	40/156 (26%)	57/153 (37%)	60/147 (41%)
<b>Endoscopic response<sup>g</sup> at Week 48</b>			
Total population	108 (37%)	137 (48%)	156 (53%)
Biologic naïve <sup>e</sup>	52/121 (43%)	68/116 (59%)	76/128 (59%)
Prior biologic failure <sup>f</sup>	49/156 (31%)	66/153 (43%)	69/147 (47%)
<b>Endoscopic remission<sup>h</sup> at Week 48</b>			
Total population	48 (16%)	72 (25%)	63 (21%)
Biologic naïve <sup>e</sup>	23/121 (19%)	39/116 (34%)	34/128 (27%)
Prior biologic failure <sup>f</sup>	21/156 (13%)	32/153 (21%)	21/147 (14%)
<b>Clinical remission<sup>i</sup> at Week 48</b>			
Total population	183 (63%)	187 (65%)	208 (70%)
Biologic naïve <sup>e</sup>	91/121 (75%)	85/116 (73%)	98/128 (77%)
Prior biologic failure <sup>f</sup>	82/156 (53%)	93/153 (61%)	94/147 (64%)
<b>Corticosteroid-free clinical remission<sup>j</sup> at Week 48</b>			
Total population	174 (60%)	182 (64%)	200 (68%)
Biologic naïve <sup>e</sup>	89/121 (74%)	82/116 (71%)	94/128 (73%)
Prior biologic failure <sup>f</sup>	75/156 (48%)	91/153 (59%)	92/147 (63%)
<b>PRO-2 remission<sup>k</sup> at Week 48</b>			
Total population	163 (56%)	169 (59%)	185 (63%)
Biologic naïve <sup>e</sup>	81/121 (67%)	76/116 (66%)	86/128 (67%)



Prior biologic failure <sup>f</sup>	73/156 (47%)	83/153 (54%)	84/147 (57%)
<sup>a</sup> Ustekinumab 6 mg/kg intravenous induction at Week 0 followed by ustekinumab 90 mg subcutaneous q8w thereafter for up to 48 weeks.			
<sup>b</sup> 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.			
<sup>c</sup> 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.			
<sup>d</sup> A combination of clinical remission and endoscopic response as defined below.			
<sup>e</sup> 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.			
<sup>f</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.			
<sup>g</sup> Endoscopic response is defined as $\geq 50\%$ improvement from baseline in SES-CD score or SES-CD Score $\leq 2$ .			
<sup>h</sup> Endoscopic remission is defined as SES-CD Score $\leq 2$ .			
<sup>i</sup> Clinical remission is defined as CDAI score $<150$ .			
<sup>j</sup> Corticosteroid-free clinical remission is defined as CDAI score $<150$ at Week 48 and not receiving corticosteroids at Week 48.			
<sup>k</sup> 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.			

In GALAXI 2 and GALAXI 3, the efficacy and safety of guselkumab was consistently demonstrated regardless of age, sex, race and body weight. Guselkumab was efficacious in biologic naive patients, as well as in patients who previously failed a biologic.

In the pooled GALAXI Phase 3 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. A clinically meaningful difference of 10 to 17 percentage points 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%).

#### *Week 48 outcomes after Week 12 clinical non-response*

Guselkumab treated patients who were not in clinical response at Week 12 after induction, received the maintenance dose regimen to which they were assigned at Week 0: guselkumab 100 mg subcutaneous q8w or guselkumab 200 mg subcutaneous q4w. In pooled GALAXI 2 and GALAXI 3, among patients without clinical response at Week 12, the proportion of patients achieving clinical remission at Week 48 was 55.6% for the guselkumab 100 mg subcutaneous q8w treatment group and 58.3% for the guselkumab 200 mg subcutaneous q4w treatment group.

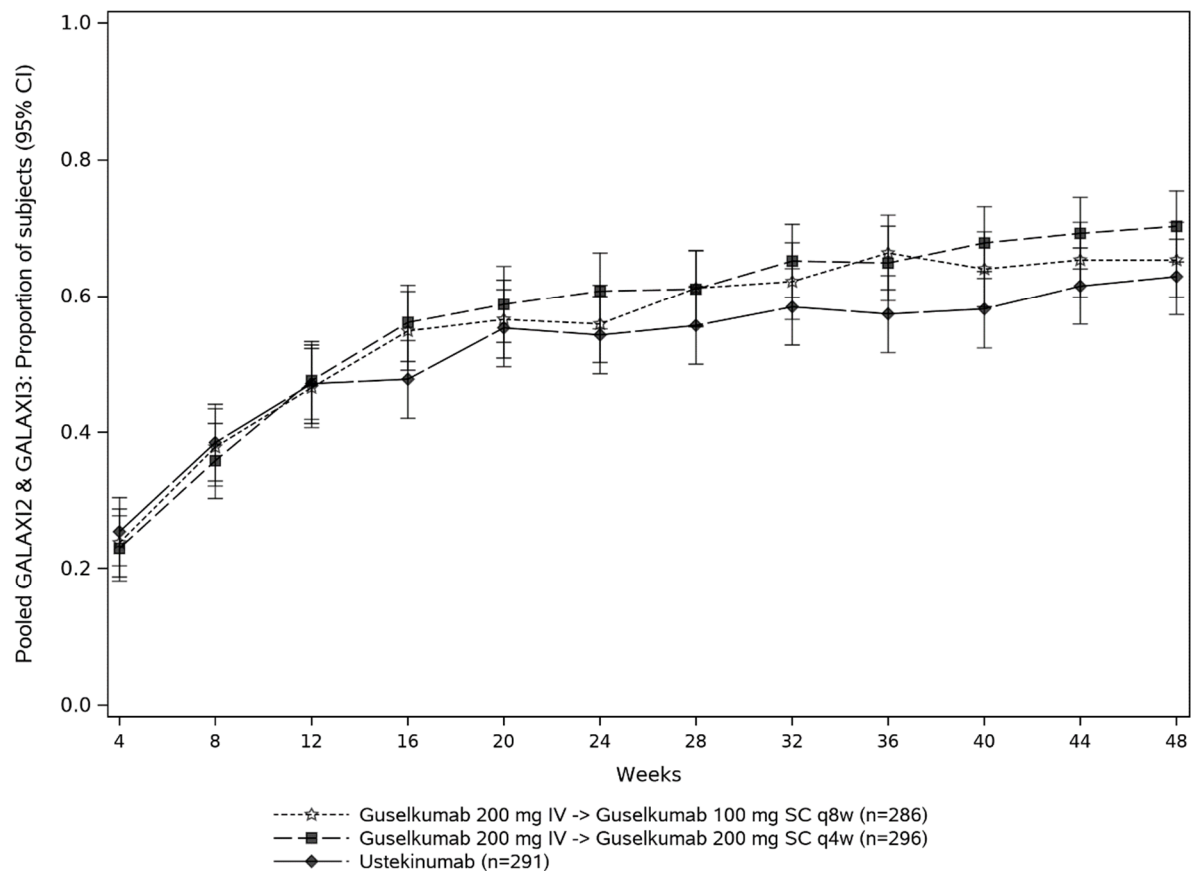
#### *Stool Frequency and abdominal pain*

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

#### *Clinical remission over time*

CDAI scores were recorded at each patient visit. Through Week 48, the proportion of patients in clinical remission with both guselkumab maintenance dose regimens was similar or greater than the proportion of patients in clinical remission observed with the ustekinumab treatment group (Figure 1).

**Figure 1: Proportion of patients in clinical remission through Week 48 in pooled GALAXI 2 and GALAXI 3**



### Health-related quality of life

At Week 12 of GALAXI 2 and GALAXI 3 in the combined guselkumab 200 mg intravenous induction group, patients showed significantly greater and clinically meaningful improvements in fatigue response compared to placebo as assessed by PROMIS Fatigue SF 7a ( $P < 0.05$  and  $p < 0.001$ , respectively).

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. All IBDQ domain scores (bowel symptoms, systemic symptoms, emotional function, and social function) and 6 of 7 general health-related quality of life domains of PROMIS-29 (i.e., depression, anxiety, physical function, pain interference, fatigue, and ability to participate in social roles and activities), as well as summary scores of overall physical health and mental health in both GALAXI 2 and GALAXI 3. Patients receiving guselkumab experienced greater improvements in overall work productivity and daily activity as assessed by the WPAI-CD questionnaire in GALAXI 2 and GALAXI 3 compared with the placebo treatment group at Week 12.

All improvements in the above measures of health-related quality of life were maintained through Week 48 in both studies.

### Crohn's disease related hospitalisations and/or surgeries

Through Week 12 of GALAXI 2 and GALAXI 3, the proportions of patients with Crohn's disease related hospitalisations and/or surgeries were low: 2.1% in the combined guselkumab 200 mg intravenous group and 5.4% in the placebo group.

Through Week 48 of GALAXI 2 and GALAXI 3, the proportions of patients with Crohn's disease related hospitalisations and/or surgeries were also low: 5.9% in the guselkumab 100 mg subcutaneous q8w treatment group, and 5.1% in the guselkumab 200 mg subcutaneous q4w treatment group.

### *GRAVITI*

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

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.

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 28.2% of the patients were receiving conventional immunomodulators.

In GRAVITI, a significantly greater proportion of patients achieved co-primary efficacy endpoints of clinical remission at Week 12 and endoscopic response at Week 12 in the guselkumab treated group compared to placebo. A significantly greater proportion of patients in the guselkumab treated group achieved PRO-2 remission at Week 12, and clinical response at Week 12, compared with the placebo treatment group (Table 8).

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% and 58.3% vs 21.4% respectively, both p-values  $<0.001$ ).

**Table 8: Proportion of patients meeting short-term efficacy endpoints with guselkumab versus placebo at Week 12 in GRAVITI**

	Placebo (N=117)	Guselkumab 400 mg subcutaneous injection <sup>a</sup> (N=230)
<b>Clinical remission<sup>b</sup> at Week 12</b>		
Total population	25 (21%)	129 (56%) <sup>c</sup>
Biologic naïve <sup>d</sup>	14/56 (25%)	52/105 (50%)
Prior biologic failure <sup>e</sup>	9/53 (17%)	65/108 (60%)
<b>Endoscopic response<sup>f</sup> at Week 12</b>		
Total population	25 (21%)	95 (41%) <sup>c</sup>
Biologic naïve <sup>d</sup>	15/56 (27%)	51/105 (49%)

Prior biologic failure <sup>e</sup>	9/53 (17%)	36/108 (33%)
<b>Clinical response<sup>g</sup> at Week 12</b>		
Total population	39 (33%)	169 (73%) <sup>c</sup>
Biologic naïve <sup>d</sup>	21/56 (38%)	71/105 (68%)
Prior biologic failure <sup>e</sup>	15/53 (28%)	84/108 (78%)
<b>PRO-2 remission<sup>h</sup> at Week 12</b>		
Total population	20 (17%)	113 (49%) <sup>c</sup>
Biologic naïve <sup>d</sup>	10/56 (18%)	46/105 (44%)
Prior biologic failure <sup>e</sup>	9/53 (17%)	56/108 (52%)

<sup>a</sup> Guselkumab 400 mg subcutaneous at Week 0, Week 4 and Week 8

<sup>b</sup> Clinical remission: CDAI score <150

<sup>c</sup> p<0.001

<sup>d</sup> 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.

<sup>e</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.

<sup>f</sup> Endoscopic response: ≥50% improvement from baseline in SES-CD score.

<sup>g</sup> Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150.

<sup>h</sup> 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.

### Stool frequency and abdominal pain

Reductions in stool frequency and abdominal pain subscores were observed as early as Week 4 in a greater proportion of patients treated with guselkumab 400 mg subcutaneous compared to placebo, and continued improvement was observed through Week 12.

### Health-related quality of life

In GRAVITI, clinically meaningful improvements were observed in IBD-specific quality of life as assessed with IBDQ total score and IBDQ domain scores, and 5 out of 7 domains of PROMIS-29 (fatigue, pain interference, physical function, ability to participate in social roles and activities and sleep disturbance), pain intensity score, and physical and mental health summary scores at Week 12. Clinically meaningful improvements in IBDQ scores as well as all 7 domains scores of PROMIS-29 were observed at Week 24.

### Ulcerative colitis (UC)

The efficacy and safety of guselkumab were evaluated in two Phase III multicentre, randomised, double-blind, placebo-controlled studies (QUASAR induction study and QUASAR maintenance study) in adult patients with moderately to severely active ulcerative colitis who had an inadequate response, loss of response, or intolerance to corticosteroids, conventional immunomodulators (AZA, 6-MP), biologic therapy (TNF blockers, vedolizumab), and/or a Janus kinase (JAK) inhibitor. 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).

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

A total of 49.1% of patients had previously failed at least one biologic therapy, and/or JAK inhibitor. Of these patients, 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 9).

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

**Table 9: Proportion of patients meeting efficacy endpoints at Week 12 in QUASAR IS**

Endpoint	Placebo (N=280)	Guselkumab 200 mg intravenous induction <sup>a</sup> (N=421)	Treatment Difference (95% CI)
<b>Clinical remission<sup>b</sup></b>			
Total population	22 (8%)	95 (23%)	15% (10%, 20%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	16/137 (12%)	64/202 (32%)	
Prior biologic and/or JAK inhibitor failure <sup>e</sup>	5/136 (4%)	26/208 (13%)	
<b>Symptomatic remission<sup>f</sup></b>			
Total population	58(21%)	210 (50%)	29% (23%, 36%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	36/137 (26%)	122/202 (60%)	
Prior biologic and/or JAK inhibitor failure <sup>e</sup>	19/136 (14%)	80/208 (38%)	
<b>Endoscopic healing<sup>g</sup></b>			
Total population	31 (11%)	113 (27%)	16% (10%, 21%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	23/137 (17%)	77/202 (38%)	
Prior biologic and/or JAK inhibitor failure <sup>e</sup>	7/136 (5%)	31/208 (15%)	
<b>Clinical response<sup>h</sup></b>			
Total population	78 (28%)	259 (62%)	34% (27%, 41%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	48/137 (35%)	144/202 (71%)	

Prior biologic and/or JAK inhibitor failure <sup>c</sup>	27/136 (20%)	107/208 (51%)	
<b>Histologic endoscopic mucosal healing<sup>i</sup></b>			
Total population	21 (8%)	99 (24%)	16% (11%, 21%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	15/137 (11%)	66/202 (33%)	
Prior biologic and/or JAK inhibitor failure <sup>c</sup>	6/136 (4%)	28/208 (13%)	
<b>Fatigue response<sup>j</sup></b>			
Total population	60 (21%)	173 (41%)	20% (13%, 26%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	40/137 (29%)	84/202 (42%)	
Prior biologic and/or JAK inhibitor failure <sup>c</sup>	18/136 (13%)	80/208 (38%)	
<b>IBDQ remission<sup>k</sup></b>			
Total population	83 (30%)	216 (51%)	22% (15%, 29%) <sup>c</sup>
Biologic and JAK inhibitor naïve <sup>d</sup>	47/137 (34%)	126/202 (62%)	
Prior biologic and/or JAK inhibitor failure <sup>c</sup>	33/136 (24%)	82/208 (39%)	

<sup>a</sup> Guselkumab 200 mg as an intravenous induction at Week 0, Week 4, and Week 8.

<sup>b</sup> A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

<sup>c</sup>  $p < 0.001$ , 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).

<sup>d</sup> 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.

<sup>e</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis.

<sup>f</sup> A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.

<sup>g</sup> An endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

<sup>h</sup> Decrease from induction baseline in the modified Mayo score by  $\geq 30\%$  and  $\geq 2$  points, with either a  $\geq 1$ -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.

<sup>i</sup> 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.

<sup>j</sup> Fatigue was assessed using the PROMIS-Fatigue Short form 7a. Fatigue response was defined as a  $\geq 7$ -point improvement from baseline which is considered clinically meaningful.

<sup>k</sup> Total Inflammatory Bowel Disease Questionnaire score  $\geq 170$ .

QUASAR IS and QUASAR induction dose-ranging study also enrolled patients with a baseline mMS of 4, including an ES of 2 or 3 and a RBS  $\geq 1$ . In these patients, 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 UC 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 10).

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

**Table 10: Proportion of patients meeting efficacy endpoints at Week 44 in QUASAR MS**

Endpoint	Placebo (N=190)	Guselkumab 100 mg q8w subcutaneous injection <sup>a</sup> (N=188)	Guselkumab 200 mg q4w subcutaneous injection <sup>b</sup> (N=190)	Treatment Difference vs Placebo (95% CI)	
				Guselkumab 100 mg	Guselkumab 200 mg
Clinical remission <sup>c</sup>					
Total population <sup>d</sup>	36 (19%)	85 (45%)	95 (50%)	25% (16%, 34%) <sup>e</sup>	30% (21%, 38%) <sup>e</sup>
Biologic and JAK- inhibitor naïve <sup>f</sup>	28/108 (26%)	53/105 (50%)	56/96 (58%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	6/75 (8%)	31/77 (40%)	35/88 (40%)		
Symptomatic remission <sup>h</sup>					
Total population <sup>d</sup>	71 (37%)	132 (70%)	131 (69%)	32% (23%, 41%) <sup>e</sup>	31% (21%, 40%) <sup>e</sup>
Biologic and JAK- inhibitor naïve <sup>f</sup>	50/108 (46%)	78/105 (74%)	73/96 (76%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	18/75 (24%)	50/77 (65%)	53/88 (60%)		
Corticosteroid-free clinical remission <sup>i</sup>					
Total population <sup>d</sup>	35 (18%)	85 (45%)	93 (49%)	26% (17%, 34%) <sup>e</sup>	29% (20%, 38%) <sup>e</sup>
Biologic and JAK- inhibitor naïve <sup>f</sup>	28/108 (26%)	53/105 (50%)	54/96 (56%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	5/75 (7%)	31/77 (40%)	35/88 (40%)		
Endoscopic healing <sup>j</sup>					
Total population <sup>d</sup>	36 (19%)	93 (49%)	98 (52%)	30% (21%, 38%) <sup>e</sup>	31% (22%, 40%) <sup>e</sup>
Biologic and JAK- inhibitor naïve <sup>f</sup>	28/108 (26%)	56/105 (53%)	57/96 (59%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	6/75 (8%)	35/77 (45%)	37/88 (42%)		
Histologic endoscopic mucosal healing <sup>k</sup>					
Total population <sup>d</sup>	32 (17%)	82 (44%)	91 (48%)	26% (17%, 34%) <sup>e</sup>	30% (21%, 38%) <sup>e</sup>
Biologic and JAK- inhibitor naïve <sup>f</sup>	25/108 (23%)	52/105 (50%)	54/96 (56%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	6/75 (8%)	29/77 (38%)	34/88 (39%)		

Clinical response <sup>l</sup>					
Total population <sup>d</sup>	82 (43%)	146 (78%)	142 (75%)	34% (25%, 43%) <sup>e</sup>	31% (21%, 40%) <sup>e</sup>
Biologic and JAK-inhibitor naïve <sup>f</sup>	58/108 (54%)	87/105 (83%)	78/96 (81%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	21/75 (28%)	54/77 (70%)	59/88 (67%)		
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 12 weeks after induction					
Total population <sup>d</sup>	20/59 (34%)	40/66 (61%)	50/69 (72%)	26% (9%, 43%) <sup>m</sup>	38% (23%, 54%) <sup>e</sup>
Biologic and JAK-inhibitor naïve <sup>f</sup>	14/41 (34%)	28/43 (65%)	38/48 (79%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	4/15 (27%)	12/20 (60%)	10/18 (56%)		
Endoscopic normalisation <sup>n</sup>					
Total population <sup>d</sup>	29 (15%)	65 (35%)	64 (34%)	18% (10%, 27%) <sup>e</sup>	17% (9%, 25%) <sup>e</sup>
Biologic and JAK-inhibitor naïve <sup>f</sup>	22/108 (20%)	40/105 (38%)	40/96 (42%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	6/75 (8%)	24/77 (31%)	21/88 (24%)		
Fatigue response <sup>o</sup>					
Total population <sup>d</sup>	56 (29%)	95 (51%)	82 (43%)	20% (11%, 29%) <sup>e</sup>	13% (3%, 22%) <sup>m</sup>
Biologic and JAK-inhibitor naïve <sup>f</sup>	39/108 (36%)	54/105 (51%)	51/96 (53%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	14/75 (19%)	36/77 (47%)	28/88 (32%)		
IBDQ remission <sup>p</sup>					
Total population <sup>d</sup>	71 (37%)	121 (64%)	122 (64%)	26% (17%, 36%) <sup>e</sup>	26% (16%, 35%) <sup>e</sup>
Biologic and JAK-inhibitor naïve <sup>f</sup>	53/108 (49%)	71/105 (68%)	71/96 (74%)		
Prior biologic and/or JAK-inhibitor failure <sup>g</sup>	14/75 (19%)	45/77 (58%)	47/88 (53%)		



- 
- <sup>a</sup> Guselkumab 100 mg as a subcutaneous injection every 8 weeks after the induction regimen.
  - <sup>b</sup> Guselkumab 200 mg as a subcutaneous injection every 4 weeks after the induction regimen.
  - <sup>c</sup> A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
  - <sup>d</sup> Patients who achieved clinical response 12 weeks following the intravenous administration of guselkumab in either QUASAR induction study or QUASAR induction dose-ranging study.
  - <sup>e</sup>  $p < 0.001$ , adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomisation stratification factors.
  - <sup>f</sup> 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.
  - <sup>g</sup> Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase [JAK] inhibitor for ulcerative colitis.
  - <sup>h</sup> A stool frequency subscore of 0 or 1 and not increased from induction baseline, and a rectal bleeding subscore of 0.
  - <sup>i</sup> 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.
  - <sup>j</sup> An endoscopy subscore of 0 or 1 with no friability present on the endoscopy.
  - <sup>k</sup> 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.
  - <sup>l</sup> Decrease from induction baseline in the modified Mayo score by  $\geq 30\%$  and  $\geq 2$  points, with either a  $\geq 1$ -point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1.
  - <sup>m</sup>  $p < 0.01$ , adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors
  - <sup>n</sup> An endoscopy subscore of 0.
  - <sup>o</sup> Fatigue was assessed using the PROMIS-Fatigue Short form 7a. Fatigue response was defined as a  $\geq 7$ -point improvement from induction baseline which is considered clinically meaningful.
  - <sup>p</sup> Total Inflammatory Bowel Disease Questionnaire score  $\geq 170$ .

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. Guselkumab was efficacious in biologic and JAK inhibitor naïve patients, as well as in patients who previously failed a biologic and/or JAK inhibitor.

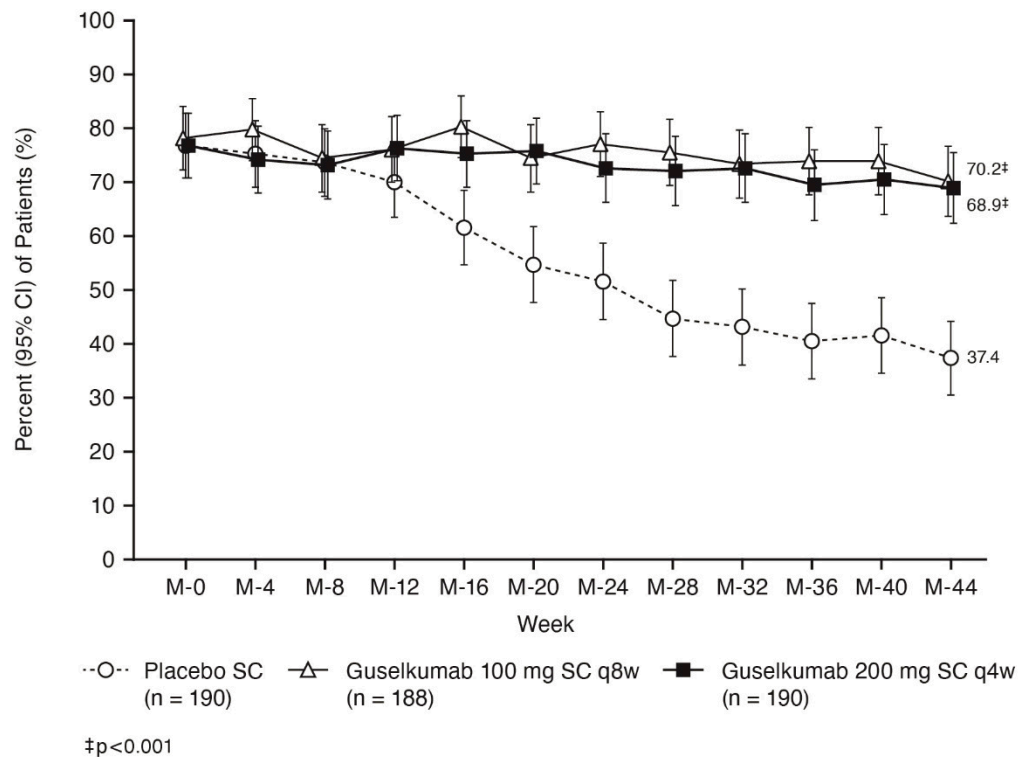
In QUASAR MS, patients with high inflammatory burden after completion of induction dosing derived additional benefit from guselkumab 200 mg subcutaneous q4w compared to 100 mg subcutaneous q8w dosing. Clinically meaningful numerical differences of  $> 15\%$  were observed between the two guselkumab dose 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 also enrolled patients with an induction baseline mMS of 4, including an ES of 2 or 3 and a RBS  $\geq 1$  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 2):

**Figure 2: Proportion of patients in symptomatic remission through Week 44 in QUASAR MS**



#### Week 24 responders to guselkumab

Guselkumab treated patients who were not in clinical response at induction Week 12, received guselkumab 200 mg subcutaneous at induction 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 induction 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 (68%) 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  $\leq 2$  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. In QUASAR MS, endoscopic normalisation at Week 44 was achieved in

35% and 34% of patients treated with guselkumab 100 mg subcutaneous q8w and guselkumab 200 mg subcutaneous q4w compared to 15% of patients on placebo.

#### Composite histologic-endoscopic mucosal outcomes

Combined endoscopic normalisation and histologic remission 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 (31% and 33% vs 14%, respectively).

Combined symptomatic remission, endoscopic healing, histologic healing, and fecal calprotectin  $\leq 250$  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 (31% and 35% vs 11%, respectively).

Combined symptomatic remission, endoscopic normalisation, histologic remission, and fecal calprotectin  $\leq 250$  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, all IBDQ domain scores (bowel symptoms including abdominal pain and bowel urgency, systemic function, emotional function, and social function) and in fatigue by PROMIS Fatigue SF 7a. Clinically meaningful improvements in general health-related quality of life were seen in all 7 domains of PROMIS-29 (i.e., depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities), as well as in summary scores of overall physical health and mental health. These improvements in health-related quality of life measures (IBDQ, PROMIS-Fatigue SF 7a, PROMIS-29) were maintained in guselkumab-treated patients in QUASAR MS through Week 44.

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

#### Ulcerative colitis (UC) related hospitalisations and surgeries

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

Through Week 44 of QUASAR MS, the proportions of patients with UC-related hospitalisation were 1.6% (3/188) in the guselkumab 100 mg subcutaneous q8w group, 1.1% (2/190) in the guselkumab 200 mg subcutaneous q4w group and 0.5% (1/190) in the placebo group. There were no reported UC-related surgeries across the guselkumab and placebo groups.

#### 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 Crohn's disease and ulcerative colitis (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 ( $\pm$  SD) maximum serum concentration ( $C_{\max}$ ) of  $8.09 \pm 3.68$  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 ( $\pm$  SD) steady-state trough serum guselkumab concentrations in two Phase III studies in patients with plaque psoriasis were  $1.15 \pm 0.73$  mcg/mL and  $1.23 \pm 0.84$  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 Crohn's disease and ulcerative colitis. 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 70.5 mcg/mL in patients with Crohn's disease, and 68.27 mcg/mL in patients with ulcerative colitis.

Following the recommended subcutaneous induction dose regimen of guselkumab 400 mg at Weeks 0, 4, and 8, mean peak serum concentration was estimated to be 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 Crohn's disease, mean steady-state trough serum guselkumab concentrations were approximately 1.2 mcg/mL and 10.1 mcg/mL, respectively.

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.

### 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 Crohn's disease and ulcerative colitis.

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, AZA, 6-MP, oral corticosteroids and csDMARDs such as methotrexate, 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 Crohn's disease or ulcerative colitis.

### Paediatric patients

The pharmacokinetics of guselkumab in paediatric patients have not been established.

### Elderly patients

No specific studies have been conducted in elderly patients. Of the 1384 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 1009 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. 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.

Population pharmacokinetic analyses in plaque psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis patients indicated no apparent changes in CL/F estimate in patients  $\geq 65$  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 (E385)  
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.

If necessary, the diluted solution may be kept in the refrigerator between 2°C to 8°C for up to 24 hours. If stored in the refrigerator, allow the solution to reach room temperature before administration. The infusion should be completed within 10 hours upon removal from refrigeration.

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 chlorobutyl 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. Tremfya does not contain preservatives. Each vial is for single use only.

Inspect Tremfya visually for particulate matter and discolouration prior to administration. Tremfya is a clear and colorless 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 micrometer).
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. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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

**9. DATE OF REVISION OF THE TEXT**

26-June-2024

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