เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

TREMFYA™

1.   NAME OF THE MEDICINAL PRODUCT

Tremfya 100 mg solution for injection in pre-filled syringe.

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

2.   QUALITATIVE AND QUANTITATIVE COMPOSITION

Tremfya 100 mg solution for injection in pre-filled syringe

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

Tremfya 100 mg solution for injection in pre-filled pen

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

Guselkumab is a fully human immunoglobulin G1 lamda (IgG1λ) 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

Solution for injection (injection)

The solution is clear and colourless to light yellow.

4.   CLINICAL PARTICULARS

4.1   Therapeutic indications

Plaque psoriasis

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

Psoriatic arthritis

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

Palmoplantar pustulosis

Tremfya is indicated for the treatment of adults with moderate to severe palmoplantar pustulosis who do not adequately response to conventional treatments.

4.2 Posology and method of administration

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

Posology

Plaque psoriasis

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

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

Psoriatic arthritis

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

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

Palmoplantar pustulosis

The recommended dose of Tremfya is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks.

Clinical response is usually achieved within 24 weeks of initiation of treatment with TREMFYA. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within 24 weeks of treatment.

Special populations

Elderly (≥ 65 years)

No dose adjustment is required (see section 5.2).

There is limited information in subjects aged ≥ 65 years and very limited information in subjects aged ≥ 75 years (see section 5.2).

Renal or hepatic impairment

Tremfya has not been studied in these patient populations. No dose recommendations can be made. 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

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

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

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

4.3   Contraindications

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

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

4.4   Special warnings and precautions for use

Traceability

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

Infections

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

Patients treated with guselkumab should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, the patient should be monitored closely and treatment should be discontinued until the infection resolves.

Pre-treatment evaluation for tuberculosis

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

Hypersensitivity

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

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

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

<u>Immunisations</u>

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.

Palmoplantar pustulosis

Fully consider using existing therapy including phototherapy before starting treatment with TREMFYA

4.5   Interaction with other medicinal products and other forms of interaction

<u>Interactions with CYP450 substrates</u>

In a Phase 1 study in subjects with moderate to severe plaque psoriasis, changes in systemic exposures (C_{max} and AUC_{inf}) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant, 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.

<u>Concomitant immunosuppressive therapy or phototherapy</u>

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

4.6   Fertility, pregnancy and lactation

<u>Women of childbearing potential</u>

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

<u>Pregnancy</u>

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 in approximately 14% of patients in the psoriasis and psoriatic arthritis clinical studies.

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis and psoriatic arthritis clinical studies as well as 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).

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	Uncommon	Hypersensitivity
	Uncommon	Anaphylaxis
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon	Urticaria
	Uncommon	Rash
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

<u>Description of selected adverse reactions</u>

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 q4w group and 8.3% in the 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 ≤ 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	guselkumab 100 mg q8w N=373	guselkumab 100 mg q4w N=371[c]	guselkumab 100 mg q8w N=373	guselkumab 100 mg q4w N=371
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.

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 subjects 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%) subjects in the guselkumab q8w group, 4 (1.1%) subjects in the guselkumab q4w group, and 1 (0.3%) subject in the placebo group. One subject 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 subjects 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.

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 neutralizing, 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 neutralizing, 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 a Phase III study in Japanese patients with Palmoplantar pustulosis, antidrug antibodies were detected in 2.6% of patients through Week 52. Of the patients who developed antidrug antibodies, no neutralizing antibodies were detected.

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.

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 IgG1λ monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL 23) protein with high specificity and affinity.. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

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

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.

<u>Clinical efficacy and safety</u>

<u>*Plaque psoriasis*</u>

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

VOYAGE 1 and VOYAGE 2

Two studies (VOYAGE 1 and VOYAGE 2) evaluated the efficacy and safety of guselkumab versus placebo and adalimumab in 1829 adult patients. Patients randomised to guselkumab (N=825) received 100 mg at Weeks 0 and 4, and every 8 weeks (q8w) thereafter through Week 48 (VOYAGE 1) and Week 20 (VOYAGE 2). Patients randomised to adalimumab (N=582) received 80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week (q2w) through Week 48 (VOYAGE 1) and Week 23 (VOYAGE 2). In both studies, patients randomised to placebo (N=422) received guselkumab 100 mg at Weeks 16, 20 and q8w thereafter. In VOYAGE 1, all patients, including those randomised to adalimumab at Week 0, started to receive open-label guselkumab q8w at Week 52. In VOYAGE 2, patients randomised to guselkumab at Week 0 who were Psoriasis Area and Severity Index (PASI) 90 responders at Week 28 were re-randomised to either continue treatment with guselkumab q8w (maintenance treatment) or receive placebo (withdrawal treatment). Withdrawal patients re-initiated guselkumab (dosed at time of retreatment, 4 weeks later and q8w thereafter) when they experienced at least a 50% loss of their Week 28 PASI improvement. Patients randomised to adalimumab at Week 0 who were PASI 90 non responders received guselkumab at Weeks 28, 32 and q8w thereafter. In VOYAGE 2, all patients started to receive open-label guselkumab q8w at Week 76.

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

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

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

Overall skin disease

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

Table 3: **Summary of clinical responses in VOYAGE 1 and VOYAGE 2**

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

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

Response over time

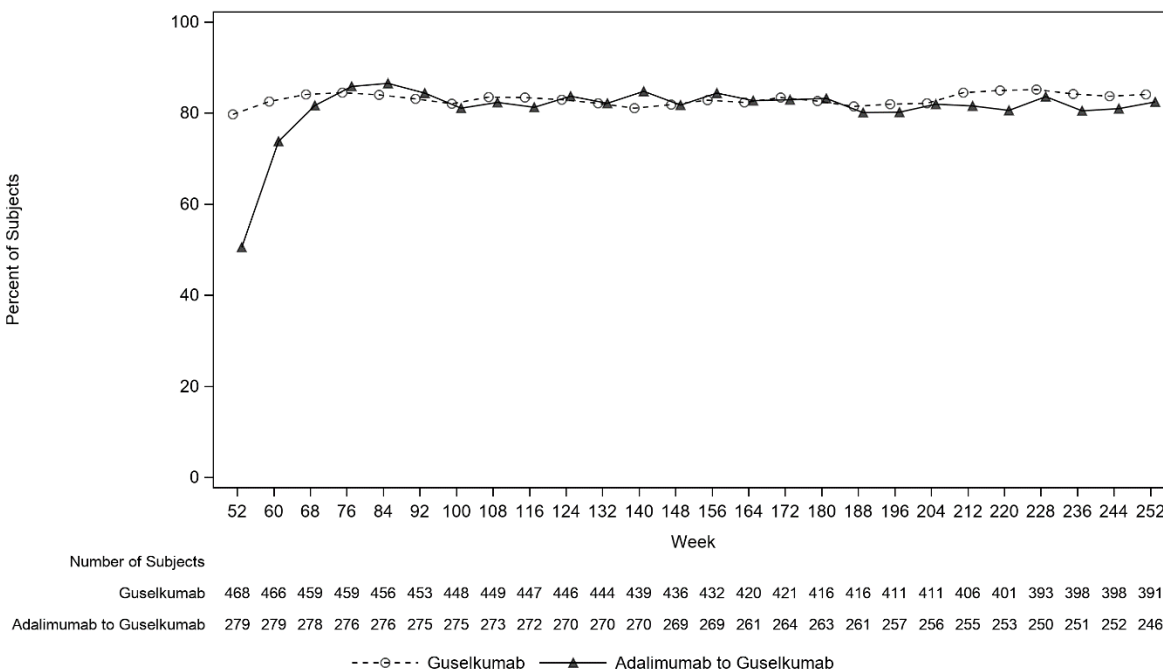Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 (p < 0.001). The percentage of patients achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the difference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

Figure 1: Percent of subjects who achieved a PASI 90 response through week 48 by visit (subjects randomised at week 0) in VOYAGE 1
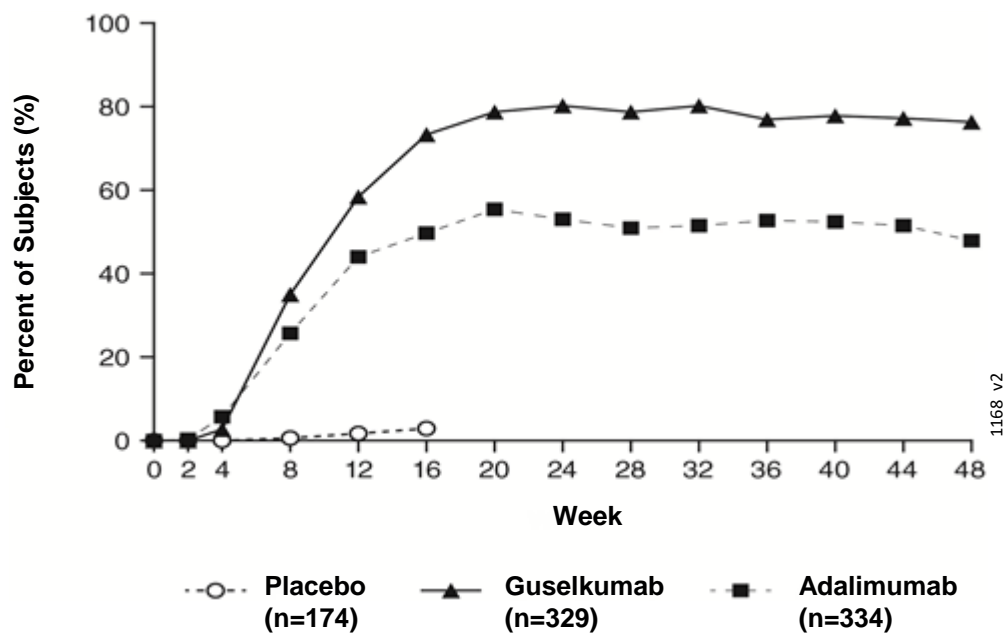
In VOYAGE 1, for patients receiving continuous guselkumab treatment, the PASI 90 response rate was maintained from Week 52 through Week 252. For patients randomised to adalimumab at Week 0 who crossed over to guselkumab at Week 52, the PASI 90 response rate increased from Week 52 through Week 76 and was then maintained through Week 252 (see Figure 2).

Figure 2: Percent of subjects who achieved a PASI 90 response by visit in the open-label phase in VOYAGE 1

Number of Subjects																										
Guselkumab	468	466	459	459	456	453	448	449	447	446	444	439	436	432	420	421	416	416	411	411	406	401	393	398	398	391
Adalimumab to Guselkumab	279	279	278	276	276	275	275	273	272	270	270	270	269	269	261	264	263	261	257	256	255	253	250	251	252	246

- - -⊖- - - Guselkumab   ▲ Adalimumab to Guselkumab

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

In VOYAGE 2, 88.6% of patients receiving guselkumab maintenance treatment at Week 48 were PASI 90 responders compared to 36.8% of patients who were withdrawn from treatment at Week 28 (p < 0.001). Loss of PASI 90 response was noted as early as 4 weeks after withdrawal of guselkumab treatment with a median time to loss of PASI 90 response of approximately 15 weeks. Among patients who were withdrawn from treatment and subsequently re-initiated guselkumab, 80% regained a PASI 90 response when assessed 20 weeks after initiation of retreatment.

In VOYAGE 2, among 112 patients randomised to adalimumab who failed to achieve a PASI 90 response at Week 28, 66% and 76% achieved a PASI 90 response after 20 and 44 weeks of treatment with guselkumab, respectively. In addition, among 95 patients randomised to guselkumab who failed to achieve a PASI 90 response at Week 28, 36% and 41% achieved a PASI 90 response with an additional 20 and 44 weeks of continued treatment with guselkumab, respectively. No new safety findings were observed in patients who switched from adalimumab to guselkumab.

Regional disease

In VOYAGE 1 and 2, significant improvements were seen in scalp, hand and foot, and nail psoriasis (as measured by the Scalp-specific Investigator Global Assessment [ss-IGA], Physician's Global Assessment of Hands and/or Feet [hf-PGA], Fingernail Physician's Global Assessment [f-PGA] and Nail Psoriasis Severity Index [NAPSI], respectively) in guselkumab treated patients compared to placebo treated patients at Week 16 (p < 0.001, Table 4). Guselkumab demonstrated superiority compared to adalimumab for scalp and hand and foot psoriasis at Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1) (p ≤ 0.001, except for hand and foot psoriasis at Week 24 [VOYAGE 2] and Week 48 [VOYAGE 1], p < 0.05).

Table 4: Summary of regional disease responses in VOYAGE 1 and VOYAGE 2

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

[a]   Includes only subjects with ss-IGA, f-PGA, hf-PGA score ≥ 2 at baseline or baseline NAPSI score > 0.
[b]   Includes only subjects achieving ≥ 2-grade improvement from baseline in ss-IGA and/or hf-PGA.
[c]   p < 0.001 for comparison between guselkumab and placebo for the major secondary endpoint.
[d]   comparisons between guselkumab and adalimumab were not performed.
[e]   p < 0.001 for comparison between guselkumab and placebo.

Health-related quality of life / Patient reported outcomes

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

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

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

[a]   p < 0.001 for comparison between guselkumab and placebo.
[b]   comparisons between guselkumab and adalimumab were not performed.
[c]   p < 0.001 for comparison between guselkumab and placebo for major secondary endpoints.

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

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

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

NAVIGATE

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

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

Figure 3: Percent of subjects who achieved an IGA Score of cleared (0) or minimal (1) and at least a 2-grade improvement in IGA from week 0 through week 24 by visit after randomisation in NAVIGATE
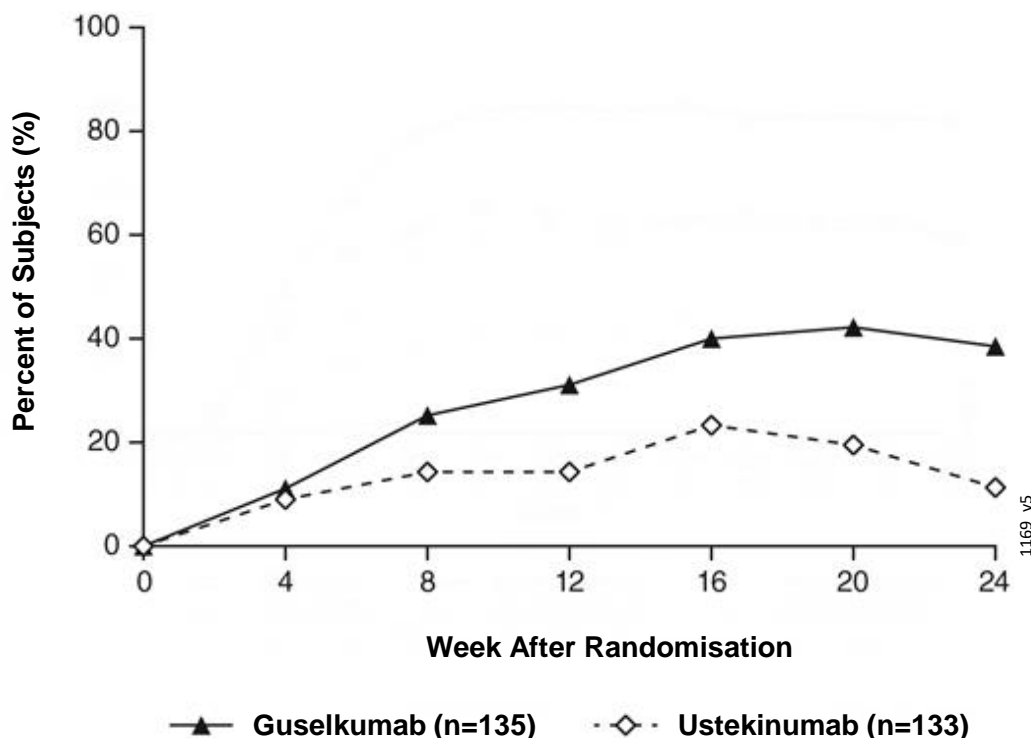
ECLIPSE

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

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

Guselkumab was superior to secukinumab as measured by the primary endpoint of PASI 90 response at Week 48 (84.5% versus 70.0%, p < 0.001). Comparative PASI response rates are presented in Table 7.

Table 7:   PASI response rates in ECLIPSE

	Number of patients (%)	
	guselkumab (N=534)	secukinumab (N=514)
Primary Endpoint PASI 90 response at Week 48	451 (84.5%) [a]	360 (70.0%)
Major Secondary Endpoints		
PASI 75 response at both Week 12 and Week 48	452 (84.6%) [b]	412 (80.2%)
PASI 75 response at Week 12	477 (89.3%) [c]	471 (91.6%)
PASI 90 response at Week 12	369 (69.1%) [c]	391 (76.1%)
PASI 100 response at Week 48	311 (58.2%) [c]	249 (48.4%)

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

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

Figure 4: Percent of subjects who achieved a PASI 90 response through week 48 by visit (Subjects randomised at Week 0) in ECLIPSE
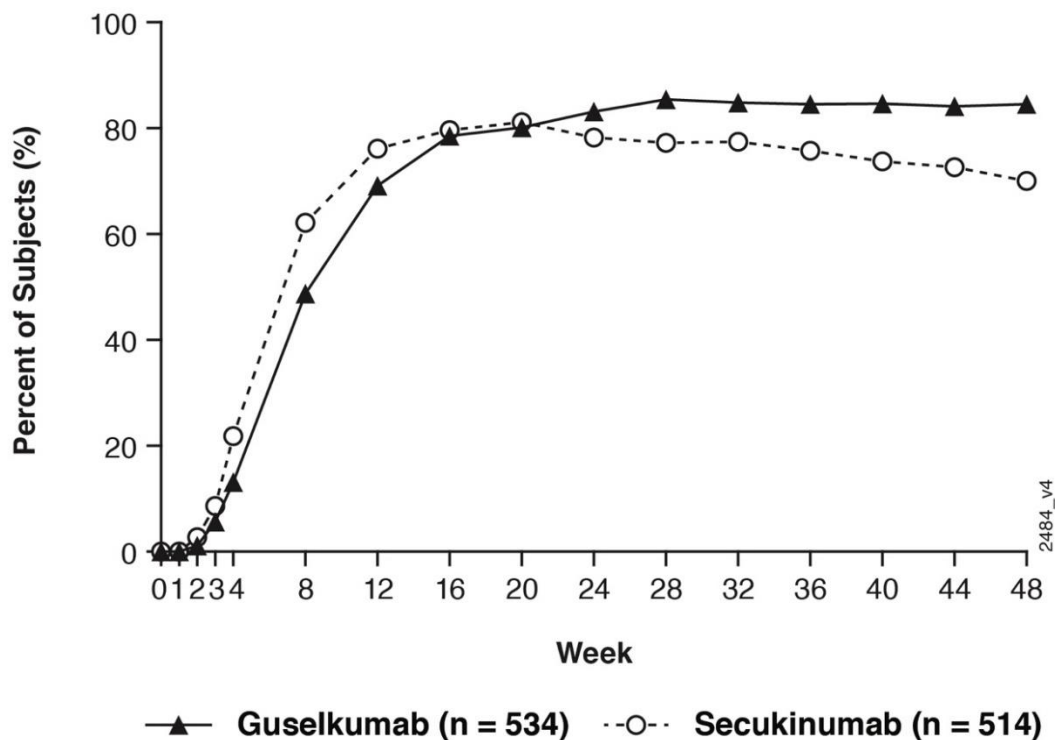
Psoriatic arthritis (PsA)

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

DISCOVER 1 and DISCOVER 2

Two randomised, double-blind, placebo-controlled Phase III studies (DISCOVER 1 and DISCOVER 2) evaluated the efficacy and safety of guselkumab versus placebo in adult patients with active PsA (≥3 swollen and ≥3 tender joints, and a C-reactive protein (CRP) level of ≥0.3 mg/dL in DISCOVER 1, and ≥5 swollen and ≥5 tender joints, and a CRP level of ≥0.6 mg/dL in DISCOVER 2), despite conventional synthetic (cs)DMARD, apremilast, or nonsteroidal anti-inflammatory drug (NSAID) therapy. Patients in these studies had a diagnosis of PsA based on the Classification criteria for Psoriatic Arthritis [CASPAR]) for a median duration of 4 years. Patients with different subtypes of PsA were enrolled in both studies, including polyarticular arthritis with the absence of rheumatoid nodules (40%), spondylitis with peripheral arthritis (30%), asymmetric peripheral arthritis (23%), distal interphalangeal involvement (7%) and arthritis mutilans (1%). Over 65% and 42% of the patients had enthesitis and dactylitis at baseline, respectively, and over 75% of patients had ≥3% BSA psoriasis skin involvement. DISCOVER 1 and DISCOVER 2 evaluated 381 and 739 patients, respectively, who received treatment with guselkumab 100 mg administered at Weeks 0 and 4 followed by every 8 weeks (q8w) or guselkumab 100 mg q4w, or placebo. At Week 24, placebo subjects in both studies crossed over to receive guselkumab 100 mg q4w. Approximately 58% of patients in both studies continued on stable doses of MTX (≤ 25 mg/week).

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

Signs and symptoms

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

Table 8:   Clinical responses in DISCOVER 1 and DISCOVER 2

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

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

Clinical response was maintained up to Week 52 as assessed by ACR 20/50/70, DAS 28 (CRP), MDA, IGA and PASI 90 response rates in DISCOVER 1 and DISCOVER 2 (see Table 9).

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

	DISCOVER 1		DISCOVER 2	
	guselkumab 100 mg q8w	guselkumab 100 mg q4w	guselkumab 100 mg q8w	guselkumab 100 mg q4w
ACR 20				
N[b]	112	124	234	228
% Response	67.9%	75.8%	79.1%	75.9%
ACR 50				
N[b]	113	124	234	228
% Response	43.4%	55.6%	51.3%	49.1%
ACR 70				
N[b]	114	124	234	228
% Response	28.9%	29.8%	29.5%	28.1%
DAS 28 (CRP) change from baseline				
N[c]	112	123	234	227
Mean (SD)	-2.03 (1.250)	-1.99 (1.062)	-2.08 (1.121)	-2.11 (1.128)
MDA				
N[b]	112	124	234	228
% Response	33.9%	40.3%	32.9%	36.8%
Patients with ≥ 3% BSA and IGA ≥ 2 at baseline				
IGA Response				
N[b]	75	88	170	173
% Response	69.3%	83.0%	77.1%	84.4%
PASI 90				
N[b]	75	88	170	173
% Response	66.7%	76.1%	77.1%	81.5%

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

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

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

	guselkumab 100 mg q8w	guselkumab 100 mg q4w
ACR 20		
N[b]	223	219
% Response	82.1%	84.9%
ACR 50		
N[b]	224	220
% Response	60.7%	62.3%
ACR 70		
N[b]	224	220

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

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

Response over time

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

Figure 5:   ACR 20 response by visit through week 24 in DISCOVER 2
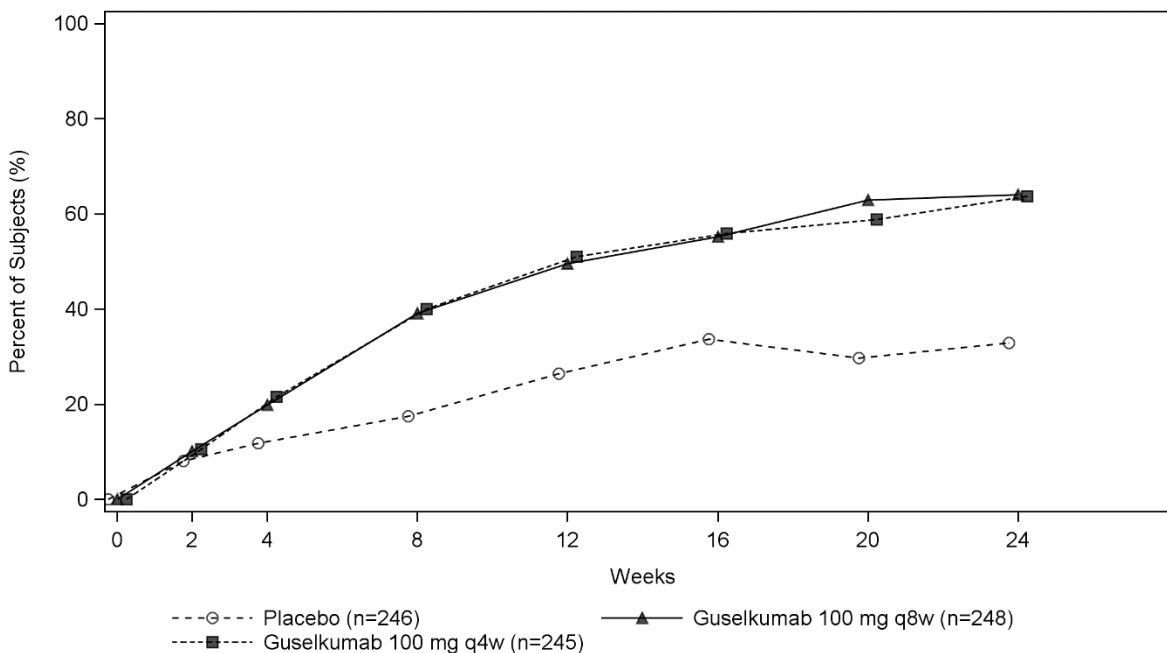
In DISCOVER 2, for subjects receiving continuous guselkumab treatment at week 24, ACR 20 response was maintained from Week 24 to Week 52 (see Figure 6). For subjects receiving continuous guselkumab treatment at week 52, ACR 20 response was maintained from Week 52

to Week 100 (see Figure 7).

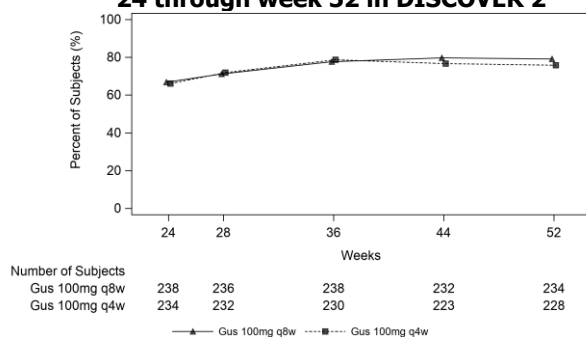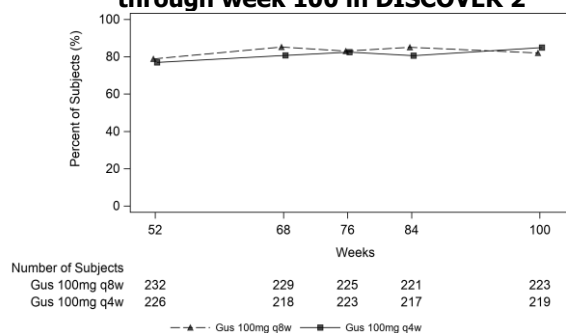**Figure 6: ACR 20 response by visit from week 24 through week 52 in DISCOVER 2**

Number of Subjects
	24	28	36	44	52
Gus 100mg q8w	238	236	238	232	234
Gus 100mg q4w	234	232	230	223	228

—▲— Gus 100mg q8w   ---■--- Gus 100mg q4w

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

Number of Subjects
	52	68	76	84	100
Gus 100mg q8w	232	229	225	221	223
Gus 100mg q4w	226	218	223	217	219

---▲--- Gus 100mg q8w   —■— Gus 100mg q4w

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

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

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

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

Radiographic response

In DISCOVER 2, inhibition of structural damage progression was measured radiographically and expressed as the mean change from baseline in the total modified van der Heijde-Sharp (vdH-S) score. At Week 24, the guselkumab q4w group demonstrated statistically significantly less radiographic progression and the guselkumab q8w group showed numerically less progression than placebo (Table 11). The observed benefit with the guselkumab q4w dosing regimen on inhibition of radiographic progression (ie, smaller mean change from baseline in total modified vdH-S score in the q4w group versus placebo) was most pronounced in subjects with both a high C-reactive protein value and high number of joints with erosions at baseline.

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

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

[a]   not statistically significant p = 0.068 (major secondary endpoint)
[b]   p = 0.006 (major secondary endpoint)
[c]   LSmean change = least squares mean change
[d]   CI = confidence interval

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

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

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

[a]   Evaluable subjects have observed change for the specified time period
[b]   SD = standard deviation
Note: no placebo group beyond Week 24

Physical function and health-related quality of life

In DISCOVER 1 and 2, guselkumab treated patients showed significant improvement (p<0.001) in physical function compared to placebo as assessed by the Health Assessment Questionnaire-

Disability Index (HAQ-DI) at Week 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52 in DISCOVER 1 and Week 100 in DISCOVER 2.

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

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 plaque psoriasis and psoriatic arthritis (see section 4.2 for information on paediatric use).

Palmoplantar Pustulosis

A double-blind, placebo-controlled study was conducted in 159 patients with moderate to severe plaque-type psoriasis (Palmo-Plantar Pustulosis Area and Severity Index; PPPASI) score ≥ 12, and PPPASI severity score≥ 2 pustules/vesicles on the palms or soles). Placebo, TREMFYA® 100mg or 200mg was administered at Week 0 and 4, and then every 8 weeks thereafter. Change from baseline in PPPASI total score at Week 16, the proportion of subjects who achieved a PPPASI-50 at Week 16, and change from baseline in PPSI (Palmoplantar Pustulosis Severity Index) at Week 16 are shown the table below.

The PPPASI score at Week 16 were statistically significantly higher in the TREMFYA® group compared to the placebo group. PPPASI-50 in the TREMFYA® 100 mg group was 57.4% (31/54 patients) at Week 16 and 83.3% (45/54 patients) at Week 52, respectively.

PPPASI and PPSI at Week 16

	Placebo (N=53)	100 mg (N=54)
Change in the PPPASI total score from the baseline [Average value (SD)]	-7.79 (10.596)	-15.08 (11.252)*
PPPASI 50	34.0% (18/53 cases)	57.4% (31/54 cases)
Change in the PPSI total score from the baseline [Average value (SD)]	-2.0 (2.41)	-3.9 (2.94)

* : p<0.001 (versus placebo, mixed-model for repeated measures)

The frequency (100mg cases) of adverse drug reactions was 31.6% (25/79), and common adverse drug reactions were injection site erythema (7.6%: 6 cases), tinea infection (5.1%: 4 cases) and upper respiratory tract infection (2.5%: 2 cases).

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.

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

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

Distribution

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

Biotransformation

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

Elimination

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

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and csDMARDs such as 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.

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.

Population pharmacokinetic analyses in plaque psoriasis and psoriatic arthritis 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.

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) and C_{max} values that were at least 49-fold and >200-fold higher, respectively, than those measured in the human clinical PK study. 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

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.

Keep medicine out of the sight and reach of children.

6.5   Nature and contents of container

<u>Tremfya 100 mg solution for injection in pre-filled syringe</u>

1 mL solution in a pre-filled glass syringe with a fixed needle and a needle shield, assembled in an automatic needle guard.

Tremfya is available in pack containing one pre-filled syringe.

<u>Tremfya 100 mg solution for injection in pre-filled pen</u>

1 mL solution in a pre-filled glass syringe 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.

MARKETING AUTHORISATION NUMBER AND DATE OF AUTHORISATION

Manufactured by	Market Authorisation Number	Date of Authorisation
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To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

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