▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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) to the interleukin (IL)-23 protein, 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

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

4.2 Posology and method of administration

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

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

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

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

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 yet 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 Tremfya according to the 'Instructions for use' provided in the carton.
For further instructions on preparation and special precautions for handling, see section 6.6 and the 'Instructions for use' leaflet.

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

Patients treated with Tremfya 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 Tremfya should be discontinued until the infection resolves.

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

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

Immunisations
Prior to initiating therapy with Tremfya, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Live vaccines should not be used

concurrently in patients treated with Tremfya. No data are available on the response to live or inactive vaccines.

Before live viral or live bacterial vaccination, treatment with Tremfya should be withheld for at least 12 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the 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 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 drug interactions between guselkumab and substrates of various CYP enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely. There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates.

Concomitant immunosuppressive therapy or phototherapy
The safety and efficacy of Tremfya in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
There are 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 in 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, or abstain from initiating treatment with Tremfya, taking into account the benefit of breast-feeding to the child and the benefit of Tremfya therapy to 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 drug reaction (ADR) was upper respiratory infection.

Tabulated list of adverse reactions

Table 1 provides a list of adverse reactions from psoriasis 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	ADR
Infections and infestations	Very common	Upper respiratory infections
	Common	Gastroenteritis
	Common	Herpes simplex infections
	Common	Tinea infections
Immune system disorders	Uncommon	Hypersensitivity
Nervous system disorders	Common	Headache
Gastrointestinal disorders	Common	Diarrhoea
Skin and subcutaneous tissue disorders	Common	Urticaria
	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Injection site erythema
	Uncommon	Injection site pain

Description of selected adverse reactions

Gastroenteritis

In two phase III clinical studies through the placebo-controlled period, gastroenteritis occurred more frequently in the Tremfya-treated group (1.1%) than in the placebo group (0.7%). Through Week 156, 4.9% of all Tremfya-treated patients reported gastroenteritis. Adverse reactions of gastroenteritis were non-serious and did not lead to discontinuation of Tremfya through Week 156.

Injection site reactions

In two phase III clinical studies through Week 48, 0.7% of Tremfya injections and 0.3% of placebo injections were associated with injection site reactions. Through Week 156, 0.5% of Tremfya injections were associated with injection site reactions. Adverse reactions of injection site erythema and injection site pain were generally mild to moderate in severity; none were serious, and none led to discontinuation of Tremfya.

Immunogenicity

The immunogenicity of Tremfya was evaluated using a sensitive and drug-tolerant immunoassay. In pooled phase II and phase III analyses, fewer than 6% of patients treated with Tremfya developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing, which equates to 0.4% of all patients treated with Tremfya. In pooled phase III analyses, approximately 9% of patients treated with Tremfya developed antidrug antibodies in up to 156 weeks of treatment. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

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 overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment 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, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalize production of these 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 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 studies. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

Clinical efficacy and safety
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 2).

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 2 below.

Table 2: 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.

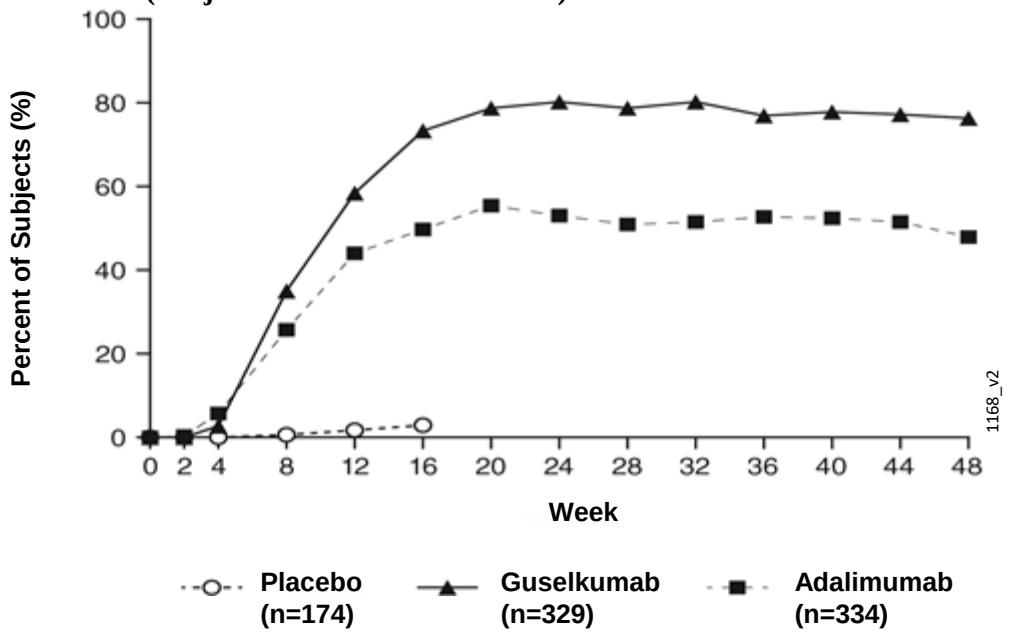
[d] comparisons between guselkumab and adalimumab were not performed.

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

Response over time

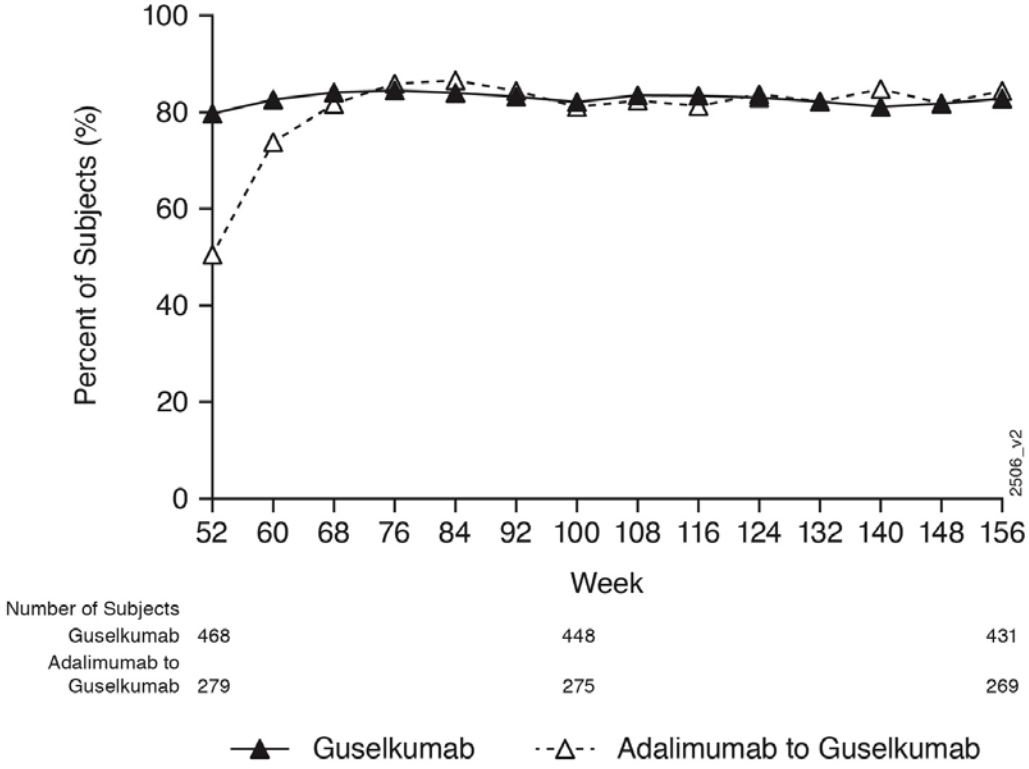
Guselkumab demonstrated rapid onset of efficacy, with a significantly higher percent improvement in PASI as compared with placebo as early as Week 2 ($p < 0.001$). The percentage of patients achieving a PASI 90 response was numerically higher for guselkumab than adalimumab starting at Week 8 with the 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 156. 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 156 (see Figure 2).

Figure 2: Percent of Subjects Who Achieved a PASI 90 Response by Visit in the Open-Label Phase in VOYAGE 1



The efficacy and safety of guselkumab was demonstrated regardless of age, gender, race, body weight, plaques location, PASI baseline severity, concurrent psoriatic arthritis, and previous treatment with a biologic therapy. Guselkumab was efficacious in conventional systemic-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 3). Guselkumab demonstrated superiority compared to adalimumab for scalp and hand and foot psoriasis at Week 24 (VOYAGE 1 and 2) and Week 48 (VOYAGE 1) ($p \leq 0.001$, except for hand and foot psoriasis at Week 24 [VOYAGE 2] and Week 48 [VOYAGE 1], $p < 0.05$).

Table 3: 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 4). 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 156 (Table 5).

Table 4: 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 5: Summary of Patient Reported Outcomes in the Open-Label Phase in VOYAGE 1

	Guselkumab		Adalimumab-Guselkumab	
	Week 76	Week 156	Week 76	Week 156
DLQI score > 1 at baseline, n	445	411	264	251
Subjects with DLQI 0/1	337 (75.7%)	307 (74.7%)	198 (75.0%)	190 (75.7%)
PSSD Symptom Score, subjects with baseline score > 0	347	319	227	214
Symptom score = 0, n (%)	136 (39.2%)	129 (40.4%)	99 (43.6%)	96 (44.9%)

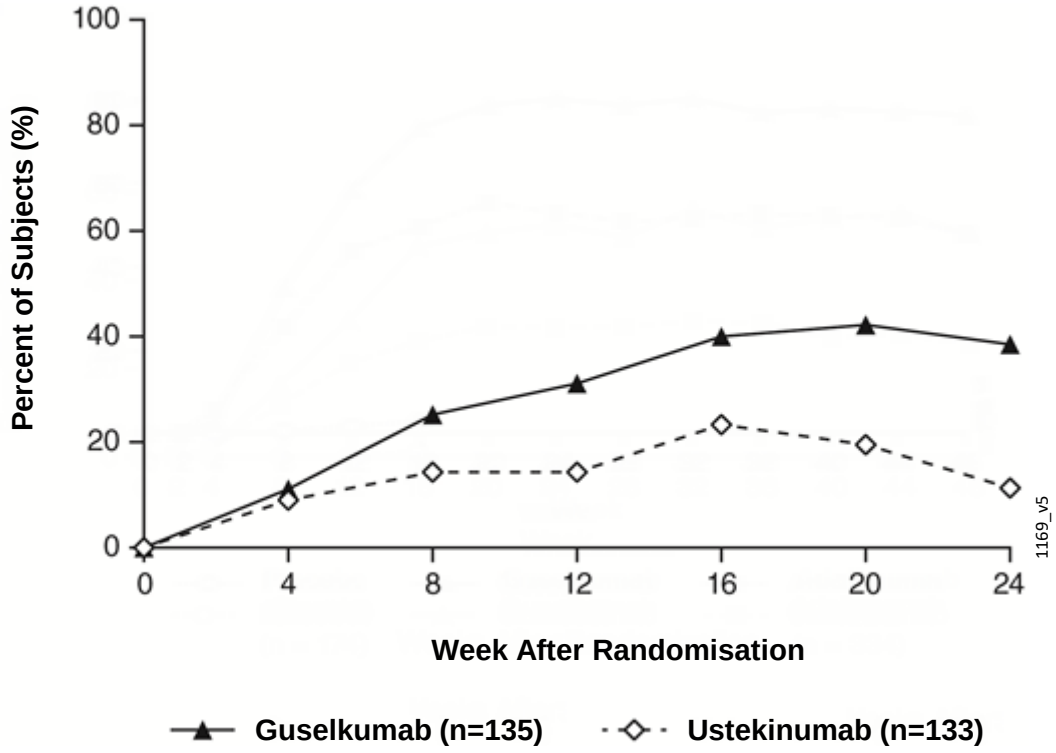
PSSD Sign score, subjects with baseline score > 0	347	319	228	215
Sign score = 0, n (%)	102 (29.4%)	93 (29.2%)	71 (31.1%)	69 (32.1%)

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 156 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 6.

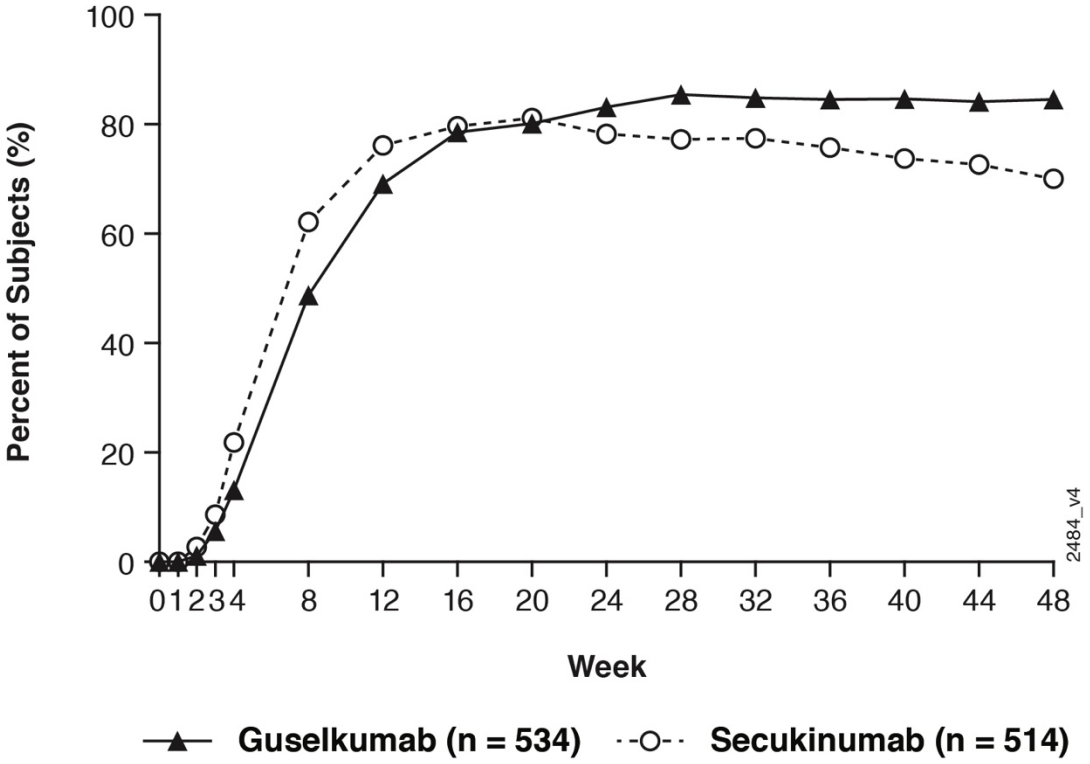
Table 6: PASI Response Rates in ECLIPSE

	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



Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Tremfya in plaque psoriasis in one or more subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose.

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 were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 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 metabolized has not been characterized. 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.

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 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. Population pharmacokinetic analyses indicated there were 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 drug 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.

6.5 Nature and contents of container

Tremfya 100 mg solution for injection in pre-filled syringe
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 a pack containing one pre-filled syringe.

Tremfya 100 mg solution for injection in pre-filled pen
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 Tremfya pack is provided with an ‘Instructions for use’ leaflet that fully describes the preparation and administration of the pre-filled syringe or pre-filled pen.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1234/001 1 pre-filled syringe
EU/1/17/1234/002 1 pre-filled pen
EU/1/17/1234/003 2 pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2017

10. DATE OF REVISION OF THE TEXT

19 September 2019

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