TREMFYA®
Guselkumab.

DOSAGE FORMS AND STRENGTHS
TREMFYA is available as a solution for injection in the following presentation:
Pre-filled syringe
Each Prefilled syringe contains 100 mg of guselkumab per 1 mL.
For excipients, see *List of Excipients* (Pharmaceutical Information).

Description
Guselkumab is a fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody (mAb) that binds selectively to the extracellular human interleukin 23 (IL-23) protein with high specificity and affinity. Guselkumab is produced in a mammalian cell line using recombinant DNA technology.

CLINICAL INFORMATION
Indications
Plaque psoriasis
Adults
TREMFYA by subcutaneous (SC) administration is indicated for the treatment of adults patients with moderate to severe plaque psoriasis who are candidates for phototherapy or 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 *Pharmacodynamic properties).*

Dosage and Administration
Dosage – Adults (18 years and older)
TREMFYA is administered by subcutaneous injection.

Plaque psoriasis
The recommended dose of TREMFYA is 100 mg to be given as subcutaneous injection at week 0, week 4 and every 8 weeks thereafter.

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

Psoriatic arthritis
The recommended dose of Tremfya 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 may be considered (see *Pharmacodynamic properties)*.

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

General considerations for administration
TREMFYA is intended for use under the guidance and supervision of a physician. TREMFYA may be administered by a health care professional, or a patient may self-inject after proper training in subcutaneous injection technique.
Comprehensive instructions for the administration of TREMFYA are given in “Instructions for use, handling, and disposal” and in the package leaflet, “Instructions for preparation and giving an injection of TREMFYA.” Full amount of TREMFYA should be injected according to the directions provided in the patient information leaflet.

Switching from other biologics to TREMFYA

TREMFYA has been shown to be safe and effective in patients with plaque psoriasis with an inadequate response to ustekinumab or adalimumab therapy (see *Clinical studies*). When switching to treatment with TREMFYA in patients with plaque psoriasis, administer TREMFYA at week 0, week 4 and every 8 weeks thereafter.

Special populations

Pediatrics (below 18 years of age)

The safety and efficacy of TREMFYA in pediatric patients have not been evaluated; therefore, no recommendations on dosing can be made (see *Pharmacokinetic Properties*).

Elderly (65 years of age and older)

Of the 3940 plaque psoriasis and psoriatic arthritis patients exposed to TREMFYA in Phase 2 and Phase 3 clinical trials, a total of 239 patients were 65 years or older, and 19 patients were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger patients who received TREMFYA in clinical studies. However, the number of patients aged 65 years and older was not sufficient to determine whether they respond differently from younger patients (see *Pharmacokinetic Properties*).

Renal impairment

Specific studies of TREMFYA have not been conducted in patients with renal insufficiency.

Hepatic impairment

Specific studies of TREMFYA have not been conducted in patients with hepatic insufficiency.

Contraindications

None.

Warnings and Precautions

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.

Infections have been observed in clinical trials in plaque psoriasis (23% in Tremfya group vs 21% in placebo group; ≤ 0.2% serious infections in both groups) and psoriatic arthritis (21% in both TREMFYA and placebo groups; ≤ 0.8% serious infections in both groups).

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing TREMFYA. Instruct patients treated with TREMFYA 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, monitor the patient closely and discontinue TREMFYA until the infection resolves.

Pre-treatment evaluation for tuberculosis

In clinical studies, subjects with latent tuberculosis (TB) who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop TB. Evaluate patients for TB infection prior to initiating treatment with TREMFYA. Initiate treatment of latent TB prior to administering TREMFYA. Patients receiving TREMFYA should be monitored for signs and symptoms of active TB during and after treatment. Do not administer TREMFYA to patients with active TB infection. Consider anti-TB therapy 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.

Immunizations

Prior to initiating therapy with TREMFYA, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA. No data are available on the response to live or inactive vaccines.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing setting. Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnea. If a serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of TREMFYA should be discontinued.

Interactions

Interactions with CYP450 substrates

Although the activity of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation, an *in vitro* study using human hepatocytes showed that IL-23 did not alter the expression or activity of multiple CYP450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).
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 (see *Pharmacokinetic Properties*), 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.

Live vaccines/therapeutic infectious agents
Live vaccines should not be given while a patient is undergoing therapy with TREMFYA (see *Warnings and Precautions - Immunizations*).

Pregnancy, Breast-feeding and Fertility
Pregnancy
The use of TREMFYA in pregnant women has not been studied. The effect of TREMFYA on human pregnancy is unknown. No maternal, embryo or fetal toxicity was observed in cynomolgus monkeys after administration of guselkumab. As with other IgG antibodies, guselkumab crosses the placenta and was detectable in newborn cynomolgus monkey serum samples indicating transplacental transfer of drug (see *Non-Clinical Information*).
As a precautionary measure, it is preferable to avoid the use of Tremfya in pregnancy.

Breast-feeding
There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys (see *Non-Clinical Information*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA.

Fertility
The effect of TREMFYA on human fertility has not been evaluated. No guselkumab-related effects on fertility parameters were identified in female and male fertility studies conducted in guinea pigs (see *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed with TREMFYA.

Adverse Reactions
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably causally associated with the use of guselkumab based on the comprehensive assessment of the available adverse event information. A causal relationship with guselkumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical studies experience in adult patients with psoriasis and psoriatic arthritis
The safety profile of TREMFYA is based on data from Phase 2 (PSO2001, PSA2001) and Phase 3 (VOYAGE 1, VOYAGE 2, NAVIGATE, ORION, ECLIPSE, DISCOVER 1, DISCOVER 2) studies in 3940 subjects, including 2711 with plaque psoriasis and 1229 subjects with psoriatic arthritis. The duration of exposure to TREMFYA is presented in Table 1.

Table 1: Long-Term Exposure to TREMFYA in Phase 2 and Phase 3 studies

Duration of exposure	Number of subjects
≥ 1 year	2975[a]
≥ 2 years	1545[b]
≥ 3 years	1482[b]
≥ 4 years	1393[b]
≥ 5 years	950[b]

[a] plaque psoriasis and psoriatic arthritis studies
[b] plaque psoriasis studies

Adverse reactions

Adverse reactions to TREMFYA are presented in Table 2. The frequency of adverse reactions was based on those that occurred during the placebo-controlled periods of the studies in psoriasis (VOYAGE 1 and VOYAGE 2) and psoriatic arthritis (DISCOVER 1 and DISCOVER 2). Overall, the safety profile was generally similar across doses and indications. Within each frequency grouping, the adverse reactions are presented within the designated system organ classes in order of decreasing frequency, using the following convention:

Very common	(≥1/10)
Common (frequent)	(≥1/100, <1/10)
Uncommon (infrequent)	(≥1/1000, <1/100)
Rare	(≥1/10000, <1/1000)

Table 2: Summary of Adverse Reactions in Clinical Studies

Infections and infestations	Very common: respiratory tract infections Uncommon: herpes simplex infections, tinea infections, gastroenteritis
Investigations	Common: transaminases increased Uncommon: neutrophil count decreased
Nervous system disorders	Common: headache
Gastrointestinal disorders	Common: diarrhea
Musculoskeletal and connective tissue disorders	Common: arthralgia
General disorders and administration site conditions	Common: injection site erythema Uncommon: injection site pain

Transaminases increased

In two Phase 3 psoriatic arthritis clinical studies, through the placebo-controlled period, adverse events of increased transaminases (includes alanine aminotransferase (ALT) Increased, aspartate aminotransferase (AST) Increased, Hepatic Enzyme Increased, Transaminases Increased, Liver Function Test Abnormal, Hypertransaminasemia) were reported more frequently in the TREMFYA-treated groups (8.6% in the 100 mg q4w group and 8.3% in the 100 mg 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, an increased incidence of liver enzyme elevations was observed in patients treated with TREMFYA q4w compared to patients treated with TREMFYA q8w or placebo. Most transaminase (ALT and AST) increases were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency (Table 3). Through 1 year, in most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

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

	Through Week 24[a]			**Through 1 Year[b]**	
	Placebo N=370	TREMFYA 100 mg q8w N=373	TREMFYA 100 mg q4w N=371	TREMFYA 100 mg q8w N=373	TREMFYA 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 randomized to TREMFYA at baseline

Gastroenteritis

In VOYAGE 1 and VOYAGE 2 through the placebo-controlled period, gastroenteritis occurred more frequently in the TREMFYA-treated group (1.1%) than in the placebo group (0.7%). Adverse events of gastroenteritis were non-serious and did not lead to discontinuation of TREMFYA through Week 48.

Injection site reactions
In VOYAGE 1 and VOYAGE 2 through Week 48, 0.7% of TREMFYA injections and 0.3% of placebo injections were associated with injection site reactions. Adverse events of injection site erythema and injection site pain were all mild to moderate in severity, none were serious, and none led to discontinuation of TREMFYA.

Postmarketing data
In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 4). Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data

Table 4: Adverse Reactions Identified During Postmarketing Experience with Guselkumab

System Organ Class Adverse Reaction	**Frequency Category Estimated from Clinical Trials with TREMFYA**
Immune System Disorders	
Hypersensitivity	Uncommon
Anaphylaxis	Uncommon
Skin and Subcutaneous Tissue Disorders	
Rash Urticaria	Uncommon Uncommon
General disorders and administration site conditions	
Injection Site Reactions	Common

Overdose
Single intravenous doses of TREMFYA up to 987 mg (10 mg/kg) have been administered in healthy volunteers and single subcutaneous doses of TREMFYA up to 300 mg have been administered in subjects with plaque psoriasis in clinical trials 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.

PHARMACOLOGICAL PROPERTIES
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 and psoriatic arthritis through blockade of the IL 23 cytokine pathway.

Pharmacodynamic effects
In a Phase 1 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 psoriatic subjects at Week 12 compared to baseline. In the same Phase 1 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 subjects in Phase 2 and Phase 3 studies in plaque psoriasis. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.
In Phase 3 studies in psoriatic arthritis, evaluated subjects had elevated 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 at baseline. Guselkumab decreased levels of these proteins within 4 weeks of initiation of treatment. By Week 24, guselkumab further reduced the levels of these proteins compared to baseline and also to placebo. In guselkumab-treated subjects, serum IL-17A and IL-17F levels were similar to those observed in a demographically matched healthy cohort at Week 24.

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The immunogenicity of TREMFYA was evaluated using a sensitive and drug-tolerant immunoassay.

Plaque psoriasis
In pooled Phase 2 (PSO2001) and Phase 3 (VOYAGE 1, VOYAGE 2 and NAVIGATE) analyses, fewer than 6% of subjects treated with TREMFYA developed antidrug antibodies in up to 52 weeks of treatment. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing which equates to 0.4% of all subjects treated with TREMFYA. In pooled Phase 3 analyses, approximately 15% of patients treated with TREMFYA developed antidrug antibodies in up to 264 weeks of treatment. Of the subjects who developed antidrug antibodies, approximately 5% had antibodies that were classified as neutralizing which equates to 0.76% of all subjects treated with TREMFYA. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

Psoriatic arthritis
In pooled Phase 3 (DISCOVER 1 and DISCOVER 2) analyses up to Week 52, 4.5% (n=49) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 5 had antibodies that were classified as neutralizing antibodies, and 3 developed injection site reactions through Week 52. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics and efficacy of guselkumab.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to TREMFYA with the incidences of antibodies to other products may be misleading.

Clinical studies
Clinical efficacy-plaque psoriasis (Adults)
The efficacy and safety of TREMFYA was assessed in four Phase 3, multicenter, randomized, double-blind, placebo and/or active controlled studies (VOYAGE 1, VOYAGE 2, NAVIGATE and ORION) in adult subjects with moderate to severe chronic plaque-type psoriasis eligible for systemic or phototherapy.
The studies enrolled adult subjects (≥ 18 years) with moderate to severe plaque psoriasis (with or without PsA) defined by Investigator's Global Assessment (IGA) ≥ 3, a Body Surface Area (BSA) involvement ≥ 10%, and Psoriasis Area and Severity Index (PASI) score ≥ 12, and were candidates for either systemic therapy or phototherapy for psoriasis. No concomitant antipsoriatic therapies for psoriasis were allowed during the study. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. The efficacy of TREMFYA was evaluated with respect to overall skin disease, and patient reported outcomes (PROs).
The IGA is a 5-category scale: 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema and scaling.
The PASI is a composite score that assesses the fraction of body surface area involved with psoriasis and the severity of psoriatic lesions within the affected regions (plaque thickness/induration, erythema, and scaling). PASI numeric scores range from 0 to 72, with higher scores representing more severe disease.
Other key efficacy assessments included:

- The Psoriasis Symptoms and Signs Diary (PSSD), includes patient reported outcomes that were designed to measure the severity of psoriasis symptoms (itch, pain, burning, skin tightness, stinging) and signs (skin dryness, cracking, shedding or flaking, scaling, redness and bleeding) using 0 to 10 numerical rating scale for

the assessment of treatment benefit. Symptom summary score and sign summary score were derived, ranging from 0 to 100. A higher score represented more severe disease.

- The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument designed to assess the impact of the disease on a patient's quality of life. DLQI scores range from 0 to 30, with a lower score representing a better quality of life.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health concepts. The SF-36 yields composite scores that provide a measure of disease impact on physical and mental health status. Higher SF-36 scores indicate a better quality of life.
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments. It consists of 2 subscales, one measuring anxiety (A-scale) and one measuring Depression (D-scale), which are scored separately. Lower HADS scores correspond to lesser psychological impairment.
- The Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations. The WLQ assesses four aspects of work and productivity: Physical Demands, Time Management, Mental-Interpersonal Demand, and Output Demand. The four subscales range from 0-100 with the lower score indicating fewer work limitations.

Placebo- and adalimumab-controlled studies – VOYAGE 1 and VOYAGE 2

VOYAGE 1 evaluated the safety and efficacy of TREMFYA vs. placebo and adalimumab in 837 subjects with plaque psoriasis. Subjects randomized to TREMFYA received TREMFYA 100 mg at Weeks 0 and 4 and every 8 weeks thereafter. Subjects randomized to adalimumab received adalimumab 80 mg at Week 0 and 40 mg at Week 1 subcutaneously followed by 40 mg every other week thereafter through Week 47. All subjects, including those randomized to adalimumab at Week 0, received TREMFYA 100 mg at Week 52 and every 8 weeks thereafter. Subjects randomized to placebo received TREMFYA at Weeks 16, 20 and every 8 weeks thereafter.

VOYAGE 2 evaluated the safety and efficacy of TREMFYA vs. placebo and adalimumab in 992 subjects with plaque psoriasis. Subjects randomized to TREMFYA received TREMFYA 100 mg at Weeks 0, 4, 12 and 20. Subjects randomized to adalimumab received adalimumab 80 mg at Week 0 and 40 mg at Week 1 subcutaneously followed by 40 mg every other week thereafter through Week 23. Subjects randomized to placebo received TREMFYA 100 mg at Weeks 16 and 20. To evaluate the therapeutic benefit of maintenance dosing with TREMFYA, subjects randomized to TREMFYA at Week 0 who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with TREMFYA maintenance therapy or withdrawal of therapy. Withdrawal subjects re-initiated TREMFYA (dosed at time of retreatment, 4 weeks later and every 8 weeks thereafter) when they experienced at least a 50% loss of their week 28 PASI improvement. Subjects randomized to adalimumab at Week 0 who were PASI 90 non-responders received TREMFYA at Weeks 28, 32 and every 8 weeks thereafter. All subjects started to receive open-label TREMFYA every 8 weeks at Week 76.

The co-primary endpoints in VOYAGE 1 and VOYAGE 2 were the proportions of subjects who achieved an IGA score of cleared (0) or minimal (1) and the proportions of subjects who achieved a PASI 90 response at Week 16, comparing the TREMFYA group and the placebo group. For both studies, secondary endpoints comparing TREMFYA and adalimumab groups included the proportions of subjects who achieved an IGA score of cleared (0) or minimal (1), a PASI 90 and a PASI 75 response at Week 16; and the proportions of subjects achieving an IGA score of cleared (0), an IGA score of cleared or minimal (0 or 1), PASI 75, PASI 90 and a PASI 100 response at Week 24, and at Week 48 for VOYAGE 1.

Baseline disease characteristics were generally consistent across all treatment groups in VOYAGE 1 and VOYAGE 2 (see Table 5). The majority of subjects were male and white. The mean age was approximately 44 years, and mean weight was approximately 90 kg.

Table 5: Baseline Disease Characteristics-VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	TREMFYA	Adalimumab	Placebo	TREMFYA	Adalimumab
Subjects randomized at Week 0	N=174	N=329	N=334	N=248	N=496	N=248
Median BSA, %	20.0	22.0	23.0	22.0	24.0	25.0
Median PASI	17.4	18.6	20.0	19.0	19.2	19.0
IGA of severe, n (%)	43 (24.7%)	77 (23.4%)	90 (26.9%)	57 (23.0%)	115 (23.2%)	53 (21.4%)
History of psoriatic arthritis, n (%)	30 (17.2%)	64 (19.5%)	62 (18.6%)	46 (18.5%)	89 (17.9%)	44 (17.7%)
Prior phototherapy, n (%)	86 (49.4%)	188 (57.3%) (N=328)	180 (53.9%)	137 (55.2%)	293 (59.1%)	135 (54.7%) (N=247)
Prior conventional systemic or biologic therapy, n (%)	106 (60.9%)	229 (69.6%)	233 (69.8%)	169 (68.1%)	361 (72.8%)	179 (72.2%)
Non-biologic systemics, n (%)	92 (52.9%)	210 (63.8%)	215 (64.4%)	149 (60.1%)	331 (66.7%)	159 (64.1%)
Biologic systemics, n (%)	34 (19.5%)	71 (21.6%)	70 (21.0%)	54 (21.8%)	101 (20.4%)	49 (19.8%)
Naïve to non-biologic systemics and biologics, n (%)	68 (39.1%)	100 (30.4%)	101 (30.2%)	79 (31.9%)	135 (27.2%)	69 (27.8%)
Failed to respond to, had contraindication for, or intolerant to conventional therapy (PUVA, Methotrexate, Cyclosporine), n/N (%)	64/82 (78.0%)	143/189 (75.7%)	154/193 (79.8%)	120/138 (87.0%)	263/308 (85.4%)	122/148 (82.4%)

Baseline disease characteristics were consistent for the study populations in VOYAGE 1 and 2 with a median BSA of 22% and 24%, a median baseline PASI score of 19 for both studies, a baseline IGA score of severe for 25% and 23% of subjects, and a history of psoriatic arthritis for 19% and 18% of subjects, respectively.
Of all subjects who were included in the VOYAGE 1 and 2 studies, 32% and 29% were naïve to conventional systemic and biologic systemic 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 systemic therapy, including 11% who had received at least one anti-tumor necrosis factor alpha (TNFα) agent, and approximately 10% who had received an anti-IL-12/IL-23 agent.

Summary of clinical outcomes

PASI and IGA outcomes, VOYAGE 1 and VOYAGE 2

In both the VOYAGE 1 and VOYAGE 2 studies, a significantly greater proportion of subjects randomized to treatment with TREMFYA achieved a PASI 90 response and IGA cleared or minimal (0 or 1) response versus placebo at Week 16 ($p < 0.001$ for all comparisons) (see Table 3).
TREMFYA demonstrated superiority to adalimumab as evaluated by efficacy endpoints of PASI 75, PASI 90 and IGA cleared or minimal (0 or 1) at Week 16 in both studies ($p < 0.001$ for all comparisons). TREMFYA also demonstrated superiority to adalimumab on PASI 75, PASI 90, PASI 100, IGA cleared (0), and IGA cleared or minimal (0 or 1) at Week 24 in both studies and at Week 48 in VOYAGE 1 ($p < 0.001$ for all comparisons) (see Table 6).
Response rates to TREMFYA were similar among the subgroups defined by age, gender, race, body weight, plaques location and baseline PASI score. Response rates in subjects with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population. TREMFYA was efficacious in systemic treatment-naïve, systemic treatment-exposed, biologic-naïve, and biologic-exposed subjects.

Table 6: Summary of Clinical Responses in Psoriasis Studies VOYAGE 1 and VOYAGE 2

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

NA=not applicable

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

[b] $p < 0.001$ for comparison between TREMFYA and adalimumab for major secondary endpoints.

[c] $p < 0.001$ for comparison between TREMFYA and adalimumab.

[d] $p < 0.001$ are for the comparisons between TREMFYA and placebo for the co-primary endpoints.

[e] comparisons between TREMFYA and adalimumab were not performed.

Response over time

TREMFYA 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 subjects achieving a PASI 90 response was numerically higher for TREMFYA than adalimumab starting at Week 8 with the difference reaching a maximum around Week 20 (VOYAGE 1 and VOYAGE 2) and maintained through Week 48 (VOYAGE 1). In VOYAGE 1, for subjects receiving continuous TREMFYA treatment, PASI 90 response was maintained from Week 52 to Week 252.

Figure 1: Percent of Subjects Who Achieved PASI 90 Response Through Week 48 by Visit (Subjects Randomized at Week 0) in VOYAGE 1

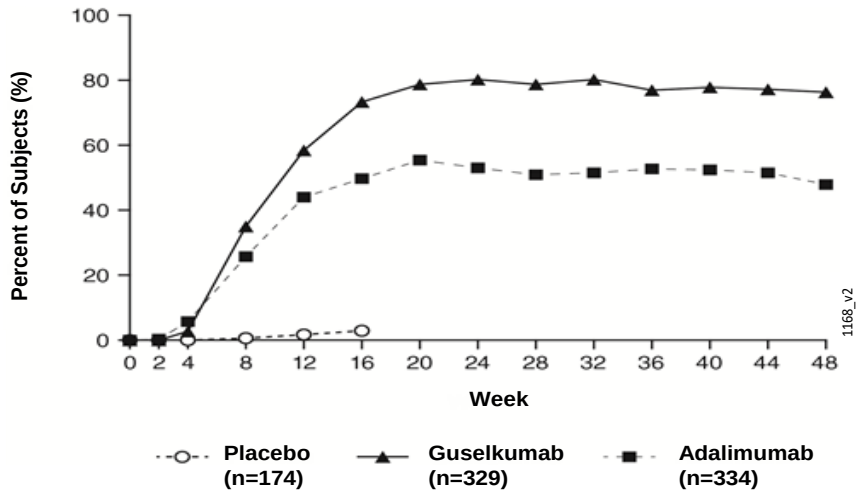
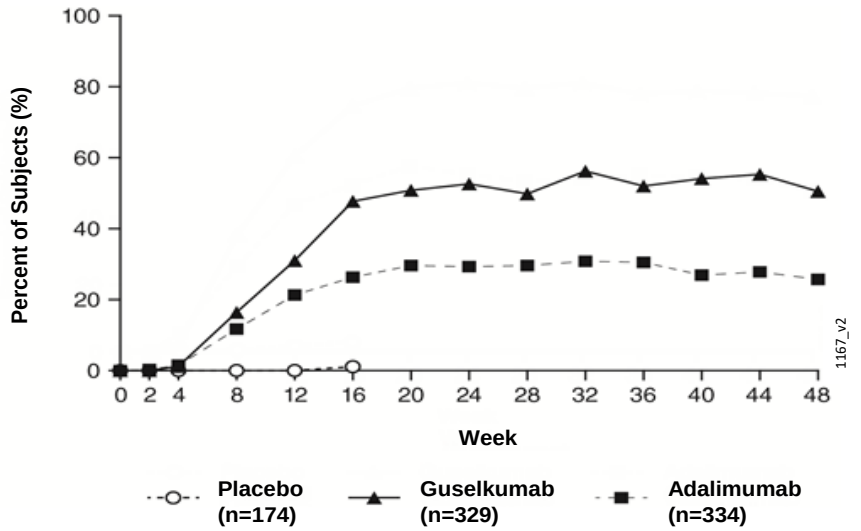


Figure 2: Percent of Subjects Who Achieved an IGA Score of Cleared (0) Through Week 48 by Visit (Subjects Randomized at Week 0) in VOYAGE 1



Maintenance and durability of response

To evaluate the maintenance and durability of response, subjects originally randomized to TREMFYA and who were PASI 90 responders at Week 28 in the VOYAGE 2 study were re-randomized to continue maintenance treatment with TREMFYA or be withdrawn from therapy (i.e. placebo). At Week 48, 88.6% of subjects in the continuous maintenance treatment group were PASI 90 responders compared with 36.8% in the withdrawal group ($p < 0.001$). Loss of PASI 90 response was noted as early as 4 weeks after withdrawal of therapy with the median time to loss of PASI 90 of approximately 15 weeks.

Therefore, a maintenance regimen of every 8 weeks is recommended.

Efficacy of retreatment

In VOYAGE 2, among subjects who were withdrawn from treatment and subsequently re-initiated TREMFYA, 80% regained a PASI 90 response when assessed 20 weeks after initiation of retreatment.

Efficacy and safety in patients switching from adalimumab to TREMFYA

In VOYAGE 2, among 112 adalimumab subjects 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 TREMFYA, respectively.

No new safety findings were observed in patients who switched from adalimumab to guselkumab.

Patient reported outcomes

In the VOYAGE 1 and VOYAGE 2 studies, patient reported outcomes of psoriasis symptoms and signs were assessed with the PSSD, and disease specific health related quality of life was evaluated with the DLQI at Weeks 16, 24, 48, 76, 100, 124, 156, 172, 204, 228 and 252. In addition, the VOYAGE 2 study also included

assessments of general health status with the SF-36, anxiety and depression with the HADS and work limitations with the WLQ in subjects treated with TREMFYA.

Psoriasis Symptoms and Signs Diary (PSSD)

In VOYAGE 1 and VOYAGE 2, TREMFYA-treated subjects demonstrated significantly greater improvement in both PSSD symptom and signs scores from baseline compared to placebo at Week 16 and compared to adalimumab at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1) (see Table 5). TREMFYA demonstrated greater improvement as compared to placebo as early as Week 2.

A significantly greater proportion of subjects treated with TREMFYA achieved a clinically meaningful improvement (≥ 40 points reduction) from baseline in PSSD symptom score and signs score compared to placebo at Week 16, and compared to adalimumab at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1) ($p \leq 0.002$, for all comparisons). A significantly greater proportion of subjects treated with TREMFYA achieved PSSD symptom and signs score of 0 (symptom free and sign free) compared to placebo at Week 16, and compared to adalimumab at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1) ($p < 0.001$, for all comparisons, except $p = 0.003$ for signs score of 0 at Week 24 in VOYAGE 2) (see Table 5).

Significantly greater improvements in each of the individual items within the PSSD symptom scale (itching, pain, burning, stinging and skin tightness) and PSSD sign scale (skin dryness, cracking, scaling, shedding or flaking, redness and bleeding) were demonstrated in TREMFYA-treated subjects when compared to placebo at Week 16, and when compared to adalimumab at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1).

In VOYAGE 1, for subjects receiving continuous TREMFYA treatment, improvements in PSSD scores were maintained from Week 52 through Week 252.

Dermatology Life Quality Index

Significantly greater improvements in the DLQI from baseline were observed in subjects treated with TREMFYA compared to placebo at Week 16 (for all comparisons, $p < 0.001$). A significantly greater proportion of subjects treated with TREMFYA achieved a DLQI 0 or 1 (no impact of psoriasis on health-related quality of life) compared to placebo at Week 16, and compared to adalimumab at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1) (for all comparisons, $p < 0.001$) (see Table 7).

In VOYAGE 1, for subjects receiving continuous TREMFYA treatment, improvements in DLQI scores were maintained from Week 52 through Week 252.

Table 7: Summary of Patient Reported Outcomes in Psoriasis Studies VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	TREMFYA	Adalimumab	Placebo	TREMFYA	Adalimumab
Change from baseline in PSSD-Symptom score						
Subjects with non-missing baseline score	129	249	274	198	411	201
At, mean (SD)						
Week 16	-3.0 (19.6)	-41.9 (24.6)[a]	-35.4 (28.5)[b]	-8.3 (23.7)	-40.4 (26.5)[a]	-32.8 (24.9)[b]
Week 24	NA	-44.0 (24.6)	-36.0 (28.4)[d]	NA	-42.1 (26.8)	-31.9 (27.0)[d]
Week 48	NA	-45.3 (25.5)	-32.5 (31.1)[d]	NA	NA	NA
Achieved a clinically meaningful change from baseline in PSSD symptom score (greater than or equal to 40 points)						
Subjects with baseline score >40	78	174	188	154	280	138
At, n (%)						
Week 16	6 (7.7%)	128 (73.6%)[c]	124 (66.0%)[b]	19 (12.3%)	203 (72.5%)[c]	72 (52.2%)[b]
Week 24	NA	139 (79.9%)	120 (63.8%)[d]	NA	213 (76.1%)	73 (52.9%)[d]
Week 48	NA	141 (81.0%)	113 (60.1%)[d]	NA	NA	NA
Achieved PSSD Symptom score of 0 among subjects with a score greater than 0 at baseline						
Subjects with baseline score>0	129	248	273	198	410	200
At, n (%)						
Week 16	1 (0.8%)	67 (27.0%)[c]	45 (16.5%)[b]	0	112 (27.3%)[c]	30 (15.0%)[b]
Week 24	NA	90 (36.3%)	59 (21.6%)[e]	NA	144 (35.1%)	45 (22.5%)[e]

Week 48	NA	104 (41.9%)	63 (23.1%)[d]	NA	NA	NA
Change from baseline in PSSD sign score						
Subjects with non-missing baseline score	129	249	274	198	411	201
At, mean (SD)						
Week 16	-4.1 (17.9)	-44.6 (22.0)[c]	-39.7 (26.4)[b]	-9.8 (22.8)	-42.9 (23.7)[c]	-34.6 (23.5)[b]
Week 24	NA	-47.2 (22.2)	-40.1 (26.5)[d]	NA	-44.5 (24.1)	-33.6 (25.3)[d]
Week 48	NA	-47.9 (23.1)	-36.6 (29.3)[d]	NA	NA	NA
Achieved a clinically meaningful change from baseline in PSSD sign score (greater than or equal to 40 points)						
Subjects with baseline score >40	95	197	221	166	305	153
At, n (%)						
Week 16	4 (4.2%)	144 (73.1%)[c]	149 (67.4%)[b]	24 (14.5%)	223 (73.1%)[c]	80 (52.3%)[b]
Week 24	NA	155 (78.7%)	144 (65.2%)[f]	NA	233 (76.4%)	79 (51.6%)[d]
Week 48	NA	162 (82.2%)	140 (63.3%)[d]	NA	NA	NA
Achieved PSSD Sign score of 0 among subjects with score of greater than 0 at baseline						
Subjects with baseline score >0	129	248	274	198	411	201
At, n (%)						
Week 16	0	50 (20.2%)[c]	32 (11.7%)[b]	0	86 (20.9%)[c]	21 (10.4%)[b]
Week 24	NA	73 (29.4%)	40 (14.6%)[d]	NA	114 (27.7%)	34 (16.9%)[g]
Week 48	NA	89 (35.9%)	51 (18.6%)[d]	NA	NA	NA
Change from baseline in DLQI						
Subjects with non-missing baseline score	170	322	328	248	495	247
At, mean (SD)						
Week 16	-0.6 (6.4)	-11.2 (7.2)[a]	-9.3 (7.8)[b]	-2.6 (6.9)	-11.3 (6.8)[a]	-9.7 (6.8)[b]
Week 24	NA	-11.6 (7.6)	-9.5 (7.9)[b]	NA	-11.9 (7.0)	-9.9 (7.4)[b]
Week 48	NA	-11.8 (7.8)	-9.2 (8.3)[b]	NA	NA	NA
Achieved DLQI of 0/1						
Subjects with baseline score >1	168	320	319	246	491	246
At, n (%)						
Week 16	7 (4.2%)	180 (56.3%)[c]	123 (38.6%)[b]	8 (3.3%)	254 (51.7%)[c]	96 (39.0%)[b]
Week 24	NA	195 (60.9%)	126 (39.5%)[d]	NA	283 (57.6%)	101 (41.1%)[d]
Week 48		200 (62.5%)	124 (38.9%)[d]	NA	NA	NA

[a] $p < 0.001$ for comparison between TREMFYA and placebo for major secondary endpoints.
[b] comparisons between TREMFYA and adalimumab were not performed.
[c] $p < 0.001$ for comparison between TREMFYA and placebo.
[d] $p < 0.001$ for comparison between TREMFYA and adalimumab.
[e] $p < 0.001$ for comparison between TREMFYA and adalimumab for major secondary endpoints.
[f] $p = 0.002$ for comparison between TREMFYA and adalimumab.
[g] $p = 0.003$ for comparison between TREMFYA and adalimumab.

SF-36

At Week 16, subjects treated with TREMFYA in VOYAGE 2 showed greater improvement from baseline in the SF-36 physical and mental component summary score compared to subjects treated with placebo ($p < 0.001$). The improvement in SF-36 physical and mental component summary score was maintained through Week 252 among subjects randomized to TREMFYA maintenance therapy.

Hospital Anxiety and Depression Scale (HADS)

Both anxiety and depression scores were significantly reduced in subjects treated with TREMFYA at Week 16 in VOYAGE 2 compared with subjects randomized to placebo ($p < 0.001$). HADS improvements were maintained through Week 252 among subjects randomized to TREMFYA maintenance therapy.

Table 8: Quality of Life Endpoints (Change from Baseline at Week 16) in VOYAGE 2

	Placebo	TREMFYA	Adalimumab
SF-36			
Physical component summary			
Subjects with non-missing baseline score	248	494	246
Mean Change (SD)	0.9 (6.6)	5.5 (7.8)[a]	3.9 (6.6)
Mental component summary			
Subjects with non-missing baseline score	248	494	246
Mean Change (SD)	0.6 (8.8)	5.7 (9.5)[a]	4.6 (9.4)
Hospital Anxiety and Depression			
Hospital Anxiety score			
Subjects with non-missing baseline score	248	495	246
Mean Change (SD)	-0.2 (2.9)	-1.7 (3.4)[a]	-1.1 (3.4)
Depression score			
Subjects with non-missing baseline score	248	495	246
Mean Change (SD)	-0.1 (2.9)	-1.6 (3.6)[a]	-1.2 (3.4)

SF-36 = Short Form Health Survey

[a] p < 0.001 for 100 mg TREMFYA compared with placebo.

Work Limitations Questionnaire

The WLQ in VOYAGE 2 showed that work productivity improved significantly more in subjects randomized to TREMFYA at Week 16 compared with subjects randomized to placebo as measured by the four WLQ subscales (Physical Demands, Time Management, Mental-Interpersonal, and Output Demands). The improvements in WLQ were maintained through Week 252 among subjects randomized to maintenance therapy.

Table 9: Summary of Change from Baseline at Week 16 in Work Limitations Questionnaire in VOYAGE 2

	Placebo	TREMFYA 100 mg	Adalimumab
Physical Demands score			
Subjects with non-missing baseline score	180	352	172
Mean Change (SD)	0.4 (15.2)	-7.5 (19.1)[a]	-2.9 (16.0)
Time Management score			
Subjects with non-missing baseline score	168	336	163
Mean Change (SD)	0.1 (19.3)	-6.0 (19.4)[b]	-7.5 (20.2)
Mental-Interpersonal score			
Subjects with non-missing baseline score	176	346	168
Mean Change (SD)	-0.7 (14.4)	-5.3 (16.2)[b]	-3.7 (13.8)
Output Demands score			
Subjects with non-missing baseline score	178	346	170
Mean Change (SD)	-2.2 (12.7)	-5.8 (18.4)[b]	-3.3 (17.2)

[a] p < 0.001 for 100 mg TREMFYA compared with placebo.

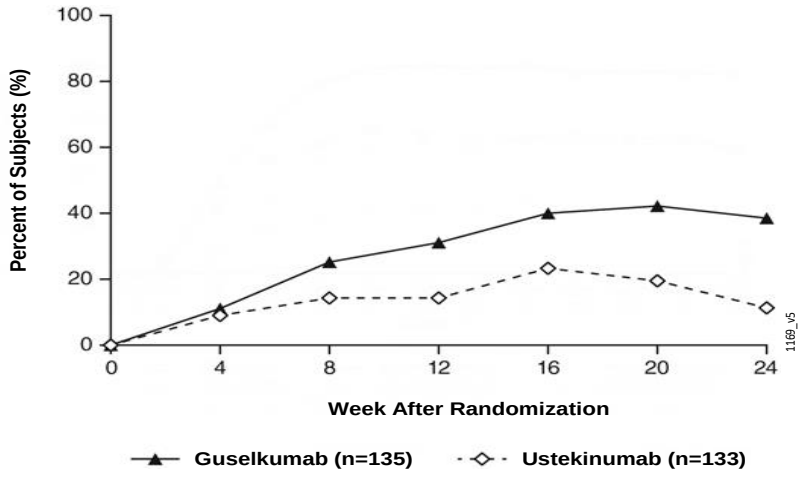
[b] p = < 0.05

Active-controlled study in ustekinumab inadequate responder–NAVIGATE

NAVIGATE evaluated the efficacy and safety of switching to TREMFYA in 268 subjects who had not achieved an adequate response (defined as IGA ≥ 2) to ustekinumab at Week 16 after initial treatment with ustekinumab (dosed at Week 0 and Week 4). Subjects were randomized to either continue ustekinumab treatment every 12 weeks or to begin TREMFYA 100 mg at Weeks 16, 20, and every 8 weeks thereafter. The primary endpoint was the number of post-randomization visits between Weeks 12 and 24 at which subjects achieved an IGA of cleared or minimal (0 or 1) and had at least a 2-grade improvement. Secondary endpoints included the number of post-randomization visits between Weeks 12 and 24 at which subjects achieved a PASI 90 response, the number of post-randomization visits between Weeks 12 and 24 at which subjects achieved an IGA of 0 and the proportion of subjects who achieved an IGA of cleared or minimal (0 or 1) and at least a 2-grade improvement

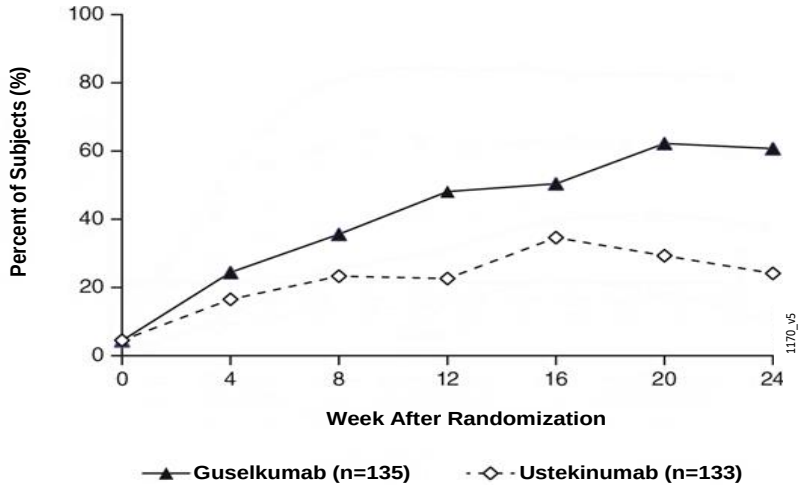
at 12 weeks post-randomization. Baseline characteristics for randomized subjects were similar to those observed in VOYAGE 1 and VOYAGE 2.
In subjects with an inadequate response to ustekinumab, significantly greater improvement of efficacy was observed in subjects who switched to TREMFYA treatment compared to subjects who continued ustekinumab treatment. Between 12 and 24 weeks after randomization, TREMFYA-treated subjects achieved an IGA score of clear or minimal (0 or 1) with at least a 2-grade improvement twice as often as ustekinumab-treated subjects (mean 1.5 vs 0.7 visits at which this outcome was observed respectively, $p < 0.001$). Similar outcomes were observed for the number of visits at which subjects achieved a PASI 90 response or an IGA score of cleared (0). At 12 weeks post-randomization, greater proportions of subjects in the TREMFYA group compared to the ustekinumab group also achieved an IGA score of cleared or minimal (0 or 1) and at least a 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 TREMFYA and ustekinumab treated subjects were noted as early as 4 weeks after randomization and reached a maximum 24 weeks after randomization (see Figure 3).

Figure 3: Percent of Subjects Who Achieved IGA Score of Cleared (0) or Minimal (1) and at least 2 Grade Improvement from Week 0 Through Week 24 by Visit After Randomization (Randomized Subjects) in NAVIGATE



No new safety findings were observed in patients who switched from ustekinumab to TREMFYA.

Figure 4: Percent of Subjects Who Achieved PASI 90 Response from Week 0 Through Week 24 by Visit After Randomization (Randomized Subjects) in NAVIGATE



Placebo-controlled study with Pre-filled pen-ORION
ORION evaluated the efficacy, safety, PK, immunogenicity, usability, and acceptability of TREMFYA delivered with a pre-filled pen. In this study, 78 subjects were randomized to receive either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter), or placebo. Baseline characteristics for randomized subjects were comparable to those observed in VOYAGE 1 and VOYAGE 2. The co-primary endpoints were the proportion of

subjects who achieved an IGA score of 0 or 1 at Week 16 and the proportion of subjects who achieved a PASI 90 response at Week 16. The secondary endpoints included the proportion of subjects who achieved an IGA score 0 at Week 16 and the proportion of subjects who achieved a PASI 100 response at Week 16.

A significantly greater proportion of subjects in the TREMFYA group achieved an IGA score of 0 or 1 or a PASI 90 response at Week 16 (80.6% and 75.8%, respectively, p<0.001 for both endpoints) than in the placebo group (0% for both endpoints). The proportion of subjects who achieved an IGA score of 0 at Week 16 was significantly higher in the TREMFYA group compared to the placebo group (56.5% vs. 0%; p < 0.001). The proportion of subjects who achieved a PASI 100 response at Week 16 was significantly higher in the TREMFYA group compared to the placebo group (50.0% vs. 0%; p < 0.001).

Patient Experience
Subject experience with the pre-filled pen was assessed on a scale of 0 (worst) to 10 (best) using a validated Self-Injection Assessment Questionnaire (SIAQ) based on subject responses across 6 domains (feelings about injections, self-image, self-confidence, pain and skin reactions during or after the injection, ease of use of the self-injection device, and satisfaction with self-injection) at weeks 0, 4 and 12. At week 12, the mean score for "Satisfaction with Self Injection" was 9.18 (with 10 indicating "Very Satisfied") and the mean score for "Ease of Use" was 9.24 (with 10 indicating "Very Easy"). The mean scores for the other domains at week 12 ranged from 8.43 to 9.84.

Active-controlled study with secukinumab – ECLIPSE
The efficacy and safety of TREMFYA were also investigated in a double-blind study compared to secukinumab. Patients were randomized to receive TREMFYA (N=534; 100 mg at Week 0, 4 and every 8 weeks thereafter) or secukinumab (N=514; 300 mg at Week 0, 1, 2, 3, 4, and every 4 weeks thereafter). The last dose was at Week 44 for both treatment groups. Demographic and disease characteristics were similar between the two treatment groups and consistent with those of the subjects enrolled in the pivotal Phase 3 psoriasis studies for TREMFYA and secukinumab. The primary endpoint was the proportion of subjects who achieved a PASI 90 response at Week 48. Major secondary endpoints were the proportion of subjects who achieved a PASI 75 response at both Week 12 and Week 48, a PASI 90 response at Week 12, PASI 75 response at Week 12, a PASI 100 response at Week 48, an IGA score of cleared (0) at Week 48, and an IGA score of cleared (0) or minimal (1) at Week 48.
TREMFYA 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 clinical response rates are presented in Table 10.

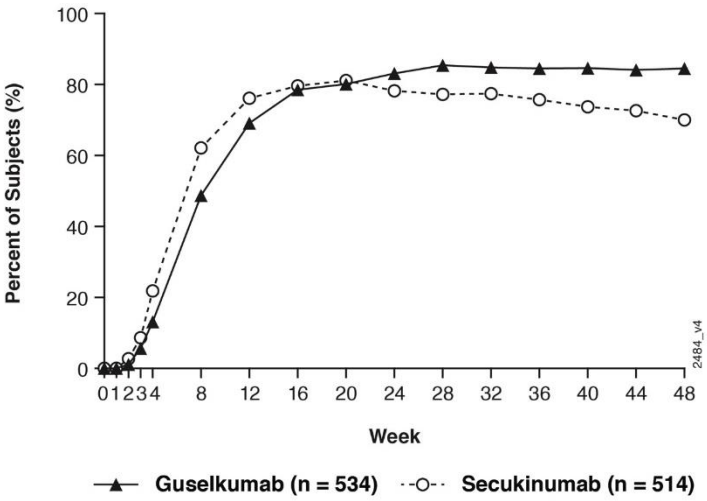
Table 10: Summary of Clinical Response Rates in ECLIPSE

	Number of patients (%)	
	TREMFYA (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%)
IGA score of cleared (0) at Week 48	332 (62.2%)[c]	259 (50.4%)
IGA score of cleared (0) or minimal (1) at Week 48	454 (85.0%)[c]	385 (74.9%)

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

The onset of PASI 90 responses occurred between Week 2 and Week 3 in both the TREMFYA and secukinumab groups. Higher PASI 90 response rates in the secukinumab group were observed between Week 4 and Week 12. Response rates were similar between the two groups at Week 16 and Week 20. TREMFYA response rates were higher from Week 24 to Week 48.

Figure 5: Percent of Subjects Who Achieved a PASI 90 Response from Week 0 Through Week 48 by Visit (Subjects Randomized at Week 0) in ECLIPSE



Clinical efficacy - Psoriatic arthritis (PsA)

The safety and efficacy of TREMFYA were assessed in 1120 patients in 2 randomized, double-blind, placebo-controlled studies (DISCOVER 1 and DISCOVER 2) in adult patients with active PsA (≥3 swollen joints, ≥3 tender joints, and a C-reactive protein (CRP) level of ≥0.3 mg/dL in DISCOVER 1 and ≥5 swollen joints, ≥5 tender joints, and a CRP level of ≥0.6 mg/dL in DISCOVER 2) who had inadequate response to standard therapies (e.g., conventional synthetic DMARDs [csDMARDs]), apremilast, or nonsteroidal anti-inflammatory drugs [NSAIDs]). Patients in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and a median duration of PsA of 4 years at baseline.

In DISCOVER 1 approximately 30% of subjects had been previously treated with up to 2 anti-tumor necrosis factor alpha (anti-TNFα) agents whereas in DISCOVER 2 all subjects were biologic naïve. Approximately 58% of subjects from both studies had concomitant methotrexate (MTX) use. 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%). At baseline, over 65% and 42% of the patients had enthesitis and dactylitis, respectively and over 75% had ≥3% body surface area (BSA) psoriasis skin involvement.

DISCOVER 1 evaluated 381 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and every 8 weeks (q8w) thereafter, or TREMFYA 100 mg SC every 4 weeks (q4w). DISCOVER 2 evaluated 739 subjects who were treated with placebo SC, TREMFYA 100 mg SC at Weeks 0, 4 and q8w thereafter, or TREMFYA 100 mg SC q4w. At Week 24, placebo subjects in both studies crossed over to receive TREMFYA 100 mg SC q4w.The primary endpoint in both studies was the percentage of patients achieving an ACR20 response at Week 24. Secondary endpoints included change from baseline in Disability Index of the Health Assessment Questionnaire (HAQ-DI), IGA, ACR 50, ACR 70, SF-36 PCS, SF-36 MCS and change from baseline in total modified van der Heijde-Sharp score (DISCOVER 2), at Week 24. Additionally, resolution of enthesitis and dactylitis based on the pooled data from DISCOVER 1 and DISCOVER 2 was assessed as a secondary endpoint in DISCOVER 2.

Signs and symptoms

In both studies, patients treated with TREMFYA 100 mg q8w or 100 mg q4wW demonstrated a greater clinical response including ACR20, ACR50, and ACR70 compared to placebo at Week 24 (Table 11). These responses were maintained from Week 24 to Week 52. Responses were seen regardless of prior anti-TNFα exposure (DISCOVER 1) and concomitant csDMARD use (DISCOVER 1 and DISCOVER 2). Additionally, in both studies, examination of age, gender, race, body weight, and previous treatment with csDMARDs did not identify differences in response to TREMFYA among these subgroups.

Table 11: Clinical Responses in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
	Placebo (N=126)	TREMFYA 100 mg q8w (N=127)	TREMFYA 100 mg q4w (N=128)	Placebo (N=246)	TREMFYA 100 mg q8w (N=248)	TREMFYA 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]
Week 24	22.2%	52.0% [a]	59.4% [a]	32.9%	64.1% [a]	63.7%[a]

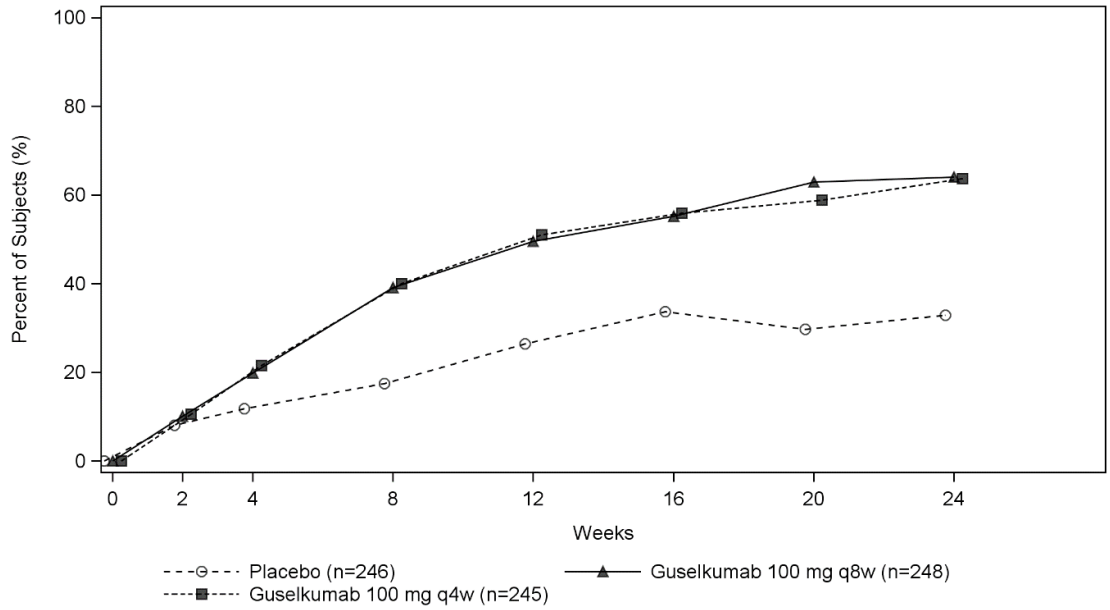
ACR 50 response						
Week 16	12.7%	22.8% [d]	26.6% [c]	9.3%	28.6% [g]	20.8% [c]
Week 24	8.7%	29.9% [b]	35.9% [b]	14.2%	31.5% [g]	33.1% [c]
ACR 70 response						
Week 24	5.6%	11.8% [d]	20.3% [b]	4.1%	18.5% [g]	13.1% [c]
DAS 28 (CRP) LS Mean Change from baseline (adjusted mean)						
Week 24	-0.70	-1.43 [b]	-1.61 [b]	-0.97	-1.59 [b]	-1.62 [b]
Minimal Disease Activity (MDA)						
Week 24	11.1%	22.8% [f]	30.5% [e]	6.1%	25.0% [e]	18.8% [e]
Modified PsA Responder Criteria (PsARC)						
Week 24	31.0%	59.8% [e]	72.7% [e]	44.7%	72.6% [e]	68.6% [e]

[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 based on hierarchical order in testing procedure, nominal p < 0.001 (major secondary endpoint)

In DISCOVER 1 and 2, patients treated with TREMFYA 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. In both studies, the improvement in BASDAI was maintained from Week 24 to Week 52.

In DISCOVER 2, a greater ACR 20 response was observed in both TREMFYA dose groups compared with the placebo group as early as Week 4 and the treatment difference continued to increase over time through Week 24 (Figure 6).

Figure 6: Subjects Achieving ACR 20 Response by Visit Through Week 24 in DISCOVER 2



ACR 20 response was maintained from Week 24 to Week 52.

In DISCOVER 1 and DISCOVER 2, improvements as assessed by mean change from baseline were observed in all components of the ACR response criteria (see Table 12).

Table 12: Mean Change from Baseline in ACR Component Scores at Week 16 and 24[a]

	DISCOVER 1		DISCOVER 2	
		TREMFYA		TREMFYA

	Placebo (N=126)	100 mg q8w (N=127)	100 mg q4w (N=128)	Placebo N=246	100 mg q8w (N=248)	100 mg q4w (N=245)
No. of Swollen Joints						
Baseline	10.1	10.9	8.6	12.3	11.7	12.9
Mean change at Week 16	-4.2	-7.3	-5.8	-5.8	-7.2	-7.5
Mean change at Week 24	-5.1	-7.3	-5.7	-6.4	-8.1	-8.8
No. of Tender Joints						
Baseline	19.8	20.2	17.7	21.6	19.8	22.4
Mean change at Week 16	-4.5	-10.2	-8.7	-6.8	-9.0	-9.9
Mean change at Week 24	-6.8	-10.5	-9.2	-5.0	-9.0	-10.0
Patient's Assessment of Pain						
Baseline	5.8	6.0	5.9	6.3	6.3	6.2
Mean change at Week 16	-0.8	-1.7	-2.0	-0.9	-2.2	-1.9
Mean change at Week 24	-0.7	-2.2	-2.4	-1.1	-2.5	-2.4
Patient Global Assessment						
Baseline	6.1	6.5	6.1	6.5	6.5	6.4
Mean change at Week 16	-1.0	-2.0	-2.2	-1.0	-2.3	-2.0
Mean change at Week 24	-0.9	-2.5	-2.6	-1.2	-2.5	-2.4
Physician Global Assessment						
Baseline	6.3	6.2	6.2	6.7	6.6	6.6
Mean change at Week 16	-1.9	-2.9	-3.5	-2.1	-3.5	-3.3
Mean change at Week 24	-2.2	-3.5	-3.9	-2.5	-3.8	-3.9
Disability Index (HAQ-DI)						
Baseline	1.1	1.0	1.0	1.2	1.2	1.1
Mean change at Week 16	-0.1	-0.3	-0.3	-0.1	-0.3	-0.4
Mean change at Week 24	-0.1	-0.3	-0.4	-0.2	-0.4	-0.4
CRP (mg/mL)						
Baseline	1.4	1.6	1.1	2.1	2.0	1.8
Mean change at Week 16	-0.2	-0.6	-0.5	-0.6	-1.0	-1.0
Mean change at Week 24	-0.0	-0.7	-0.5	-0.5	-1.1	-1.0
[a] based on observed data						

In DISCOVER 1 and DISCOVER 2, median percent improvement from baseline was observed in all components of the ACR response criteria (see Table 13). In both studies, the median percent improvement was maintained from Week 24 to Week 52.

Table 13: Median Percent Improvement from Baseline in ACR Component Scores at Week 24[a]

	DISCOVER 1			**DISCOVER 2**		
		TREMFYA			TREMFYA	
	Placebo (N=126)	100 mg q8w (N=127)	100 mg q4w (N=128)	Placebo N=246	100 mg q8w (N=248)	100 mg 4w (N=245)
No. of Swollen Joints	60.0%	83.3%	87.5%	65.5%	85.7%	81.5%
No. of Tender Joints	37.8%	66.7%	66.7%	33.3%	60.0%	66.7%
Patient's Assessment of Pain	8.2%	37.5%	39.3%	11.6%	37.2%	38.5%
Patient Global Assessment	10.2%	42.9%	44.0%	13.3%	34.0%	37.1%
Physician Global Assessment	32.4%	58.3%	70.2%	34.6%	62.9%	63.9%
Disability Index (HAQ-DI)	6.9%	25.0%	33.3%	8.3%	27.3%	33.3%
CRP	21.2%	24.4%	37.4%	17.5%	53.2%	48.2%
[a] based on observed data						

Psoriasis Skin Response

In DISCOVER 1 and DISCOVER 2, among subjects with mild to severe psoriasis (BSA ≥3% and IGA ≥2) at baseline, a greater proportion of subjects in both TREMFYA dose groups achieved a psoriasis response, defined as an IGA of 0 (cleared) or 1 (minimal) and a ≥2-grade reduction from baseline, compared with the placebo group at Week

24. Results from psoriasis skin response endpoints in DISCOVER 1 and DISCOVER 2 are presented in Table 13. Responses for both IGA and PASI endpoints were maintained from Week 24 to Week 52.

Table 14: Psoriasis Skin Response in Subjects with ≥ 3% BSA and IGA ≥ 2 at Baseline

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo (n=78)	100 mg q8w (n=82)	100 mg q4w (n=89)	Placebo (n=183)	100 mg q8w (n=176)	100 mg q4w (n=184)
IGA response *IGA 0/1 and ≥2 grade improvement*						
Week 24	15.4%	57.3% [a]	75.3% [a]	19.1%	70.5% [a]	68.5% [a]
PASI 90 response						
Week 16	10.3%	45.1% [b]	52.8% [b]	8.2%	55.1% [b]	53.8% [b]
Week 24	11.5%	50.0% [b]	62.9% [b]	9.8%	68.8% [b]	60.9% [b]
PASI 100 response						
Week 16	7.7%	23.2% [c]	32.6% [b]	3.8%	27.3% [b]	33.2% [b]
Week 24	6.4%	25.6% [b]	44.9% [b]	2.7%	45.5% [b]	44.6% [b]

[a] $p < 0.001$ (major secondary endpoint)
[b] nominal $p < 0.001$
[c] nominal $p=0.006$

Enthesitis and Dactylitis

Enthesitis and dactylitis were assessed based on pooled data from DISCOVER 1 and DISCOVER 2. Among subjects with dactylitis at baseline, a greater proportion of subjects in both the TREMFYA 100 mg q8w and the TREMFYA 100 mg q4w groups achieved dactylitis resolution at Week 24 compared with the placebo group (Table 15). Among subjects with enthesitis at baseline, a greater proportion of subjects in both the TREMFYA 100 mg q8w group and q4w group achieved enthesitis resolution at Week 24 compared with the placebo group (Table 16). Based on the combined data from DISCOVER 1 and DISCOVER 2, resolution of dactylitis and enthesitis were maintained from Week 24 to Week 52.

Table 15: Dactylitis and Enthesitis Resolution at Week 24; Pooled Data from DISCOVER 1 and DISCOVER 2

		TREMFYA	
	Placebo	**100 mg q8w**	**100 mg q4w**
Dactylitis			
Subjects with dactylitis at baseline (n)	154	160	159
Dactylitis resolution at Week 24	42.2%	59.4% [b]	63.5%[a]
Enthesitis			
Subjects with enthesitis at baseline (n)	255	230	243
Enthesitis resolution at Week 24	29.4%	49.6% [c]	44.9%[a]

[a] $p=0.006$ (major secondary endpoint)
[b] not formally tested based on hierarchical order in testing procedure, nominal $p=0.001$ (major secondary endpoint)
[c] not formally tested based on hierarchical order in testing procedure, nominal $p<0.001$ (major secondary endpoint)

The results from the individual studies are presented in Table 16.

Table 16: Dactylitis and Enthesitis Resolution at Week 24 in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo	**100 mg q8w**	**100 mg q4w**	**Placebo**	**100 mg q8w**	**100 mg q4w**
Dactylitis						
Subjects with dactylitis at baseline (n)	55	49	38	99	111	121
Dactylitis resolution at Week 24	49.1%	65.3%[a]	63.2%[b]	38.4%	56.8%[c]	63.6%[d]
Enthesitis						

Subjects with enthesitis at baseline (n)	77	72	73	178	158	170
Enthesitis resolution at Week 24	27.3%	40.3%[e]	47.9%[f]	30.3%	53.8%[d]	43.5%[g]
[a] nominal p=0.088 [b] nominal p=0.212 [c] nominal p=0.007 [d] nominal p<0.001 [e] nominal p=0.094 [f] nominal p=0.013 [g] nominal p=0.017						

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.

TREMFYA q4w inhibited the progression of structural damage compared to placebo at Week 24. TREMFYA q8w did not demonstrate statistically significant inhibition of structural damage compared to placebo at Week 24. These results are shown in Table 17.

Table 17: Change from Baseline in vdH-S score at Week 24 in DISCOVER 2

	N	LS Mean change from baseline in vdH-S score at Week 24
Placebo	246	0.95
TREMFYA 100 mg q4w	245	0.29[a]
TREMFYA 100 mg q8w	248	0.52[b]
[a] p=0.006 (major secondary endpoint) [b] not statistically significant p=0.068 (major secondary endpoint)		

At Week 52, the mean change from baseline in total modified vdH-S was similar in the guselkumab q8w and q4w groups (0.97 and 1.07, respectively).

Physical function and health-related quality of life

TREMFYA-treated patients in both the 100 mg q8w and q4w dose groups in both DISCOVER 1 and DISCOVER 2 showed greater mean improvement from baseline in physical function compared to patients treated with placebo as assessed by HAQ-DI at Weeks 16 and 24. Improvements in HAQ-DI were maintained from Week 24 to Week 52. In both studies, the proportion of HAQ-DI responders (≥0.35 improvement in HAQ-DI score) was greater in both TREMFYA dose groups compared to placebo at weeks 16 and 24. The proportion of HAQ-DI responders was maintained from Week 24 to Week 52.

Table 18: HAQ-DI Response at Weeks 16 and 24 in DISCOVER 1 and DISCOVER 2

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo (N=126)	100 mg q8w (N=127)	100 mg q4w (N=128)	Placebo N=246	100 mg q8w (N=248)	100 mg q4w (N=245)
HAQ-DI Mean change from baseline[f]						
Baseline	1.2391	1.2057	1.0938	1.2949	1.2848	1.2490
Mean change at Week 16	-0.1131	-0.2620 [d]	-0.3393 [c]	-0.1167	-0.3177 [c]	-0.3442 [c]
Mean change at Week 24	-0.0743	-0.3225 [a]	-0.3968 [a]	-0.1300	-0.3672 [a]	-0.4004 [a]
HAQ-DI Responders (≥ 0.35 improvement from baseline)						
Week 16	30.9%	46.4% [e]	57.3% [c]	30.9%	50.0% [c]	51.8% [c]
Week 24	29.1%	50.9% [b]	57.3% [c]	31.4%	50.0% [c]	56.1% [c]
[a] p<0.001 (major secondary endpoint) [b] nominal p=0.001 [c] nominal p<0.001 [d] nominal p=0.008 [e] nominal p=0.019 [f] adjusted mean change						

At Week 24, subjects in both the TREMFYA 100 mg q8w and q4w dose groups in both DISCOVER 1 and DISCOVER 2 showed greater improvement from baseline in the SF-36 PCS with no worsening in the SF-36 MCS compared with placebo. At Week 24 there was consistent evidence of effect in the physical functioning, role-physical, bodily-pain, general health, social-functioning and vitality domains but not in the role-emotional and mental health domains. Subjects in both the TREMFYA 100 mg q8w and q4w dose groups in both DISCOVER 1 and DISCOVER 2 showed greater improvement compared with placebo in fatigue measured with FACIT-fatigue at Week 24. 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. In DISCOVER 2, greater improvements were also observed in overall work impairment and activity impairment as assessed by the Work Productivity and Activity Impairment (WPAI)-PsA questionnaire compared to placebo at Week 24. Improvements in SF-36 PCS, SF-36 MCS, FACIT-F, DLQI and WPAI-PsA scores were maintained from Week 24 to Week 52.

Table 19: Mean Change from Baseline in Health-Related Quality of Life Endpoints at Week 24[f]"

	DISCOVER 1			DISCOVER 2		
		TREMFYA			TREMFYA	
	Placebo (N=126)	100 mg q8w (N=127)	100 mg q4w (N=128)	Placebo N=246	100 mg q8w (N=248)	100 mg q4w (N=245)
SF-PCS						
Mean change at Week 24	1.96	6.10[a]	6.87[a]	3.42	7.39[b]	7.04 [c]
SF-MCS						
Mean change at Week 24	2.37	3.20	3.60	2.14	4.17[d]	4.22[c]
FACIT-F						
Mean change at Week 24	2.206	5.609[e]	5.841[e]	3.559	7.550[e]	7.111[e]
DLQI[g]						
Mean change at Week 24	-	-	-	-2.129	-8.954[e]	-8.853[e]

[a] p<0.001 (major secondary endpoint)
[b] not formally tested based on hierarchical order in testing procedure, nominal p<0.001 (major secondary endpoint)
[c] p=0.006 (major secondary endpoint)
[d] not formally tested based on hierarchical order in testing procedure, nominal p=0.007 (major secondary endpoint)
[e] nominal p<0.001
[f] adjusted mean change
[g] in subjects with ≥ 3% BSA of Psoriasis and IGA ≥ 2 at baseline

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 3 in plaque psoriasis studies were 1.15 ± 0.73 mcg/mL and 1.23 ± 0.84 mcg/mL. Serum guselkumab concentrations did not appear to accumulate over time when given subcutaneously every 8 weeks.

The pharmacokinetics of guselkumab in subjects with psoriatic arthritis was similar to that in subjects with plaque 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 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 (Vz) following a single intravenous administration to healthy subjects ranged from approximately 7 to 10 L (98 to 123 mL/kg) across studies.

Metabolism

The exact pathway through which guselkumab is metabolized has not been characterized. As a human IgG monoclonal antibody, 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 (3.6 to 6.0 mL/day/kg) across studies.
Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in subjects with plaque psoriasis across studies.

Dose 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 subjects with plaque psoriasis.

Population pharmacokinetic analysis
In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.516 L/d and 13.5 L, respectively, and the $T_{1/2}$ was approximately 18 days in subjects with psoriasis. In the population pharmacokinetic analysis, the effects of baseline demographics (weight, age, sex, and race), immunogenicity, baseline disease characteristics, comorbidities (past and current history of diabetes, hypertension, and hyperlipidemia), past use of therapeutic biologics, past use of methotrexate or cyclosporine, concomitant medications (NSAIDs, corticosteroids and conventional synthetic DMARDS such as methotrexate), use of alcohol, or current smoking status, on pharmacokinetics of guselkumab was evaluated. Only the effects of body weight on CL/F and V/F were found to be significant, with a trend towards higher CL/F in heavier subjects. However, subsequent exposure-response modeling analysis suggested that no dose adjustment would be warranted for body weight.

Cytochrome P450 Substrates
An *in vitro* study using human hepatocytes showed that IL-23 did not alter the expression or activity of multiple CYP450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).
The effects of guselkumab on the pharmacokinetics of representative probe substrates of CYP isozymes (midazolam [CYP3A4], warfarin [CYP2C9], omeprazole [CYP2C19], dextromethorphan [CYP2D6], and caffeine [CYP1A2]) were evaluated in subjects with moderate to severe plaque psoriasis. Results from this study indicate that changes in C_{max} and AUC_{inf} of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant (see *Interactions*).
There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates.

Special populations
Pediatrics ([17] years of age and younger)
The safety and efficacy of guselkumab have not been established in pediatric patients.

Elderly ([65] years of age and older)
Of the 1384 plaque psoriasis subjects exposed to TREMFYA in Phase 3 clinical studies and included in the population pharmacokinetic (pop PK) analysis, 70 subjects were 65 years of age or older, including 4 subjects who were 75 years of age or older. Population pharmacokinetic analyses indicated there were no apparent changes in CL/F estimate in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly patients. Of the 746 psoriatic arthritis patients exposed to TREMFYA in Phase 3 clinical studies and included in the pop PK analysis, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older.

Renal impairment
No specific study has been conducted to determine the effect of renal impairment on the pharmacokinetics of guselkumab.

Hepatic impairment
No specific study has been conducted to determine the effect of hepatic impairment on the pharmacokinetics of guselkumab.

NON-CLINICAL INFORMATION

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well-tolerated at weekly doses up to 50 mg/kg intravenously for 5 weeks or 50 mg/kg subcutaneously for up to 24 weeks. There were no effects on cardiovascular, respiratory and nervous system function, and clinical pathology or anatomical pathology parameters. Safety margins at the NOAEL dose (50 mg/kg once weekly) were approximately 206-fold and 50-fold higher for AUC_{last} and C_{max}, respectively, than those following a single administration of a 100 mg SC dose to psoriasis subjects.

Carcinogenicity and Mutagenicity

Routine genotoxicity and carcinogenicity studies were not performed as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive Toxicology

There were no effects on reproduction or development in a prenatal and postnatal developmental toxicity (ePPND) study in which pregnant cynomolgus monkeys were administered guselkumab SC at doses up to 50 mg/kg/week from gestation day 20 through natural delivery. Peak serum concentrations in pregnant monkeys were 152-fold and 36-fold higher for C_{max} and AUC, respectively than those observed in psoriasis subjects following a single administration of a 100 mg SC dose. Guselkumab was detectable in newborn cynomolgus monkey serum samples indicating transplacental transfer of drug. Guselkumab was undetectable in breast milk at 4 weeks postpartum. There was a slightly higher incidence of pregnancy losses in the guselkumab treatment groups (10 or 50 mg/kg/week SC) relative to controls but without clear dose-response relationship. The clinical significance of these findings is unknown.

Immunization of infant monkeys with KLH at 4 to 6 months of age showed no impairment in the ability of the infants to mount a T-cell dependent anti-KLH antibody response to KLH immunization.

Fertility

No effects on fertility parameters were identified in female and male fertility studies conducted in guinea pigs. Results from the studies indicated no effects on male or female reproductive parameters, including no localization of guselkumab by immunohistochemistry (IHC) in any female reproductive tissues at 3 time points following mating in one mechanistic study. Safety margins for C_{max} and AUC_{last} at the 100 mg/kg twice-weekly NOAEL dose were at least 106-fold and 12-fold higher, respectively than those following a single administration of a 100 mg SC dose to psoriasis subjects.

PHARMACEUTICAL INFORMATION

List of Excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Sucrose
Water for injection

Incompatibilities

Not applicable.

Shelf Life

Pre-filled Syringe: 24 months
See expiry date on the outer pack.

Storage Conditions

- Store in a refrigerator at 2^0C to 8^0C (36^0F to 46^0F).
- Store in original carton until time of use.
- Protect from light.
- Do not freeze.
- Do not shake.

Keep out of the sight and reach of children.

Nature and Contents of Container

TREMFYA is a clear, colorless to light yellow solution for subcutaneous injection.

TREMFYA is supplied as a single-use sterile solution in a 1mL glass syringe with a fixed 27G, half inch needle assembled in a passive needle guard delivery system.
The formulation is composed of 100 mg/mL TREMFYA, containing L-Histidine, L-Histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection. Each mL of TREMFYA contains 100 mg of guselkumab, 0.6 mg L-histidine and 1.5 mg L-histidine monohydrochloride monohydrate, 79 mg sucrose, 0.5 mg polysorbate 80, and Water for Injection, USP.
TREMFYA is essentially free of visible particulate material with a pH of approximately 5.8.
TREMFYA does not contain preservatives.
TREMFYA is available as:

- 100 mg (100 mg/mL in1.0 mL syringe volume)

TREMFYA is available in the following packaging presentations:

- 1 single-use pre-filled syringe in a passive needle guard delivery system.

Instructions for Use and Handling and Disposal
Following administration of TREMFYA, discard any unused portion. The syringe should be disposed of using accepted medical practices for used syringes. The syringe and needle must never be re-used.

HOW SUPPLIED
Tremfya solution for injection
Box, 1 prefilled syringe @ 1ml
Reg. No.: DKI2160001843A1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Manufactured by Cilag AG, Schaffhausen, Switzerland
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
~~Imported by PT Johnson & Johnson Indonesia, Jakarta – Indonesia~~
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935-3935

Based on CCDS ~~ver.12 26Feb21 (PsA indication) + CCDS ver.13 11Feb21 _ IHI~~ Stopping rules PsO

INFORMASI PRODUK UNTUK PASIEN

TREMFYA 100mg larutan untuk injeksi
guselkumab

Baca semua informasi produk ini secara seksama sebelum Anda mulai menggunakan obat ini.
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau perawat Anda.

Apa yang ada dalam informasi produk ini

1. Apakah TREMFYA dan digunakan untuk apa

Apakah TREMFYA itu?
TREMFYA mengandung zat aktif guselkumab yaitu kelompok protein yang disebut antibodi monoklonal. Obat ini bekerja dengan menetralisir aktivitas suatu protein yang disebut IL-23, yang meningkat pada orang dengan psoriasis.

TREMFYA digunakan untuk mengobati:
- orang dewasa dengan "plak psoriasis" sedang hingga berat, yang merupakan kandidat untuk diobati dengan fototerapi atau terapi sistemik.
- orang dewasa dengan psoriatis artritis aktif, yaitu penyakit inflamasi pada sendi, biasanya disertai psoriasis. Jika Anda memiliki psoriatis artritis aktif, Anda akan diberikan TREMFYA saja atau dikombinasikan dengan *Disease Modifying Anti-Rheumatic Drugs* (DMARD) seperti metotreksat.

2. Apa saja yang perlu Anda ketahui sebelum menggunakan TREMFYA

Peringatan dan Perhatian
Bicaralah dengan dokter, apoteker atau perawat Anda sebelum menggunakan TREMFYA.

Infeksi
Sebelum memulai TREMFYA, beritahu penyedia layanan kesehatan Anda jika Anda:
- sedang dirawat karena infeksi
- memiliki infeksi yang tidak hilang atau yang terus kambuh
- memiliki tuberkulosis (TB) atau berhubungan dekat dengan seseorang dengan TB
- berpikir Anda memiliki infeksi atau memiliki gejala infeksi seperti:
  - seperti gejala demam atau flu
  - nyeri otot
  - batuk
  - sesak napas
  - darah di dahak Anda (lendir)
  - penurunan berat badan
  - diare atau sakit perut
  - kulit yang hangat, merah, atau menyakitkan atau luka di tubuh Anda yang berbeda dengan psoriasis
  - sensasi terbakar ketika Anda buang air kecil atau kencing lebih sering daripada biasanya

Setelah memulai TREMFYA, hubungi penyedia layanan kesehatan Anda segera jika Anda memiliki salah satu gejala infeksi yang tercantum di atas.

TREMFYA dapat menurunkan kemampuan Anda untuk melawan infeksi dan dapat meningkatkan risiko infeksi. Jangan gunakan TREMFYA jika Anda memiliki gejala infeksi kecuali Anda diperintahkan oleh penyedia layanan kesehatan Anda.

Vaksinasi:
Beritahu dokter Anda jika Anda baru saja melakukan vaksinasi atau jika Anda akan melakukan vaksinasi selama perawatan dengan TREMFYA.

Anda tidak boleh diberikan jenis vaksin tertentu (vaksin hidup) saat menggunakan TREMFYA.

Jika Anda tidak yakin apakah hal-hal di atas terjadi pada Anda, bicarakan dengan dokter, apoteker, atau perawat Anda sebelum menggunakan TREMFYA.

Reaksi alergi
Reaksi alergi yang serius, yang dapat mencakup gejala bengkak pada wajah, bibir, mulut, lidah atau tenggorokan, kesulitan menelan atau bernapas, gatal-gatal dan sesak napas, telah terjadi dengan TREMFYA. Beri tahu dokter Anda atau dapatkan bantuan medis darurat segera jika Anda merasa mengalami alergi.

Anak-anak dan remaja
TREMFYA tidak disarankan untuk anak-anak dan remaja di bawah 18 tahun karena belum diteliti dalam kelompok usia ini.

Obat-obatan lainnya dan TREMFYA
Beritahu dokter Anda tentang semua obat yang Anda gunakan, termasuk obat resep dan non-resep, vitamin, dan suplemen herbal.

Kehamilan
Efek obat ini pada wanita hamil tidak diketahui. Bicarakan dengan dokter Anda jika Anda sedang hamil, atau berpikir mungkin hamil atau berencana untuk hamil.
Sebagai bentuk kehati-hatian, disarankan untuk menghindari penggunaan TREMFYA selama kehamilan.

Kontrasepsi
Jika Anda adalah wanita yang berpotensi hamil, gunakan kontrasepsi yang memadai saat menggunakan TREMFYA dan setidaknya 12 minggu setelah dosis TREMFYA terakhir. Bicarakan dengan dokter Anda tentang pilihan kontrasepsi Anda.

Menyusui
Bicarakan dengan dokter Anda jika Anda menyusui atau berencana untuk menyusui. Anda dan dokter Anda harus memutuskan apakah Anda akan menyusui saat menggunakan TREMFYA.

3. Bagaimana TREMFYA digunakan

Selalu gunakan obat ini sama seperti yang dikatakan oleh dokter atau perawat Anda. Tanyakan kepada dokter, perawat, atau apoteker Anda jika Anda tidak yakin.

TREMFYA diberikan dengan suntikan di bawah kulit Anda (injeksi subkutan). Anda dan dokter atau perawat Anda harus memutuskan apakah Anda harus menyuntikkan TREMFYA sendiri.

Hal yang penting untuk tidak mencoba menyuntik diri sendiri sampai Anda telah dilatih oleh dokter atau perawat Anda. Perawat Anda juga dapat memberi Anda injeksi TREMFYA setelah mendapatkan pelatihan yang tepat.

Sebelum digunakan, keluarkan karton dari kulkas dan simpan jarum suntik yang sudah terisi (*pre-filled syringe*) di bagian dalam karton dan biarkan mencapai suhu kamar dengan menunggu selama 30 menit. Baca "Petunjuk Penggunaan" untuk jarum suntik dengan hati-hati sebelum menggunakan TREMFYA.

Berapa banyak TREMFYA diberikan dan untuk berapa lama

Dokter Anda akan memutuskan berapa banyak TREMFYA yang Anda butuhkan dan untuk berapa lama.

Untuk psoriasis tipe plak:

- Dosis pertama adalah 100 mg (isi dari 1 *pre-filled syringe*) secara injeksi subkutan. Ini mungkin diberikan oleh dokter atau perawat Anda.
- Setelah dosis pertama, Anda akan diberikan dosis berikutnya 4 minggu kemudian, dan kemudian setiap 8 minggu. Dosis yang digunakan adalah sama dengan dosis pertama, 100mg.

Untuk psoriatis artritis:

- Dosis awal diberikan 100 mg (isi dari 1 *pre-filled syringe*) melalui injeksi subkutan oleh dokter atau perawat Anda.
- Setelah dosis awal, Anda akan diberikan dosis berikutnya 4 minggu kemudian, lalu diikuti setiap 8 minggu atau setiap 4 minggu.

Jika Anda menggunakan TREMFYA lebih dari yang seharusnya
Jika Anda menerima TREMFYA lebih dari yang seharusnya atau dosis yang diberikan lebih cepat dari yang ditentukan, beri tahu dokter Anda.

Jika Anda lupa menggunakan TREMFYA
Jika Anda lupa menggunakan dosis TREMFYA Anda, suntikkan dosis segera saat Anda ingat. Kemudian, ambillah dosis berikutnya pada waktu rutin Anda yang dijadwalkan. Jika Anda tidak yakin apa yang harus lakukan, hubungi dokter Anda.

Jika Anda berhenti menggunakan TREMFYA
Anda tidak dianjurkan untuk berhenti menggunakan TREMFYA tanpa berbicara dengan dokter Anda terlebih dahulu. Jika Anda menghentikan pengobatan, gejala Anda dapat kembali.

4. Apa Efek samping yang mungkin terjadi selama menggunakan TREMFYA

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping:
- infeksi pada hidung, sinus atau tenggorokan (*common cold*), infeksi pada paru dan saluran napas bawah
- infeksi pada lambung dan usus (gastroenteritis)
- infeksi jamur pada kulit, misalnya antara jari-jari kaki (kaki atlet)
- infeksi herpes simpleks, misalnya bibir (cold sores) atau alat kelamin (herpes alat kelamin)
- sakit kepala
- diare
- nyeri sendi
- kemerahan, nyeri dan iritasi di tempat suntikan
- reaksi alergi
- ruam kulit
- gatal-gatal
- penurunan jumlah sel darah putih yang dinamakan neutrofil
- peningkatan kadar enzim hati dalam darah

Efek samping diatas tidak mencakup semua efek samping yang berkaitan dengan TREMFYA. Beritahu dokter Anda mengenai efek samping yang mengganggu Anda atau yang tidak hilang.

Informasi umum mengenai TREMFYA
Obat-obatan kadang-kadang diresepkan untuk tujuan yang tidak disebutkan dalam lembar informasi pasien. Jangan gunakan TREMFYA pada kondisi yang tidak diresepkan.

5. Bagaimana cara menyimpan TREMFYA

Jika Anda menggunakan TREMFYA di rumah, penting untuk menyimpan produk ini di lemari es Anda meskipun tidak di dalam *freezer*. TREMFYA tidak boleh dibekukan. Simpan produk dalam kardus asli untuk melindunginya dari cahaya hingga waktu penggunaan.

Apa saja kandungan TREMFYA?
Zat aktifnya adalah guselkumab.

TREMFYA 100 mg untuk injeksi subkutan (di bawah kulit). Bahan kandungan lainnya termasuk: L histidin, L-histidin monohidroklorida monohidrat, polisorbat 80 dan sukrosa. Tidak ada pengawet didalamnya.

6. Isi kemasan dan informasi lainnya

Larutan TREMFYA 100 mg untuk injeksi subkutan adalah larutan yang jernih, tidak berwarna hingga kuning muda dan mengandung partikel protein yang jernih atau putih. Bentuk ini bukanlah bentuk yang tidak biasa untuk larutan yang mengandung protein.

TREMFYA tidak boleh digunakan:
- setelah tanggal kedaluwarsa pada label;
- jika segel rusak;
- jika cairan berubah warna, keruh atau Anda dapat melihat partikel lain mengambang di dalamnya.

Selalu jauhkan obat dari jangkauan anak-anak.

Cara Membuang TREMFYA
Jarum suntik bekas harus ditempatkan dalam wadah yang tahan tusukan, seperti wadah untuk benda tajam. Buang wadah benda tajam Anda sesuai dengan peraturan di negara Anda. Tisu antiseptik, dan persediaan lainnya dapat ditempatkan di tempat sampah biasa Anda. Jarum suntik, tidak boleh digunakan kembali. Buang bagian TREMFYA yang tidak digunakan.

Lembar informasi ini merangkum informasi paling penting tentang TREMFYA. Anda dapat meminta penyedia layanan kesehatan Anda untuk informasi tentang TREMFYA yang ditulis untuk tenaga kesehatan profesional.

Dus, 1 pre-filled syringe @ 1ml

No. Reg: DKI2160001843A1

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

Diproduksi oleh
Cilag AG, Schaffhausen, Switzerland.

Didaftarkan oleh:
PT Integrated Healthcare Indonesia, Jakarta – Indonesia

Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935

Based on CPPI Sep 2019 + Nov 2019 + indikasi PsA _IHI_JJID removal