PRODUCT NAME
TREMFYA® (guselkumab)

DOSAGE FORM AND STRENGTHS
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.

TREMFYA® is available as a solution for injection in the following presentation:

Pre-filled syringe
Each 100 mg pre-filled syringe contains 100 mg of guselkumab per 1 mL.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
TREMFYA® is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

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.

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.

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 *Pharmacodynamic Properties*).

Elderly (65 years of age and older)

Of the 2177 plaque psoriasis subjects exposed to TREMFYA® in Phase 2 and Phase 3 clinical trials, a total of 111 subjects were 65 years or older, and 9 subjects 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. In clinical trials, infections occurred in 23% of subjects in the TREMFYA® group versus 21% of subjects in the placebo group through 16 weeks of treatment. The rate of serious infections for the TREMFYA® group and the placebo group were ≤ 0.2%. Treatment with TREMFYA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

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

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*).

TREMFYA® should be used during pregnancy only if clearly needed.

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 TREMFYA® based on the comprehensive assessment of the available adverse event information. A causal relationship with TREMFYA® 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

The safety profile of TREMFYA® in subjects with moderate to severe plaque psoriasis is based on data from the Phase 2 (PSO2001) and Phase 3 (VOYAGE 1, VOYAGE 2 and NAVIGATE) studies. Of the 2177 TREMFYA® treated subjects, 1748 subjects were exposed for at least 1 year, and 1516 and 692 subjects were exposed for at least 2 and 3 years, respectively. Most subjects (n=2012) received a dosage regimen of 100 mg TREMFYA® as subcutaneous injection every 8 weeks.

Adverse Reactions

Adverse reactions to TREMFYA® are presented in Table 1. The frequency of adverse reactions reflects treatment with TREMFYA® 100 mg administered subcutaneously in 823 subjects with moderate to severe plaque psoriasis in the 16-week, placebo-controlled period of VOYAGE 1 and VOYAGE 2. 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 1: Summary of Adverse Reactions in Clinical Studies

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

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®.

Infections
Infections occurred in 23% of the TREMFYA® group compared to 21% of the placebo group. The most common (≥ 1%) infections were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of TREMFYA®.

Elevated Liver Enzymes
Elevated liver enzymes were reported more frequently in the TREMFYA® group (2.6%) than in the placebo group (1.9%). Of the 21 subjects who were reported to have elevated liver enzymes in the TREMFYA® group, all events except one were mild to moderate in severity and none of the events led to discontinuation of TREMFYA®.

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. 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®. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

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.

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 2). 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 2: 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 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. These results are consistent with the clinical benefit observed with guselkumab treatment in plaque psoriasis.

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 and NAVIGATE) 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, regional disease (scalp, hand and foot, and nails) 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 Scalp-specific Investigator Global Assessment (ss-IGA), is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed based on a 5 point scale in terms of clinical signs of redness, thickness, and scaliness with 0 indicating absence of disease and a score of 4 representing severe disease.
- Physician's Global Assessment of Hands and/or Feet (hf-PGA), assesses the severity of hand and foot psoriasis. The plaques are scored on a 5-point scale with a score of 0 indicating clear to 4 being severe.
- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of fingernail involvement. The scale consists of 4 components of nail matrix disease and 4 components of nail bed disease with scores from 0 to 8, with a lower score representing milder disease. Fingernail Physician's Global Assessment (f-PGA), is also a physician assessed score that is used to evaluate fingernail psoriasis on a scale of 0 to 4 with 4 indicating severe disease.
- 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® 100mg 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 3). The majority of subjects were male and white. The mean age was approximately 44 years, and mean weight was approximately 90 kg.

Table 3: 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 4).

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 4).

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 4: 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 156.

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

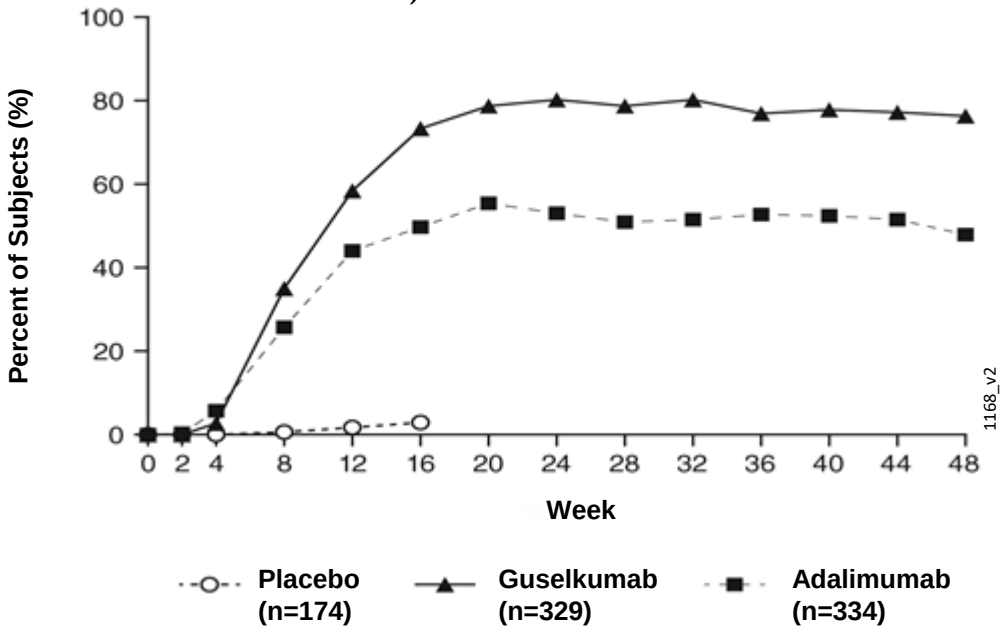
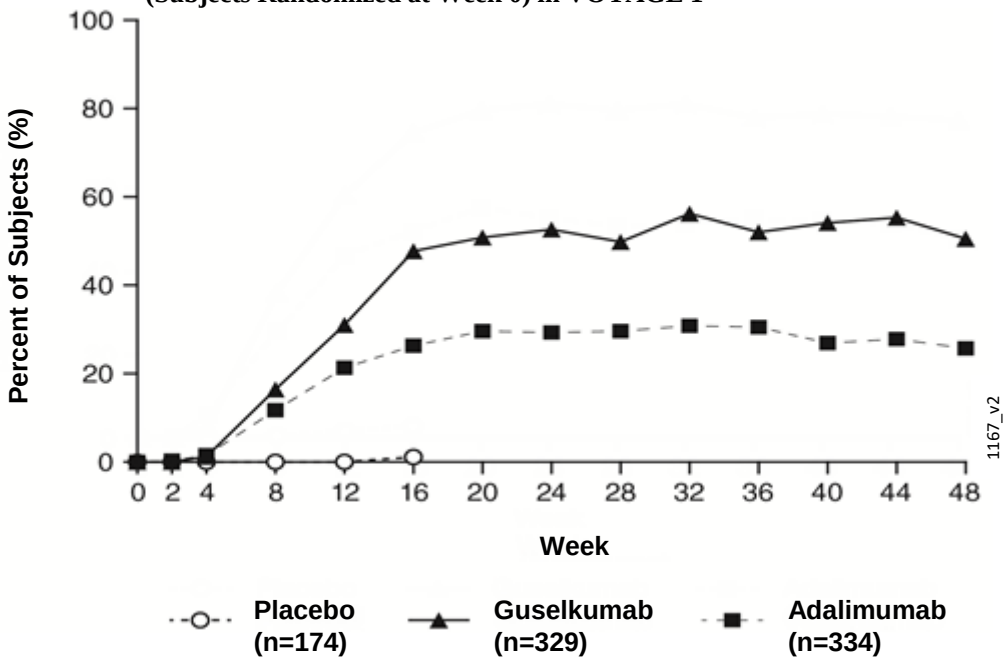


Figure 2: Percent of Subjects Who Achieved an IGA Score of Cleared (0) Through Week 48 by Visit (Subjects Randomized at Week 0) in VOYAGE 1



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.

Analyses related to regional psoriasis disease
Significant improvements were seen in psoriasis involving the scalp, hands and feet, and nails in subjects randomized to TREMFYA® compared to placebo at Week 16. TREMFYA® demonstrated superiority compared to adalimumab for treatment of psoriasis involving the scalp, or hands and feet at Week 24 (VOYAGE 1 and VOYAGE 2) and Week 48 (VOYAGE 1) ($p \leq 0.001$ for all comparisons, except $p<0.05$ for hf-PGA 0/1 and f-PGA 0/1 at Week 48 in VOYAGE 1, and for hf-PGA 0/1 at Week 24 in VOYAGE 2).

Table 5: Summary of Regional Psoriasis Responses in VOYAGE 1 and VOYAGE 2

	VOYAGE 1			VOYAGE 2		
	Placebo	TREMFYA®	Adalimumab	Placebo	TREMFYA®	Adalimumab
Scalp-Specific Investigator Global Assessment (ss-IGA) (N)[a]	145	277	286	202	408	194
ss-IGA 0[b,c], n (%)						
Week 16	11 (7.6%)	191 (69.0%)	155 (54.2%)	18 (8.9%)	256 (62.7%)	102 (52.6%)
Week 24	NA	193 (69.7%)	161 (56.3%)	NA	286 (70.1%)	109 (56.2%)
Week 48	NA	181 (65.3%)	146 (51.0%)	NA	NA	NA
ss-IGA 0/1[b], n (%)						
Week 16	21 (14.5%)	231 (83.4%)[d]	201 (70.3%)[e]	22 (10.9%)	329 (80.6%)[d]	130 (67.0%)[e]
Week 24	NA	234 (84.5%)	198 (69.2%)[g]	NA	348 (85.3%)	131 (67.5%)[g]
Week 48	NA	217 (78.3%)	173 (60.5%)[g]	NA	NA	NA
Physician's Global Assessment of Hands and/or Feet (hf-PGA) (N)[a]	43	90	95	63	114	56
hf-PGA 0[b,c], n (%)						
Week 16	4 (9.3%)	57 (63.3%)	41 (43.2%)	8 (12.7%)	74 (64.9%)	29 (51.8%)
Week 24	NA	67 (74.4%)	47 (49.5%)	NA	86 (75.4%)	29 (51.8%)
Week 48	NA	64 (71.1%)	51 (53.7%)	NA	NA	NA
hf-PGA 0/1[b], n (%)						

Week 16	6 (14.0%)	66 (73.3%)[f]	53 (55.8%)[e]	9 (14.3%)	88 (77.2%)[f]	40 (71.4%)[e]
Week 24	NA	71 (78.9%)	54 (56.8%)[g]	NA	93 (81.6%)	37 (66.1%)[h]
Week 48	NA	68 (75.6%)	59 (62.1%)[h]	NA	NA	NA
Fingernail Physician's Global Assessment (f-PGA) (N)[a]	88	174	173	123	246	124
f-PGA 0[c], n (%)						
Week 16	2 (2.3%)	16 (9.2%)	32 (18.5%)	6 (4.9%)	36 (14.6%)	24 (19.4%)
Week 24	NA	42 (24.1%)	45 (26.0%)	NA	73 (29.7%)	38 (30.6%)
Week 48	NA	74 (42.5%)	73 (42.2%)	NA	NA	NA
f-PGA 0/1, n (%)						
Week 16	14 (15.9%)	68 (39.1%)[f]	88 (50.9%)[e]	18 (14.6%)	128 (52.0%)[f]	74 (59.7%)[e]
Week 24	NA	98 (56.3%)	108 (62.4%)[i]	NA	154 (62.6%)	83 (66.9%)[i]
Week 48	NA	130 (74.7%)	107 (61.8%)[h]	NA	NA	NA
Nail Psoriasis Area and Severity Index (NAPSI)[a] (N)	99	194	191	140	280	140
Percent Improvement, Mean (SD)						
Week 16	-0.9 (57.9)	34.4 (42.4)[f]	38.0 (53.9)[e]	1.8 (53.8)	39.6 (45.6)[f]	46.9 (48.1)[e]
Week 24	NA	49.8 (44.2)	49.4 (60.0)[i]	NA	55.0 (46.8)	53.7 (49.5)[i]
Week 48	NA	68.1 (43.0)	61.4 (49.2)[i]	NA	NA	NA

NA=not applicable

[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] no formal comparisons were performed between any treatment groups for this endpoint.

[d] $p < 0.001$ for comparison between TREMFYA® and placebo for the major secondary endpoint.

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

[f] $p \leq 0.001$ for comparison between TREMFYA® and placebo.

[g] $p \leq 0.001$ for comparison between TREMFYA® and adalimumab.

[h] $p < 0.05$ for comparison between TREMFYA® and adalimumab.

[i] p = not significant for comparison between TREMFYA® and adalimumab.

Scalp psoriasis

At Week 16, in subjects with a baseline ss-IGA score ≥ 2, 83.4% and 80.6% in the TREMFYA® group in VOYAGE 1 and VOYAGE 2, respectively, achieved a ss-IGA score of 0/1 and at least a 2-grade improvement from baseline compared to 14.5% and 10.9% in the placebo group, respectively ($p < 0.001$ for all comparisons).

Additionally, at Week 24, 84.5% and 85.3% in the TREMFYA® group in VOYAGE 1 and VOYAGE 2, respectively, achieved a ss-IGA score of 0/1 and at least a 2-grade improvement from baseline compared to 69.2% and 67.5% in the adalimumab group, respectively ($p < 0.001$ for all comparisons). At Week 48, this outcome was achieved in 78.3% of TREMFYA® subjects compared to 60.5% of adalimumab subjects in VOYAGE 1 ($p < 0.001$).

Hand/foot psoriasis

At Week 16, in subjects with a baseline hf-PGA score ≥ 2, 73.3% and 77.2% in the TREMFYA® group in VOYAGE 1 and VOYAGE 2, respectively, achieved a hf-PGA score of 0/1 and at least

a 2-grade improvement from baseline compared to 14.0% and 14.3% in the placebo group, respectively ($p < 0.001$ for all comparisons).

Additionally, at Week 24, 78.9% and 81.6% in the TREMFYA® group in VOYAGE 1 and VOYAGE 2, respectively, achieved a hf-PGA score of 0/1 and at least a 2-grade improvement from baseline compared with 56.8% and 66.1% in the adalimumab group, respectively ($p = 0.001$ for VOYAGE 1; $p<0.05$ for VOYAGE 2). At Week 48, this outcome was achieved in 75.6% of TREMFYA® subjects compared to 62.1% of adalimumab subjects in VOYAGE 1 ($p<0.05$).

Nail psoriasis

At Week 16, in subjects with a baseline f-PGA score ≥ 2, 39.1% and 52.0% in the TREMFYA® group in VOYAGE 1 and VOYAGE 2, respectively, achieved a f-PGA score of 0/1 compared to 15.9% and 14.6% in the placebo group, respectively ($p < 0.001$ for all comparisons). In subjects with a baseline NAPSI score > 0, the median percent improvement in NAPSI is 33.3 and 50.0 in VOYAGE 1 and VOYAGE 2, respectively, for the TREMFYA® group and 0 for both studies for the placebo group ($p < 0.001$ for all comparisons).

At Week 48, a significantly higher proportion of subjects (74.7%) treated with TREMFYA® achieved a f-PGA score of 0/1 compared to subjects (61.8%) randomized to adalimumab in VOYAGE 1 ($p<0.05$).

No significant differences were seen in f-PGA at Week 24 and in NAPSI at Weeks 24 and 48 in subjects randomized to TREMFYA® compared to adalimumab.

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 and 156. 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 6). 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 6).

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 156.

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 6).

In VOYAGE 1, for subjects receiving continuous TREMFYA® treatment, improvements in DLQI scores were maintained from Week 52 through Week 156.

Table 6: 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%)[d]
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 156 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 156 among subjects randomized to TREMFYA® maintenance therapy.

Table 7: 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] $p \leq 0.001$ 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 156 among subjects randomized to maintenance therapy.

Table 8: 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] $p \leq 0.001$ for 100 mg TREMFYA® compared with placebo.
[b] $p = < 0.05$

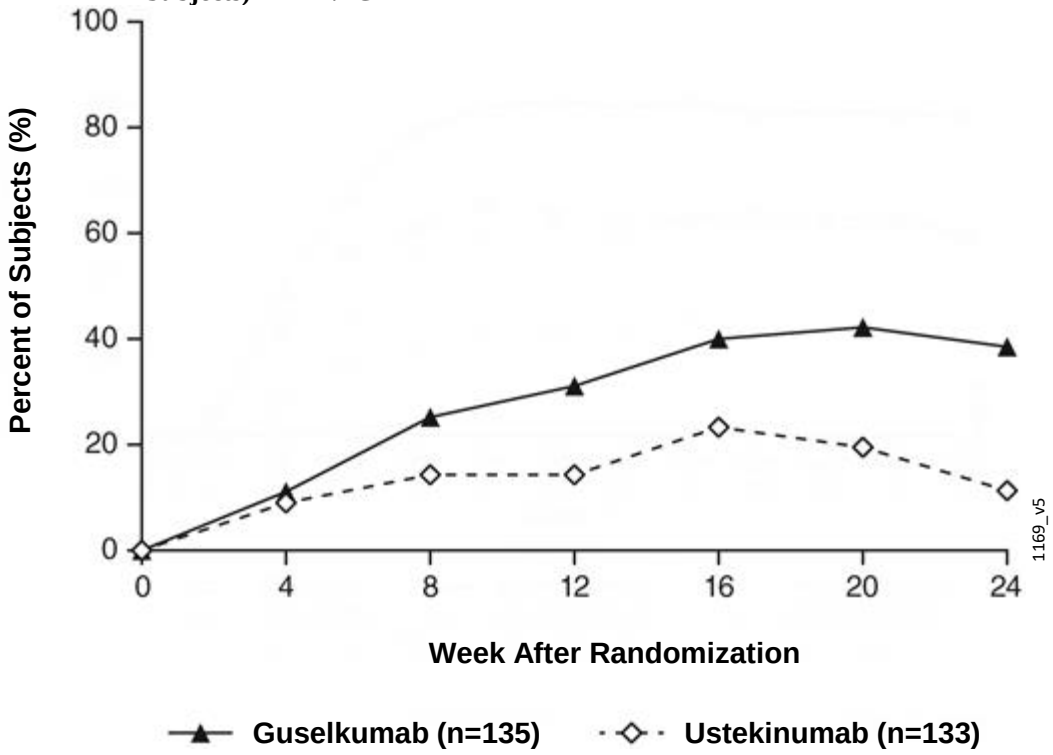
Active-controlled study in ustekinumab inadequate responder – NAVIGATE

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

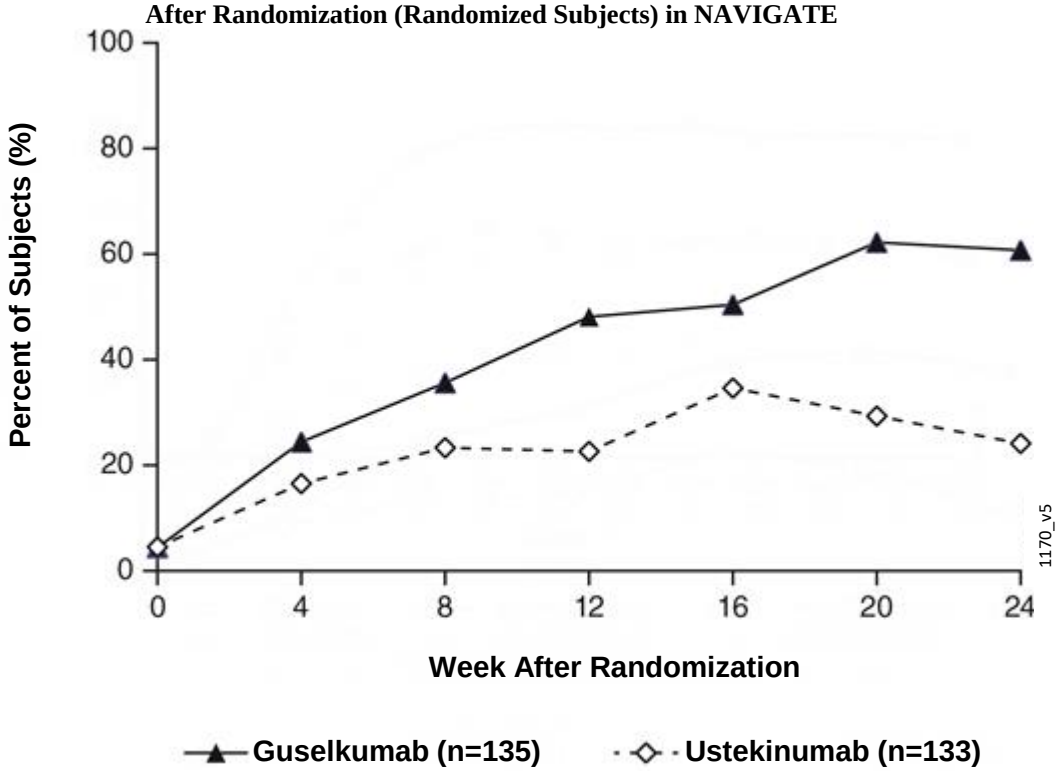
ustekinumab treated subjects were noted as early as 4 weeks after randomization and reached a maximum 24 weeks after randomization (see Figure 3).

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



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 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 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 (ibuprofen, paracetamol, acetylsalicylic acid, and isoniazid), 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® and included in the population pharmacokinetic 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.

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 Keyhole Limpet Hemocyanin (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 100mg 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

Refer to expiry date on the outer pack.

Storage Conditions

- Store in a refrigerator between 2ºC to 8ºC.
- 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 in 1.0 mL syringe volume)

TREMFYA® is available in the following packaging presentation:

- 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.

BATCH RELEASER

Cilag AG
Hochstrasse 201
8200 Schaffhausen
Switzerland

PRODUCT REGISTRANT

Johnson & Johnson International (Singapore) Pte. Ltd.
2 Science Park Drive
#07-13, Ascent
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