

เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

TREMFYA®

TREMFYA® IV

FULL PRESCRIBING INFORMATION

1. Name of the Medicinal Product

1.1 Product Name

TREMFYA and TREMFYA IV

1.2 Strength

Subcutaneous Injection

- TREMFYA 100 mg solution for injection in pre-filled syringe.
- TREMFYA 100 mg solution for injection in One-Press.
- TREMFYA 200 mg solution for injection in pre-filled syringe.
- TREMFYA 200 mg PushPen solution for injection in pre-filled pen

Intravenous Infusion

- TREMFYA IV 200 mg/20mL (10 mg/mL) solution in a single-dose vial.

1.3 Pharmaceutical Dosage Form

Solution for injection

TREMFYA is a clear and colorless to light yellow solution that may contain small translucent particles.

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

Guselkumab, an interleukin-23 antagonist, is a human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody. Guselkumab is produced in a mammalian cell line using recombinant DNA technology and has an approximate molecular weight of approximately 147 kDa.

TREMFYA (guselkumab) injection is a sterile, preservative free, clear, and colorless to light yellow solution.

2.2 Quantitative Declaration

TREMFYA 100 mg solution for injection in pre-filled syringe

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

TREMFYA 100 mg solution for injection in One-Press

Each One-Press contains 100 mg of guselkumab in 1 mL solution.

TREMFYA 200 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 200 mg of guselkumab in 2 mL solution.

TREMFYA 200 mg PushPen solution for injection in pre-filled pen

Each pre-filled pen contains 200 mg of guselkumab in 2 mL solution.

TREMFYA IV 200 mg solution for injection in a single-dose vial.

Each vial contains 200 mg of guselkumab in 20 mL solution.

3. Pharmaceutical Form

Solution for injection

4. Clinical Particulars

4.1 Therapeutic indication

4.1.1 Plaque Psoriasis

TREMFYA is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

4.1.2 Psoriatic Arthritis

TREMFYA is indicated for the treatment of adult patients with active psoriatic arthritis.

4.1.3 Ulcerative Colitis

TREMFYA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

4.1.4 Crohn's Disease

TREMFYA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.

4.1.5 Palmoplantar pustulosis

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

4.2 Posology and Method of Administration

4.2.1 Recommended Evaluations and Immunizations Prior to Treatment

Initiation

- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TREMFYA [see *Special Warning and Precautions for Use (4.4.3)*].
- For the treatment of Crohn's disease or ulcerative colitis, obtain liver enzymes and bilirubin levels prior to initiating treatment with TREMFYA [see *Special Warning and Precautions for Use (4.4.4)*].
- Complete all age-appropriate vaccinations according to current immunization guidelines [see *Special Warning and Precautions for Use (4.4.5)*].

4.2.2 Recommended Dosage for Plaque Psoriasis

TREMFYA is administered by subcutaneous injection. The recommended dosage is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

4.2.3 Recommended Dosage for Psoriatic Arthritis

TREMFYA is administered by subcutaneous injection. The recommended dosage is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.

TREMFYA may be administered alone or in combination with a conventional disease-modifying antirheumatic drug (e.g., methotrexate).

4.2.4 Recommended Dosage for Ulcerative Colitis

Induction:

The recommended induction dosage of TREMFYA is 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8 [see *Posology and Method of Administration(4.2.6)*].

Maintenance:

The recommended maintenance dosage of TREMFYA is:

- 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or
- 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter.

Use the lowest effective recommended dosage to maintain therapeutic response.

4.2.5 Recommended Dosage for Crohn's Disease

Induction:

The recommended induction dosage of TREMFYA is:

- 200 mg administered by intravenous infusion over at least one hour at Week 0, Week 4, and Week 8 or
- 400 mg administered by subcutaneous injection (given as two consecutive injections of 200 mg each) at Week 0, Week 4, and Week 8.

Maintenance:

The recommended maintenance dosage of TREMFYA is:

- 100 mg administered by subcutaneous injection at Week 16, and every 8 weeks thereafter, or
- 200 mg administered by subcutaneous injection at Week 12, and every 4 weeks thereafter.

Use the lowest effective recommended dosage to maintain therapeutic response.

4.2.6 Preparation and Administration Instructions for Subcutaneous Injection

TREMFYA is available for subcutaneous use in the following presentations: prefilled pen, One-Press, and prefilled syringes [see *Strength (1.2) and Nature and contents of container (6.5)*].

- Administer TREMFYA subcutaneously. Each prefilled pen, One-Press, or prefilled syringe is for one time use in one patient only. Instruct patients to inject the full amount: 100 mg or 200 mg of TREMFYA (1 mL or 2 mL, respectively).
- TREMFYA is intended for use under the guidance and supervision of a healthcare professional. TREMFYA may be administered by a healthcare professional, or a patient/caregiver after proper training on correct subcutaneous injection technique.
- Before injection, remove TREMFYA from the refrigerator and allow to reach room temperature (30 minutes) without removing the needle cap.
- Inject into the front of the thighs, the lower abdomen except for the 2 inches around the navel, or the back of the upper arms (healthcare professional or caregiver only).
- Do not inject TREMFYA into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis [see *Instructions for Use*].
- The TREMFYA *Instructions for Use* contains more detailed patient instructions on the preparation and administration of TREMFYA [see *Instructions for Use*].
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.
- Inspect TREMFYA visually for particulate matter and discoloration prior to administration. TREMFYA is a clear and colorless to light yellow solution that may contain small translucent particles. Do not use if the liquid contains large particles, is discolored or cloudy. TREMFYA does not contain preservatives; therefore, discard any unused product remaining in the prefilled pen, One-Press, or prefilled syringe.

4.2.7 Preparation and Administration Instructions for Intravenous Infusion (Ulcerative Colitis and Crohn's Disease)

Preparation Instructions:

1. Withdraw and then discard 20 mL of the 0.9% Sodium Chloride Injection from the 250 mL infusion bag which is equal to the volume of TREMFYA to be added.
2. Withdraw 20 mL of TREMFYA from the vial and add it to the 250 mL intravenous infusion bag of 0.9% Sodium Chloride Injection for a final concentration of 0.8 mg/mL. Gently mix the diluted solution. Discard the vial with any remaining solution.
3. Visually inspect the diluted solution for particulate matter and discoloration before infusion. Infuse the diluted solution over a period of at least one hour.
4. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein binding filter (pore size 0.2 micrometer).
5. Do not infuse TREMFYA concomitantly in the same intravenous line with other medicinal products.
6. Dispose any unused medicinal product in accordance with local requirements.

Administration Instructions:

- TREMFYA solution for intravenous infusion must be diluted, prepared, and infused by a healthcare professional using aseptic technique. TREMFYA does not contain preservatives. Each vial is for one time use in one patient only.
- Inspect TREMFYA visually for particulate matter and discoloration prior to administration. TREMFYA is a clear and colorless to light yellow solution that may contain small translucent particles. Do not use if the liquid contains large particles, is discolored, or is cloudy.

Storage of Diluted Solution:

- The diluted infusion solution may be kept at room temperature up to 25°C (77°F) for up to 10 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 10 hours after the dilution in the infusion bag.
- Do not freeze.
- Discard any unused portion of the infusion solution.

4.2.8 Palmoplantar pustulosis

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

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

4.2.9 Pediatric Use

The safety and efficacy of TREMFYA in pediatric patients (less than 18 years of age) have not been established.

4.2.10 Geriatric Use

Of the 5392 subjects with plaque psoriasis, psoriatic arthritis, ulcerative colitis, or Crohn's disease exposed to TREMFYA, a total of 285 subjects were 65 years or older, and 28 subjects were 75 years or older. Clinical studies of TREMFYA, within each indication, did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

No clinically meaningful differences in the pharmacokinetics of guselkumab were observed based on age [*see Pharmacokinetic Properties (5.2)*].

4.3 Contraindication

TREMFYA is contraindicated in patients with a history of serious hypersensitivity reaction to guselkumab or to any of the excipients [*see Special Warning and Precautions for Use (4.4.1)*].

4.4 Special Warning and Precautions for Use

4.4.1 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with post market use of TREMFYA. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, discontinue TREMFYA and initiate appropriate therapy.

4.4.2 Infections

TREMFYA may increase the risk of infection [*see Undesirable Effects (4.8.1)*].

In placebo-controlled clinical trials of up to 48 weeks in subjects with ulcerative colitis and Crohn's disease, serious infections occurred in $\leq 2\%$ of subjects who received TREMFYA. In the 16-week placebo-controlled trials in subjects with plaque psoriasis, the rate of serious infections for the TREMFYA group and the placebo group was $\leq 0.2\%$. A similar rate of serious infections was seen in placebo-controlled trials in subjects with psoriatic arthritis. The overall rates of infections were similar between subjects in the TREMFYA groups and subjects in the placebo groups in clinical trials for all indicated populations [*see Undesirable Effects (4.8.1)*].

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 to seek medical help 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.

4.4.3 Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating TREMFYA treatment. Do not administer TREMFYA to patients with active TB infection. Initiate treatment of latent TB prior to administering TREMFYA. 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. Monitor all patients for signs and symptoms of active TB during and after TREMFYA treatment.

In clinical trials, 105 subjects with plaque psoriasis, 71 subjects with psoriatic arthritis, 43 subjects with ulcerative colitis, and 36 subjects with Crohn's disease with latent TB who were concurrently treated with TREMFYA, and appropriate TB prophylaxis did not develop active TB. In clinical trials of TREMFYA in subjects with Crohn's disease, active TB was reported in 2 subjects during treatment with TREMFYA [*see Undesirable Effects (4.8)*].

4.4.4 Hepatotoxicity

A serious adverse reaction of drug-induced liver injury was reported in a clinical trial subject with Crohn's disease following three doses of a higher than the recommended induction regimen. This subject had peak alanine aminotransferase (ALT) of 18x the upper limit of normal (ULN), aspartate aminotransferase (AST) of 11x ULN, and total bilirubin of 2.4x ULN. TREMFYA was subsequently discontinued, and the liver test abnormalities resolved following administration of corticosteroids [*see Undesirable Effects (4.8.1)*].

In patients with ulcerative colitis or Crohn's disease, evaluate liver enzymes and bilirubin at baseline, for at least 16 weeks of treatment, and periodically thereafter according to routine patient management.

In patients with plaque psoriasis or psoriatic arthritis, if clinically indicated, evaluate liver enzymes and bilirubin at baseline, and periodically thereafter according to routine patient management.

Consider other treatment options in patients with evidence of acute liver disease or cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

4.4.5 Immunizations

Avoid use of live vaccines in patients treated with TREMFYA. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with TREMFYA, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

4.4.6 Palmoplantar pustulosis

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

4.5.1 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , interferon) during chronic inflammation.

Results from an exploratory drug-drug interaction trial in subjects with moderate-to-severe plaque psoriasis suggested a low potential for clinically relevant drug interactions for drugs metabolized by CYP3A4, CYP2C9, CYP2C19 and CYP1A2 but the interaction potential cannot be ruled out for drugs metabolized by CYP2D6. However, the results were highly variable because of the limited number of subjects in the trial.

Upon initiation of TREMFYA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed [*see Pharmacokinetic Properties (5.2)*].

4.6 Pregnancy and lactation

4.6.1 Pregnancy

Risk Summary

Available data from literature, post-marketing reports, and ongoing pregnancy registry with TREMFYA use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Monoclonal antibodies are actively transported across the placenta [*see Clinical Studies*].

In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of guselkumab during organogenesis through parturition at doses up to 18 times the exposure (AUC) in humans administered 200 mg intravenously and 16 times the exposure (AUC) to the 400 mg dose given subcutaneously. Neonatal deaths in monkeys were observed at 4 to 18 times the exposure (AUC) in humans administered 200 mg intravenously and 4 to 16 times the exposure (AUC) to the 400 mg dose given subcutaneously (see Data). The clinical significance of these nonclinical findings is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses and peaks during the third trimester. Therefore, TREMFYA may be present in infants exposed *in utero*. The potential clinical impact of guselkumab exposure in infants exposed *in utero* should be considered.

Data

Animal Data

In a combined embryofetal development and pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of guselkumab from the beginning of organogenesis to parturition at a dose (50 mg/kg) resulting in exposures (AUC) 18 times the exposure in humans administered 200 mg intravenously and 16 times the human exposure at 400 mg given subcutaneously. Neonatal deaths occurred in the offspring of one control monkey, three monkeys administered guselkumab at 10 mg/kg/week (4 times the exposure (AUC) in humans administered 200 mg intravenously or 400 mg given subcutaneously) and three monkeys administered guselkumab at 50 mg/kg/week (18 times the exposure (AUC) in humans administered 200 mg intravenously and 16 times the exposure (AUC) following a 400 mg subcutaneous dose). The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

4.6.2 Lactation

Risk Summary

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. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. The effects of local gastrointestinal exposure and the extent of systemic exposure in the breastfed infant to guselkumab are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TREMFYA and any potential adverse effects on the breastfed infant from TREMFYA or from the underlying maternal condition.

4.7 Effect on Ability to Drive and Use Machine

No studies on the effects on the ability to drive and use machines have been performed with TREMFYA.

4.8 Undesirable Effects

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Hypersensitivity Reactions [*see Contraindication (4.3) and Special Warning and Precautions for Use (4.4.1)*]
- Infections [*see Special Warning and Precautions for Use (4.4.2)*]
- Tuberculosis [*see Special Warning and Precautions for Use (4.4.3)*]

- Hepatotoxicity [see *Special Warning and Precautions for Use (4.4.4)*]

4.8.1 Clinical Trials Experience

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 practice.

Adverse Reactions in Adults with Plaque Psoriasis

In clinical trials, a total of 1823 adult subjects with moderate-to-severe plaque psoriasis received TREMFYA. Of these, 1393 subjects were exposed to TREMFYA for at least 6 months and 728 subjects were exposed for at least 1 year.

Data from two placebo- and active-controlled trials (PsO1 and PsO2) in 1441 subjects (mean age 44 years; 70% males; 82% white) were pooled to evaluate the safety of TREMFYA (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 8 weeks).

Weeks 0 to 16:

In the 16-week placebo-controlled period of the pooled clinical trials (PsO1 and PsO2), adverse events occurred in 49% of subjects in the TREMFYA group compared to 47% of subjects in the placebo group and 49% of subjects in the U.S. licensed adalimumab group. Serious adverse events occurred in 1.9% of subjects in the TREMFYA group (6.3 events per 100 patient-years of follow-up) compared to 1.4% of subjects in the placebo group (4.7 events per 100 patient-years of follow-up), and in 2.6% of subjects in U.S. licensed adalimumab group (9.9 events per 100 patient-years of follow-up).

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA group than in the placebo group during the 16-week placebo-controlled period.

Table 1: Adverse Reactions Occurring in $\geq 1\%$ of Adult Subjects with Moderate-to-Severe Plaque Psoriasis through Week 16 in Trials PsO1 and PsO2

	TREMFYA^a 100 mg N=823 n (%)	Adalimumab^b N=196 n (%)	Placebo N=422 n (%)
Upper respiratory infections ^c	118 (14.3)	21 (10.7)	54 (12.8)
Headache ^d	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions ^e	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis ^f	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections ^g	9 (1.1)	0	0
Herpes simplex infections ^h	9 (1.1)	0	2 (0.5)

^a Subjects receiving 100 mg of TREMFYA at Week 0, Week 4, and every 8 weeks thereafter

^b U.S. licensed adalimumab

^c Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.

^d Headache includes headache and tension headache.

^e Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.

^f Gastroenteritis includes gastroenteritis and viral gastroenteritis.

^g Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.

^h Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the TREMFYA group and at a higher rate than in the placebo group through Week 16 in trials PsO1 and PsO2 were migraine, candida infections, and urticaria.

Specific Adverse Reactions

- *Infections*

Infections occurred in 23% of subjects in the TREMFYA group compared to 21% of subjects in the placebo group through 16 weeks of treatment.

The most common ($\geq 1\%$) infections that occurred more frequently in the TREMFYA group than in the placebo group 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. The rate of serious infections for the TREMFYA group and the placebo group was $\leq 0.2\%$.

- *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.

- *Safety through Week 48*

Through Week 48, no new adverse reactions were identified with TREMFYA use and the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment.

Adverse Reactions in Pediatric Subjects with Plaque Psoriasis

The safety of TREMFYA was studied in one placebo- and active-controlled clinical trial (PsO5) that included 120 pediatric subjects 6 years of age and older with moderate-to-severe plaque psoriasis [see *Clinical Studies*]. The safety profile observed in pediatric subjects 6 years of age and older treated with TREMFYA up to 52 weeks was consistent with the safety profile observed in adult subjects with moderate-to-severe plaque psoriasis.

Adverse Reactions in Adults with Psoriatic Arthritis

TREMFYA was studied in two placebo-controlled trials in adult subjects with psoriatic arthritis (748 subjects on TREMFYA and 372 subjects on placebo). Of the 748 subjects who received TREMFYA, 375 subjects received TREMFYA 100 mg at Week 0, Week 4, and every 8 weeks thereafter and 373 subjects received TREMFYA 100 mg every 4 weeks. The overall safety profile observed in adult subjects with psoriatic arthritis treated with TREMFYA is generally consistent with the safety profile in adult subjects with plaque psoriasis with the addition of bronchitis and neutrophil count decreased. In the 24-week placebo-controlled period, combined across the two studies, bronchitis occurred in 1.6% of subjects in the TREMFYA q8w group and 2.9% of subjects in the TREMFYA q4w group compared to 1.1% of subjects in the placebo group. Neutrophil count decreased occurred in 0.3% of subjects in the TREMFYA q8w and 1.6% of subjects in the TREMFYA q4w group compared to 0% of subjects in the placebo group. The majority of events of neutrophil count decreased were mild,

transient, not associated with infection and did not lead to discontinuation. A similar risk of infection and serious infections was seen in placebo-controlled trials in subjects with psoriatic arthritis as in subjects with plaque psoriasis.

Adverse Reactions in Adults with Ulcerative Colitis

TREMFYA was studied up to 12 weeks in adult subjects with moderately to severely active ulcerative colitis in a randomized, double-blind, placebo-controlled induction trial (UC1) and a randomized, double-blind, placebo-controlled, induction dose-finding trial (UC3; NCT04033445). Long-term safety up to 44 weeks was evaluated in subjects who responded to induction therapy in trials UC1 or UC3 in a randomized, double-blind, placebo-controlled maintenance trial (UC2). In a randomized, double-blind, placebo-controlled trial (UC4), subjects received subcutaneous TREMFYA at Weeks 0, 4, and 8 followed by one of two recommended subcutaneous TREMFYA dosing regimens for a total duration of up to 24 weeks [see *Clinical Studies*].

Trials UC1, UC2 and UC3

In the induction trials (UC1 and UC3), 522 subjects received at least one dose of the TREMFYA intravenous induction regimen (i.e., 200 mg at Week 0, Week 4, and Week 8). Clinical response was defined as a decrease in modified Mayo score (mMS) of $\geq 30\%$ and ≥ 2 points from baseline with either a ≥ 1 decrease from baseline in rectal bleeding subscore (RBS) or RBS of 0 or 1. In the maintenance trial (UC2), subjects who achieved clinical response after 12 weeks of TREMFYA intravenous induction treatment were randomized and received either TREMFYA 100 mg every 8 weeks (with the first dose given at Week 4 of trial UC2) or TREMFYA 200 mg every 4 weeks (with the first dose given at Week 0 of trial UC2), by subcutaneous (SC) injection for up to an additional 44 weeks.

Respiratory tract infections occurred in $\geq 2\%$ of subjects treated with TREMFYA and at a higher rate than placebo (8.8% TREMFYA-treated subjects vs. 7.3% placebo-treated subjects) through Week 12 in the induction trials (UC1 and UC3). Respiratory tract infections included COVID-19, influenza, nasopharyngitis, respiratory tract infection, upper respiratory tract infection, and viral respiratory tract infection.

Adverse reactions that occurred in $\geq 3\%$ of subjects treated with TREMFYA and at a higher rate than placebo through Week 44 in the maintenance trial (UC2) are shown in Table 2.

Table 2: Adverse Reactions Occurring in $\geq 3\%$ of Adult Subjects with Moderately to Severely Active Ulcerative Colitis through Week 44 in Trial UC2

	TREMFYA^a 100 mg Subcutaneous Injection N=186 n (%)	TREMFYA^a 200 mg Subcutaneous Injection N=190 n (%)	Placebo N=192 n (%)
Injection site reactions ^b	2 (1.1)	17 (8.9) ^c	2 (1)
Arthralgia	8 (4.3)	15 (7.9)	13 (6.8)
Upper respiratory tract infection	6 (3.2)	13 (6.8)	8 (4.2)

^a Subjects receiving TREMFYA 100 mg at Week 16 and every 8 weeks thereafter or TREMFYA 200 mg at Week 12 and every 4 weeks thereafter.

^b Injection site reactions include administration site pain, injection site hematoma, injection site hemorrhage, injection site hypersensitivity, injection site erythema, injection site pain, injection site pruritus, injection site rash, injection site reaction, and injection site urticaria.

^c TREMFYA 200 mg was administered as two 100 mg injections.

Trial UC4

In trial UC4, 418 subjects were enrolled, of whom 279 subjects were randomized to receive TREMFYA. Randomization was 1:1:1 to subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg every 8 weeks (with the first dose given at Week 16) for up to an additional 8 weeks (from Week 16 through Week 24); subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg every 4 weeks (with the first dose given at Week 12 for up to an additional 12 weeks (from Week 12 through Week 24); or placebo.

Adverse reactions reported in trial UC4 through Week 24 in $\geq 3\%$ of subjects treated with either subcutaneous TREMFYA dosing regimen and at a higher rate than placebo are shown in Table 3.

Table 3: Adverse Reactions Occurring in $\geq 3\%$ of Adult Subjects with Moderately to Severely Active Ulcerative Colitis through Week 24 in Trial UC4

	TREMFYA 400 mg/100 mg Subcutaneous Injection^a N=139 n (%)	TREMFYA 400 mg/200 mg Subcutaneous Injection^b N=140 n (%)	Placebo N=139 n (%)
Arthralgia	11 (7.9)	7 (5.0)	3 (2.2)
Upper respiratory tract infections ^c	11 (7.9)	5 (3.6)	9 (6.5)
Injection site reactions ^d	7 (5.0)	9 (6.4)	4 (2.9)
Headache ^e	8 (5.8)	7 (5.0)	3 (2.2)
Gastroenteritis	4 (2.9)	3 (2.1)	0
Fatigue	2 (1.4)	4 (2.9)	1 (0.7)
Pyrexia	1 (0.7)	4 (2.9)	2 (1.4)
Rash ^f	4 (2.9)	1 (0.7)	1 (0.7)

^a TREMFYA 400 mg as a subcutaneous injection at Weeks 0, 4, and 8, followed by TREMFYA 100 mg as a subcutaneous injection at Week 16 and every 8 weeks thereafter.

^b TREMFYA 400 mg as a subcutaneous injection at Weeks 0, 4, and 8, followed by TREMFYA 200 mg as a subcutaneous injection at Week 12 and every 4 weeks thereafter.

^c Upper respiratory tract infections include upper respiratory tract infection and viral upper respiratory tract infection.

^d Injection site reactions include injection site erythema, injection site swelling, injection site pain, injection site paresthesia, injection site edema, injection site bruising, injection site induration, injection site pruritus, application site edema, application site erythema, and application site pain.

^e Headache includes headache, migraine, and sinus headache.

^f Rash includes rash and rash pruritic.

Specific Adverse Reactions

Infections

In the 44-week trial (UC2), serious infections occurred in 0.8% of subjects treated with TREMFYA versus 0% of subjects in the placebo group. In the 24-week trial (UC4), serious infections occurred in 1.8% of subjects treated with TREMFYA versus 0.7% of subjects in the placebo group.

Adverse Reactions in Adults with Crohn's Disease

TREMFYA was studied in four clinical trials in adult subjects with moderately to severely active Crohn's disease [see *Clinical Studies*]. In two randomized, double-blind, placebo-controlled trials (CD1, CD2) and one randomized, double-blind, dose-ranging trial (CD4, NCT03466411); subjects received intravenous TREMFYA at Weeks 0, 4, and 8 followed by one of two recommended subcutaneous TREMFYA dosing regimens for a total duration of up to 48 weeks. In a randomized, double-blind, placebo-controlled trial (CD3); subjects received subcutaneous TREMFYA at Weeks 0, 4, and 8 followed by one of two recommended subcutaneous TREMFYA dosing regimens for a total duration of up to 48 weeks.

Trials CD1, CD2, and CD4

In trials CD1, CD2, and CD4; 1349 subjects were enrolled, of whom 649 were randomized to intravenous TREMFYA 200 mg at Weeks 0, 4, and 8 followed by either subcutaneous TREMFYA 100 mg every 8 weeks (with the first dose given at Week 16) for up to an additional 32 weeks (from Week 16 through Week 48) or subcutaneous TREMFYA 200 mg every 4 weeks (with the first dose given at Week 12) for up to an additional 36 weeks (from Week 12 through Week 48); and 211 subjects were randomized to receive placebo.

Through Week 12 in trials CD1, CD2, and CD4; headache (including headache, migraine, and sinus headache) was reported in $\geq 3\%$ of subjects treated with intravenous TREMFYA and at a greater rate than placebo (3.4% TREMFYA-treated subjects vs. 1.9% placebo-treated subjects). In TREMFYA-treated subjects in trial CD2, one case of active extrapulmonary TB was reported between Weeks 12-48 and one case of active pulmonary TB was reported after Week 48. Both subjects had negative baseline screenings and resided in TB-endemic regions [see *Warnings and Precautions (5.3)*]. In general, the safety profile in subjects treated with subcutaneous TREMFYA from Week 12 up to Week 48 in these trials was generally similar to that reported with intravenous TREMFYA through Week 12.

Trial CD3

In trial CD3, 347 subjects were enrolled, of whom 230 subjects were randomized to receive TREMFYA. Randomization was 1:1:1 to subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg every 8 weeks (with the first dose given at Week 16) for up to an additional 32 weeks (from Week 16 through Week 48); subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg every 4 weeks (with the first dose given at Week 12) for up to an additional 36 weeks (from Week 12 through Week 48); or placebo.

Adverse reactions reported in trial CD3 through Week 48 in $\geq 3\%$ of subjects treated with either subcutaneous TREMFYA dosing regimen and at a higher rate than placebo are shown in Table 4.

Table 4: Adverse Reactions Occurring in $\geq 3\%$ of Adult Subjects with Moderately to Severely Active Crohn's Disease Treated with Either Recommended Subcutaneous TREMFYA Regimen through Week 48 in Trial CD3

	TREMFYA 400 mg/100 mg Subcutaneous Injection^a N=115 n (%)	TREMFYA 400 mg/200 mg Subcutaneous Injection^b N=115 n (%)	Placebo N=117 n (%)
Respiratory tract infections ^c	44 (38.3)	35 (30.4)	30 (25.6)
Abdominal pain ^d	14 (12.2)	16 (13.9)	8 (6.8)
Injection site reactions ^e	5 (4.3)	4 (3.5)	0
Fatigue	3 (2.6)	4 (3.5)	0
Headache ^f	7 (6.1)	9 (7.8)	5 (4.3)
Arthralgia	6 (5.2)	5 (4.3)	4 (3.4)
Diarrhea	6 (5.2)	4 (3.5)	3 (2.6)
Gastroenteritis	4 (3.5)	2 (1.7)	1 (0.9)

^a TREMFYA 400 mg as a subcutaneous injection at Weeks 0,4, and 8, followed by TREMFYA 100 mg as a subcutaneous injection at Week 16 and every 8 weeks thereafter.

^b TREMFYA 400 mg as a subcutaneous injection at Weeks 0,4, and 8, followed by TREMFYA 200 mg as a subcutaneous injection at Week 12 and every 4 weeks thereafter.

^c Respiratory tract infections include bronchitis, COVID-19, H1N1 influenza, influenza, influenza like illness, nasopharyngitis, pneumonia, respiratory tract infection, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.

^d Abdominal pain includes abdominal pain, abdominal pain lower, and abdominal pain upper.

^e Injection site reactions includes application site hypersensitivity, application site pruritus, injection site edema, injection site erythema, injection site hemorrhage, injection site mass, injection site rash, injection site reaction, and injection site swelling.

^f Headache includes headache and tension headache.

Specific Adverse Reactions

Infections

In the 48-week clinical trial in subjects with Crohn's disease (CD3), serious infections occurred in 1.5% of subjects treated with TREMFYA versus 0% of subjects in the placebo group.

Elevated Liver Enzymes

Through Week 12 in CD1, CD2, and CD4; ALT $\geq 5x$ ULN was reported in 2/645 (0.3%) subjects treated with intravenous TREMFYA 200 mg at Weeks 0, 4, and 8 and 0/211 subjects treated with placebo. These elevations occurred without concomitant elevations in total bilirubin.

Through Week 48 in CD3, ALT $\geq 5x$ ULN was reported in 0/115 subjects treated with subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg every 8 weeks; 2/115 (1.7%) subjects treated with subcutaneous TREMFYA 400 mg

at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg every 4 weeks; and 0/117 subjects treated with placebo. These elevations occurred without concomitant elevations in total bilirubin.

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

4.8.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval of TREMFYA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to TREMFYA exposure.

Immune system disorders: Hypersensitivity, including anaphylaxis [see Special Warning and Precautions for Use (4.4.1)]

Skin and subcutaneous tissue disorders: Rash [see Special Warning and Precautions for Use (4.4.1)]

4.9 Overdose

TREMFYA intravenous doses up to 1200 mg as well as subcutaneous doses up to 400 mg at a single dosing visit have been administered in clinical studies without dose-limiting toxicity.

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

5. Pharmacological Properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC16.

5.1 Pharmacodynamic Properties

5.1.1 Mechanism of Action

Guselkumab is a human IgG1 λ monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL 23) protein with high specificity and affinity through the antigen binding site. IL 23, 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 subjects with plaque psoriasis. In patients with ulcerative colitis, and Crohn's Disease, levels of IL-23 are elevated in the colon tissue. In in vitro models, guselkumab was shown to inhibit the bioactivity of IL 23 by blocking its interaction with cell surface IL 23 receptor, disrupting IL 23 mediated signaling, activation and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis, psoriatic

arthritis, ulcerative colitis, and Crohn's Disease through blockade of the IL 23 cytokine pathway.

Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, Crohn's disease, and ulcerative colitis. Guselkumab has demonstrated in vitro: blocking of IL-23 and binding to CD64. These results indicate that guselkumab is able to neutralize IL-23 at the cellular source of inflammation.

5.1.2 Pharmacodynamics

In evaluated subjects with plaque psoriasis, guselkumab reduced serum levels of IL-17A, IL-17F and IL-22 relative to pre-treatment levels based on exploratory analyses of the pharmacodynamic markers.

In evaluated subjects with psoriatic arthritis, serum levels of acute phase proteins C-reactive protein, serum amyloid A and IL-6, and Th17 effector cytokines IL-17A, IL-17F and IL-22 were elevated at baseline. Serum levels of these proteins measured at Week 4 and Week 24 were decreased compared to baseline following guselkumab treatment at Week 0, Week 4, and every 8 weeks thereafter.

The relationship between these pharmacodynamic markers and the mechanism(s) by which guselkumab exerts its clinical effects is unknown.

5.2 Pharmacokinetic Properties

Guselkumab exhibited linear pharmacokinetics in healthy subjects and subjects with plaque psoriasis following subcutaneous injections. In subjects with plaque psoriasis, following subcutaneous administration of 100 mg of TREMFYA at Weeks 0 and 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.

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 TREMFYA at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was approximately 1.2 mcg/mL.

Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks or 200 mg TREMFYA every 4 weeks in subjects with ulcerative colitis, mean steady-state trough serum guselkumab concentrations were approximately 1.4 mcg/mL and 10.7 mcg/mL, respectively.

Following subcutaneous maintenance dosing of 100 mg TREMFYA every 8 weeks, or 200 mg TREMFYA every 4 weeks, in subjects with Crohn's disease mean steady-state trough serum guselkumab concentrations were approximately 1.2 mcg/mL and 10.1 mcg/mL, respectively.

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (\pm SD) maximum serum concentration of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose. The absolute bioavailability of guselkumab following a single 100 mg subcutaneous injection was estimated to be approximately 49% in healthy subjects.

Following the recommended intravenous induction dose regimen of TREMFYA 200 mg at Weeks 0, 4, and 8, mean (\pm SD) peak serum guselkumab concentration at Week 8 was 68.3 ± 17.3 mcg/mL in subjects with ulcerative colitis.

Following the recommended intravenous induction dose regimen of TREMFYA 200 mg at Weeks 0, 4, and 8, mean (\pm SD) peak serum guselkumab concentration at Week 8 was 70.5 ± 24.5 mcg/mL in subjects with Crohn's disease.

Following the recommended subcutaneous induction dose regimen of TREMFYA 400 mg at Weeks 0, 4, and 8, mean (\pm SD) peak serum guselkumab concentration was estimated to be 27.7 ± 9.1 mcg/mL in subjects with Crohn's disease. The total systemic exposure (AUC) after the recommended induction dose regimen was similar following subcutaneous and intravenous induction.

Distribution

In subjects with plaque psoriasis, apparent volume of distribution was 13.5 L. In subjects with ulcerative colitis, apparent volume of distribution at steady-state was 10.1 L. In subjects with Crohn's disease, apparent volume of distribution at steady-state was 11.4 L.

Elimination

Apparent clearance in subjects with plaque psoriasis was 0.516 L/day. Mean half-life of guselkumab was approximately 15 to 18 days in subjects with plaque psoriasis across trials.

The apparent clearance in subjects with ulcerative colitis was 0.531 L/day. Mean half-life of guselkumab was approximately 17 days in subjects with ulcerative colitis.

The apparent clearance in subjects with Crohn's disease was 0.568 L/day. Mean half-life of guselkumab was approximately 17 days in subjects with Crohn's disease.

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.

Specific Populations

No apparent differences in clearance were observed in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly subjects. Clearance and volume of distribution of guselkumab increases as body weight increases, however, observed clinical trial data indicate that dose adjustment for body weight is not warranted. No specific trials have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of guselkumab.

Drug Interactions

Population pharmacokinetic analyses indicated that concomitant use of NSAIDs, oral corticosteroids and conventional DMARDs such as methotrexate (MTX), azathioprine (AZA), and 6-mercaptopurine (6-MP), did not affect the clearance of guselkumab.

Cytochrome P450 Substrates

The effects of guselkumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), dextromethorphan

(metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in an exploratory study with 6 to 12 evaluable subjects with moderate-to-severe plaque psoriasis. Changes in AUC_{inf} of midazolam, S-warfarin, omeprazole, and caffeine after a single dose of guselkumab were not clinically relevant. For dextromethorphan, changes in AUC_{inf} after guselkumab were not clinically relevant in 9 out of 10 subjects; however, a 2.9-fold change in AUC_{inf} was observed in one individual [*see Interaction with Other Medicinal Products and Other Forms of Interactions (4.5)*].

Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of guselkumab or of other guselkumab products.

Plaque Psoriasis

Up to Week 52, approximately 6% of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing antibodies. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subjects who experienced loss of efficacy after developing high antibody titers. Up to Week 156, approximately 9% of subjects treated with TREMFYA developed antidrug antibodies and of these subjects approximately 6% were classified as neutralizing antibodies. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions.

Psoriatic Arthritis

Up to Week 24, 2% (n=15) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 1 had antibodies that were classified as neutralizing antibodies. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics, efficacy and safety of guselkumab.

Ulcerative Colitis

Up to Week 56 in Studies UC1, UC2 and UC3, 11% (n=48) of subjects treated with TREMFYA at the recommended dosage developed antidrug antibodies. Of these subjects who tested positive for anti-guselkumab antibodies and were evaluable for neutralizing antibodies, 16% (n=6) had antibodies that were classified as neutralizing antibodies. Most of the subjects who were positive for antibodies to guselkumab had low titers. Two subjects with the highest antibody titers exhibited low trough levels of guselkumab. There was no identified clinically significant effect of antidrug antibodies on injection site reactions, or effectiveness of guselkumab, over the treatment duration of 56 weeks.

Crohn's Disease

Up to Week 48 in CD1, CD2, and CD4; 5% (30/634) of subjects treated with a recommended dosage of TREMFYA developed antidrug antibodies. Of the subjects who tested positive for anti-guselkumab antibodies and were evaluable for neutralizing antibodies, 5% (1/22) had antibodies that were classified as neutralizing antibodies. Up to Week 48 in CD3, 9% (24/273)

of subjects treated with TREMFYA developed antidrug antibodies. Of the subjects who tested positive for anti-guselkumab antibodies and were evaluable for neutralizing antibodies, none had antibodies that were classified as neutralizing antibodies. Most of the subjects who were positive for antibodies to guselkumab had low titers. There were no identified clinically significant effects of antidrug antibodies on pharmacokinetics, injection site reactions, or effectiveness of guselkumab, over the treatment duration of 48 weeks.

5.3 Preclinical Safety Data

5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TREMFYA.

No effects on fertility parameters were observed after male guinea pigs were subcutaneously administered guselkumab at a dose of 25 mg/kg twice weekly (6 times the exposure (AUC) in humans administered 200 mg intravenously and 5 times the exposure (AUC) at the 400 mg subcutaneous dose).

No effects on fertility parameters were observed after female guinea pigs were subcutaneously administered guselkumab at doses up to 100 mg/kg twice weekly (12 times the exposure (AUC) in humans administered 200 mg intravenously and 10 times the exposure (AUC) at the 400 mg subcutaneous dose).

Clinical Studies

Four multicenter, randomized, double-blind trials (PsO1 [NCT02207231], PsO2 [NCT02207244], PsO3 [NCT02203032], and PsO4 [NCT02905331]) enrolled subjects 18 years of age and older with moderate-to-severe plaque psoriasis who were eligible for systemic therapy or phototherapy. Subjects had an Investigator's Global Assessment (IGA) score of ≥ 3 ("moderate") on a 5-point scale of overall disease severity, a Psoriasis Area and Severity Index (PASI) score ≥ 12 , and a minimum affected body surface area (BSA) of 10%. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded.

Trials PsO1 and PsO2

In PsO1 and PsO2, 1443 subjects were randomized to either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter) administered with a prefilled syringe, placebo or U.S. licensed adalimumab (80 mg at Week 0 and 40 mg at Week 1, followed by 40 mg every other week thereafter).

Both trials assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an IGA score of 0 ("cleared") or 1 ("minimal");
- the proportion of subjects who achieved at least a 90% reduction from baseline in the PASI composite score (PASI 90).

Comparisons between TREMFYA and U.S. licensed adalimumab were secondary endpoints at the following time points:

- at Week 16 (PsO1 and PsO2), the proportions of subjects who achieved an IGA score of 0 or 1, a PASI 90, and a PASI 75 response;
- at Week 24 (PsO1 and PsO2), and at Week 48 (PsO1), the proportions of subjects achieving an IGA score of 0, an IGA score of 0 or 1, and a PASI 90 response.

Other evaluated outcomes included improvement in psoriasis symptoms assessed on the Psoriasis Symptoms and Signs Diary (PSSD) and improvements in psoriasis of the scalp at Week 16.

In both trials, subjects were predominantly men and white, with a mean age of 44 years and a mean weight of 90 kg. At baseline, subjects had a median affected BSA of approximately 21%, a median PASI score of 19, and 18% had a history of psoriatic arthritis. Approximately 24% of subjects had an IGA score of severe. In both trials, 23% had received prior biologic systemic therapy.

Clinical Response

Table 5 presents the efficacy results at Week 16 in PsO1 and PsO2.

Table 5: Efficacy Results at Week 16 in Adults with Plaque Psoriasis (NRI^a)

Endpoint	PsO1		PsO2	
	TREMFYA (N=329) n (%)	Placebo (N=174) n (%)	TREMFYA (N=496) n (%)	Placebo (N=248) n (%)
IGA response of 0/1^{b, c}	280 (85)	12 (7)	417 (84)	21 (8)
PASI 90 response^b	241 (73)	5 (3)	347 (70)	6 (2)

^a NRI = Non-Responder Imputation

^b Co-Primary Endpoints

^c IGA response of 0 (cleared) or 1 (minimal)

Table 6 presents the results of an analysis of all the North America sites (i.e., U.S. and Canada), demonstrating superiority of TREMFYA to U.S. licensed adalimumab.

Table 6: Efficacy Results in Adults with Plaque Psoriasis (NRI^a)

Endpoint	PsO1		PsO2	
	TREMFYA (N=115) ^b n (%)	Adalimumab ^c (N=115) ^b n (%)	TREMFYA (N=160) ^b n (%)	Adalimumab ^c (N=81) ^b n (%)
IGA response of 0/1 (cleared or minimal)				
Week 16	97 (84)	70 (61)	119 (74)	50 (62)
Week 24	97 (84)	62 (54)	119 (74)	46 (57)
Week 48	91 (79)	62 (54)	NA	NA
IGA response of 0 (cleared)				
Week 24	61 (53)	27 (23)	76 (48)	23 (28)
Week 48	54 (47)	28 (24)	NA	NA
PASI 75 response				
Week 16	105 (91)	80 (70)	132 (83)	51 (63)

PASI 90 response				
Week 16	84 (73)	47 (41)	102 (64)	34 (42)
Week 24	92 (80)	51 (44)	113 (71)	41 (51)
Week 48	84 (73)	53 (46)	NA	NA

^a NRI = Non-Responder Imputation

^b Subjects from sites in the United States and Canada

^c U.S. licensed adalimumab

An improvement was seen in psoriasis involving the scalp in subjects randomized to TREMFYA compared to placebo at Week 16.

Examination of age, gender, race, body weight, and previous treatment with systemic or biologic agents did not identify differences in response to TREMFYA among these subgroups.

Maintenance and Durability of Response

To evaluate maintenance and durability of response (PsO2), subjects randomized to TREMFYA at Week 0 and who were PASI 90 responders at Week 28 were re-randomized to either continue treatment with TREMFYA every 8 weeks or be withdrawn from therapy (i.e., receive placebo).

At Week 48, 89% of subjects who continued on TREMFYA maintained PASI 90 compared to 37% of subjects who were re-randomized to placebo and withdrawn from TREMFYA. For responders at Week 28 who were re-randomized to placebo and withdrawn from TREMFYA, the median time to loss of PASI 90 was approximately 15 weeks.

Patient Reported Outcomes

Greater improvements in symptoms of psoriasis (itch, pain, stinging, burning and skin tightness) at Week 16 in TREMFYA compared to placebo were observed in both trials based on the Psoriasis Symptoms and Signs Diary (PSSD). Greater proportions of subjects on TREMFYA compared to U.S. licensed adalimumab achieved a PSSD symptom score of 0 (symptom-free) at Week 24 in both trials.

Trial PsO3

PsO3 [NCT02203032] evaluated the efficacy of 24 weeks of treatment with TREMFYA in subjects (N=268) who had not achieved an adequate response, defined as IGA ≥ 2 at Week 16 after initial treatment with U.S. licensed ustekinumab (dosed 45 mg or 90 mg according to the subject's baseline weight at Week 0 and Week 4). These subjects were randomized to either continue with U.S. licensed ustekinumab treatment every 12 weeks or switch to TREMFYA 100 mg at Weeks 16, 20, and every 8 weeks thereafter. Baseline characteristics for randomized subjects were similar to those observed in PsO1 and PsO2.

In subjects with an inadequate response (IGA ≥ 2 at Week 16 to U.S. licensed ustekinumab), greater proportions of subjects on TREMFYA compared to U.S. licensed ustekinumab achieved an IGA score of 0 or 1 with a ≥ 2 grade improvement at Week 28 (31% vs. 14%, respectively; 12 weeks after randomization).

Trial PsO4

PsO4 [NCT02905331] evaluated the efficacy, safety, and pharmacokinetics of TREMFYA administered with the One-Press. In this study, 78 subjects were randomized to receive either TREMFYA (100 mg at Weeks 0 and 4 and every 8 weeks thereafter) [N=62], or placebo

[N=16]. Baseline characteristics for subjects were comparable to those observed in PsO1 and PsO2. The co-primary endpoints were the same as those for PsO1 and PsO2. Secondary endpoints included the proportion of subjects who achieved an IGA score of 0 at Week 16 and the proportion of subjects who achieved a PASI 100 response at Week 16.

A greater proportion of subjects in the guselkumab group achieved an IGA score of 0 or 1 or a PASI 90 response at Week 16 (81% and 76%, respectively) than in the placebo group (0% for both endpoints). The proportion of subjects who achieved an IGA score of 0 at Week 16 was higher in the guselkumab group compared to the placebo group (56% vs. 0%). The proportion of subjects who achieved a PASI 100 response at Week 16 was higher in the guselkumab group compared to the placebo group (50% vs. 0%).

Psoriatic Arthritis

The safety and efficacy of TREMFYA were assessed in 1120 subjects in 2 randomized, double-blind, placebo-controlled trials (PsA1 [NCT03162796] and PsA2 [NCT03158285]) in adult subjects with active psoriatic arthritis (PsA) (≥ 3 swollen joints, ≥ 3 tender joints, and a C-reactive protein (CRP) level of ≥ 0.3 mg/dL in PsA1 and ≥ 5 swollen joints, ≥ 5 tender joints, and a CRP level of ≥ 0.6 mg/dL in PsA2) who had inadequate response to standard therapies (e.g., conventional DMARDs [cDMARDs]), apremilast, or nonsteroidal anti-inflammatory drugs [NSAIDs]). Subjects in these trials 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 PsA1 approximately 31% of subjects had been previously treated with up to 2 anti-tumor necrosis factor alpha (anti-TNF α) agents whereas in PsA2 all subjects were biologic naïve. Approximately 58% of subjects from both trials had concomitant methotrexate (MTX) use. Subjects with different subtypes of PsA were enrolled in both trials, 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 subjects had enthesitis and dactylitis, respectively and 79% had $\geq 3\%$ body surface area (BSA) psoriasis skin involvement.

PsA1 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). PsA2 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. The primary endpoint in both trials was the percentage of subjects achieving an ACR20 response at Week 24.

Clinical Response

In both trials, subjects treated with TREMFYA 100 mg q8w demonstrated a greater clinical response including ACR20, compared to placebo at Week 24 (Tables 7 and 8). Similar responses were seen regardless of prior anti-TNF α exposure in PsA1, and in both trials similar responses were seen regardless of concomitant cDMARD use, previous treatment with cDMARDs, gender and body weight.

Table 7: Percent of Subjects with ACR Responses in PsA1

	Placebo (N=126)	TREMFYA 100 mg q8w (N=127)	
	Response Rate	Response Rate	Difference from Placebo (95% CI)

ACR 20 response^a			
Week 16	25%	52%	27 (15, 38)
Week 24	22%	52%	30 (19, 41)
ACR 50 response^a			
Week 16	13%	23%	10 (1, 19)
Week 24	9%	30%	21 (12, 31)
ACR 70 response^a			
Week 16	6%	8%	2 (-4, 8)
Week 24	6%	12%	6 (-0.3, 13)

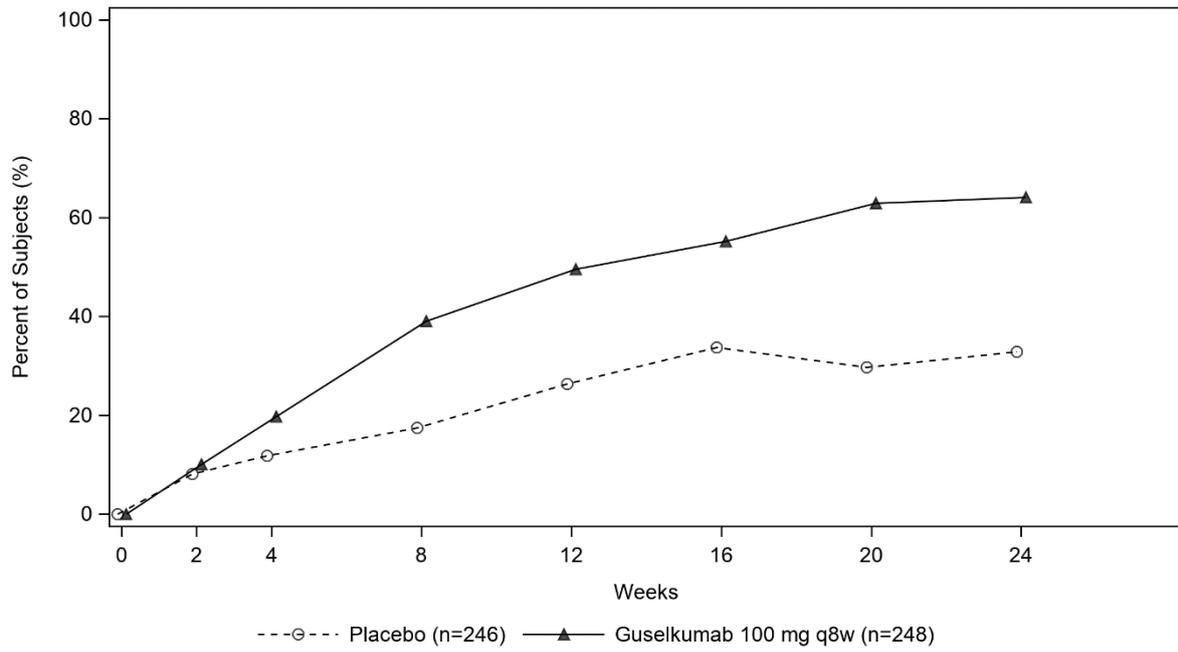
^a Subjects with missing data at a visit were imputed as non-responders at that visit. Subjects who met escape criteria (less than 5% improvement in both tender and swollen joint counts) at Week 16 were allowed to initiate or increase the dose of the permitted concomitant medication and remained on the randomized group. Subjects who initiated or increased the dose of non-biologic DMARD or oral corticosteroids over baseline, discontinued study/study medication or initiated protocol prohibited medications/therapies for PsA prior to a visit were considered non-responders at that visit.

Table 8: Percent of Subjects with ACR Responses in PsA2

	Placebo (N=246)	TREMFYA 100 mg q8w (N=248)	
	Response Rate	Response Rate	Difference from Placebo (95% CI)
ACR 20 response^a			
Week 16	34%	55%	22 (13, 30)
Week 24	33%	64%	31 (23, 40)
ACR 50 response^a			
Week 16	9%	29%	19 (13, 26)
Week 24	14%	32%	17 (10, 24)
ACR 70 response^a			
Week 16	1%	14%	13 (9, 17)
Week 24	4%	19%	15 (9, 20)

^a Subjects with missing data at a visit were imputed as non-responders at that visit. Subjects who met escape criteria (less than 5% improvement in both tender and swollen joint counts) at Week 16 were allowed to initiate or increase the dose of the permitted concomitant medication and remained on the randomized group. Subjects who initiated or increased the dose of non-biologic DMARD or oral corticosteroids over baseline, discontinued study/study medication or initiated protocol prohibited medications/therapies for PsA prior to a visit were considered non-responders at that visit.

The percentage of subjects achieving ACR20 response in PsA2 by visit is shown in Figure 1.

Figure 1: Subjects Achieving ACR 20 Response by Visit Through Week 24 in PsA2

The results of the components of the ACR response criteria are shown in Table 9.

Table 9: Mean change (SD^a) from Baseline in ACR Component Scores at Week 16 and 24 based on Observed Data

	PsA1		PsA2	
	Placebo (N=126)	TREMFYA 100 mg q8w (N=127)	Placebo N=246	TREMFYA 100 mg q8w (N=248)
No. of Swollen Joints				
Baseline	10.1 (7.1)	10.9 (9.3)	12.3 (6.9)	11.7 (6.8)
Mean change at Week 16	-4.2 (7.0)	-7.3 (7.0)	-5.8 (7.1)	-7.2 (6.0)
Mean change at Week 24	-5.1 (6.9)	-7.3 (8.0)	-6.4 (7.2)	-8.1 (6.1)
No. of Tender Joints				
Baseline	19.8 (14.4)	20.2 (14.5)	21.6 (13.1)	19.8 (11.9)
Mean change at Week 16	-4.5 (10.8)	-10.2 (10.4)	-6.8 (10.5)	-9.0 (9.4)
Mean change at Week 24	-6.8 (13.0)	-10.5 (12.0)	-7.3 (11.2)	-10.4 (9.5)
Patient's Assessment of Pain^b				
Baseline	5.8 (2.2)	6.0 (2.1)	6.3 (1.8)	6.3 (2.0)
Mean change at Week 16	-0.8 (2.3)	-1.7 (2.4)	-0.9 (2.3)	-2.2 (2.5)
Mean change at Week 24	-0.7 (2.4)	-2.2 (2.6)	-1.1 (2.4)	-2.5 (2.5)
Patient Global Assessment^b				
Baseline	6.1 (2.2)	6.5 (2.0)	6.5 (1.8)	6.5 (1.9)
Mean change at Week 16	-1.0 (2.3)	-2.0 (2.6)	-1.0 (2.3)	-2.3 (2.6)
Mean change at Week 24	-0.9 (2.5)	-2.5 (2.7)	-1.2 (2.6)	-2.5 (2.5)
Physician Global Assessment^b				
Baseline	6.3 (1.7)	6.2 (1.7)	6.7 (1.5)	6.6 (1.6)
Mean change at Week 16	-1.9 (2.2)	-2.9 (2.4)	-2.1 (2.2)	-3.5 (2.3)
Mean change at Week 24	-2.2 (2.3)	-3.5 (2.4)	-2.5 (2.3)	-3.8 (2.3)
Disability Index (HAQ-DI)^c				
Baseline	1.2 (0.7)	1.2 (0.6)	1.3 (0.6)	1.3 (0.6)
Mean change at Week 16	-0.1 (0.5)	-0.3 (0.5)	-0.1 (0.5)	-0.3 (0.5)
Mean change at Week 24	-0.1 (0.5)	-0.3 (0.6)	-0.2 (0.5)	-0.4 (0.5)
CRP (mg/dL)				
Baseline	1.4 (1.9)	1.6 (2.4)	2.1 (2.7)	2.0 (2.4)
Mean change at Week 16	-0.2 (1.5)	-0.6 (2.2)	-0.6 (2.5)	-1.0 (2.2)
Mean change at Week 24	-0.0 (2.8)	-0.7 (2.1)	-0.5 (2.5)	-1.1 (2.2)

^a SD= standard deviation^b Assessment based on Visual Analog Scale (cm) with the left end indicating "no pain" (for patient's assessment of pain), "very well" (for patient global assessment), or "no arthritis activity" (for physician global assessment) and the right end indicating

“the worst possible pain” (for patient assessment of pain), “poor” (for patient global assessment), or “extremely active arthritis (for physician global assessment).

- ^c Disability Index of the Health Assessment Questionnaire; 0 = no difficulty to 3 = inability to perform, measures the patient’s ability to perform the following: dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living

Treatment with TREMFYA resulted in an improvement in the skin manifestations of psoriasis in subjects with PsA.

Treatment with TREMFYA resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis.

Physical Function

TREMFYA treated subjects in the TREMFYA 100 mg q8w group in both PsA1 and PsA2 showed greater mean improvement from baseline in physical function compared to subjects treated with placebo as assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Weeks 16 and 24. In both studies, the proportion of HAQ-DI responders (≥ 0.35 improvement in HAQ-DI score) was greater in the TREMFYA q8w dose group compared to placebo at Weeks 16 and 24.

Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). At Week 24, subjects in the TREMFYA 100 mg q8w dose group in both PsA1 and PsA2 showed greater improvement from baseline in the SF-36 physical component summary (PCS) compared with placebo. There was not a statistically significant improvement observed in the SF-36 MCS. At Week 24, there was numerical improvement 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. Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue score (FACIT-F) in Studies PsA1 and PsA2. Treatment with TREMFYA resulted in improvement in fatigue as measured by FACIT-F.

Ulcerative Colitis

Induction Trial: UC1

In the 12-week induction study (UC1; NCT04033445), 701 subjects with moderately to severely active ulcerative colitis were randomized 3:2 to receive either TREMFYA 200 mg or placebo by intravenous infusion at Week 0, Week 4, and Week 8. Disease activity was assessed by the modified Mayo score (mMS), a 3-component Mayo score (0-9) which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally reviewed endoscopy (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, friability, and/or erosions; an ES of 3 was defined by spontaneous bleeding and ulceration. Enrolled subjects with a mMS between 5 and 9 and an ES of 2 or 3 were classified as having moderately to severely active ulcerative colitis. Subjects with inadequate response, loss of response, or intolerance to corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine), biologic therapy (TNF blockers, vedolizumab), and/or Janus kinase (JAK) inhibitors were enrolled.

At baseline in UC1, the median mMS was 7, 64% of subjects had severely active disease (mMS ≥ 7), and 68% of subjects had an ES of 3. In UC1, 49% of subjects had previously failed (inadequate response, loss of response, or intolerance) treatment with at least one biologic therapy and/or JAK inhibitor, 48% were biologic and JAK inhibitor naïve, and 3% had

previously received but not failed a biologic or JAK inhibitor. The median age was 39 years (ranging from 18 to 79 years); 43% were female; and 72% identified as White, 21% as Asian, 1% as Black or African American, <1% as American Indian or Alaskan Native, and <1% as multiple racial groups.

Enrolled subjects were permitted to use stable doses of oral aminosalicylates, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or oral corticosteroids (up to 20 mg/day prednisone or equivalent). At baseline, 72% of subjects were receiving aminosalicylates, 21% of subjects were receiving immunomodulators, and 43% of subjects were receiving corticosteroids. Concomitant biologic therapies or JAK inhibitors were not permitted.

In UC1, the primary endpoint was clinical remission at Week 12 as defined by the mMS. Secondary endpoints at Week 12 included endoscopic improvement, clinical response, and histologic endoscopic mucosal improvement (see Table 10).

Table 10: Proportion of Subjects with Ulcerative Colitis Meeting Efficacy Endpoints at Week 12 in UC1

Endpoint	Placebo	TREMFYA 200 mg Intravenous Infusion ^a	Treatment Difference (95% CI)
Clinical remission^b			
Total Population	N=280 8%	N=421 23%	15% (10%, 20%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 4%	N=208 13%	
Without prior biologic or JAK inhibitor failure ^e	N=144 12%	N=213 32%	
Endoscopic improvement^f			
Total Population	N=280 11%	N=421 27%	16% (10%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 5%	N=208 15%	
Without prior biologic or JAK inhibitor failure ^e	N=144 17%	N=213 38%	
Clinical response^g			
Total Population	N=280 28%	N=421 62%	34% (27%, 41%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 20%	N=208 51%	
Without prior biologic or JAK inhibitor failure ^e	N=144 35%	N=213 71%	
Histologic endoscopic mucosal improvement (HEMI)^h			
Total Population	N=280 8%	N=421 24%	16% (11%, 21%) ^c
Prior biologic and/or JAK inhibitor failure ^d	N=136 4%	N=208 13%	
Without prior biologic or JAK inhibitor failure ^e	N=144 10%	N=213 33%	

^a TREMFYA 200 mg as an intravenous infusion at Week 0, Week 4, and Week 8

^b A stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability

^c $p < 0.001$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method (adjusted for stratification factors: biologic and/or JAK-inhibitor failure status and concomitant use of corticosteroids at baseline)

^d Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis

^e Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 7 subjects in the placebo group and 11 subjects in the TREMFYA group were previously exposed to, but did not fail, a biologic or JAK inhibitor

^f An endoscopy subscore of 0 or 1 with no friability

^g Decrease from induction baseline in the modified Mayo score by $\geq 30\%$ and ≥ 2 points, with either a ≥ 1 point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1

^h An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in $< 5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

Study UC1 was not designed to evaluate the relationship of histologic endoscopic mucosal improvement at Week 12 to disease progression and long-term outcomes.

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 4 in subjects treated with TREMFYA compared to placebo.

Endoscopic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. At Week 12 of UC1, a greater proportion of subjects treated with TREMFYA compared to placebo-treated subjects achieved endoscopic remission (15% vs 5%).

Fatigue Response

In UC1, subjects treated with TREMFYA experienced a clinically meaningful improvement in fatigue, assessed by the PROMIS-Fatigue Short form 7a, at Week 12, compared to placebo-treated subjects. The effect of TREMFYA to improve fatigue after 12 weeks of induction has not been established.

Maintenance Trial: UC2

The maintenance trial (UC2) evaluated 568 subjects who received one of two intravenous TREMFYA induction regimens, including the recommended 200 mg regimen, for 12 weeks in Studies UC1 or UC3 (induction dose-finding study) and demonstrated clinical response per mMS after 12 weeks. Subjects were re-randomized to receive a subcutaneous maintenance regimen of either TREMFYA 100 mg every 8 weeks, TREMFYA 200 mg every 4 weeks, or placebo for up to an additional 44 weeks.

In UC2, 42% of subjects had failed (inadequate response, loss of response, or intolerance) treatment with one or more biologics or JAK inhibitors.

The primary endpoint was clinical remission at Week 44 defined by mMS. Secondary endpoints included corticosteroid-free clinical remission, endoscopic improvement, histologic endoscopic mucosal improvement, all at Week 44 and maintenance of clinical remission at Week 44 in subjects who achieved clinical remission 12 weeks after intravenous TREMFYA induction treatment (see Table 11).

Table 11: Proportion of Subjects with Ulcerative Colitis Meeting Efficacy Endpoints at Week 44 in UC2

Endpoint	Placebo	TREMFYA 100 mg Every 8 Weeks Subcutaneous Injection ^a	TREMFYA 200 mg Every 4 Weeks Subcutaneous Injection ^b	Treatment Difference vs Placebo (95% CI)	
				TREMFYA 100 mg	TREMFYA 200 mg
Clinical remission^c					
Total population ^d	N=190 19%	N=188 45%	N=190 50%	25% (16%, 34%) ^e	30% (21%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 59%		
Corticosteroid-free clinical remission^h					
Total population ^d	N=190 18%	N=188 45%	N=190 49%	26% (17%, 34%) ^e	29% (20%, 38%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 7%	N=77 40%	N=88 40%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 49%	N=102 57%		
Endoscopic improvementⁱ					
Total population ^d	N=190 19%	N=188 49%	N=190 52%	30% (21%, 38%) ^e	31% (22%, 40%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 45%	N=88 42%		
Without prior biologic or JAK inhibitor failure ^g	N=115 26%	N=111 52%	N=102 60%		
Histologic endoscopic mucosal improvement (HEMI)^j					
Total population ^d	N=190 17%	N=188 44%	N=190 48%	26% (17%, 34%) ^e	30% (21%, 38%) ^e

Prior biologic and/or JAK inhibitor failure ^f	N=75 8%	N=77 38%	N=88 39%		
Without prior biologic or JAK inhibitor failure ^g	N=115 23%	N=111 48%	N=102 56%		
Maintenance of Clinical Remission at Week 44 in subjects who achieved clinical remission after 12 weeks of induction					
Total population ^k	N=59 34%	N=66 61%	N=69 72%	26% (9%, 43%) ^l	38% (23%, 54%) ^e
Prior biologic and/or JAK inhibitor failure ^f	N=15 27%	N=20 60%	N=18 56%		
Without prior biologic or JAK inhibitor failure ^m	N=44 36%	N=46 61%	N=51 78%		

^a TREMFYA 100 mg as a subcutaneous injection every 8 weeks after the induction regimen

^b TREMFYA 200 mg as a subcutaneous injection every 4 weeks after the induction regimen

^c A stool frequency subscore of 0 or 1 and not increased from induction baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability

^d Subjects who achieved clinical response 12 weeks following the intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3

^e $p < 0.001$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors

^f Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) and/or a Janus kinase (JAK) inhibitor for ulcerative colitis

^g Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 7 subjects in the placebo group, 6 subjects in the TREMFYA 100 mg group, and 6 subjects in the TREMFYA 200 mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor

^h Not requiring any treatment with corticosteroids for at least 8 weeks prior to week 44 and also meeting the criteria for clinical remission at week 44

ⁱ An endoscopy subscore of 0 or 1 with no friability

^j An endoscopy subscore of 0 or 1 with no friability and Geboes score ≤ 3.1 (indicating neutrophil infiltration in $< 5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue)

^k Subjects who achieved clinical remission 12 weeks following intravenous administration of TREMFYA in either induction study UC1 or induction dose-finding study UC3

^l $p < 0.01$, adjusted treatment difference (95% CI) based on Cochran-Mantel-Haenszel method adjusted for randomization stratification factors

^m Includes subjects that were biologic and/or JAK inhibitor naïve and subjects with biologic and/or JAK inhibitor exposure who did not meet criteria for failure. Of these, 3 subjects in the placebo group, 3 subjects in the TREMFYA 100 mg group, and 3 subjects in the TREMFYA 200 mg group were previously exposed to, but did not fail, a biologic or JAK inhibitor.

Study UC2 was not designed to evaluate the relationship of histologic endoscopic mucosal improvement at Week 44 to disease progression and long-term outcomes.

Endoscopic Assessment

Normalization of the endoscopic appearance of the mucosa (endoscopic remission) was defined as ES of 0. In UC2, greater proportions of subjects treated with TREMFYA 100 mg every 8 weeks or TREMFYA 200 mg every 4 weeks achieved endoscopic remission at Week 44 compared to placebo-treated subjects (35% and 34%, respectively, vs. 15%).

Crohn's Disease

The efficacy and safety of TREMFYA were assessed in three randomized, double-blind, placebo-controlled trials that enrolled adult subjects with moderately to severely active Crohn's disease who had a history of inadequate response, loss of response, or intolerance to oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or biologic therapy (TNF blockers or vedolizumab). Moderately to severely active Crohn's disease was defined as a Crohn's Disease Activity Index (CDAI) score of ≥ 220 and a Simple Endoscopic Score for Crohn's Disease (SES-CD) of ≥ 6 (or ≥ 4 for subjects with isolated ileal disease). Subjects were permitted to use stable doses of oral corticosteroids (prednisone ≤ 40 mg/day or equivalent), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or aminosalicylates.

Trials CD1 and CD2

In CD1 (NCT03466411), 361 subjects were randomized to receive intravenous TREMFYA 200 mg at Weeks 0, 4, and 8 (N = 285) or placebo (N = 76). The median age of subjects enrolled into CD1 was 33 years (range: 18 - 83 years); 46% were female; and 75% identified as White, 22% as Asian, 1% as Black or African American, <1% as Native Hawaiian or Pacific Islander, and 2% did not report their racial group. The median baseline CDAI score was 285 (range: 220 - 442), and the median baseline SES-CD score was 11 (range: 4 - 39). Of the randomized subjects, 52% of subjects had previously failed (inadequate response, loss of response, or intolerance) treatment with at least one biologic therapy, 43% were biologic-naïve, and 6% had previously received but had not failed a biologic. At baseline, 37% of subjects were receiving oral corticosteroids and 30% of subjects were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate).

In CD2 (NCT03466411), 360 subjects were randomized to receive intravenous TREMFYA 200 mg at Weeks 0, 4, and 8 (N = 288) or placebo (N = 72). The median age of subjects enrolled into CD2 was 33 years (range: 18 - 72 years); 39% were female; and 73% identified as White, 23% as Asian, 1% as Black or African American, <1% as Native Hawaiian or Pacific Islander, and 2% did not report their racial group. The median baseline CDAI score was 286 (range: 220 - 442) and the median baseline SES-CD score was 11 (range: 4 - 42). Of the randomized subjects, 52% of subjects had previously failed (inadequate response, loss of response, or intolerance) treatment with at least one biologic therapy, 41% were biologic-naïve, and 7% had previously received but had not failed a biologic. At baseline, 36% of the subjects were receiving oral corticosteroids and 31% of the subjects were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate).

The results of efficacy endpoints at Week 12 for CD1 and CD2 are shown in Table 12.

Table 12: Proportion of Subjects with Crohn's Disease Meeting Efficacy Endpoints at Week 12 in CD1 and CD2

Endpoint	CD1			CD2		
	Placebo	TREMFY A 200 mg Intravenous Infusion ^a	Treatment Difference vs Placebo (95% CI) ^b	Placebo	TREMFY A 200 mg Intravenous Infusion ^a	Treatment Difference vs Placebo (95% CI) ^b
Clinical remission^c at Week 12						
Total population	N=76 20%	N=285 47%	27% (17%, 38%) ^d	N=72 15%	N=288 47%	31% (21%, 41%) ^d
Prior biologic failure ^e	N=39 21%	N=147 44%		N=39 15%	N=148 47%	
Without prior biologic failure ^f	N=37 19%	N=138 49%		N=33 15%	N=140 48%	
Endoscopic response^g at Week 12						
Total population	N=76 9%	N=285 36%	27% (19%, 35%) ^d	N=72 13%	N=288 34%	21% (11%, 30%) ^d
Prior biologic failure ^e	N=39 3%	N=147 26%		N=39 8%	N=148 28%	
Without prior biologic failure ^f	N=37 16%	N=138 47%		N=33 18%	N=140 40%	
Clinical remission^c at Week 12 and endoscopic response^g at Week 12						
Total population	N=76 3%	N=285 20%	17% (11%, 23%) ^d	N=72 3%	N=288 21%	18% (12%, 24%) ^d
Prior biologic failure ^e	N=39 3%	N=147 14%		N=39 3%	N=148 19%	
Without prior biologic failure ^f	N=37 3%	N=138 26%		N=33 3%	N=140 24%	

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- ^a TREMFYA 200 mg as an intravenous infusion at Weeks 0, 4, and 8.
- ^b The adjusted treatment difference and the confidence intervals (CIs) were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤ 300 or > 300), baseline SES-CD score (≤ 12 or > 12), BIO-Failure status (Yes or No), and baseline corticosteroid use (Yes or No).
- ^c Clinical remission is defined as CDAI score < 150 .
- ^d $p < 0.001$
- ^e Includes inadequate response, loss of response, or intolerance to biologic therapy (TNF blockers, vedolizumab) for Crohn's disease.
- ^f Includes subjects that were biologic naïve and subjects with prior biologic exposure who did not meet criteria for failure. In CD1, 3 subjects in the placebo group and 18 subjects in the intravenous TREMFYA 200 mg group were previously exposed to but did not fail a biologic therapy. In CD2, 6 subjects in the placebo group and 19 subjects in the intravenous TREMFYA 200 mg group were previously exposed to but did not fail a biologic therapy.
- ^g Endoscopic response is defined as $> 50\%$ improvement from baseline in SES-CD score.

Stool Frequency and Abdominal Pain

Greater reductions in stool frequency and abdominal pain were observed as early as Week 4 in subjects treated with intravenous TREMFYA compared to placebo.

Trial CD3

In CD3, 340 subjects were randomized in a 1:1:1 ratio to receive subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg every 8 weeks (with the first dose given at Week 16); subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg every 4 weeks (with the first dose given at Week 12); or placebo. The median age of subjects enrolled into CD3 was 36 years (range: 18 - 83 years); 41% were female; and 66% identified as White, 22% as Asian, 3% as Black or African American, and 9% did not report their racial group. The median baseline CDAI score was 291 (range: 220 - 447), and the median baseline SES-CD score was 10 (range: 4 - 40). Of the randomized subjects, 46% of subjects had previously failed (inadequate response, loss of response, or intolerance) treatment with at least one biologic therapy, 47% were biologic naïve, and 7% had previously received but had not failed a biologic. At baseline, 30% of the subjects were receiving oral corticosteroids and 29% of the subjects were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate).

In CD3, the coprimary endpoints were clinical remission at Week 12 and endoscopic response at Week 12 compared to placebo. Additional efficacy endpoints included clinical response at Week 12, clinical remission at Week 24, clinical remission at Week 48, and endoscopic response at Week 48. The results of analyses of multiplicity-controlled efficacy endpoints in CD3 are shown in Table 13.

Table 13: Proportion of Subjects with Crohn's Disease Meeting Efficacy Endpoints in CD3

Endpoint	Placebo	TREMFYA 400 mg Subcutaneous Injection at Weeks 0, 4, and 8^a		Treatment Difference vs Placebo (95% CI)^b	
Week 12					
Clinical Remission^c					
Total population	N=115 22%	N=225 56%		34% (24%, 44%) ^d	
Prior biologic failure ^e	N=53 17%	N=104 60%			
Without prior biologic failure ^f	N=62 26%	N=121 52%			
Endoscopic Response^g					
Total population	N=115 15%	N=225 34%		19% (10%, 28%) ^d	
Prior biologic failure ^e	N=53 11%	N=104 27%			
Without prior biologic failure ^f	N=62 18%	N=121 40%			
Clinical Response^h					
Total population	N=115 33%	N=225 72%		39% (29%, 50%) ^d	
Prior biologic failure ^e	N=53 28%	N=104 76%			
Without prior biologic failure ^f	N=62 37%	N=121 69%			
Weeks 24 and 48					
Endpoint	Placebo	TREMFYA 100 mg Subcutane ous Injection every 8 weeks starting at Week 16	TREMFYA 200 mg Subcutane ous Injection every 4 weeks starting at Week 12	Treatment difference vs Placebo (95% CI)^b	
				TREMFYA 100 mg	TREMFYA 200 mg
Clinical Remission^c at Week 24					
Total population	N=115 21%	N=114 61%	N=111 58%	39% (28%, 51%) ^d	37% (25%, 48%) ^d
Prior biologic failure ^e	N=53 19%	N=54 63%	N=50 52%		
Without prior biologic failure ⁱ	N=62 23%	N=60 58%	N=61 62%		
Clinical Remission^c at Week 48					

Total population	N=115 17%	N=114 59%	N=111 65%	41% (30%, 52%) ^d	47% (36%, 58%) ^d
Prior biologic failure ^e	N=53 9%	N=54 56%	N=50 60%		
Without prior biologic failure ^f	N=62 24%	N=60 62%	N=61 69%		
Endoscopic Response^g at Week 48					
Total population	N=115 5%	N=114 39%	N=111 48%	34% (24%, 44%) ^d	42% (32%, 53%) ^d
Prior biologic failure ^e	N=53 0%	N=54 33%	N=50 52%		
Without prior biologic failure ^f	N=62 10%	N=60 45%	N=61 44%		

^a At baseline, subjects were randomized 1:1: 1 to receive subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg every 8 weeks; subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg every 4 weeks; or placebo. Because dosing is identical through Week 12, subjects in both TREMFYA groups are combined for the analysis of the Week 12 endpoints.

^b The adjusted treatment difference and the CIs were based on the common risk difference test using Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used were baseline CDAI score (≤ 300 or >300), baseline SES-CD score (≤ 12 or >12), BIO-Failure status (Yes or No). CI = confidence interval

^c Clinical remission is defined as CDAI score <150 .

^d $p < 0.001$

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

^f Includes subjects that were biologic naïve and subjects with prior biologic exposure who did not meet criteria for failure. Of these, 8 subjects in the placebo group and 17 subjects in the subcutaneous TREMFYA 400 mg group, were previously exposed to but did not fail a biologic therapy.

^g Endoscopic response is defined as $>50\%$ improvement from baseline in SES-CD score.

^h Clinical response is defined as ≥ 100 -point decrease from baseline in CDAI total score.

ⁱ Includes subjects that were biologic naïve and subjects with prior biologic exposure who did not meet criteria for failure. Of these, 8 subjects in the placebo group, 7 subjects in the subcutaneous TREMFYA 100 mg group, and 10 subjects in the subcutaneous TREMFYA 200 mg group were previously exposed to but did not fail a biologic therapy.

Stool Frequency and Abdominal Pain

Greater reductions in stool frequency and abdominal pain were observed as early as Week 4 in subjects treated with TREMFYA 400 mg subcutaneous compared to placebo.

Endoscopic Remission at Week 48

Endoscopic remission was defined as an SES-CD score ≤ 4 and at least a 2-point reduction from baseline and no subscore greater than 1 in any individual component. In CD3, a greater proportion of subjects treated with either TREMFYA regimen (i.e., subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 100 mg at Week 16 and every 8 weeks thereafter or subcutaneous TREMFYA 400 mg at Weeks 0, 4, and 8 followed by subcutaneous TREMFYA 200 mg at Week 12 and every 4 weeks thereafter) achieved endoscopic remission, compared to placebo-treated subjects (31% and 40%, respectively, vs. 6%).

Palmoplantar Pustulosis

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

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

PPPASI and PPSI at Week 16

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

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

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

6. Pharmaceutical Particulars

6.1 List of excipients

Each TREMFYA 1 mL prefilled syringe or One-Press contains 100 mg guselkumab, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection

Each TREMFYA 2 mL prefilled syringe or prefilled pen contains 200 mg guselkumab, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection.

Each TREMFYA 20 mL vial contains 200 mg guselkumab, EDTA disodium dihydrate, L-histidine, L-histidine monohydrochloride monohydrate, L-methionine, polysorbate 80, sucrose and water for injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

TREMFYA is sterile and preservative-free. Discard any unused portion.

- Store in a refrigerator between 2°C to 8°C
- Store in original carton until time of use.
- Protect from light until use.
- Do not freeze.
- Do not shake.
- Not made with natural rubber latex.

Keep out of reach of children.

6.5 Nature and contents of container

TREMFYA 100 mg solution for injection in pre-filled syringe

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

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

TREMFYA 100 mg solution for injection in One-Press

1 mL solution in a pre-filled glass syringe assembled in a One-Press with an automatic needle guard.

TREMFYA is available in a pack containing one One-Press and in a multipack containing 2 (2 packs of 1) One-Press.

TREMFYA 200 mg solution for injection in pre-filled syringe

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

TREMFYA is available in packs containing one prefilled syringe and in multipacks containing 2 (2 packs of 1) pre-filled syringes.

TREMFYA 200 mg PushPen solution for injection in pre-filled pen

2 mL solution in a pre-filled glass syringe assembled in a pre-filled pen with an automatic needle guard.

TREMFYA is available in a pack containing one pre-filled pen and in a multipack containing 2 (2 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

TREMFYA IV 200 mg solution for injection in a single-dose vial.

200 mg solution for infusion in a type I clear glass vial closed with a chlorobutyl rubber stopper, an aluminium seal and polypropylene flip top.

Tremfya is available in a 1 vial pack.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (*Instructions for Use*) before starting TREMFYA therapy, and each time the prescription is renewed, as there may be new information they need to know.

Hypersensitivity Reactions

Advise patients to discontinue TREMFYA and seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [*see Special Warning and Precautions for Use (4.4.1)*].

Infections

Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection [*see Special Warning and Precautions for Use (4.4.2)*].

Tuberculosis

Advise patients to contact their healthcare provider if they experience symptoms suggestive of TB (e.g., unexplained fever, cough, or difficulty breathing) [*see Special Warning and Precautions for Use (4.4.3)*].

Hepatotoxicity

Inform patients that TREMFYA may cause liver injury. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of liver dysfunction (e.g., unexplained rash, nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) [*see Special Warning and Precautions for Use (4.4.4)*].

Immunizations

Advise patients treated with TREMFYA to avoid use of live vaccines [*see Special Warning and Precautions for Use (4.4.5)*].

Crohn's Disease Subcutaneous Induction Dosing Instructions (400 mg Subcutaneous dose)

If patients are to receive the 400 mg subcutaneous induction dosage for Crohn's disease, instruct patients or caregivers to administer two 200 mg prefilled pens or prefilled syringes to achieve the full 400 mg dose [*see Instructions for Use*].

Instruction on Injection Technique

Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique including injection of the full dose [*see Instructions for Use*].

Proper Sharps Disposal Instructions

Counsel patients and caregivers on the proper technique of needle and syringe disposal. Instruct patients to dispose needles and syringes in a puncture-resistant container. Advise patients and caregivers not to reuse needles or syringes.

Administration Instructions

Instruct patients that if they forget to administer a dose of TREMFYA, then they should administer TREMFYA as soon as they remember. Instruct patients to administer the next dose at the regular scheduled time.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in patients exposed to TREMFYA during pregnancy [see *Pregnancy and lactation (4.6.1)*].

7. Marketing Authorization Holder

Janssen-Cilag Ltd., Bangkok, Thailand

8. Marketing Authorization Numbers

Manufactured by	Market Authorization Number	Date of First Authorization
Cilag AG, Schaffhausen, Switzerland	1C 15015/62 (NBC)	26-Feb-2019
	1C 25/68 (NBC)	03-Nov-2025

9. Date of First Authorization

Product Name	Market Authorization Number	Date of First Authorization
TREMFYA	1C 15015/62 (NBC)	26-Feb-2019
TREMFYA IV	1C 25/68 (NBC)	03-Nov-2025

10. Date of revision of the text

USPI version Sep-2025_Safety + JP PPP indication

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com