Data from the **VOYAGE** and **DISCOVER** **TREMFYA® (guselkumab)** Clinical Trials

Presented at the 2021 European Academy of Dermatology and Venereology (EADV) Congress

VOYAGE 1 and **VOYAGE 2** were Phase 3, randomized, double-blind trials comparing TREMFYA with placebo and adalimumab in adult patients with moderate to severe plaque psoriasis (PsO) who were candidates for systemic therapy or phototherapy. Results showed patients treated with TREMFYA, a selective interleukin (IL)-23 inhibitor therapy, had greater improvements in the signs and symptoms of moderate to severe plaque PsO versus placebo and adalimumab based on Psoriasis Area Severity Index (PASI) 90 response and Investigator Global Assessment (IGA) 0/1 at week 16.[1,2]

Separate post-hoc analyses of VOYAGE data being presented at EADV show **TREMFYA provided durable skin clearance responses and was well-tolerated through up to five years (week 252).**

- With TREMFYA, mean percentage improvement from baseline in PASI response at week 48 was 94% compared to 73.4% with adalimumab. At week 252, mean percentage improvement from baseline in PASI response was 92.9% among patients who crossed over at week 48 from adalimumab to TREMFYA (P1432).[3,a]

- Among TREMFYA patients who acheived an absolute PASI ≤2 at week 16, durable maintenance of PASI ≤2 was observed through five years (week 252) (P1318).[4,b]

- Through the end of five years (week 252), 15% of patients developed anti-drug antibodies (ADA) to TREMFYA and of these, 5% (representing 0.8% of all TREMFYA-treated patients) had antibodies that were classified as neutralizing. The development of ADA or neutralizing antibodies were not associated with decreased clinical efficacy or an increase in the incidence of injection site reactions (P1427).[5,c]

- There were no reported opportunistic infections or tuberculosis throughout five years (week 252) of treatment (n=1721 patients, 7,166 patient-years [PYs] of follow up; P1290)[6,d]

- Serious infections and infection-related treatment-emergent adverse events (TEAEs) of special interest were infrequent; the results support TREMFYA as a generally tolerated therapy for the long-term treatment of patients with moderate to severe plaque PsO (P1290)[6-10,d]
Please refer to the Important Safety Information for TREMFYA on page 3.

About Psoriasis

PsO is an immune-mediated disease resulting in an overproduction of skin cells, which causes raised, red, scaly plaques that may be itchy or painful.[11] Nearly one-quarter of all people with PsO have cases that are considered moderate to severe.[12] Living with PsO can be a challenge and impact life beyond a person's physical health, including emotional health, relationships, and handling the stressors of life.[13]

- Moderate PsO covers between 3 and 10% of the body.[14]
- Severe PsO covers more than 10% the body.[14]

Psoriasis Area and Severity Index

PASI 75/90/100 responses are defined as at least 75/90/100 percent improvement in the PASI score from baseline. The PASI score grades the amount of surface area covered by PsO plaques in each body region, and the degree of plaque redness, thickness, and scaliness.[15]

Absolute PASI

The achievement of an absolute PASI score lower than 2 or 3 has been proposed as an indication of treatment success. A score exceeding 5 usually indicates that an alteration of treatment is needed.[16]

DISCOVER-1 and -2 are Phase 3, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of TREMFYA in adult patients with active psoriatic arthritis (PsA). Results showed that patients treated with TREMFYA had greater improvements in the signs and symptoms, including joint symptoms, of active PsA based on American College of Rheumatology 20 (ACR 20) response compared with placebo at week 24.[17,18]

Separate post-hoc analyses of DISCOVER data presented at EADV show **TREMFYA provided improvement in the signs and symptoms of active PsA, including axial symptoms, and was well-tolerated through one year (week 52).**

- TREMFYA treatment resulted in lower mean scores for all six Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) components and greater improvements in Ankylosing Spondylitis Disease Activity Score (ASDAS) compared with placebo through week 24 and as early as week 8, with similar mean scores at week 52 in patients with axial symptoms and sacroiliitis (P1434).[19,e]

- TREMFYA showed improvement in signs and symptoms of active PsA regardless of patients' baseline characteristics (P1428).[20,f]
    - Week 24 ACR 20 response rates showed overall continued improvement at week 52 in the TREMFYA 100mg every 4 weeks (q4w) (72%) and every 8 weeks (q8w) (70%) groups and also within multiple patient subgroups defined by baseline patient and disease characteristics. ACR 50 and 70 response patterns were similar to ACR 20.
    - Week 24 cleared or almost cleared skin response rates were similar at week 52 in the overall TREMFYA q4w (80%) and q8w (71%) groups and also within patient subgroups assessed.
      TREMFYA is not approved in the U.S. for q4w dosing.

- Time-adjusted (per 100 PYs) incidence rates for serious adverse events (AEs), serious infections, malignancy, major adverse cardiovascular events (MACE), and AEs leading to discontinuation were low and generally similar between TREMFYA PsO and PsA patient populations. No anaphylaxis, serum sickness-like reactions, opportunistic infections, or active tuberculosis were reported in TREMFYA-treated patients through one year of treatment (P1466).[21,g]
  Please refer to the Important Safety Information for TREMFYA on page 3.

About Psoriatic Arthritis
PsA is a chronic, immune-mediated disease characterized by psoriatic skin lesions, as well as by joint pain, stiffness and swelling in the fingers, toes, or lower back. Symptoms such as pain and fatigue and other related health concerns can increase the risk of anxiety and depression in people with PsA.[22]

About Sacroiliitis
Sacroiliitis occurs in the PsA subtype of spondylitis, where inflammation reaches the spine and causes stiffness as well as pain and difficulty moving the neck, lower back, sacroiliac joints, and pelvis. This type of PsA can also affect joints in the arms, legs, hands, and feet. Occurs in 5-28% of patients with early PsA, and in over 40% of patients with established disease.[23,24]

BASDAI
A six-item questionnaire using a 0-10 rating scale to assess the severity of the symptoms of ankylosing spondylitis, including fatigue, spinal pain, peripheral joint pain, pain at entheseal sites, severity of morning stiffness, and duration of morning stiffness. BASDAI has demonstrated statistically significant reliability.[25]

ASDAS
A composite index to measure disease activity in ankylosing spondylitis based on patient assessment of symptoms (0-10 rating scale for back pain, duration of morning stiffness, patient global assessment, peripheral pain and swelling,) and laboratory data from blood tests. The ASDAS-CRP (preferred clinical standard) incorporates levels of C-reactive protein, which increase when inflammation is present in the body, in the ultimate composite score.[26]

ACR
At least 20/50/70 percent improvement from baseline in both the number of tender and number of swollen joints, and at least 20/50/70 percent improvement from baseline in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein.[27]

Important Safety Information

What is the most important information I should know about TREMFYA®?
TREMFYA® is a prescription medicine that may cause serious side effects, including:

- **Serious Allergic Reactions.** Stop using TREMFYA® and get emergency medical help right away if you develop any of the following symptoms of a serious allergic reaction:
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - swelling of your face, eyelids, lips, mouth, tongue or throat
  - trouble breathing or throat tightness
  - chest tightness
  - skin rash, hives
  - itching

- **Infections.** TREMFYA® may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with TREMFYA® and may treat you for TB before you begin treatment with TREMFYA® if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with TREMFYA®.

  Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:
  - fever, sweats, or chills
  - muscle aches
  - weight loss
  - cough
  - warm, red, or painful skin or sores on your body different from your psoriasis
  - diarrhea or stomach pain
  - shortness of breath
  - blood in your phlegm (mucus)
  - burning when you urinate or urinating more often than normal

Do not take TREMFYA® if you have had a serious allergic reaction to guselkumab or any of the ingredients in TREMFYA®.

Before using TREMFYA®, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about TREMFYA®?"**
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with TREMFYA®.
- are pregnant or plan to become pregnant. It is not known if TREMFYA® can harm your unborn baby.

- are breastfeeding or plan to breastfeed. It is not known if TREMFYA® passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

What are the possible side effects of TREMFYA®?
TREMFYA® may cause serious side effects. See "What is the most important information I should know about TREMFYA®?"

The most common side effects of TREMFYA® include: upper respiratory infections, headache, injection site reactions, joint pain (arthralgia), diarrhea, stomach flu (gastroenteritis), fungal skin infections, herpes simplex infections, and bronchitis.

These are not all the possible side effects of TREMFYA®. Call your doctor for medical advice about side effects.

Use TREMFYA® exactly as your healthcare provider tells you to use it.

Please read the full Prescribing Information, including Medication Guide for TREMFYA®, and discuss any questions that you have with your doctor.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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About VOYAGE 1[1]
Patients were randomized to receive placebo (n=174) at weeks 0, 4 and 12, followed by crossover to TREMFYA (n=165) at weeks 16 and 20 followed by every q8w dosing; TREMFYA 100 mg (n=329) at weeks 0, 4 and 12, followed by q8w dosing; or adalimumab 80 mg (n= 334) at week 0, followed by 40 mg at week 1, then dosing every two weeks (q2w) through week 47, with crossover to TREMFYA q8w at week 52. The co-primary endpoints were the proportions of patients receiving TREMFYA vs. patients receiving placebo achieving Investigator's Global Assessment (IGA) 0/1 (clear/almost clear) [73% vs. 3%, respectively; p<0.001 vs. placebo] and PASI 90 [85% vs. 7%, respectively; p<0.001 vs. placebo] at week 16. Through week 48, non-responder imputation (NRI) rules were used for missing data (after the application of Treatment Failure Rules [TFR] where patients discontinuing due to lack of efficacy, worsening of PsO, or use of a prohibited treatment were considered non-responders). During the open-label extension period, which started at week 52, all patients continued open-label treatment with TREMFYA through week 252. Efficacy assessments included proportions of patients achieving PASI 90, PASI 100, IGA of 0/1, and IGA of 0. Efficacy was analyzed using prespecified TFR for the primary analysis, while NRI and observed (OBS) methodologies were used for the secondary analyses.

About VOYAGE 2[2]

Patients (N=992) were randomized to receive SC injections of TREMFYA 100 mg (n=496) at weeks 0, 4 and q8w thereafter; placebo (n=248) at weeks 0, 4, and 12 followed by crossover to TREMFYA 100 mg at week 16; or adalimumab 80 mg (n=248) at week 0, 40 mg at week 1, then 40 mg q2w until week 23. Weeks 28-72 incorporated a randomized withdrawal study design. During the open-label period (weeks 76-252), all patients received TREMFYA 100 mg q8w. Physician- and patient-reported outcomes were assessed. Efficacy was analyzed using pre-specified TFR. Data were combined for patients randomized to TREMFYA and for those originally randomized to placebo who later crossed over to TREMFYA at week 16. Patients were treated and followed for up to 264 weeks. Co-primary endpoints of the study were proportions of patients receiving TREMFYA vs. patients receiving placebo achieving IGA 0/1 (clear/almost clear) [84% vs. 9%, respectively; p<0.001 vs. placebo] and PASI 90 [70% vs. 2%, respectively; p<0.001 vs. placebo] at week 16. Efficacy was analyzed using pre-specified TFR, NRI, and OBS methodologies.

About DISCOVER-1[14]

DISCOVER-1 is a Phase 3 study of TREMFYA in participants with active PsA (n=381) who had inadequate response to standard therapies, including participants previously treated with anti-tumor necrosis factor (TNF) alpha biologics. Group 2 participants received subcutaneous (SC) TREMFYA 100 mg at weeks 0 and 4, then q8w (weeks 12, 20, 28, 36, and 44) and placebo injections at other visits (weeks 8, 16, 24, 32, 40, 48) to maintain the blind. Group 3 participants received SC placebo q4w from week 0 to week 20, and crossover at week 24 to receive TREMFYA 100 mg q4w from week 24 through week 48. Efficacy was assessed using the proportion of patients achieving ACR20 response (59% and 52% respectively, vs. 22 percent on placebo) at week 24 as a primary endpoint, as well as change from baseline in HAQ-DI scores, ACR50, and IGA of 0/1.

About DISCOVER-2[15]

DISCOVER-2 is a Phase 3 study of TREMFYA in participants (n=739) with active PsA who are biologic naive and have had inadequate response to standard therapies. Patients were divided into three groups with different dosing regimens: Group 1 participants received SC TREMFYA 100 mg q4w from week 0 through week 100. Group 2 participants received SC TREMFYA 100 mg at weeks 0 and 4 then q8w (weeks 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, and 100) and placebo injections at other visits (weeks 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, and 96) to maintain the blind. Group 3 participants received SC placebo q4w from week 0 to week 20 and crossed over at week 24 to receive SC TREMFYA 100 mg q4w from week 24 through week 100. Efficacy was assessed using the proportion of patients achieving ACR20 response (64% vs. 33% on placebo) at week 24 as a primary endpoint, as well as change from baseline in HAQ-DI scores, ACR50, and IGA of 0/1.

Details of Post-Hoc Analyses

a. Patients randomized to TREMFYA at baseline were combined with those randomized to placebo who crossed over to TREMFYA at week 16 to form the TREMFYA group (n=468) from week 52. Treatment groups analyzed included the TREMFYA group and adalimumab with crossover to TREMFYA group (n=279).[2]
b. Absolute PASI thresholds of 0, ≤1, ≤2, ≤3, and ≤5 were evaluated through week 252 among patients randomized to TREMFYA at baseline who achieved absolute PASI ≤2 at week 16.[3]
c. The incidence and titres of ADA were summarized through week 264 for all patients who were treated with at least one dose of TREMFYA and who had evaluable serum samples following treatment. The incidence of neutralizing antibodies (NAb) to TREMFYA was summarized among patients positive for ADA. The proportions of patients achieving clinical response at week 252 or experiencing ISRs at week 264 were evaluated by positive/negative ADA status. Clinical response was defined as the achievement of at least 90% improvement or 100% improvement in the Psoriasis Area and Severity Index (PASI 90 and PASI 100, respectively) and a score of 0/1 (clear or minimal) or 0 (complete clearance) on the Investigator's Global Assessment (IGA 0/1 and IGA 0, respectively).[4]
d. The analysis included data from VOYAGE 1 and VOYAGE 2. In VOYAGE 2, all patients entered a randomized withdrawal and TREMFYA retreatment period from week 28 to week 72; from week 76 through the end of the study, all patients received open-label TREMFYA q8w. Pooled safety data were analyzed in the TREMFYA group, the adalimumab with crossover to TREMFYA group, and the combined TREMFYA group. Infection-related

outcomes of interest included rates per 100 PY of overall, serious, and opportunistic infections (including active tuberculosis), along with TEAEs of Candida and herpes zoster infections.[6]

e. Included 312 patients identified by the investigator as having axial symptoms and sacroiliitis (based on prior X-ray or magnetic resonance imaging or screening X-ray). BASDAI scores were assessed at week 0, 8, 16, 24, and 52. Mean BASDAI component scores (0, "none"; 10, "very severe") were analyzed using OBS data; total BASDAI scores with missing components were set to missing. Patients with missing data or who met treatment failure criteria were considered non-responders at all subsequent timepoints. Axial endpoints were summarized by baseline HLA-B*27 status.[18]

f. Patients randomized to placebo received TREMFYA 100 mg q4w starting at week 24 and were excluded from these analyses assessing maintenance of effect from week 24 to week 52. TREMFYA effects on joint (ACR20/50/70) and skin (IGA=0/1 + ≥2-grade reduction from baseline] in patients with ≥3% body surface area [BSA] with PsO and IGA ≥2 at baseline) endpoints were evaluated by patient baseline demographics (sex and body mass index), skin (% BSA with PsO, PASI score, and IGA score) and joint characteristics, C reactive protein level, PsA duration, and conventional synthetic disease-modifying antirheumatic drug (csDMARD) use. Missing data were imputed as non-response through week 52.[19]

g. AEs and laboratory parameters, analyzed by National Cancer Institute-Common Terminology Criteria for AEs, toxicity grades, were summarized through the placebo-controlled and one-year periods.[21]

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