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Role of Spevigo® (spesolimab-sbzo) Injection in the Treatment of Generalized Pustular Psoriasis

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening, and chronic neutrophilic skin disease.^{1,2} Characterized by flares of unpredictable duration and severity, GPP can result in more inpatient visits and a longer length of hospital stay, as well as increased outpatient and emergency department (ED) visits relative to patients in the general population, creating a burden for patients and the health care system.³⁻⁵ According to a patient survey published in 2022, the chronic and unpredictable nature of GPP causes a constant emotional and physical burden.¹

Historically, treatment options for GPP (eg, topical steroids, tumor necrosis factor [TNF] inhibitors, and methotrexate) have been limited.^{5,6} A consensus statement published by the National Psoriasis Foundation advocates for timely access to FDA-approved treatments for GPP.⁷ Spevigo® (spesolimab-sbzo) injection is the first and only FDA-approved agent for the treatment of GPP in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.^{8,9} This article provides an overview of GPP and its clinical and economic impact, and reviews findings of Effisayil® 2, the first trial to study subcutaneous (SC) SPEVIGO in patients with GPP when not experiencing a flare.¹⁰

INDICATION

SPEVIGO is indicated for the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.

IMPORTANT SAFETY INFORMATION CONTRAINDICATIONS

SPEVIGO is contraindicated in patients with severe or life-threatening hypersensitivity to spesolimab-sbzo or to any of the excipients in SPEVIGO. Reported hypersensitivity reactions have included drug reaction with eosinophilia and systemic symptoms (DRESS).

WARNINGS AND PRECAUTIONS

Infections: SPEVIGO may increase the risk of infections. In patients with a chronic infection or a history of recurrent infection, consider the potential risks and expected clinical benefits of treatment prior to prescribing SPEVIGO. Treatment with SPEVIGO is not recommended in patients with any clinically important active infection until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur during or after treatment with SPEVIGO. If a patient develops a clinically important active infection, discontinue SPEVIGO therapy until the infection resolves or is adequately treated.

Please see **Prescribing Information for SPEVIGO,**
including **Medication Guide and Instructions for Use.**

OVERVIEW

GPP flares are characterized by widespread eruption of pustules, erythema, and scaling on large areas of the body, arms, and legs.^{2,11-13} Potentially life-threatening complications that require emergency treatment can occur in patients with GPP.^{14,15} These could include sepsis, severe infection, and organ failure such as heart, kidney, hepatic, and respiratory failure.¹⁵ Between flares, approximately 83% of dermatologists and 74% of patients report residual skin symptoms.^{2,16} GPP flares can be unpredictable, even in patients who are otherwise well managed.³

GPP is phenotypically and genetically different from plaque psoriasis (PsO).^{2,11,14,17} Unlike PsO, GPP may be life-threatening, and it could cause hepatic, renal, respiratory, and cardiovascular failure.¹⁴ In GPP, erythema and scaling may take up to 3 months to resolve.² Whereas PsO is driven by interleukin (IL)-23/IL-17 and involves adaptive responses and autoimmunity,¹⁸ the pathology of GPP is thought to be driven primarily by the IL-36 pathway.¹⁹ Dysregulated IL-36 receptor (IL-36R) signaling leads to a neutrophilic inflammatory response and the eruption of pustules, a distinct GPP flare syndrome.^{13,20}

Although GPP is rare, it can occur more frequently among certain groups in the United States. The prevalence range is 7 to 9 cases per 100,000 patients.²¹ Incidence peaks at 40 to 59 years of age.^{14,22} In the United States, approximately 4000 patients seek treatment across a 5-year period.²³⁻²⁵ Not all patients who experience a flare are captured within this figure, however, as they may not seek care at the time of the flare.²⁴

CLINICAL IMPACT

Patients with GPP can experience symptoms for years before receiving a diagnosis. Results of an analysis of an online survey of 66 patients with GPP conducted in 2020 showed that variability of health care practitioner (HCP) knowledge led to misdiagnosis and delays in treatment. Further, 51% of patients reported having to visit multiple HCPs/specialists before a diagnosis was made.¹

Moreover, flare episodes are frequently identified in a variety of high-cost health care settings. In a retrospective cohort study of electronic health record (EHR) data from 1535 adult patients with GPP, 45% of flare episodes were identified at inpatient (36%) and ED (9%) sites. Results of the study, which used data from the Optum database (2015-2020), demonstrated that 83% of flare episodes identified in the outpatient setting were treated by specialists.²⁶

The clinical burden remains high after flares, which are common in patients with this chronic inflammatory disease.^{27,28} Results of a retrospective study of medical records (2005-2019) from 5 university medical centers demonstrated that among 85 patients with GPP who had clear documentation, 63 (74.1%) had chronic symptoms at their last visit with their HCP.¹⁶ Indeed, approximately 1 of 3 of patients demonstrate persistent pustular lesions, even when receiving systemic therapy.²⁹ In a retrospective study of longitudinal EHR data (2007-2018) involving 95 adults with GPP, approximately 36% of patients with at least 6 months of follow-up data (n/N = 19/53) were hospitalized for GPP symptoms after an initial encounter.³⁰

The duration and severity of GPP flares is unpredictable; flares could last weeks to months and could require extended hospitalizations.^{3,5} In a retrospective study of medical data for 53 patients enrolled in the Effisayil® 1 trial, 85.8% of patients reported their longest past flare lasting 3 weeks or longer, and 28.6% had flares lasting 12 weeks or longer. Furthermore, 74.2% of patients required hospitalization for their most severe flare, with a typical stay lasting 1 to 2 weeks.⁵

Results of a study of outpatient EHR data (2017-2023) drawn from 6 specialty dermatology networks demonstrated that, among 404 patients with GPP who experienced a flare, 66% had a subsequent flare within 6 months, and 87% had a subsequent flare within 1 year.³¹

Patients with GPP have a higher risk of all-cause mortality compared with matched general population and PsO cohorts. In a study of Inovalon Insights claims data (2015-2020), 2630 patients with GPP, 128,924 matched patients with PsO, and 19,641,441 matched patients in the general population were identified. For patients with GPP

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Risk of Tuberculosis: Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SPEVIGO. Avoid use of SPEVIGO in patients with active TB infection. Consider initiating anti-TB therapy prior to initiating SPEVIGO in patients with latent TB or a history of TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SPEVIGO treatment.

Hypersensitivity and Infusion-Related Reactions:

- SPEVIGO-associated hypersensitivity reactions may include immediate reactions, such as anaphylaxis, and delayed reactions, such as drug reaction with eosinophilia and systemic symptoms (DRESS).
- Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in clinical trials with spesolimab-sbzo in subjects with GPP.
- If a patient develops signs of anaphylaxis or other serious hypersensitivity, discontinue SPEVIGO immediately and initiate appropriate treatment.

and/or PsO, all-cause mortality was assessed from time of diagnosis until the study period ended or the patient experienced an event (maximum follow-up). At maximum follow-up, patients with GPP had a 3.98-times higher risk of all-cause mortality versus the general population (95% CI, 2.92-5.43; $P < .001$) and a 1.49-time higher risk versus the PsO cohort (95% CI, 1.20-1.85; $P < .001$).³²

ECONOMIC IMPACT

Patients with GPP place a significant burden on health care resources. In the aforementioned study of Inovalon Insights data, relative to patients with PsO, patients with GPP had 51% more outpatient visits, a 48% higher likelihood of having an ED visit, and a 63% higher likelihood of having an inpatient visit.³²

In a separate study of IBM MarketScan Research Database data (2015-2018), 637 patients with GPP had inpatient visits at roughly twice the rate as matched general population controls in the 12 months after index diagnosis (12.2% vs 6.2%, respectively). During this period, patients with GPP also had a longer mean (SD) length of hospital stay (11.5 [16.0] vs 6.7 [7.8] days, respectively).⁴

GPP is associated with lost productivity and related costs. A retrospective cohort study of OptumHealth Care Solutions private-payer employer database data from 2015 to 2017 analyzed indirect costs for 66 adults with GPP aged 18 to 64 years. When compared with a non-GPP control group, patients with GPP had higher odds of medically related absenteeism (OR, 40.8; 95% CI, 5.5-301.4). These patients also had more days per month of medically related absenteeism (rate ratio, 2.1; 95% CI, 1.7-2.6) and higher odds of taking a leave of absence (OR, 8.5; 95% CI, 1.04-69.2) along with higher absenteeism costs (mean difference, \$83; $P = .001$).³³

HISTORICAL TREATMENT OPTIONS

Treatment goals should address the chronic and heterogenous nature of GPP.²⁸ Treatment options for GPP have been limited.⁵ A real-world study demonstrated that patients with GPP are treated

with medications indicated or typically used for PsO such as topical steroids, TNF inhibitors, and methotrexate.⁶

In the current landscape, treatment discontinuation rates are high regardless of initial treatment.^{30,34} Results of a retrospective study of EHR data (2017-2023) for patients with GPP demonstrated that 360 days after treatment initiation, 83% of patients treated with a biologic ($n = 30$) and 96% of patients treated with other systemic agents ($n = 41$) had discontinued treatment.³⁴

A consensus statement published by the National Psoriasis Foundation advocates timely access to FDA-approved therapies for GPP.⁷

SPEVIGO FOR GPP

SPEVIGO is the first and only FDA-approved agent for the treatment of GPP in adults and pediatric patients 12 years of age and older and weighing at least 40 kg.^{8,9} SPEVIGO inhibits IL-36 signaling by binding to the IL-36R, preventing subsequent activation of IL-36R1.⁹ SPEVIGO was studied in 2 multicenter, randomized, placebo-controlled trials.^{9,35,36}

EFFISAYIL 1 (NCT03782792) was a multicenter, randomized, double-blind, placebo-controlled trial of intravenous (IV) SPEVIGO in patients with GPP presenting with a flare.^{9,35} EFFISAYIL 2 (NCT04399837) was the first trial to study SC SPEVIGO in patients with GPP when they were not experiencing a flare.^{9,36}

EFFISAYIL 2 Trial

Study Objectives

Primary objectives for the 48-week EFFISAYIL 2 trial ($N = 123$) included demonstrating a non-flat dose response curve and evaluating the dose-response relationship for 3 SC dosing regimens of SPEVIGO versus placebo on the primary end point, which was the time to the first GPP flare onset up to week 48. If the primary objective was met, the secondary objective was to demonstrate superiority versus placebo for each of the regimens known as SPEVIGO-High (300 mg SC given every 4 weeks) and SPEVIGO-Medium (300 mg SC given every 12 weeks) on the primary end point (the time to the first GPP flare onset

IMPORTANT SAFETY INFORMATION (Continued) WARNINGS AND PRECAUTIONS (Continued)

Hypersensitivity and Infusion-Related Reactions (Continued):

- If a patient develops mild or moderate hypersensitivity during an intravenous infusion or other infusion-related reactions, stop SPEVIGO infusion and consider appropriate medical therapy (eg, systemic antihistamines and/or corticosteroids). Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion.

Vaccinations: Prior to initiating SPEVIGO for treatment of GPP, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid use of live vaccines in patients during and for at least 16 weeks after treatment with SPEVIGO. No specific studies have been conducted in SPEVIGO-treated patients who have recently received live viral or live bacterial vaccines.

up to week 48) and the key secondary end point (the occurrence of at least 1 GPP flare up to 48 weeks).³⁶

Inclusion Criteria

Select inclusion criteria included adolescents and adults aged 12 to 75 years with a weight of at least 40 kg, a documented diagnosis of GPP as defined by the European Rare and Severe Psoriasis Expert Network, a history of at least 2 GPP flares in a lifetime with fresh pustulation (new appearance or worsening), and a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of zero or 1 point at screening and randomization. Patients not on concurrent GPP treatment at randomization must have had at least 2 moderate to severe flares in the previous year, at least 1 of which must have been associated with systemic symptoms.³⁶

Additionally, patients on concurrent GPP treatment in the 12 weeks prior to randomization were required to have a history of flaring during, or after dose reduction or discontinuation of, concurrent treatment and were required to stop concurrent treatment with retinoids, methotrexate, and/or cyclosporin on the day of randomization.³⁶

Exclusion Criteria

Patients were required to have a diagnosis of GPP and a history of GPP flares but could not be experiencing a flare at screening and randomization.^{9,36}

Patients who presented with any of the following were excluded from the EFFISAYIL 2 trial: synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome; primary erythrodermic psoriasis vulgaris; severe, progressive, or uncontrolled hepatic disease; and treatment with a restricted medication, any drug the investigator considered could interfere with the safe conduct of the study, or prior exposure to SPEVIGO or another IL-36 receptor inhibitor biologic agent. Patients also could not take a biologic treatment in the 12 weeks prior to randomization (or 5 half-lives, whichever was shorter) or use systemic immunomodulatory treatments such as corticosteroids in the 4 weeks prior to randomization.³⁶

Study End Points

The primary end point of EFFISAYIL 2 was time to first GPP flare, defined as a GPPPGA pustulation subscore of at least 2 points and an increase of at least 2 points in GPPPGA total score from baseline, up to week 48. The key secondary end point was the occurrence of at least 1 GPP flare, defined by an increase in GPPPGA score by at least 2 points from baseline and the pustular component of GPPPGA by at least 2 points, up to week 48.^{9,36}

Other secondary, exploratory end points included time to first worsening of the Psoriasis Symptoms Scale score, defined as at least a 4-point increase in total score from baseline, up to week 48; time to first worsening of Dermatology Life Quality Index, defined as at least a 4-point increase in total score from baseline, up to week 48; and sustained remission defined as a GPPPGA score 0 or 1 point at all visits up to week 48 without intake of open-label SPEVIGO or investigator-prescribed other medication for GPP.³⁶

The safety end point included occurrence of treatment-emergent adverse events (TEAEs) by week 48.³⁶

GPPPGA Score

The GPPPGA is used to evaluate flare symptoms and treatment efficacy. The severity of pustules, scaling, and erythema is assessed using a 5-point scale ranging from 0 to 4 points, with higher scores indicating greater disease severity. The GPPPGA is not used in clinical practice.³⁷

Results: Primary End Point

The [Figure](#) shows the Kaplan-Meier curve illustrating the estimated probability of a first GPP flare over 48 weeks. The steps in the graph represent GPP flares that occurred in individual patients. The numbers below the graph correspond with the number of patients remaining in each dosing group who are at risk for a GPP flare at that point in time.^{9,10}

SPEVIGO reached statistical significance compared to placebo with respect to time to development of first GPP flare. The high-dose SC SPEVIGO group experienced only 3 flare events, all occurring within the first 4 weeks. After week 4, no additional at-risk patients

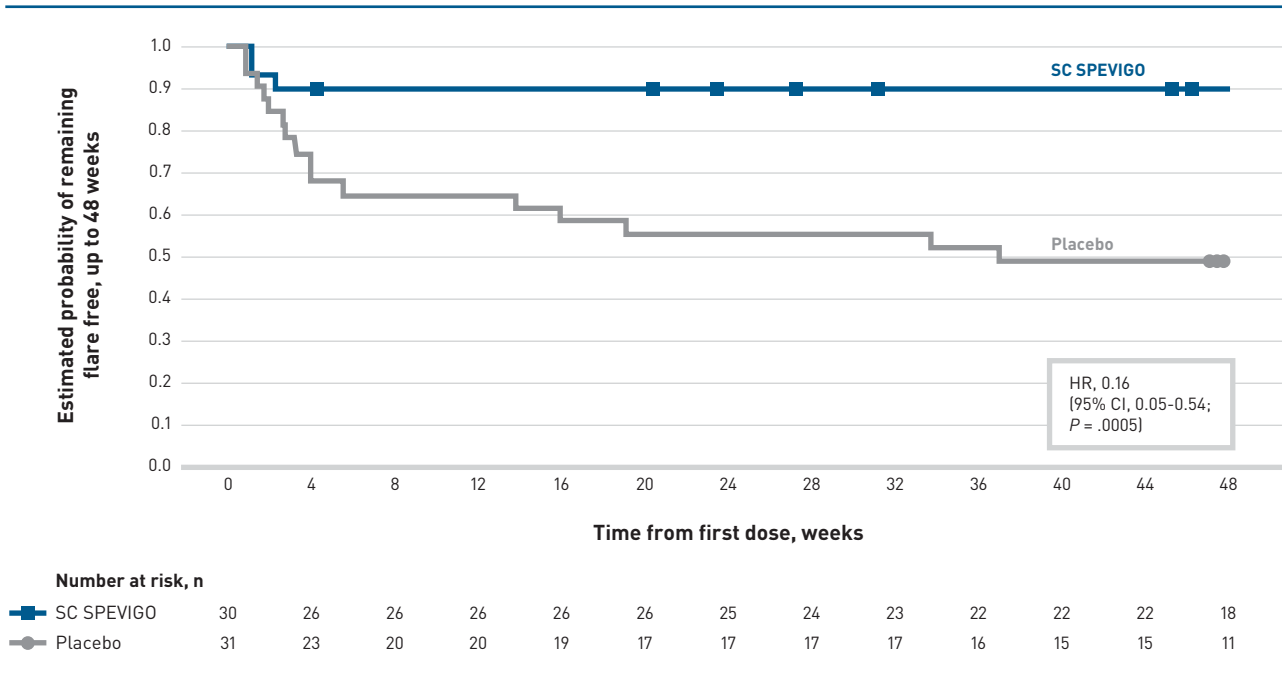
IMPORTANT SAFETY INFORMATION (Continued) ADVERSE REACTIONS

Intravenous SPEVIGO for Treatment of GPP Flare (Study Effisayil-1): Most common adverse reactions reported in $\geq 5\%$ of patients treated with SPEVIGO in the clinical trial were asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, and urinary tract infection (UTI).

Specific Adverse Reactions

- **Infections:** The most frequent adverse reactions that occurred in subjects treated with intravenous SPEVIGO were infections. During the 1-week placebo-controlled period in Study Effisayil-1, infections were reported in 14% of subjects treated with SPEVIGO compared with 6% of subjects treated with placebo. Serious infection (UTI) was reported in 1 subject (3%) in the SPEVIGO group and no subjects in the placebo group. Infections observed through Week 1 in Study Effisayil-1 in subjects treated with SPEVIGO were mild (29%) to moderate (71%).
- **Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS):** Two cases of DRESS were reported in Study Effisayil-1 in subjects with GPP who were treated with intravenous SPEVIGO. RegiSCAR DRESS validation scoring (with the following categories: “no,” “possible,” “probable,” or “definite” DRESS) was applied to the reported cases. Reported cases were assessed as “no DRESS” and “possible DRESS.”

Figure. Time to First GPP Flare up to Week 48 in Adults and Pediatric Subjects (12 Years and Older and Weighing at least 40 kg) With a History of GPP in Study EFFISAYIL 2 (SC SPEVIGO)^{9,10}



GPP, generalized pustular psoriasis; SC, subcutaneous.

in the high-dose SC SPEVIGO group experienced a flare event for the duration of the 48-week study.¹⁰

Results: Key Secondary End Point

The key secondary end point was also achieved. The results showed that 87.3% of patients in the high-dose SC SPEVIGO group (exposure adjusted) did not experience a flare event while they were on treatment in the trial, compared to 48.4% of patients in the placebo group.¹⁰

Adverse Reactions

AEs occurring during the randomized treatment period are summarized in the [Table](#).⁹ All patients in EFFISAYIL 2 who received SC SPEVIGO are included in the adverse reaction reporting.⁹ Injection-site reactions were reported with SC SPEVIGO, most commonly as injection-site erythema, but did not lead to treatment discontinuation. Three patients discontinued SC SPEVIGO due to TEAEs of psoriasis compared to no patients in the placebo group.¹⁰

IMPORTANT SAFETY INFORMATION (Continued)
ADVERSE REACTIONS (Continued)

Subcutaneous SPEVIGO for Treatment of GPP When Not Experiencing a Flare (Study Effisayil-2): Regarding the exposure-adjusted incidence rates for subjects on randomized treatment prior to receiving rescue treatment for flare or completing trial without a flare, the rate per 100-patient years for injection site reaction (including erythema, pain, swelling, induration, urticaria, and warmth at the injection site) was 31.6 for the subcutaneous SPEVIGO cohort (600 mg loading dose followed by 300 mg every 4 weeks) vs 12.7 for the placebo cohort. The rate per 100-patient years for UTI was 18 for SPEVIGO vs 0 for placebo. The rate per 100-patient years for pruritus was 8.8 for SPEVIGO vs 0 for placebo. The rate per 100-patient years for arthralgia was 13.3 for SPEVIGO vs 6 for the placebo cohort. There were 3 subjects who discontinued subcutaneous SPEVIGO due to treatment-emergent adverse events of psoriasis compared to no subjects in the placebo cohort who discontinued placebo for any treatment-emergent adverse event.

The safety profile of open-label SC SPEVIGO use after treatment of GPP flare with open-label IV SPEVIGO use was consistent with the safety profiles of use of SPEVIGO from EFFISAYIL 1 and randomized controlled data from EFFISAYIL 2.⁹

Available Formulations

SPEVIGO is available in 2 formulations. The SC formulation can be used to treat GPP when patients are not experiencing a flare or when initiating or reinitiating SC SPEVIGO after treatment of a GPP flare with IV SPEVIGO. The IV formulation can be used to treat patients experiencing a GPP flare.⁹

Potential Scenarios Leading to SC Therapy

For treatment initiation, a patient may have a GPP flare and receive SPEVIGO IV 900 mg as treatment and then receive subsequent doses of SC SPEVIGO 300 mg via prefilled syringe every 4 weeks. A loading dose is not required if dosing is initiated at 4 weeks after

receiving IV treatment. A non-flaring patient prescribed SC therapy may receive a loading dose of SC SPEVIGO 600 mg (4 × 150 mg) via prefilled syringe followed by a subsequent dose of SC SPEVIGO 300 mg (2 × 150 mg) via prefilled syringe every 4 weeks. For treatment continuation, in the absence of a flare, a patient would be expected to receive a dose of SC SPEVIGO 300 mg (2 × 150 mg) via prefilled syringe every 4 weeks.^{9,23}

Testing and Procedures Prior to Treatment Initiation

Patients with GPP should be evaluated for active or latent tuberculosis (TB) infection. SPEVIGO initiation is not recommended in patients with active TB infection. Prior to initiation of SPEVIGO, initiation of treatment for latent TB should be considered and all age-appropriate vaccinations should be completed according to current immunization guidelines.⁹

CONCLUSIONS

Treatment goals for GPP should address the chronic and heterogeneous nature of GPP.²⁸ GPP is a debilitating systemic skin disease with life-threatening potential.² Patients with GPP have a high mortality risk compared to those with PsO and the general population.³² This chronic condition often relapses over time.²⁷

In the EFFISAYIL 2 trial, SC SPEVIGO reduced the risk of GPP flares over 48 weeks versus placebo.^{9,10} In all, 87.3% of patients in the SC SPEVIGO group (exposure adjusted) did not experience a flare as compared to 48.4% of patients in the placebo group.¹⁰ A consensus statement published by the National Psoriasis Foundation advocates for timely access to FDA-approved therapies for GPP.⁷ •

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Table. Adverse Reactions With SC SPEVIGO for Treatment of GPP When Not Experiencing a Flare (EFFISAYIL 2): Exposure-Adjusted Incidence Rates Per 100-Patient Years Through Week 48^{9,a,b}

Adverse reaction	SPEVIGO N = 30	Placebo N = 30
Injection site reactions ^c	31.6	12.7
Urinary tract infection	18	0
Pruritus	8.8	0
Arthralgia	13.3	6

GPP, generalized pustular psoriasis; SC, subcutaneous.

^aAll patients in EFFISAYIL 2 who received SC SPEVIGO are included in Adverse Reaction reporting.

^bIncidence rates include subjects on randomized treatment prior to receiving rescue treatment for flare or completing the trial without a flare.

^cIncludes erythema, pain, swelling, induration, urticaria, and warmth at the injection site. Injection site reactions observed in EFFISAYIL 2 were typically mild to moderate in severity.

IMPORTANT SAFETY INFORMATION (Continued) ADVERSE REACTIONS (Continued)

Safety in Study Effisayil-2 After Flare: In Effisayil-2, subjects who experienced a GPP flare and received at least one dose of an open-label single intravenous 900 mg dose of SPEVIGO were treated with open-label subcutaneous SPEVIGO 300 mg. These subjects (n=19) received subcutaneous dosing at every 12 weeks, which could have been increased to every 4 weeks based on GPPGA total score or pustulation subscore increased by ≥1 from any previous open-label maintenance visit. The reported safety profile of open-label subcutaneous SPEVIGO use after treatment of GPP flare with open-label intravenous SPEVIGO use was consistent with the safety profiles of use of SPEVIGO from Trial Effisayil-1 and randomized controlled data from Trial Effisayil-2.

Clinical Development of Spesolimab-sbzo

- **Guillain-Barre Syndrome (GBS):** Among approximately 835 subjects exposed to spesolimab-sbzo during clinical development, GBS was reported in 3 subjects who received various doses of spesolimab-sbzo via various methods of administration in clinical trials for unapproved indications.

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IMPORTANT SAFETY INFORMATION (Continued) SPECIFIC POPULATIONS

Pediatric Use: The safety and effectiveness of SPEVIGO for the treatment of GPP have been established in pediatric patients 12 years of age and older and weighing at least 40 kg. Use of SPEVIGO for this indication is supported by data from a randomized, placebo-controlled study, which included 6 pediatric subjects 14 to 17 years of age with a history of GPP treated with subcutaneous SPEVIGO (Study Effisayil-2), and evidence from an adequate and well-controlled study of intravenous SPEVIGO in adults with GPP (Study Effisayil-1), with additional pharmacokinetic analyses showing similar drug exposure levels in adults and pediatric subjects 12 years of age and older and weighing 40 kg or more. The safety and effectiveness of SPEVIGO in pediatric patients younger than 12 years of age or in pediatric patients weighing less than 40 kg have not been established.

Please see [Prescribing Information](#) for SPEVIGO, including [Medication Guide](#) and [Instructions for Use](#).

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