Spesolimab-sbzo (SPEVIGO) in Generalized Pustular Psoriasis
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Spesolimab-sbzo (from here on referred to as spesolimab) is a humanized monoclonal IgG1 antibody against human interleukin-36 receptors (IL-36Rs).[1] Binding to the IL-36R leads to inhibition of downstream pro-inflammatory and pro-fibrotic pathways. The mechanism of spesolimab effects in generalized pustular psoriasis (GPP) has not been determined; however, the etiopathogenesis of pustular psoriasis is believed to involve IL-36 overexpression or mutation of its IL-36R antagonist.[2]
- Spesolimab is a first-in-class therapy for GPP flares. The FDA granted it Orphan Drug status and designated it as Breakthrough Therapy.

Indication Under Review in This Document

- Treatment of GPP flares in adults.

Pretreatment Tests and Evaluations

- Tuberculosis (TB) screening

Dosage Regimen and Dosage Form(s) Under Review

- **Recommended Dose**: 900 mg IV infusion over 90 minutes (single dose). A second single dose (900 mg IV infusion over 90 minutes) may be given 1 week after the initial dose if flare symptoms persist.
- **Dosage Form**: Injection of 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial

Efficacy Considerations

- No active-controlled trials or phase 3 trials have been performed to date.
- A phase 2 placebo-controlled randomized clinical trial (RCT), Effisayil 1, showed the efficacy of a single dose of spesolimab in terms of the percentage of patients who achieved clearance of pustules at Week 1 in adults with moderate to severe GPP flare.[3,4]
- Two ongoing phase 2 RCTs provided supportive evidence of efficacy.
- Ongoing trials include a 5-year open-label extension to evaluate long-term therapy and the Effisayil 2 trial evaluating spesolimab in prevention of flares.

Pivotal Phase 2 Randomized Clinical Trial

- Table 1 summarizes the methods of the pivotal phase 2 RCT.

Table 1 Methods of Pivotal RCT

Topic	Effisayil 1 Trial
Study Design	12-week, single-dose, Phase 2 multinational DB PC RCT (2:1) Stratified by Japanese / non-Japanese ethnicity A hierarchical method was used to control for type I error Placebo patients could crossover to open-label spesolimab at Day 8
Major Entry Criteria	Main Inclusion Criteria • Age 18–75 years • Known, documented history of GPP, or first acute GPP flare with diagnosis confirmed retrospectively, as per diagnostic criteria of the European Rare and Severe Psoriasis Expert Network (ERASPEN), regardless of IL-36RN gene mutation status. Those with a previous history of GPP had previous evidence of fever and/or asthenia and/or myalgia and/or elevated CRP and/or leukocytosis with neutrophilia (above ULN). • GPP flare of moderate to severe intensity (defined as GPP-PGA total score of ≥ 3 / Moderate, new or worsening pustules, GPP-PGA-P subscore of ≥ 2 / Mild, and ≥ 5% of BSA with erythema and pustules Main Exclusion Criteria • SAPHO (synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome • Primary erythrodermic psoriasis vulgaris • Plaque psoriasis without pustules or with pustules restricted to psoriatic plaques • Drug-induced acute generalized exanthematous pustulosis (AGEP) • Immediate life-threatening flare of GPP warranting intensive care treatment as per physician judgment, mainly including but not limited to cardiovascular / cytokine driven shock, pulmonary distress syndrome, renal failure • Severe, progressive, or uncontrolled hepatic disease defined as AST, ALT or alkaline phosphatase > 3 times ULN or total bilirubin > 2 times ULN • Dose escalation or initiation of cyclosporine, methotrexate, or retinoids within the previous 2 weeks • Concurrent corticosteroids, methotrexate, cyclosporine, retinoids, or other restricted medications including but not limited to IL-17A inhibitors (ixekizumab, secukinumab), IL-17RA (brodalumab); IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab), IL-12/23 inhibitor (ustekinumab), TNF-alpha inhibitors (adalimumab, etanercept, infliximab); JAK inhibitor (tofacitinib), PDE4 inhibitor (apremilast), fumarates, photochemotherapy, natalizumab, alemtuzumab, rituximab, anakinra, topical medications for psoriasis or other skin condition, and granulocytes and monocytes adsorptive apheresis (GMA). *Note: Certolizumab might be used for GPP but was not mentioned.* • Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
Interventions	Day 1, single dose: • Spesolimab 900 mg IV • Placebo *For Inadequate Response / Retreatment*. Day 8: Option to receive a second dose of open-label spesolimab for persistent symptoms defined as GPP-PGA total score of ≥ 2 at end of Week 1 and mPGA and GPP-PGA-P subscore of ≥ 2 at Week 1. *For Loss of Response / Rescue Therapy*. After Week 1: Spesolimab could be given as rescue for reoccurrence of flare, defined as an increase of ≥ 2 points (from a GPP-PGA total score of 0 or 1) on both the GPP-PGA total score and GPP-PGA-P. *Escape Therapy*: Defined as standard-of-care therapy as per physician discretion. Escape therapy was allowed during Week 1 for worsening disease requiring immediate treatment and after Week 1 for worsening disease in patients not qualified for rescue medication.

Topic	Effisayil 1 Trial
Maintenance Phase or Long-term Extension	No maintenance phase. 5-year open-label extension trial for patients who had clinical improvement and completed the randomized phase without flare
Primary and Key Secondary Efficacy Measure(s)	GPP-PGA-P subscore of 0 / No Visible Pustules at Week 1 / Day 8 GPP-PGA total score of 0 / Clear or 1 / Almost Clear at Week 1 / Day 8. The total score averages the subscores for pustulation, erythema, and scaling.
Baseline Patient Characteristics	85 screened, 53 (62.4%) enrolled The spesolimab and placebo groups differed at baseline in terms of female sex (60% vs 83%, respectively), Asian race (46% and 72%, respectively), and median GPP-PASI total score (27.4 and 20.9, respectively) Age 43 y — GPP-PGA total score of 3 / 4: 82% / 19% Weight 72 kg — GPP-PGA-P subscore of 2 / 3 / 4: 22% / 42% / 35% Female 70% — Median GPP-PASI: 24.2 Race Asian / White: 59% / 41% — IL-36RN mutation positive: 13%

BSA, Body surface area; **CRP**, C-reactive protein; **GPP-PASI**, Psoriasis Area and Severity Index modified for GPP by substitution of the induration component with a pustule component; **GPP-PGA**, GPP Physician global assessment (scale: 0 / Clear skin to 4 / Severe); **GPP-PGA-P**, GPP PGA pustulation (scale: 0 / No visible pustules to 4 / Severe pustulation); **IL-36RN**, Interleukin-36 receptor gene that encodes for the interleukin-36 receptor antagonist; **mPGA**, Modified physician global assessment; **ULN**, Upper limit of normal

Results

- Key efficacy data are summarized in Table 2 and Table 3.

Table 2 Day-8 Efficacy results from Effisayil 1 Trial

Outcome	Spesolimab	PBO	Relative Risk (95% CI)	Difference (95% CI)
GPP-PGA-P–0, n/N (%)	19/35 (54.3)	1/18 (5.6)	9.8 (1.42, 67.24)	49 (21, 67)
GPP-PGA–0/1, n/N (%)	15/35 (42.9)	2/18 (11.1)	3.9 (0.99, 15.05)	32 (2, 53)

Sources: 3, FDA Multi-discipline Review[5]

GPP-PGA–0/1, GPP Physicians Global Assessment total score of 0 / Clear or 1 / Almost Clear; **GPP-PGA-P–0**, GPP Physicians Global Assessment Pustulation subscore of 0 / Clear

Table 3 Absolute Effects for Achieving Key Outcomes with Spesolimab vs Placebo at Day 8

Outcome Measure	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
GPP-PGA-P subscore of 0	489 (291, 683) more	3 (2, 5)	L[α]
GPP-PGA total score of 0/1	317 more (98 fewer, 536 more)	4 (2, 16)	L[α]

AAE, Anticipated absolute effect for achieving the outcome (calculated using modified SIGN [Scottish Intercollegiate Guidelines Network] method); **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (H = High, M = Moderate, L = Low, VL = Very low)

[α] Downgraded for inconsistency between outcomes and imprecision (optimal information size not met; wide CIs).

  - A GPP physician's global assessment pustulation subscore of 0 (zero) (GPP-PGA-P–0) was reported in 19 (54%), 18 (51%), 18 (51%), 17 (49%) and 15 (43%) of patients at Day 8 and Weeks

2, 4, 8, and 12, respectively, following the single dose of spesolimab, as compared with 1 (6%) at Day 8 then 2 (11%) for each of the other time points (to Week 12) in the placebo group.
    - Post hoc sensitivity analyses adjusting for the baseline imbalances in sex, race, and the Psoriasis Area and Severity Index modified for GPP (GPP-PASI) score showed results consistent with the primary analysis.
- Exploratory efficacy results after Day 8
    - The primary and key secondary efficacy results over time are summarized by treatment path in Table 4.

Table 4 Exploratory Results After Day 8

Group by Treatment Path	N	Outcome	Day 8	Week 2	Week 4	Week 8	Week 12
Spesolimab, one dose (Day 1 only) or two doses (Day 1 + Day 8), n (%)	35	GPP-PGA-P–0	19 (54)	23 (66)	23 (66)	22 (63)	21 (60)
		GPP-PGA–0/1	15 (43)	18 (51)	23 (66)	21 (60)	21 (60)
Spesolimab, one dose (Day 1) only, n (%)	23	GPP-PGA-P–0	19 (83)	18 (78)	18 (78)	17 (74)	15 (65)
		GPP-PGA–0/1	15 (65)	16 (70)	17 (74)	16 (70)	14 (60)
Spesolimab, two doses (Day 1 + OL Day 8), n (%)	12	GPP-PGA-P–0	0 (0)	5 (42)	5 (42)	5 (42)	6 (50)
		GPP-PGA–0/1	0 (0)	2 (17)	6 (50)	5 (42)	7 (58)
Placebo + one dose spesolimab (OL Day 8), n (%)	15	GPP-PGA-P–0	0 (0)	11 (73)	9 (60)	7 (47)	6 (40)
		GPP-PGA–0/1	0 (0)	8 (53)	7 (47)	10 (67)	8 (53)

GPP-PGA–0/1, GPP Physicians Global Assessment total score of 0 / Clear or 1 / Almost Clear; **GPP-PGA-P–0**, GPP Physicians Global Assessment Pustulation subscore of 0 / Clear; **OL**, Open-label

- GPP-PASI-75 (≥ 75% reduction in GPP-PASI) response was 34.3% (12/35) at Day 8.
- Dermatology Life Quality Index (DLQI) decreased from baseline by a median of 2.5, 9, 10, 11, and 12 points at Day 8 and Weeks 2, 4, 8, and 12, respectively. The minimal clinically important change in the DLQI in patients with inflammatory skin diseases is 4.[6]
- Scores on the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire (range of scores 0 to 52, with lower scores indicating greater impact of fatigue on daily activities) changed from baseline by a median of 7.0 points at Day 8 and 22.0 points at Week 4 in patients who received one dose (Day 1 only) or two doses (Day 1 + Day 8) of spesolimab.

Onset of Treatment Benefit and Duration of an Adequate Therapeutic Trial

- Onset of effects (earliest significant treatment difference): Day 8 based on the GPP-PGA-P–0 response rates. Response to spesolimab treatment was first evaluated on Day 8.
- Duration of an adequate therapeutic trial (time of peak response): Day 8 based on the GPP-PGA-P–0 response rates.

Durability of Response

- The GPP-PGA-P–0 response rate increased from 54% on Day 8 to 60% at Week 12. No further assessments were reported beyond Week 12.

Safety Considerations

Safety Profile from US Prescribing Information

- **Boxed Warnings**: None
- **Contraindications**: Severe or life-threatening hypersensitivity to spesolimab or excipients. Reactions have included drug reaction with eosinophilia and systemic symptoms (DRESS).
- **Other Warnings / Precautions**: Infections, risk of TB, hypersensitivity and infusion-related reactions, avoid live vaccines

- **Common Adverse Events (≥ 5%)**: Asthenia and fatigue; nausea and vomiting; headache; pruritus and prurigo; infusion site hematoma and bruising; urinary tract infection
- **Specific Adverse Events**
    - *Latent tuberculosis* was reported in 4% of patients treated with a single dose of spesolimab by Week 17 in EFFISAYIL-1.[1]
    - *DRESS* occurred in 2 spesolimab-treated patients in EFFISAYIL-1.[1] Based on RegiSCAR DRESS validation scoring, one case was deemed "no DRESS" and the other was scored as "possible DRESS."
    - *Guillain-Barre syndrome* was reported in 3 of 750 spesolimab-exposed subjects during the clinical development program.[1]

Safety Results from Clinical Trials

- **Deaths and Serious Adverse Events**: No deaths occurred during Effisayil 1. Serious adverse events occurred in 6% (2/35; 309.5 per 100 patient-years [PY]) and 0% (0/18) of spesolimab and placebo patients, respectively, at Week 1. At Week 12, serious adverse events occurred in 12% (6/51; 49.7 per 100 PY) of patients on spesolimab at Week 12.
    - Serious adverse events reported up to Week 1 and Week 12 included DRESS, urinary tract infection, drug-induced liver injury, and arthritis in the spesolimab group. None of the placebo patients reported these events.
    - Additional serious adverse events occurring in the spesolimab group up to Week 12 were worsening of chronic plaque psoriasis, influenza and squamous cell carcinoma of the skin.
- **Discontinuations Due to Adverse Events**: None in either treatment group at Week 1 and none in the spesolimab group at Week 12.
- **Severe adverse events (Rheumatology Common Toxicity Criteria grade 3 or 4)**: 6% (2/35; 309.5 per 100 PY) and 6% (1/18; 304.4 per 100 PY) in the spesolimab and placebo groups, respectively, up to Week 1. At Week 12, the rate was 10% (5/51; 40.9 per 100 PY) on spesolimab.
- **Any Adverse Event**: 66% (23/35) vs 56% (10/18) in the spesolimab vs placebo groups, respectively.

Evidence Gaps

- Survival / Mortality
- Hospitalization or readmission
- Functional ability / Disability (relative to placebo)
- Patient Satisfaction

Network Meta-analyses

- Spesolimab was not included in any meta-analyses to date.

Other Considerations

- **Storage**. After reconstitution, diluted solution should be refrigerated at 2°C to 8°C (36°F to 46°F) for not more than 4 hours.

Other Therapeutic Options

- There has been no standard therapy for GPP in the US and there has been a lack of clinical trials in GPP because of the rarity of this condition. As a consequence, there are few clinical practice guidelines that address GPP,[7,8] and recommendations are based on expert opinions informed by case reports, case series,

or uncontrolled, open-label observational studies and indirect evidence.[2,9] Placebo-controlled trials are necessary because GPP can resolve spontaneously.

- Spesolimab is the only GPP treatment studied in placebo-controlled, randomized trials.

Expert-recommended therapies for GPP

- Since there is a lack of high-quality evidence and lack of comparative studies, expert-recommended therapies for GPP are summarized in Table 5 for reference, listed in no particular order. Optimal doses and duration of therapy are unknown.

Table 5 Expert-suggested therapies for GPP

Therapy	Safety Considerations	Other Considerations
Retinoids • Acitretin (0.75–1 mg/kg/d PO; maintenance 0.125–0.25 mg/kg/d for several months)[8,13]	• Retinoic acid-associated respiratory failure / capillary leak syndrome • Teratogenic • Skeletal toxicity	• Considered 1st-line therapy for GPP NOS in NPF Guidelines (2012)[8] and for severe or recalcitrant disease, or with prednisone for acute GPP.[13] • Etretinate (no longer available in US) can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • Retrospective studies in EU and Asia: Used in 89% of patients as 1st-line therapy.[9] Considered by authors as most effective systemic therapy at the time.[9] • Response in 7–10 d.[9]
IL-2 Inhibitor • Cyclosporine[8,10] (1.5–5 mg/kg/d for > 6 wks; taper to lowest effective dose[13] or 3.5–5 mg/kg/d; if response is adequate, taper down by 0.5 mg/kg every 2 wks[13])	• Renal toxicity • Hypertension • Infections • Malignancy • Discontinuation of cyclosporine has triggered pustular psoriasis[8]	• Considered alternative 1st-line therapy for GPP NOS in NPF Guidelines (2012),[8] for severe, acute GPP in UpToDate,[10] and for nonpregnant patients with GPP NOS.[2] • Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • For severe or recalcitrant disease.[13] • Historically considered treatment of choice for acute, severe GPP.[10] • Mostly case reports.[9] • 71.2% of 66 patients responded in a retrospective study.[9] • More history of use than IL-17 inhibitors and IL-23 inhibitors[10] • Can be rapid-acting;[10] usual onset in 4–8 wks
Folate Antagonist • Methotrexate (5–15 mg/wk PO, IM, or IV; increase by 2.5 mg/wk until response; max 25 mg/wk)[13]	• Teratogenic	• Considered alternative 1st-line therapy for GPP NOS in NPF Guidelines (2012).[8] • Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • For severe or recalcitrant disease[13] • "Effective" in 76.2% of 24 patients and 80% of 41 patients in two retrospective studies.[9] • Slow onset[13]

Therapy	Safety Considerations	Other Considerations
Corticosteroids		
• Prednisone equivalent (1 mg/kg/d or 30–60 mg/d[7,13]; taper dose after symptoms improve[13])	• Discontinuation of systemic corticosteroids can trigger acute GPP flare. • Corticosteroids should be used with caution and discontinued slowly after response is achieved.	• Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.[7] Recommended for GPP-related respiratory failure.[7] • Last-line alternative therapy for GPP NOS if other treatments are not possible.[13]
PDE4 Inhibitors		
• Apremilast (titrate from 10 mg QAM to 50 mg/d in 2 divided doses over the first 5 days, then 30 mg twice daily)	• Associated with triggering paradoxical recurrent GPP.[11] • Diarrhea, nausea, vomiting, depression, weight decrease • Strong CYP450 inducers may reduce apremilast effects • Overall, has a favorable safety profile.	• Least used treatment for GPP (2 of 121 treatment courses) and lowest probability of drug survival in a German retrospective multicenter study.[12] Of the 2 treatment courses, 1 was associated with an excellent response.
TNF-α Inhibitors		
• Infliximab[8,10] (5 mg/kg at Wks 0, 2, and 6 then every 8 wks as needed[13])	• May paradoxically trigger flares of acute GPP.[8] • Infusion-related reactions may stress the cardiovascular system, a concern because patients with GPP can develop cardiorespiratory failure.[7] • May use in pregnancy up to first 30 weeks of gestation[13]	• Can be considered but evidence is insufficient for acute GPP as per Japanese Guidelines (2018)[7] Recommended for GPP-related respiratory failure.[7] • Considered 1st-line therapy for extensive or severe, acute GPP NOS in NPF Guidelines (2012)[8] and for severe, acute GPP in UpToDate,[10] or 3rd-line therapy for nonpregnant patients with GPP NOS.[2] • Use of TNFIs, mostly infliximab, are based mainly on case reports / series.[9] • Of 55 cases treated with TNFIs, 58% had complete remission and 28% partial response.[9] • More history of use than IL-17 inhibitors and IL-23 inhibitors[10] • Historically considered treatment of choice[10] • Approved for GPP in Japan, Taiwan, and Thailand. • Rapid onset[9,13]
• Adalimumab[8] (80 mg SC every wk for 2 wks then 40 mg every 2 wks[13])	• May paradoxically trigger flares of acute GPP.[8]	• Considered 2nd-line therapy in NPF Guidelines (2012)[8] or 3rd-line therapy for nonpregnant patients with GPP NOS.[2] • Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • 52-wk MC OL SA OS of 10 Japanese patients with mainly mild–moderate GPP: Complete remission 50% at 2 wks and 70% at 16 wks.[14] First TNFI shown to be safe and effective in a clinical study.[9] • Approved for GPP in Japan, Taiwan, and Thailand.
• Certolizumab[2]	• May be preferred TNFI in pregnancy	• Considered 2nd-line therapy for nonpregnant patients with GPP NOS,[2] above other TNFIs. • Approved for GPP in Japan, Taiwan, and Thailand.
• Etanercept[8] (50 mg SC every 2 wks for 3 months then 50 mg every wk[13])	• May paradoxically trigger flares of acute GPP[8] or worsen pustular psoriasis especially in patients with RA or IBD[13]	• Considered 2nd-line therapy in NPF Guidelines (2012)[8] or 3rd-line therapy for nonpregnant patients with GPP NOS.[2] • Least reported evidence of the TNFIs; case reports.[9]

Therapy	Safety Considerations	Other Considerations
IL-17 inhibitors		
• Ixekizumab[13] (160 mg SC at Wk 0, 80 mg at Wks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 wks[13]) • Secukinumab[13] (300 mg weekly for 3 wks then every 4 wks[13]) • Brodalumab[13] (210 mg SC at Wks 0, 1, and 2, then every 2 wks[13])	• Fungal infections (e.g., oral candidiasis, tinea) • Upper respiratory tract infection • Inflammatory bowel disease • Potential suicide ideation / behavior with brodalumab (REMS)	• Considered 1st-line therapy for severe, acute GPP in UpToDate[10] or 2nd-line therapy for nonpregnant patients with GPP NOS.[2] • Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • Approved for GPP in Japan, Taiwan, and Thailand. • 60% of 5 patients with GPP resolved or improved on ixekizumab at 52 wks in a MC OL SA OS.[15,16] • 83.3% of 10 patients with GPP achieved treatment success on secukinumab at 16 wks in a 52-wk MC OL SA OS.[17] • 91.7% of 12 patients with GPP achieved remission or improvement on brodalumab at 52 wks in a 52-wk MC OL SA OS.[18] • Better safety profile than cyclosporine[10] • Improvement in 3 weeks (secukinumab) and 2 weeks (brodalumab).[10]
IL-12/23 inhibitor		
• Ustekinumab[10] (45 mg at Wks 0, 4, and 16; maintenance 45 mg every 12 wks[13])	• Associated with new or worsening pustular psoriasis[8,10]	• Considered 1st-line therapy in UpToDate[10] or 3rd-line therapy for nonpregnant patients with GPP NOS.[2] • Can be considered but evidence is insufficient for acute GPP as per Japanese guidelines.7 • Better safety profile than cyclosporine[10]
IL-23 inhibitors		
• Guselkumab[10] (50 mg or 100 mg SC at Wks 0 and 4, then every 8 wks[13])	• Associated with cutaneous squamous cell carcinoma in patients with GPP or erythrodermic psoriasis[10]	• Considered 1st-line therapy for severe, acute GPP in UpToDate[10] or 3rd-line therapy for nonpregnant patients with GPP NOS.[2] • Approved for GPP in Japan, Taiwan, and Thailand. • 77.8% of 9 patients with GPP achieved treatment success in a 52-wk MC OL SA OS.[19] • Better safety profile than cyclosporine[10]
• Risankizumab (75 or 100 mg SC at Wks 0 and 4 then every 12 wks[20])	• 3 of 8 patients developed possible drug-induced liver injury: 1 case deemed related to risankizumab; none led to discontinuation of therapy	• Approved for GPP in Japan, Taiwan, and Thailand. • 100% of 8 patients with mild–moderate GPP achieved clinical response at 16 wks regardless of risankizumab dose, and 25%–50% maintained clinical response through Wk 160 in a dose-controlled MC OL RCT.[20]
IL-1 inhibitors		
• Anakinra (100 mg SC daily[13,13])		• Phase 2 OL SA OS of 18 patients with pustular psoriasis including 5 with GPP: 50% of 14 evaluable patients achieved clinical response at 12 wks.[21]

MC, Multicenter; OL, Open-label; OS, Observational study; SA, Single-arm

Projected Place in Therapy

- **Epidemiology and Prevalence of Acute Generalized Pustular Psoriasis (GPP)**. The European Rare and Severe Psoriasis Expert Network (ERASPEN) categorized pustular psoriasis into three phenotypes: GPP and two localized subtypes, acrodermatitis continua of Hallopeau (ACH) and the most common subtype palmoplantar pustulosis (PPP).[22] IL-36RN gene mutations have been found in 25% of GPP, 20% of ACH, and 2% of PPP cases in European and Asian populations.[22] The clinical presentations of GPP include acute GPP (aka generalized pustular psoriasis of von Zumbusch) and a subacute generalized annular pustular

psoriasis.[23] GPP is a rare, relapsing or persistent, dermatologic disease that has a widely variable clinical course. The Japanese guidelines consider GPP to be a systemic inflammatory response syndrome (SIRS).[7] The prevalence of GPP varies from 1.76 per million in Europe to 7.46 per million in Japan, suggesting that it is 5 times more common in Asia than the EU and US.[24,25,26]. Acute GPP is manifested by rapid onset of erythematous, inflamed skin with generalized, extremely painful, small or coalesced, noninfectious, neutrophilic, pustular, nonacral skin lesions.[7,22] Systemic (fever, malaise, fatigue), mucosal, eye (keratoconjunctivitis, uveitis, iritis), and arthritic manifestations may occur. Acute GPP can be a life-threatening medical emergency and about 50% of patients require hospitalization.[27]. Complications include sepsis, pneumonia, neutrophilic cholangitis, neutrophilic pneumonitis, acute kidney, liver, and/or high-output heart failure, acute respiratory distress syndrome, amyloidosis, and death. Mortality rates have ranged from 2% to 16%.[5] Older individuals have a worse prognosis. Most cases are idiopathic but a number of potential precipitants have been identified, including withdrawal of systemic or potent topical corticosteroids in patients with plaque psoriasis, lithium, stress, infection, and pregnancy (pregnancy-induced GPP was known as impetigo herpetiformis). GPP flares often last 2–5 weeks but may last longer than 3 months.[27]

- **Potential Place in Therapy Based on the Evidence**. Although no active-controlled trials were available, low-quality evidence from a phase 2 placebo-controlled trial supports the first-line use of spesolimab in patients with acute, non–life-threatening, moderate to severe GPP flare. Overall, clearance of pustules and global skin clearance are small to moderate and clinically meaningful. Spesolimab increased the risks of infection and serious adverse events including DRESS and drug-induced liver injury. The efficacy, safety, and optimal dosing of other potential alternative treatments, such as cyclosporine, TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors, have not been confirmed in placebo-controlled randomized clinical trials. The safety and efficacy of more than 2 doses of spesolimab have not been evaluated to date.
- **Potential Place in Therapy in VHA**. Spesolimab may be used in the treatment of patients with acute GPP flares as recommended in its prescribing information.

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