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REVIEW ARTICLE

Spesolimab for the Treatment of Generalized Pustular Psoriasis

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Abstract

Generalized pustular psoriasis (GPP) is a rare but severe skin inflammatory disorder characterized by the eruption of widespread sterile neutrophilic pustules, often accompanied by systemic inflammation. Given its life-threatening potential, GPP requires prompt accurate diagnosis and effective treatment, but its rarity and relapsing-remitting nature pose challenges in performing large-scale randomized controlled clinical trials. Established international guidelines are currently lacking and management guidance often follows that for plaque psoriasis. However, while it can co-exist with plaque psoriasis and has traditionally been classified as a most severe form of psoriasis, GPP is now recognized as a distinct entity, with its own clinicopathological, autoinflammatory, immunologic and genetic features. Research conducted over the past decade revealed that an imbalance of interleukin (IL)-36 signaling favoring the proinflammatory activity is the central driver of the pathogenesis of GPP, thereby laying the groundwork for the development of targeted therapies for the disease. This article reviews the evidence thus far on spesolimab, a selective humanized antibody against the IL-36 receptor that was recently licensed in Europe and the United States for the treatment of GPP flares in adults. In phase II, randomized controlled clinical trials, spesolimab led to rapid and effective skin clearance in patients experiencing a GPP flare and demonstrated superiority to placebo in preventing flares for up to 48 weeks with maintenance treatment, with reassuring safety and tolerability profiles. Spesolimab is considered to be a first-in-class medication establishing itself as the standard of care for the treatment of GPP flares, thus changing the paradigm of the management of GPP to a new era of scientifically- and evidence-based targeted therapy for this distinctive disease.

Key Points

The interleukin (IL)-36 signaling pathway is now recognized as the key driver of the pathogenesis of generalized pustular psoriasis (GPP).

Spesolimab is a humanized monoclonal antibody against the IL-36 receptor.

Spesolimab has been shown to be effective in the management of GPP, both in the rapid control of the flares and in preventing their recurrence in the long-term, while maintaining a favorable safety profile.

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1 Introduction

Pustular psoriasis is a rare variant of psoriasis distinguished by the occurrence of sterile pustules, which can appear either in a generalized or localized distribution. In Europe and the United States (US), pustular psoriasis commonly develops in association with pre-existing plaque psoriasis but may occur independently [1–3]. Pustular psoriasis may be categorized into three main phenotypes: palmoplantar pustulosis (PPP), acrodermatitis continua of Hallopeau (ACH), and generalized pustular psoriasis (GPP) [3, 4].

GPP is the most severe form, characterized by the eruption of widespread neutrophilic sterile pustules that are frequently accompanied by signs of systemic inflammation [1, 2]. It is a rare condition and scarce epidemiological data are available. The exact prevalence of GPP is unknown, but, globally, can be estimated as 1–7 cases per million persons, with significant regional variability. It is predominantly reported in Asia, while its prevalence in Caucasians has been suggested to be considerably lower [5–8]. GPP primarily affects adults, with the median reported age at diagnosis being around 50 years, but can also occur in children [6]. There does not appear to be

a strong gender predilection, although some series have pointed to a female preponderance [6, 8, 9].

The clinical course of GPP can be heterogeneous and the spectrum of severity is broad. GPP can not only manifest as an acute flare but also as a relapsing disease with recurrent flares without pustulation between the episodes, and for months can also be a persistent disease with chronic pustulation, in which flares of greater severity may overlap. Distinct phenotypes of GPP have been described. GPP of the von Zumbusch type is the acute form, characterized by the abrupt eruption of widespread numerous pustules arising on painful erythematous skin, which may coalesce to form 'lakes' of pus. Erythroderma may occur and is often associated with systemic involvement, as denoted by fever, leukocytosis with neutrophilia, and elevated C-reactive protein levels. Secondary bacterial infections and kidney, liver and cardiorespiratory failure are potential complications. Thus, acute GPP flares can be life-threatening and often require hospitalization to ensure adequate surveillance and supportive care. Flares may occur without any evident cause, although corticosteroid withdrawal, infections, medications, stress and pregnancy have been reported as the main precipitating factors. The term 'impetigo herpetiformis' is used to refer to acute GPP that appears during pregnancy. Other less common clinical variants of GPP include generalized annular pustular psoriasis and infantile/juvenile pustular psoriasis [2–4, 6, 10].

The pathogenesis of GPP is only partially understood. Although GPP may arise in parallel with plaque psoriasis, it is currently recognized as a separate entity, with distinct genetic basis and immune activation pattern [1, 10, 11]. A timely and accurate differential diagnosis is important given the potential life-threatening nature of GPP flares, which may require prompt treatment [9, 10]. The classification and diagnosis of GPP can be challenging given its rarity, heterogeneity, potential overlap and clinical similarity to other skin conditions, thus prompting some international groups to propose consensus guidelines [3, 6, 12]. The European Rare and Severe Psoriasis Expert Network (ERASPEN) consensus diagnostic criteria (2017) define GPP based on the clinical features, defined as primary, macroscopic, sterile pustules not limited to the palms and soles (and excluding cases of pustulation limited to psoriatic plaques), with or without systemic inflammation, and manifesting with a relapsing (more than one episode) or persistent (more than 3 months) pattern [3]. Japanese diagnostic criteria (2018) state that the definitive diagnosis of GPP can be made if the following four criteria are met: (1) presence of systemic symptoms; (2) widespread erythematous skin with numerous sterile pustules; (3) histopathological evidence of neutrophilic subcorneal pustules (Kogoj's spongiform pustules),;and (4) recurrence of these clinical and histological criteria. GPP should also be considered if only criteria 2 and 3 are present [12].

The rarity of GPP and lack of large-scale clinical trials pose challenges in finding evidence-based therapeutic options. Current management of GPP flares often relies on conventional systemic therapies used for moderate to severe plaque psoriasis, with retinoids, cyclosporine and methotrexate being commonly used. Biologic agents targeting tumor necrosis factor (TNF), interleukin (IL)-17A or IL-17 RA (receptor) and IL-23 have emerged as potential therapies for GPP, with several approved in Japan based on short, open, small size, nonrandomized clinical trials. However, there is a clear demand for targeted GPP treatments that offer higher and sustained efficacy, as well as rapid onset of action [9, 11, 13, 14].

Over the past decade, advances in the knowledge of the molecular basis behind GPP immunopathogenesis, namely the discovery of IL36RN mutations and the central role of the IL-36 pathway in the pathogenesis of GPP, has resulted in the development of targeted therapies for the disease [14–17]. Spesolimab is an IL-36 receptor antagonist that was recently approved by the US Food and Drug Administration (FDA; September 2022) and European Medicines Agency (EMA; December 2022) for the treatment of GPP flares in adults [18].

This article aims to review the most recent data on the management of GPP, the role of IL-36 in the pathogenesis of GPP, and the efficacy and safety of spesolimab, which made it the first licensed treatment for GPP flares in the US and Europe. A comprehensive literature review was conducted (to October 2023) using the PubMed database, employing the keywords 'spesolimab', 'interleukin 36' and 'generalized pustular psoriasis'. The articles were selected by the relevance of the abstract and established objectives. When pertinent, the bibliographic references present in the selected articles were assessed and included. Additional data were obtained from the ClinicalTrials.gov database and the FDA and EMA websites.

2 Overview of Current Treatment Options in Generalized Pustular Psoriasis (GPP)

The management of GPP flares varies depending on the extent and severity of skin and systemic involvement, but overall includes a combination of topical therapies, systemic medications, and supportive care within a hospital inpatient setting. Topical treatments, such as corticosteroids, may provide symptomatic relief but are usually employed as adjuncts since systemic treatment is typically required [2, 12, 14].

Currently, established international guidelines for the pharmacologic treatment of GPP are lacking, mainly due to

the scarcity of high-quality evidence data on its efficacy. The management of GPP has been globally based on recommendations designed for plaque psoriasis [14, 19, 20]. In fact, before spesolimab approval in 2022, no specific treatments for GPP were approved by the FDA or EMA.

Overall, with the possible exception of impetigo herpetiformis, systemic corticosteroids are usually discouraged in GPP given the potential risk of rebound flares upon withdrawal [2, 11]. Systemic retinoids (acitretin), methotrexate and cyclosporine have been widely used as first-line conventional systemic therapeutic options for GPP flares, but they are limited by their toxicities and/or slow onset of response (methotrexate and retinoids). Furthermore, none of these agents targets any specific aspect of the GPP pathogenesis [2, 13, 14].

Furthermore, various biologic agents approved for moderate to severe plaque psoriasis, such as TNF inhibitors (infliximab, adalimumab, certolizumab), IL-12/23 and IL-23 inhibitors (ustekinumab, guselkumab and risankizumab) and IL-17 inhibitors (brodalumab, secukinumab, ixekizumab) have emerged as potential options for the treatment of GPP, with several being licensed in Japan, as well as brodalumab in Taiwan and Thailand. These agents have also been frequently used off-label to treat GPP flares in other countries, although evidence supporting its efficacy is mainly derived from case series and small open-label, single-arm trials [9, 13, 14, 20–23]. There are also case reports of GPP exhibiting a positive response to IL-1 inhibition with anakinra, canakinumab and gevokizumab [14, 24, 25].

Setting strong recommendations for the GPP treatment strategy presents a challenge. The infrequency of GPP and its sudden relapsing-remitting nature make it difficult to perform large-scale randomized controlled clinical trials of suitable patients with active acute disease. Hence, the evidence thus far predominantly relies on case series, small open-label trials, retrospective studies, and expert opinions, with the majority of clinical trials hailing from a single country, i.e. Japan [14, 23]. Furthermore, making comparisons between the therapeutic agents is not appropriate because of the high heterogeneity of study designs.

Over the past decade, advances in the knowledge of the molecular basis behind GPP pathogenesis, in particular identification of the central role of the IL-36 pathway, led to the development of new therapies tailored specifically for this condition [1, 16]. Spesolimab, which has already been FDA- and EMA-approved, and imsidolimab are two monoclonal antibodies targeting the IL-36 signaling that are undergoing phase II and III clinical trials evaluating its efficacy and safety in the management of GPP. Imsidolimab showed efficacy in an open-label study that involved eight patients experiencing a GPP flare and is presently progressing into a phase III clinical trial [26].

3 The Role of Interleukin-36 in the Pathogenesis of GPP

The pathogenesis of GPP remains incompletely elucidated. GPP may arise with pre-existing plaque psoriasis, thus suggesting an overlap and interlink between the immunologic pathways of both entities. However, while plaque psoriasis is known to be primarily driven by an adaptive immune response highlighting the IL-23/IL-17 axis, recent evidence from histopathological, molecular, and genetic studies indicates that GPP mainly relies on the hyperactivation of innate immunity triggered by genetic factors, with a central role of the IL-36 pathway [1, 2, 15, 22]. It has prompted some authors to consider GPP as a representative clinical entity within the spectrum of autoinflammatory keratinization diseases [27]. However, both pathways are interconnected and modulate each other through an inflammatory loop [1, 15].

IL-36 cytokines belong to the IL-1 superfamily and comprise the proinflammatory agonists IL-36α, IL-36β and IL-36γ, as well as the IL-36 receptor antagonist (IL-36Ra). These cytokines are expressed by, and act through, various cell types in the skin, including keratinocytes and cells of the immune system, following stimulation by TNF, IL-17A, IL-22 and IL-1β. After proteolytic activation, binding of IL-36 agonists to the heterodimeric receptor complexes (IL-36R and IL-1 receptor accessory protein [IL-1RAcP]) prompts the activation of downstream pathways mediated by protein myeloid differentiated protein 88 (MyD88), mitogen-activated protein kinase (MAPK), and nuclear factor-kappa B (NF-κB) signaling. It results in the release of various proinflammatory mediators, including neutrophil-attracting chemokines (e.g. CXCL1, CXCL2 and CXCL8), more IL-36 precursors, TNF, and IL-1β and IL-17 cytokines that promote recruitment and activation of neutrophils, T cells and dendritic cells through a self-amplifying loop. IL-36Ra acts as a regulator by competing with the IL-36 agonists for binding to the IL-36R, thus balancing this inflammatory cascade [1, 2, 15, 28]. IL-36 cytokines are involved in the first-line defense of the skin against external insults and contribute to the interconnection between the innate and adaptive immunity, including the T-helper (Th) 1 and Th17 pathways [29]. The IL-36 signaling pathway is schematized in Figs. 1 and 2.

Dysregulation of the IL-36 inflammatory pathway seems to be the primary driver in the pathogenesis of GPP [1]. Genetic studies in both familiar and sporadic cases of GPP have identified loss-of-function mutations affecting IL36RN, the gene that codes the IL-36Ra, resulting in the inability of IL-36Ra to antagonize and limit the proinflammatory effects of IL-36 [30, 31]. This leads to a self-perpetuating loop of uncontrolled signaling and excessive production of

chemokines that promote epidermal neutrophil infiltration, clinically manifesting as pustules, as well as systemic symptoms [1, 2, 29].

IL36RN mutations are the most common genetic abnormality associated with GPP and have been reported in approximately one in four patients, with a higher prevalence in those experiencing an earlier age onset and greater severity of the disease [32]. IL36RN mutations do not seem to be associated with plaque psoriasis and are more frequent in patients with GPP without plaque psoriasis [29, 32, 33]. More recently, mutations and allelic variations in other genes functionally connected with the IL-36 pathway favoring the positive inflammatory feedback (e.g., loss-of-function of AP1S3, SERPINA3 and MPO; gain-of-function of CARD14) have also been found to be associated with GPP [2, 34].

Further evidence supporting the key role of the IL-36 pathway in GPP comes from gene expression studies of lesional skin biopsies demonstrating overexpression of IL-36 agonists (IL-36α, β and γ) in keratinocytes that surround the neutrophilic pustules when compared with healthy controls. Significant contributions for TNF, IL-17A, IL-23, IL-1 and interferons (IFNs) in the pathogenesis of GPP were also observed, although in comparison with plaque psoriasis, GPP lesions were shown to have higher IL-1 and IL-36 and lower IL-17A and IFN-γ. Furthermore, strongly enhanced expression of neutrophil chemokines (CXCL1, CXCL2 and CXCL8) as well as IL-1- and IL-36-related transcripts were observed in GPP lesions, significantly higher than in plaque psoriasis [31, 32].

Therefore, although GPP pathogenesis includes some mediators that overlap with plaque psoriasis, it was found to be mainly driven by a distinctive pathway centered on the IL-36 signaling, through an imbalance stemming from either an overexpression of IL-36 agonists or a loss-of-function of the antagonist IL-36Ra [1, 31]. These findings provided the rational basis for the development of new therapies targeting the IL-36 pathway.

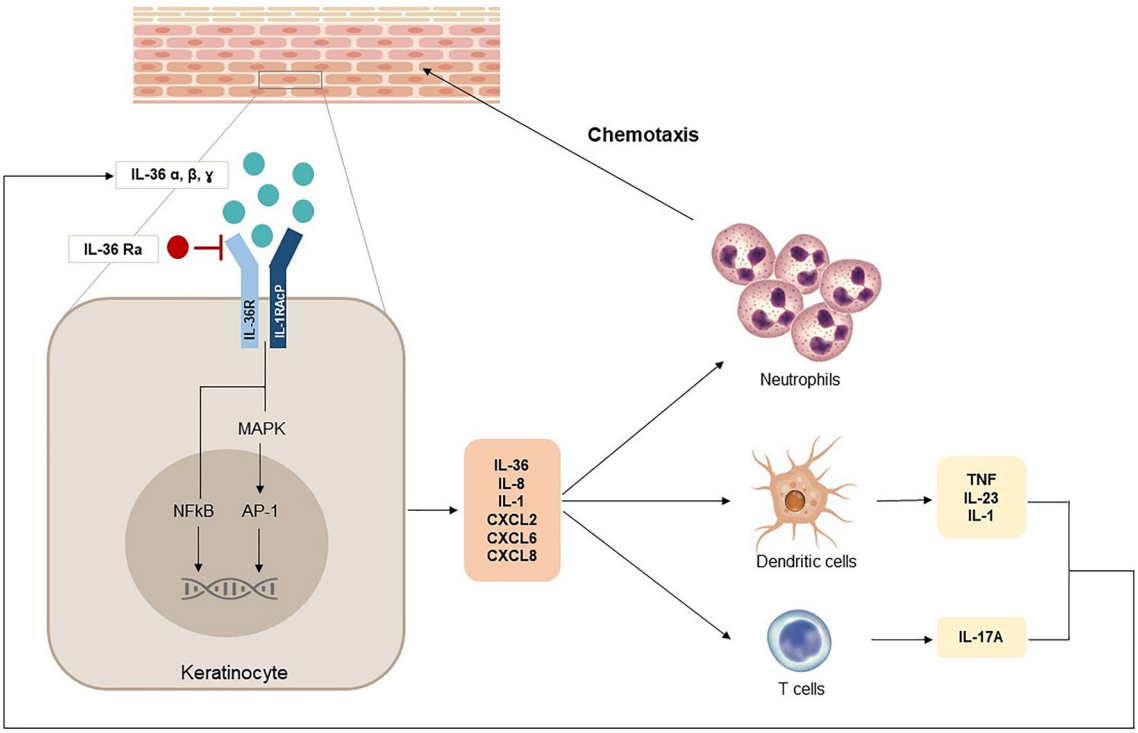

Fig. 1 Overview of IL-36 signaling. After processing by neutrophil-derived proteases, mature IL-36 agonists (α, β and γ) bind to IL-36R on the surface of keratinocytes, inducing an inflammatory cascade that promotes expression of more IL-36 percursors, neutrophilic chemokines (CXCL1, CXCL2, CXCL8) and various cytokines (IL-1β, IL-17A, IL-23, TNF), thus promoting recruitment and activation of neutrophils, T cells and dendritic cells through a self-amplifying loop. Hyperactivation of IL-36 pathways plays a key role in the pathogenesis of GPP. *AP-1* activating protein-1, *CXCL* chemokine (C–X–C motif) ligand, *GPP* generalized pustular psoriasis, *IL* interleukin, *MAPK* mitogen-activated protein kinase, *NFκB* nuclear factor kappa-light-chain-enhancer of activated B cells, *R* receptor, *Ra* receptor antagonist, *RAcP* receptor accessory protein, *TNF* tumor necrosis factor. Adapted from Marrakchi et al. [1]

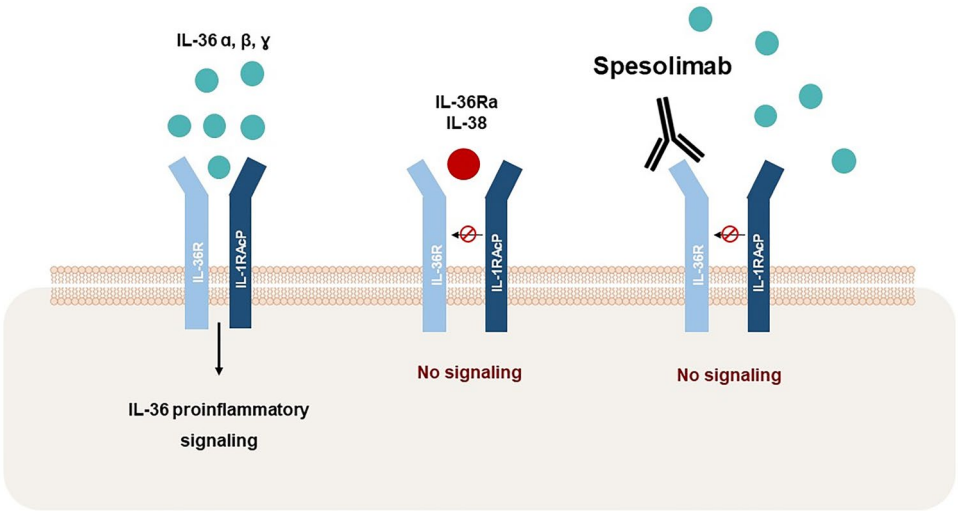

Fig. 2 Signaling through the IL-36 heterodimeric receptor and the mechanism of action of spesolimab. Binding of agonists (IL-36α, β and γ) leads to heterodimerization of the IL-36R/IL-1RAcP receptor and activation of the downstream proinflammatory IL-36-mediated cascade that is schematized in Fig. 1. IL-36Ra and IL-38 are endogenous regulators of this inflammatory respose. Spesolimab is a humanized monoclonal antibody that specifically binds to the IL-36R with high affinity, thus preventing ligands from activating downstream inflammatory pathways. *IL* interleukin, *R* receptor, Ra, receptor antagonist; *RAcP* receptor accessory protein. Adapted from Iznardo et al. [28]

4 Mechanism of Action and Pharmacology of Spesolimab

Spesolimab is a humanized monoclonal IgG1 antibody that specifically binds to the IL-36R with high affinity, thus preventing ligands (IL-36α, β and γ) from activating IL-36R and blocking downstream activation of proinflammatory and profibrotic IL-36-mediated pathways [35]. The mechanism of action of spesolimab is schematized in Fig. 2.

Spesolimab is administered by intravenous infusion and has shown linear dose-proportional pharmacokinetics in a dose range of 0.3–20 mg/kg. Age, sex and race do not seem to affect the pharmacokinetics. Plasma levels are lower in subjects with higher body weight, but the clinical implication of this finding is unknown [35].

The terminal half-life of spesolimab is 25.5 days. Its metabolic pathway has not been characterized but, as a humanized IgG1 antibody, hepatic or renal impairment is not expected to influence elimination of spesolimab. Data on the drug–drug interactions of spesolimab are currently unavailable [35].

5 Clinical Efficacy of Spesolimab in GPP

5.1 Phase I Trial

First evidence of the efficacy and safety of spesolimab in GPP arose from a proof-of-concept phase I open-label study (NCT02978690) of seven biologic-naive adult patients experiencing a moderate-to-severe GPP flare. The activity of the disease was evaluated using the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score, which has subsequently been validated [17].

At baseline, all patients had an average GPPGA score of 3 (moderate disease). A single intravenous dose of 10 mg/kg of spesolimab was administered at baseline. A GPPGA score of 0 or 1 was achieved in five patients by week 1 and in all patients by week 4, sustained up to week 20. A rapid reduction in C-reactive protein and absolute neutrophil count was also observed. Of note, total clearance of the pustules was seen within 48 h in three patients (47%). Response was obtained regardless of the IL36RN mutation status (present in three of the seven patients). Drug-related adverse effects were mild to moderate in severity and no serious adverse events were reported [17].

5.2 Phase II Trials

The phase II Effisayil clinical trial program assessing spesolimab in GPP consists of three key studies, including Effisayil 1 (NCT03782792), which assessed the efficacy and safety of spesolimab in GPP flares; the phase IIb Effisayil 2 (NCT04399837), which has been conducted to evaluate the effectiveness of the maintenance treatment with spesolimab in preventing recurrence of flares; and the long-term extension of both these trials, Effisayil ON (NCT03886246). The available results to date are summarized in Table 1.

The Effisayil 1 trial was a randomized, placebo-controlled, double-blind, phase II, multicenter study designed

to evaluate the efficacy, safety and tolerability of spesolimab in patients with GPP presenting with an acute flare. A total of 53 adults with GPP experiencing an acute flare of moderate-to-severe intensity (required to have a GPPGA score of ≥ 3, new appearance or worsening of existing pustules, a GPPGA pustulation subscore ≥ 2, and a body surface covered with erythema and pustules ≥ 5%, excluding immediately life-threatening flares) were randomly distributed in a 2:1 ratio to receive a single 900 mg intravenous dose of spesolimab ($n = 35$) or placebo ($n = 18$) on day 1 [5, 36]. Participants ranged in age from 21 to 69 years (mean 43 years), with female (68%) and Asian (55% vs. 45% Caucasians) predominance [5, 35]. The primary endpoint, defined as the achievement of a GPPGA pustulation subscore of 0 at the end of week 1, was achieved by 19 of the 35 patients (54%) receiving spesolimab versus 1 of 18 (6%) patients receiving placebo ($p < 0.001$). A GPPGA score of 0 or 1 at week 1, measured as a key secondary endpoint, was reached by 15 of the 35 patients (43%) in the spesolimab group, as compared with 2 of 18 patients (11%) in the placebo group ($p = 0.02$) [5, 37].

At day 8, patients from both groups were eligible to receive an open-label, single intravenous dose of 900 mg of spesolimab without compromising the initial blinding if they had persistent symptoms (GPPGA ≥ 2 and GPPGA pustulation subscore ≥ 2). Of the 35 patients initially randomized for spesolimab, 34% ($n = 12$) received a second dose, while 15 of the 18 (83%) patients who were assigned to placebo required the rescue dose. As a result, comparisons between the effect of spesolimab and that of placebo could not be carried out after week 1. Among the 15 patients from the placebo group who later received an open-label spesolimab infusion at week 1, 11 (73%) achieved a GPPGA pustulation subscore of 1 by week 2 (1 week after the infusion) and 8 (53%) reached a GPPGA total score of 0 or 1. After day 8, rescue treatment with a single intravenous dose of 900 mg of spesolimab could be administered in case of reoccurrence of a flare, which occurred in 6 of the 49 patients who completed the 12-week follow-up period [5, 37].

Furthermore, patients treated with spesolimab achieved clinically significant improvements in patient-reported outcomes, such as the pain Visual Analog Scale (VAS), Psoriasis Symptom Score (PSS), and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) scores, as well as the Dermatology Life Quality Index (DLQI). There was a numerical trend for early separation between the spesolimab and placebo groups during the first week, favoring the spesolimab group. Curves began to converge after day 8 and both the spesolimab and placebo groups showed comparable improvements. Sustained response over the 12-week duration of the study was observed in both mentioned clinician- and patient-reported outcomes [5, 37].

Regarding IL36RN mutation status, seven patients (five in the spesolimab group and two in the placebo group) were identified to have IL36RN mutations. Clinical response was obtained regardless of the presence or absence of mutations, although patients with mutations showed faster onset of response [5, 37, 38]. Subanalyses revealed that spesolimab efficacy and safety seem to also be independent of sex, race, body mass index, background medication and clinical characteristics at baseline, such as GPPGA and presence of plaque psoriasis [38].

Effisayil 2 is a multinational, phase IIb, randomized, double-blind, placebo-controlled clinical trial that has been conducted to assess whether maintenance treatment with spesolimab can prevent the occurrence of GPP flares and yield sustained control of the disease, as well as determine the optimal dosing regimen to achieve this aim. A total of 123 patients aged 12–75 years with a documented history of GPP with frequent flares and a GPPGA score of 0 or 1 (clear or almost clear) at baseline were randomized 1:1:1:1 to receive (1) a 600 mg subcutaneous loading dose of spesolimab, followed by a 300 mg maintenance dose every 4 weeks (q4w) [high dose] or (2) every 12 weeks (q12w) [medium dose]; or (3) a 300 mg loading dose followed by a 150 mg maintenance dose q12w (low-dose); or (4) placebo q4w, during a period of 44 weeks with follow-up to week 48. The objectives of the trial included the establishment of dose-response curves and assess whether higher doses of spesolimab demonstrate superiority. The primary endpoint was time to first GPP flare. If a patient experienced a GPP flare during the maintenance treatment period, an open-label intravenous infusion of 900 mg of spesolimab was administered, with an option for a second intravenous dose after 1 week. Secondary outcomes on efficacy included the occurrence of at least one GPP flare by week 48 (key secondary endpoint) and time to worsening (defined as an increase of 4 points from baseline for each score) of the PSS and DLQI up to week 48 [39, 40].

A preponderance of Asian (64%) and female (62%) patients was also documented in this trial and the mean age was 40.4 years. At week 48, 30 of the 31 patients receiving placebo, 27 of 31 patients receiving low-dose spesolimab, 28 of 31 patients receiving medium-dose spesolimab, and 26 of 30 patients receiving high-dose spesolimab completed the trial, with no demonstrated pattern with respect to the reasons for discontinuation between the groups. At week 48, 23% of patients in the low-dose spesolimab group, 29% in the medium-dose group, 10% in the high-dose group, and 52% in the placebo group had at least one GPP flare. The estimated probability of a GPP flare occurring started to diverge between the spesolimab and placebo groups shortly after randomization and remained sustained up to week 48. A non-flat dose-response relationship for spesolimab was shown for the three arms of spesolimab versus placebo on

Table 1 Summary of available results evaluating Spesolimab in the management of generalized pustular psoriasis

Trial	Study design	Endpoints	Main results	Main AE
Phase I [17]	Single-arm, open-label, proof-of-concept $N = 7$ adults Ongoing moderate to severe GPP flare SD of spesolimab 10 mg/kg IV at baseline Follow-up 20 weeks	Primary: Safety and tolerability (% AE) Secondary: Percentage change in GPPGA, FACIT-F and Pain-VAS at week 2 GPPGA 0/1 at week 2	GPPGA 0 in 43% of patients within 48 h GPPGA 0/1 achieved in 71% of patients by week 1 and in 100% of patients by week 4, sustained up to week 20 Mean percentage change in GPPASI of 73.2% at week 2, sustained up to week 20 Improvement in Pain-VAS (− 46%) and FACIT-F (− 12%) at week 2, sustained at week 4 Rapid reduction in CRP and absolute neutrophil count	Mild to moderate eosinophilia, infections, vomiting, pain, infusion-related reaction No severe AE
Phase II Effisayil 1 [5, 37]	Randomized, placebo-controlled, double-blind $N = 53$ adults Ongoing moderate to severe GPP flare 2:1 Spesolimab 900 mg SD Placebo Rescue SD 900 mg IV of spesolimab allowed by day 8 in both groups if persistent symptoms, and after day 8 if recurrence of a flare 12 weeks	Primary: GPPGA pustulation subscore 0 at week 1 Secondary: *Week 1* GPPGA score of 0 or 1 GPPASI 50 Percentage change in GPPASI from baseline *Week 4* GPPASI 75 Change from baseline in Pain-VAS, FACIT-F and PSS Percentage change in GPPASI from baseline GPPGA pustulation subscore 0	Significant GPPGA pustulation subscore 0 at week 1 vs. placebo (54% vs. 6%; $p < 0.001$), sustained over 12 weeks GPPGA total 0/1 higher than placebo (43% vs. 11%) at week 1 ($p = 0.02$), sustained over 12 weeks Improvements from baseline (median) in pain VAS (−21.3), FACIT–Fatigue (7.0), DLQI (−2.5), and PSS (−4.0) within 1 week after spesolimab, sustained over 12 weeks	Infections (17% during the first week vs. 6% of placebo); 82% at week 12 Asthenia and fatigue, nausea, vomiting, headache, pruritus, infusion site hematoma and bruising (<10%) Antidrug antibodies (46%) DRESS (controversial data)

Table 1 (continued)

Trial	Study design	Endpoints	Main results	Main AE
Phase IIb Effisayil 2 [39, 40]	Randomized, placebo-controlled, double-blind $N = 123$ adults and adolescents No active flare at baseline 1:1:1:1 Spesolimab LD 600 mg, followed by maintenance 300 mg q4w Spesolimab LD 600 mg, followed by maintenance 300 mg q12w Spesolimab LD 300 mg, followed by maintenance 150 mg q12w Placebo Subcutaneous administration 48 weeks	Primary: Time to first GPP flare Secondary: Occurrence of ≥ 1 GPP flare Time to first worsening of PSS and DLQI GPPGA score of 0 or 1 up to week 48 (sustained remission) Occurrence of TEAE	Non-flat dose-response relationship for the three arms of spesolimab vs. placebo High-dose spesolimab showed statistically significant superiority on time to GPP flare vs. placebo ($p = 0.0005$) Risk differences for the occurrence of a GPP flare compared with placebo: −0.31 ($p = 0.0068$) for low-dose spesolimab; − 0.23 ($p = 0.036$) for medium-dose spesolimab; − 0.39 ($p = 0.0013$) for high-dose spesolimab Risk of PSS worsening vs. placebo (HR): 0.46 ($p = 0.0079$) for low-dose spesolimab; 0.56 ($p = 0.052$) for medium-dose spesolimab; 0.42 ($p = 0.013$) for high-dose spesolimab Risk of DLQI worsening vs. placebo (HR): 0.58 ($p = 0.043$) for low-dose spesolimab; 0.60 ($p = 0.048$) for medium-dose spesolimab; 0.26 ($p = 0.001$) for high-dose spesolimab Patients with IL36RN mutation: 0% of patients had a flare on high-dose spesolimab vs. 75% on placebo Patients without IL36RN mutation: 16% of patients had a flare on high-dose vs. 41% on placebo	Similar incidence of (including severe AE and an investigator-defined drug-related AE) between spesolimab and placebo Greater proportion of serious AEs in the spesolimab groups (10% vs. 3% placebo), mostly unrelated to drug treatment Infections (33%, same as placebo), injection-site erythema (14%), arthralgias (9%)

AE adverse event, *CRP* C-reactive protein, *DLQI* Dermatology Quality of Life Index, *DRESS* Drug Reaction with Eosinophilia and Systemic Symptoms, *FACIT-F* Functional Assessment of Chronic Illness Therapy–Fatigue, *GPP* generalized pustular psoriasis, *GPPASI* Psoriasis Area and Severity Index for Generalized Pustular Psoriasis, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *GPPASI* Generalized Pustular Psoriasis Area and Severity Index, *HR* hazard ratio, *IV* intravenous, *LD* loading dose, *PSS* Psoriasis Symptom Scale, *q4w* every 4 weeks, *q12w* every 12 weeks, *SD* single dose, *TEAE* treatment-emergent adverse event, *VAS* visual analog scale

time to first GPP flare, achieving the primary trial objective. No flares were observed after week 4 of spesolimab treatment in the high-dose group, which demonstrated a statistical superiority versus placebo in both primary and key secondary endpoints. On the other hand, lower doses of spesolimab did not achieve statistical significance on the time to GPP flare when compared with placebo [40]. Regarding IL36RN mutation status, among patients with an IL36RN mutation, no patients who received the high-dose spesolimab regimen experienced a flare versus 3 of 4 (75%) patients in the placebo regimen. For patients without an IL36RN mutation, 3 of 19 (16%) patients in the high-dose spesolimab group had a flare, in comparison with 9 of 22 (41%) patients in the placebo group [40].

In numerical terms, spesolimab reduced the risk of PSS and DLQI worsening in the 48-week period compared with placebo, but, with the exception of the reduction in DLQI in the high-dose spesolimab regimen (hazard ratio vs. placebo 0.26, $p = 0.001$), the threshold of statistical significance was not achieved by the remaining secondary measures [40].

Patients who completed the treatment period were eligible to enter Effisayil ON (NCT03886246), an open-label, 5-year extension trial of spesolimab in GPP [41]. The primary endpoint is to assess the occurrence of treatment-emergent AEs up to week 252 of maintenance treatment with spesolimab. Secondary key endpoints that will be assessed include the recurrence of a flare defined by GPPGA and time required to achieve a GPPGA of 0 or 1 in patients who received a rescue dose of spesolimab for a flare. Additional outcome measures include the change from baseline in PSS and the achievement of a GPPGA pustulation subscore of 0, assessed in each visit throughout the 252 weeks [41].

5.3 Phase III Trials

Phase III, open-label expanded access trials are underway in Japan (NCT05200247) [42] and China (NCT05239039) [43] to provide access to spesolimab to patients experiencing a GPP flare-up who have no alternative treatment options. These trials have already been completed but the results have not yet been published.

6 Safety

Spesolimab was generally well tolerated in GPP patients. During the first week of the Effisayil 1 trial, adverse events (AE) were reported in 66% of patients assigned to the spesolimab group and 56% of those in the placebo group, with the incidence of infections being numerically higher in patients receiving spesolimab (17%) versus placebo (6%) [37]. Other AEs occurring in more than 5% of patients receiving spesolimab (and more frequently than in those receiving placebo) were asthenia and fatigue (9 vs. 0%), nausea and vomiting (6 vs. 9%), headache (9 vs. 6%), pruritus (6 vs. 0%), and infusion site hematoma and bruising (6 vs. 0%) [18, 35, 37]. AEs were mild-to-moderate in intensity and did not require treatment discontinuation [37].

Over the 12-week period, a total of 82% of all patients who received at least one dose of spesolimab reported an AE, with 12% being considered serious AEs. [37] Infections were reported in 47% of patients who had received spesolimab, with no patterns identified in terms of affected site and nature of the culprit agent. One case of serious infection (urinary tract infection) was reported in a patient treated with spesolimab, with the remaining cases being considered mild to moderate [35, 37]. Two cases of drug reaction with eosinophilia and systemic symptoms (DRESS) in patients who received spesolimab were reported. In one of the cases, the onset of symptoms occurred within 2 days of spesolimab exposure. Both patients were concurrently taking multiple medications, including various antibiotics, at the time of the onset of the symptoms [37]. Reported cases were subsequently assessed as 'no DRESS' and 'possible DRESS' by RegiSCAR (Registry of Severe Cutaneous Adverse Reactions) DRESS validation scoring [35].

Safety data in Effisayil 2 seem to be in line with previously conducted trials. An equivalent proportion of patients receiving spesolimab (90%) and placebo (87%) experienced an AE over the 48-week period and the incidence did not follow a dose-dependent pattern. Most AEs were non-serious and non-severe and none led to death. The incidence of severe AEs and investigator-defined drug-related AEs were also similar between spesolimab (19% and 40%, respectively) and placebo (23% and 33%, respectively). The most common AEs reported were pustular psoriasis (25% of patients receiving spesolimab vs. 53% of those receiving placebo), psoriasis (14% vs. 10%) and injection-site erythema (14% vs. 3%). Infections were reported in 33% of all patients who received spesolimab, the same rate that was seen in the placebo group, and did not follow a dose-dependent pattern with spesolimab. A greater proportion of patients receiving spesolimab experienced serious AEs (10% vs. 3% received placebo), including viral encephalitis/hypertensive encephalopathy, pneumonia, skin bacterial infection, angioedema, drug eruption, palpitations, breast cancer, cholelithiasis and pustular psoriasis. A total of 5.4% of patients receiving spesolimab had AEs that led to treatment discontinuation, none of which were due to hypersensitivity reactions [40].

Spesolimab carries the potential for immunogenicity [18]. Antidrug antibodies (ADAs) were detected in 46% of patients who received at least one dose of spesolimab in Effisayil 1, with a median onset of 2.3 weeks after exposure [37]. There was no apparent impact on spesolimab pharmacokinetics for ADA titers < 4000, while a significant reduction in the plasma concentrations of spesolimab was

documented in patients with ADA titers ≥ 4000, although its impact on safety and efficacy is unclear [35, 37]. Data from spesolimab-treated patients across three clinical trials (phase I, Effisayil 1 and some limited data from Effisayil ON) showed that after treatment with intravenous spesolimab, 24–33% of patients had an ADA titer > 4000, more frequently in females (30%) than in males (12%). Furthermore, treatment effect over time has shown to be maintained irrespective of the presence of ADAs or neutralizing antibodies, and there was no evidence that ADAs are associated with hypersensitivity events [44]. However, more data on the impact upon retreatment of a GPP flare with spesolimab is needed. A multicenter, open-label, single-arm, postmarketing (phase IV) trial is expected to be performed to evaluate efficacy and safety, as well as the impact of immunogenicity on the efficacy, safety, and pharmacokinetics of spesolimab in patients with GPP presenting with a recurrent flare, following an initial GPP flare treated with spesolimab [45].

Since spesolimab only received approval for GPP in late 2022, data on postmarketing surveillance are not yet available. The occurrence of treatment-emergent AEs during the long-term maintenance treatment with spesolimab will be assessed as the primary endpoint in the open-label, 5-year extension trial [41].

Ongoing clinical trials investigating spesolimab for the treatment of GPP are listed in Table 2.

7 Discussion

GPP is an orphan auto-inflammatory disorder of the keratinocytes, characterized by severe flares of widespread pustulation, and often accompanied by systemic inflammation [1, 2]. As a potentially life-threatening disease, it requires prompt diagnosis and treatment, although there are several unmet needs in the current management of GPP [14, 40]. Optimal treatment for GPP would offer rapid onset of action, skin clearance and avoidance of systemic manifestations, as well as a reduction of the burden and the ability to prevent the recurrence of flares, while providing a favorable safety profile both in the short- and long-term [14, 23, 40].

Current treatment of GPP flares often relies on the off-label use of medications licensed for moderate to severe plaque psoriasis, but the limited evidence that supports this practice is derived from case reports and small single-arm studies [9, 14, 20]. Actually, while it can co-exist with plaque psoriasis and is traditionally classified as a subtype of psoriasis, GPP stands apart due to its distinctive clinical and immune-histopathologic features, as well as genetics [1, 11]. Following the identification of loss-of-function mutations in the IL36RN gene in 2011, several additional studies corroborated the central role of IL-36 axis overactivation in the pathogenesis of GPP, providing the rational basis for

Table 2 Ongoing clinical trials investigating Spesolimab for the treatment of generalized pustular psoriasis

ClinicalTrials.gov identifier	Title	Phase	Estimated enrollment (*n*)	Status	Estimated study completion date
NCT03886246 [41]	Effisayil™ ON: A study to test long-term treatment with spesolimab in people with generalized pustular psoriasis who took part in a previous study	II	131	Active, not recruiting	January 2028
NCT05200247 [42]	An expanded access trial in Japan to provide spesolimab to people with a flare-up in generalized pustular psoriasis who have no other treatment options	III	11	Completed (waiting for results)	March 2023
NCT05239039 [43]	An expanded access program in China to provide spesolimab to people with a flare-up in generalized pustular psoriasis who have no other treatment options	III	39	Completed (waiting for results)	July 2023
NCT05670821 [49]	Post-marketing surveillance of spesolimab IV infusion in improvement of generalized pustular psoriasis with acute symptoms in Japan	IV	40	Recruiting	December 2025
NCT06013969 [45]	An open-label, multicenter, single-arm, post-marketing trial to evaluate efficacy and safety and the impact of immunogenicity on efficacy, safety, and pharmacokinetics of spesolimab IV in treatment of patients with generalized pustular psoriasis presenting with a recurrent flare following their initial GPP flare treatment with spesolimab IV	IV	40	Not yet recruiting	December 2026

IV intravenous

the development of a novel treatment paradigm for GPP by targeting IL-36 [18].

Spesolimab is an antibody against the IL-36 receptor that has been developed for the treatment of various immune-mediated disorders. To date, spesolimab has been approved by regulatory authorities for the treatment of GPP flares in adults in almost 40 countries, including Japan, the US and the European Union. The recommended dosage for GPP flares is a single spesolimab 900 mg intravenous infusion, which may be repeated 1 week after the initial administration if flare symptoms persist [18].

The first evidence came from an initial phase I proof-of-concept study of seven patients experiencing a GPP flare in whom a single intravenous infusion of 10 mg/kg of spesolimab resulted in rapid, effective and sustained clearance of skin manifestations, with no significant AEs [17]. In light of these results, subsequent analyses of the molecular and cellular expression profiles in skin specimens and blood from GPP patients revealed that a single intravenous dose of spesolimab resulted in rapid and strong downregulation of biomarkers linked to key inflammatory pathways, which was found to be in line with the clinical improvements [27].

The phase II Effisayil clinical trial program has been investigating the largest and broadest population of patients with GPP. The Effisayil 1 trial, conducted with a multicentric cohort of 53 individuals, provided further evidence of the efficacy of spesolimab versus placebo in clearing GPP lesions within 1 week, as well as improving patient-reported pain, fatigue, quality of life and cutaneous symptoms [5, 37]. Beyond the initial week of the trial, there was no notable placebo effect, since more than 80% of patients in the placebo arm subsequently required a rescue infusion of spesolimab at day 8. After receiving spesolimab, these patients also experienced similar improvements in clinician- and patient-reported outcomes, and, in both arms, the response was sustained throughout the 12-week duration of the trial [5, 37]. As previously observed in the phase I trial, the efficacy of spesolimab was not affected by the IL36RN mutational status [38].

The Effisayil 2 clinical trial evaluated spesolimab maintenance treatment for the prevention of GPP flares. In this multinational trial that included 123 adolescents and adults with a history of GPP, high-dose spesolimab was shown to be significantly superior to placebo in preventing the occurrence of GPP flares over 48 weeks and reduced the risk of quality-of-life decline. Despite the numerical benefit of spesolimab that was observed for the other dose regimens, it was not possible to obtain statistical significance. Since spesolimab acts by inhibiting the IL-36R rather than the IL-36 cytokines directly, there might be a requirement for a more frequent injection schedule (q4w instead of q12w) to maintain sustained receptor inhibition and the resulting prolonged downstream effects. The clinical benefit of spesolimab maintenance treatment for flare prevention was also independent of IL36RN mutation status [40].

In clinical trials, spesolimab was shown to be safe and well-tolerated by GPP patients, with most AEs being non-serious, non-severe, and not leading to treatment discontinuation. The primary concern arises from the increased frequency of infections among patients in the spesolimab arm observed in Effisayil 1, despite the absence of a predilection for any particular microorganism or affected organ [37]. IL-36 cytokines are predominantly expressed at barrier surfaces of the body, such as the skin, intestines, and bronchi [15]. They are involved in the first-line protection of the host against exogenous pathogens and contribute to the interlink between the innate and adaptive immune systems, but these roles are less well-defined in other organs than in the skin [15, 29]. Phenotyping studies of individuals carrying loss-of-function mutations in the IL-36 receptor gene show that immune function is globally preserved in these patients, suggesting that IL-36 blockade is unlikely to substantially compromise host defenses [30]. Since it is not possible to exclude that IL-36 inhibition may confer higher vulnerability of the host to infections, the risk-benefit must be weighed in patients with a chronic infection or a history of recurrent infections. Spesolimab is not recommended for use in patients with any ongoing clinically significant active infection. Screening and treatment of patients for tuberculosis infection is recommended prior to initiating treatment with spesolimab [35]. This could be a limitation of spesolimab in the management of acute flares due to necessity for screening for tuberculosis (TB), which can delay prompt use of the treatment.

In Effisayil 2, infection rates were similar across the placebo and spesolimab arms and there was no evidence pointing to an increase in rates with a higher dose. A higher rate of treatment discontinuation was reported in the high-dose group, but the reasons were predominantly unrelated to spesolimab treatment, like breast cancer and pregnancy. There were no hypersensitivity events leading to treatment discontinuation and no deaths were documented during the study period [40]. The safety data thus far for spesolimab in GPP seem to be reassuring and are expected to be confirmed by data on postmarketing surveillance and the ongoing 5-year, open-label extension trial evaluating continuous long-term treatment with spesolimab in GPP [41].

Spesolimab has also been studied for PPP and other inflammatory disorders, including ulcerative colitis, Crohn's disease and hidradenitis suppurativa, with reassuring results regarding tolerability and safety. There was no evidence for significant hypersensitivity reactions or severe, serious, or opportunistic infections related to spesolimab [18, 46, 47]. Of note, in two phase II trials for PPP, the primary endpoint was not met, indicating potential modest benefits on PPP [46, 48].

Establishing evidence-based guidelines and recommendations for the management of GPP will be essential to address issues related to treatment availability and accessibility. For now, further investigations are required, including additional data on the long-term efficacy and safety and real-world evidence. Data on the use of spesolimab in special populations, such as children, elderly over 75 years of age, pregnant women and patients with multiple comorbidities, is currently missing since they were excluded from clinical trials. Studies thus far may not have represented the total diversity of patients worldwide, given the overt predominance of Asian and European participants. Furthermore, there is still a gap regarding the awareness of GPP and its features and clinical course. It would be important to establish consensus regarding the diagnostic criteria to avoid potential misclassifications, delay in treatment and inadequate inclusion or exclusion of patients in clinical trials. It is also essential to set and validate scoring systems for assessing disease burden, as well as to establish objective outcome measures and clinical endpoints to be uniformly adopted in the clinical trials, facilitating comparisons between therapies. GPPGA score and subscores were first used in Effisayil 1 and subsequently validated, but they only assess the severity of skin manifestation and do not consider systemic signs and symptoms, including disease burden of the disease.

Despite these limitations, data published to date suggest that spesolimab was shown to have a faster and more complete clinical response in GPP than other biologics and has been shown to be able to prevent the occurrence of flares over 48 weeks, with a favorable safety profile. Current data suggest that targeting IL-36 is a highly effective target in treating GPP flares and controlling the disease relapses in the long-term, and support the hypothesis that IL-36 is the central mediator of the pathogenesis of GPP. Spesolimab appears to address the main unmet needs in GPP and it is expected that spesolimab will soon become the established standard of care for this life-threatening orphan disease.

8 Conclusion

The IL-36 pathway is now recognized as the key driver of the autoinflammatory responses involved in GPP. Spesolimab is a selective, humanized antibody targeting IL-36R that has been shown to be effective in the management of GPP, both in the rapid control of the flares and in preventing their recurrence in the long-term, while maintaining a favorable safety profile.

Declarations

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