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Design of Effisayil™ 2: A randomized, double-blind, placebo-controlled study of spesolimab in preventing flares in patients with generalized pustular psoriasis

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STUDY PROTOCOL

Design of Effisayil™ 2: A Randomized, Double-Blind, Placebo-Controlled Study of Spesolimab in Preventing Flares in Patients with Generalized Pustular Psoriasis

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ABSTRACT

Introduction: Generalized pustular psoriasis (GPP) is a rare autoinflammatory skin disease characterized by flares of widespread erythema with sterile pustules, and can be relapsing with recurrent flares, or persistent with intermittent flares. Spesolimab, a humanized anti-

interleukin-36 (IL-36) receptor monoclonal antibody, targets the key IL-36 pathogenetic pathway in GPP. A previous study showed that spesolimab treatment led to rapid pustular and skin clearance in patients with GPP flares, which was sustained for up to 12 weeks. This study investigates the long-term effects of spesolimab on GPP flares, for which no specific treatments are currently available. The Eff-

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isayil™ 2 study will assess whether maintenance treatment with subcutaneous spesolimab prevents the occurrence of GPP flares and determine the optimal dosing regimen to achieve this aim.

Methods: Patients will have a documented history of GPP with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 (clear or almost clear) at screening and randomization. Patients will be randomized 1:1:1:1 to three groups receiving a 600-mg subcutaneous loading dose of spesolimab followed by a 300-mg maintenance dose administered every 4 or 12 weeks, or a 300-mg loading dose followed by a 150-mg maintenance dose administered every 12 weeks, and one group receiving placebo, for 48 weeks. The primary endpoint is time to first GPP flare. If a patient experiences a GPP flare during the randomized maintenance treatment period, an open-label intravenous dose of 900-mg spesolimab will be administered, with an option for a second intravenous dose after 1 week.

Conclusions: Effisayil™ 2 is the first placebo-controlled study in patients with GPP to investigate whether maintenance treatment with spesolimab can prevent flares and provide sustained disease control. This study will provide valuable insights on the long-term management of patients with this potentially life-threatening skin disease.

Trial Registration Number: NCT04399837.

PLAIN LANGUAGE SUMMARY

The aim of the Effisayil™ 2 study is to see whether long-term treatment with the antibody spesolimab helps prevent skin flares in people with generalized pustular psoriasis (GPP). Patients can take part in the Effisayil™ 2 study if they have well-controlled GPP before they begin treatment in the study; that is, they will have skin that is clear or almost clear. Patients will be randomly divided into four groups, with similar numbers of patients in each group. In three of the four groups, patients will be given different doses of spesolimab for 48 weeks. In the fourth group, patients will be given a

placebo for 48 weeks. The main goal of the study is to see how long it takes patients to have a GPP flare, while they are being given spesolimab or placebo. If any patient has a GPP flare during the study, they can be treated with another dose of spesolimab (and possibly a second dose 1 week later if needed), to help control the GPP flare. In this way, the Effisayil™ 2 study will help doctors and patients to learn how to manage GPP over time, so that GPP flares can be avoided.

Keywords: Spesolimab; Generalized pustular psoriasis; Biologics; Clinical trials; Immunomodulatory therapies; Inflammatory skin diseases

Key Summary Points

Why carry out this study?

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening autoinflammatory skin disease; standard treatment guidance for this condition often follows that of plaque psoriasis, despite limited evidence on the efficacy of anti-psoriatic drugs, including biologics, in GPP.

Spesolimab is effective in treating GPP flares, but the relapsing nature of GPP means that there is an unmet need for treatments to prevent the occurrence of GPP flares, which the Effisayil™ 2 study (NCT04399837) will assess.

What was learned from the study?

Effisayil™ 2 is the first placebo-controlled study in patients with GPP that focuses on flare prevention, through maintenance treatment with subcutaneous spesolimab.

The efficacy and safety data from Effisayil™ 2 will provide valuable information on the use of maintenance spesolimab treatment in preventing GPP flares and delivering sustained symptom management.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, severe, autoinflammatory skin disease characterized by recurrent flares of widespread erythema and edema with sterile pustules that may coalesce to form lakes of pus [1–4]. During a GPP flare, patients may experience fever, leukocytosis, fatigue, and painful skin [1, 2, 5, 6]. GPP may also lead to potentially life-threatening complications including kidney, liver, respiratory and heart failure, and sepsis [1, 5, 7]. Standard treatment guidance for GPP often follows that of plaque psoriasis, despite limited evidence on the efficacy of anti-psoriatic drugs, including biologics, in GPP [8]. In Japan, Taiwan, and Thailand, a number of biologic agents targeting pro-inflammatory pathways associated with GPP have been approved for patient use, but the rarity of the disease means that their approval is based on a limited number of open-label clinical trials with small numbers of participants [2, 9–12].

In an open-label, proof-of-concept study (NCT02978690), patients experiencing a GPP flare became clear or almost clear of GPP by Week 4 post treatment with a single dose of spesolimab (a humanized anti-interleukin-36 receptor monoclonal antibody) [14]. After this, the Effisayil™ 1 study (NCT03782792) was the first randomized clinical trial to investigate a targeted treatment for GPP, and reported that adult patients with a GPP flare treated with spesolimab achieved rapid pustular and skin clearance [15]. The results from this study were integral to the recent approval of spesolimab by the US FDA as a first treatment option for GPP flares [16]. The relapsing nature of GPP (recurrent flares or persistent disease with intermittent flares) highlights the need to develop treatments to prevent flares [3], with a recent survey revealing that among dermatologists whose patients experience frequent flares, 67% felt that currently available treatments fail to adequately prevent new flares [13].

The aims of the Effisayil™ 2 study were to assess whether maintenance treatment with subcutaneous (SC) dosing regimens of spesolimab prevent the occurrence of GPP flares, and

to determine the optimal dosing regimen of spesolimab SC maintenance treatment.

METHODS

Study Design

Effisayil™ 2 (NCT04399837) is a phase 2, multicenter, randomized, parallel-group, double-blind, placebo-controlled, dose-finding study to evaluate the efficacy and safety of spesolimab in preventing GPP flares in patients with a history of GPP. Patients will be randomized 1:1:1:1 to three groups receiving a SC 600-mg loading dose of spesolimab followed by a 300-mg maintenance dose administered every 4 weeks (q4w) or every 12 weeks (q12w), or a 300-mg loading dose of spesolimab followed by a 150-mg maintenance dose administered q12w, and one group receiving placebo, for 48 weeks (Fig. 1). To maintain treatment blinding, patients in all treatment arms will receive one loading dose, administered as four injections of 150-mg spesolimab or placebo at Week 1/Day 1, followed by a maintenance dose administered as two injections of 150-mg spesolimab or placebo at subsequent dosing visits in the 4-week schedule. Patients who complete the treatment period in this study will be offered the option of entering into an ongoing open-label extension (OLE) study to assess the long-term safety and efficacy of spesolimab treatment in patients with GPP (NCT03886246), providing they agree to participate in the OLE study and meet the OLE study eligibility criteria.

Randomization

Randomization of patients will be conducted according to the use of systemic GPP medications at randomization, region (Japan versus outside of Japan) and age at screening (adults aged 18–75 years versus adolescents aged 12– < 18 years). The randomization list will be generated using a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. An

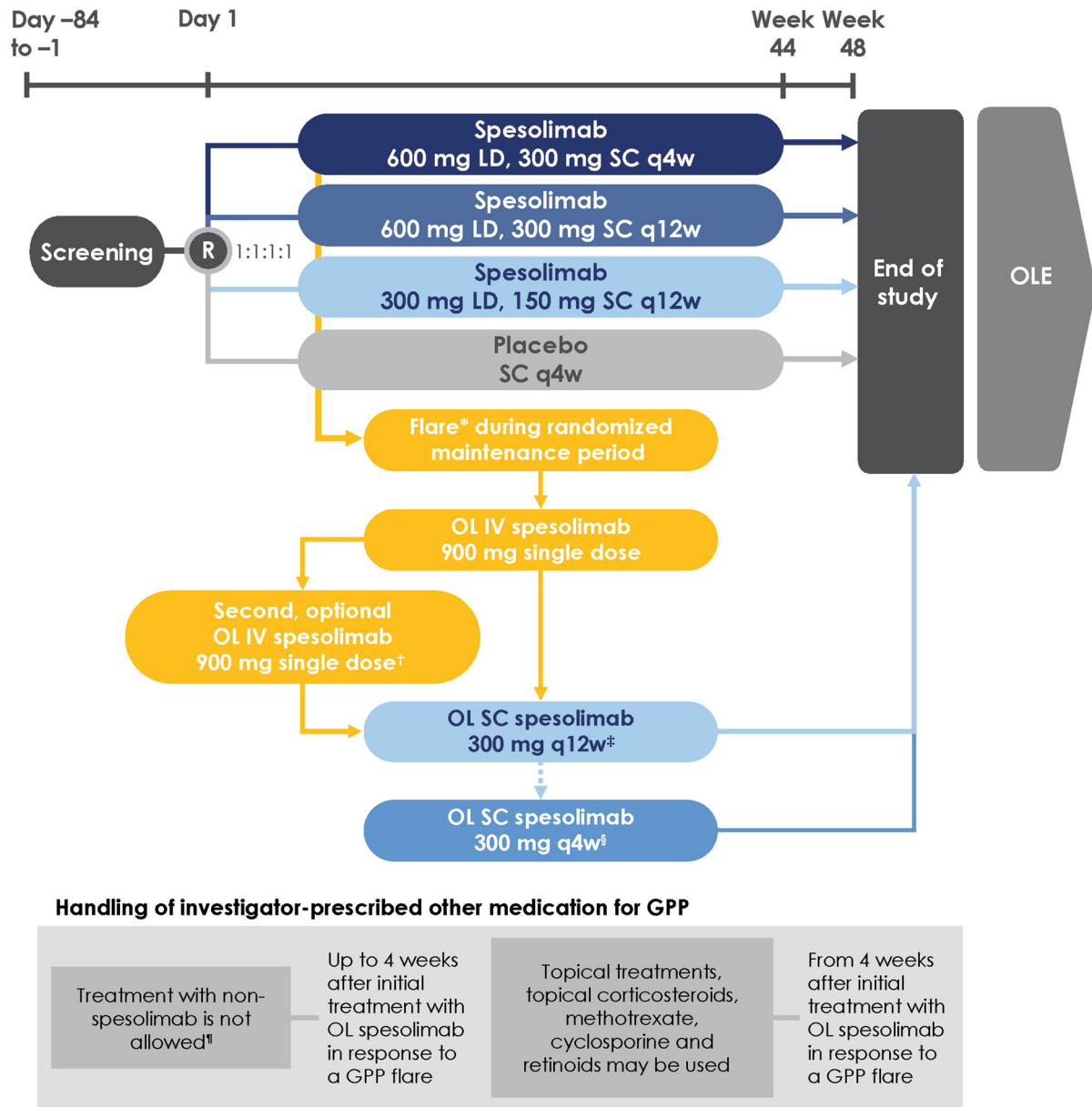


Fig. 1 Overall study design, with loading and maintenance phase treatment arms, and handling of GPP flares during the randomized maintenance treatment period. *GPP flare defined as an increase in GPPGA total score of ≥ 2 from baseline and the pustular component of GPPGA of ≥ 2 . [†]Administered 1 week after initial treatment with OL spesolimab in response to a GPP flare if patients meet qualifying criteria: for patients with GPPGA total score of ≥ 3 and a pustular component of GPPGA of ≥ 2 at baseline, if the GPPGA total score is ≥ 2 and the pustular component of GPPGA is ≥ 2 ; and for patients with GPPGA total score of 2 and a pustular component of

GPPGA of ≥ 2 at baseline, if the pustular component of GPPGA is ≥ 2 . [‡]12 weeks after initial treatment with OL spesolimab in response to a GPP flare. [§]Other medication for GPP may be prescribed, but intensified spesolimab maintenance should be attempted first. [¶]Patients may be treated with other medication for GPP at the investigator's discretion, but the patient will be discontinued from any further study drug. *GPP* generalized pustular psoriasis, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *IV* intravenous, *LD* loading dose, *OL* open-label, *OLE* open-label extension, *q4w* every 4 weeks, *q12w* every 12 weeks, *R* randomization, *SC* subcutaneous

Interactive Response Technology will be used to screen eligible patients, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The sponsor will remain blinded to the randomized treatment assignments until the last patient has completed or discontinued early from the 48-week treatment period of the trial and the database is considered ready for unblinding to perform the primary analysis of the trial.

Patient Population

Study participants will be male or female aged ≥ 12 –75 years at screening and weigh ≥ 40 kg, with a known and documented history of GPP as per the European Rare and Severe Psoriasis Expert Network (ERASPEN) criteria [3], regardless of *IL36RN* mutation status, with at least two prior presentations of GPP flares with fresh pustulation. At screening and randomization, patients must present with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 (clear or almost clear). The GPPGA score is a minimally modified version of the Physician Global Assessment (PGA) that is widely used and understood by dermatologists, created with the help of leading global experts in GPP and psoriasis vulgaris [17]. Patients not on concurrent GPP treatment at randomization must have had at least two flares within the past year, at least one of which must have been associated with fever, elevated C-reactive protein or white blood cell count, asthenia, and/or myalgia. Patients on concurrent GPP treatment until shortly before randomization (≤ 12 weeks prior to randomization) must have a history of flaring during concurrent treatment, or after dose reduction or discontinuation of concurrent treatment. Those on concurrent treatment with retinoids, methotrexate and/or ciclosporin must stop this treatment on the day of randomization. At randomization, participants will be tested for mutations in the *IL36RN*, *CARD14*, and *AP1S3* genes to evaluate the potential influence of these mutations on disease activity and/or spesolimab efficacy, but mutation status will not factor into decisions

regarding patient inclusion or randomization. A full list of inclusion and exclusion criteria is provided in Table 1. Participants will be recruited in 34 countries and areas across global regions: Argentina, Australia, Belgium, Bulgaria, Chile, China, Columbia, Croatia, Czech Republic, Egypt, France, Georgia, Germany, Greece, Italy, Israel, Japan, Republic of Korea, Malaysia, Mexico, the Netherlands, Philippines, Poland, Russia, Singapore, South Africa, Spain, Thailand, Tunisia, Turkey, Taiwan, Ukraine, USA, and Vietnam.

A total of 120 patients are planned to be recruited to achieve a power of over 90% for at least one successful dose of spesolimab in the 300-mg q4w and 300-mg q12w maintenance dose groups versus placebo for the primary and key secondary endpoints.

Treatment Administration in Response to Patients Experiencing a GPP flare

If a patient experiences a first GPP flare, defined as an increase in GPPGA total score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2 , during the randomized maintenance treatment period of this study, an open-label intravenous (IV) dose of 900-mg spesolimab will be administered (Fig. 1). After treatment with open-label IV 900-mg spesolimab in response to a GPP flare, a patient may qualify to receive a second dose of open-label IV 900-mg spesolimab 1 week later if flare symptoms persist, as defined by criteria shown in Fig. 1. Patients who respond to one or two doses of open-label IV 900-mg spesolimab before Week 34 of randomization will be switched back to maintenance treatment (open-label SC spesolimab) at 12 weeks after the first 900-mg IV dose, either in this study or as part of the ongoing OLE study.

Handling of Investigator-Prescribed Other Medication for GPP

During the randomized maintenance treatment period, it is strongly recommended that investigators avoid prescription of medication currently used for the treatment of GPP. During the randomized maintenance treatment period, and during the first 4 weeks following spesolimab treatment in response to a GPP flare, if a

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male or female patients aged ≥ 12 –75 years at screening	Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome
History of GPP with ≥ 2 past GPP flares with fresh pustulation (new appearance or worsening). At screening, the confirmation of history (diagnosis) of GPP is based on the consensus diagnostic criteria defined by the ERASPEN [3] and the patients must have had previous evidence (for past GPP flares) of either fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN)	Primary erythrodermic psoriasis vulgaris
GPPGA total score of 0 or 1 at screening and randomization	Severe, progressive, or uncontrolled hepatic disease
Patients not on concurrent GPP treatment at randomization must have had ≥ 2 flares in the previous year, ≥ 1 of which must have been associated with fever, elevated CRP or WBC count, asthenia, and/or myalgia	Treatment with any defined restricted medication, any drug considered by the investigator to interfere with the safe conduct of the study, or prior exposure to spesolimab or another IL-36R inhibitor biologic. Biologic treatments must not be taken for 12 weeks, or 5 half-lives (whichever is shorter), prior to randomization. Systemic immunomodulatory treatments (e.g., corticosteroids) are not permitted 4 weeks prior to randomization
Patients on concurrent GPP treatment within 12 weeks prior to randomization must have a history of flaring during, or after dose reduction or discontinuation of, concurrent treatment	Increased risk of infectious complications
Patients on concurrent treatment with retinoids, methotrexate, and/or ciclosporin must stop this treatment on the day of randomization	Acute or chronic infections at randomization
Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the study	Active or latent tuberculosis
Women of child-bearing potential must be ready and able to use highly effective methods of birth control	History of allergy/hypersensitivity to the systemically administered study medication agent
	Malignancy within 5 years prior to screening
	Currently enrolled or < 30 days since ending another investigational device or drug study
	Pregnant or nursing women, or women planning to become pregnant during the study
	Patients who have undergone major surgery within 12 weeks prior to the study or have surgery planned during the study
	Evidence of a current or previous disease, medical condition other than GPP or other condition/finding that would compromise the safety of the patient or compromise the quality of the data

CRP C-reactive protein, *GPP* generalized pustular psoriasis, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *ICH-GCP* International Conference on Harmonisation Good Clinical Practice, *IL-36R* interleukin-36 receptor, *ULN* upper limit normal, *WBC* white blood cells

patient is given any investigator-prescribed medication other than spesolimab for treatment of GPP symptoms or worsening of GPP clinical status, the patient will be discontinued from any further study drug (Fig. 1). The exception to this is that patients may be

prescribed topical treatments/topical corticosteroids, methotrexate, ciclosporin and retinoids, at the discretion of investigators, 4 weeks following a dose of open-label IV 900-mg spesolimab in response to a GPP flare, and also

during the open-label maintenance treatment period.

Study Objectives

The aims of the Effisayil™ 2 study are to investigate whether administration of a maintenance dosing regimen of spesolimab prevents the occurrence of GPP flares, and to evaluate which of the three investigated maintenance dosing regimens optimally achieves this aim. Effisayil™ 2 includes both a dose-finding and a confirmatory component; the primary objective is to evaluate the dose–response relationship for three SC dosing regimens of spesolimab versus placebo on the primary endpoint, and demonstrate a non-flat dose–response curve, which would indicate a benefit of spesolimab over placebo. If the primary objective is met, the secondary objective is to demonstrate superiority versus placebo for each of spesolimab 300-mg q4w and spesolimab 300-mg q12w regimens for the primary and key secondary endpoints. Further objectives are to evaluate the safety and tolerability of multiple SC doses of spesolimab in patients with a history of GPP, and to evaluate the safety and efficacy of an IV dose of spesolimab (with the option of a second dose) for treating patients with onset of a GPP flare.

Study Endpoints

The primary efficacy endpoint of the study is time to first GPP flare (increase of ≥ 2 in GPPGA total score from baseline and GPPGA pustulation subscore ≥ 2) up to Week 48. The key secondary efficacy endpoint is the occurrence of at least one GPP flare up to Week 48. Other secondary endpoints are listed in Table 2, and outcomes measures for assessment of efficacy are listed in Table 3.

Safety and Adverse Event Assessment

Safety will be assessed descriptively based on treatment-emergent adverse events, adverse events (AEs) of special interest, serious AEs and clinical laboratory values. Intensity of AEs will

be assessed using the Rheumatology Common Toxicity Criteria version 2.0, physical examination, vital signs (blood pressure, pulse rate, body temperature), electrocardiogram and immunogenicity (anti-drug antibodies).

Statistical Analysis

The primary analysis for the primary objective will consist of a multiple comparison and modelling (MCPMod)-based testing with respect to a non-flat dose–response curve, to evaluate several possible dose–response models and to identify the best-fitting model or subset of models. The generalized MCPMod procedure for time-to-event endpoints is based on the log hazard ratio of the active doses versus placebo, obtained via a stratified Cox regression model on the time to first GPP flare up to Week 48, stratified by the systemic concomitant use of GPP medications at randomization. The primary analysis for the secondary objective on the time to first GPP flare up to Week 48 for each dose of spesolimab versus placebo will be tested using the stratified log-rank test, stratified by the systemic concomitant use of GPP medications at randomization. In addition to the GPP flare definition per protocol, any use of investigator-prescribed spesolimab or other non-spesolimab medication for GPP will be considered to indicate the onset of a flare. In the event of missing data, only observed GPP flare events will be included in the analysis for the primary endpoint.

Ethics

The study will be conducted in compliance with the ethical principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonised Guideline for Good Clinical Practice (GCP), relevant Boehringer Ingelheim Standard Operating Procedures, the EU directive 2001/20/EC, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations.

Table 2 Study endpoints

		Definition
Primary endpoint	Time to first GPP flare up to Week 48	GPP flare defined as an increase of ≥ 2 in GPPGA total score from baseline and GPPGA pustulation subscore of ≥ 2
Key secondary efficacy endpoint	Occurrence of at least one GPP flare up to Week 48	GPP flare defined as an increase of ≥ 2 in GPPGA total score from baseline and GPPGA pustulation subscore of ≥ 2
Secondary endpoints	Time to worsening of PSS score up to Week 48	≥ 4 -point increase in total PSS score from baseline; intake of open-label IV spesolimab or investigator-prescribed other medication for GPP will be considered as onset of worsening
	Time to first worsening of DLQI up to Week 48	≥ 4 -point increase in total DLQI score from baseline; intake of open-label IV spesolimab or investigator-prescribed other medication for GPP will be considered as onset of worsening

Table 2 continued

		Definition
	Sustained remission	GPPGA total score of 0 or 1 at all visits up to Week 48 without intake of open-label IV spesolimab or investigator-prescribed other medication for GPP
Safety endpoint	Occurrence of treatment-emergent adverse events	

DLQI Dermatology Life Quality Index, *GPP* generalized pustular psoriasis, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *IV* intravenous, *PSS* Psoriatic Symptom Scale

DISCUSSION

Rationale for Conducting the Trial

GPP is a disease with a considerable clinical burden for patients, substantially impacting their quality of life [18]. While spesolimab has recently been approved for the treatment of GPP flares [16], current therapies do not completely resolve symptoms, prevent reoccurrence of flares, or provide sustained efficacy. Furthermore, the majority of therapies for treatment or prevention of GPP flares are based on anecdotal retrospective case reports. Preventing GPP flares with a well-tolerated and effective treatment that primarily targets the key inflammatory pathway operating in GPP, will meet a high unmet need to have a proven treatment available for patients with recurrence of this disruptive condition, which is associated with high morbidity and associated mortality. Results of the EffisayilTM 1 study showed that spesolimab is efficacious in the treatment of GPP flares [15].

Table 3 Outcome measures for assessment of efficacy

Outcome	Measure for assessment
Skin condition	GPPGA
	GPPASI
Systemic aspects of the GPP flare	Systemic components of the JDA GPP Severity Score
	CGI-I instrument (as per JDA severity index)
	TPSS (measured in patients with concurrent plaque psoriasis, if applicable)
Patient-reported outcomes	PSS
	Pain VAS
	DLQI
	EQ-5D-5L health questionnaire
	WPAI questionnaire
	SF-36
	PGI-S PGI-C

CGI-I Clinical Global Impression-Improvement, *DLQI* Dermatology Life Quality Index, *EQ-5D-5L* EuroQoL 5 Dimension 5 Level, *GPP* generalized pustular psoriasis, *GPPASI* Generalized Pustular Psoriasis Area and Severity Index, *GPPGA* Generalized Pustular Psoriasis Physician Global Assessment, *JDA* Japanese Dermatological Association, *PGI-C* Patients' Global Impressions of Change, *PGI-S* Patients' Global Impressions of Severity, *PSS* Psoriatic Symptom Scale, *SF-36* 36-Question Short Form, *TPSS* Target Plaque Severity Score, *VAS* visual analogue scale, *WPAI* Work Productivity and Activity Impairment

In this placebo-controlled trial design, Effisayil™ 2 will provide data on the efficacy, sustainability of efficacy, safety, and tolerability of spesolimab in preventing the occurrence of GPP flares in patients with a history of recurrent GPP flares. These data will also build on the results of Effisayil™ 1 by gathering further data on the treatment of flares with open-label IV spesolimab.

Rationale for Patient Selection

The Effisayil™ 2 study will be conducted in patients who are known to experience frequent GPP flares. Patients may be included who are not receiving ongoing treatment for control of GPP, who are receiving ongoing treatment to control their GPP, but the disease would not be controlled if their medication was reduced or discontinued. These criteria place the study population as the optimal population of patients in which to study GPP flare prevention. Confirmation of GPP diagnosis and flare history will be based on ERASPEN consensus diagnostic criteria [3]. At screening and randomization, patient GPP status will be defined according to the GPPGA, which is a GPP-specific measure adapted from the widely used PGA endpoint [17]. The GPPGA is a robust assessment of disease severity in GPP, and was successfully used as an endpoint in the Effisayil™ 1 study [15]. Blocking for region (Japan versus outside of Japan) and age (adults versus adolescents) will be done to ensure that there are a sufficient number of patients to demonstrate efficacy and safety in each group, and to ensure that there will be a sufficient number of adolescent patients randomized in each treatment group for pediatric investigation. These blocking factors will be treated as operational factors and will not be included in the analyses of efficacy endpoints.

Rationale for Study Endpoints and Outcomes

The study endpoints were selected with the aim of establishing the efficacy and safety of spesolimab for the prevention of GPP flares, with maximal statistical power. Systemic aspects of the GPP flares were assessed using measures including components of the Japanese Dermatological Association GPP severity score, which was developed for the Japanese Ministry of Health as a diagnostic tool for measuring the severity of GPP at presentation [2]. A range of patient-reported outcomes (PROs) will be measured as these provide unique insights into the impact of GPP and the trial intervention from

the patients' perspective, and PROs are considered an important factor by dermatologists when making treatment decisions in patients with psoriasis [19, 20]. Some of these PROs (Psoriasis Symptom Scale, Pain Visual Analogue Scale, Dermatology Life Quality Index) were used successfully in the Effisayil™ 1 study [15], and will evaluate participants' health-related quality of life, ability to participate in daily activities, and experience of pain.

Rationale for Dose Selection for Flare Prevention, and Using IV Spesolimab in Response to a Flare

The three dosing regimens in the Effisayil™ 2 study were selected to test a wide range in exposure, allowing a thorough evaluation of the exposure–response relationship of spesolimab in patients with GPP. Loading doses of 600 or 300 mg were included to evaluate whether either exposure is efficacious in preventing GPP flares if other regimens are discontinued. The 300-mg q4w and 300-mg q12w maintenance doses are assumed to be closely effective, while the 150-mg q12w dose is assumed to be subtherapeutic. The dosing intervals of q12w versus q4w were selected to evaluate whether flare prevention could be achieved with a dose administered every 3 months, or whether monthly dosing would be required. Since the incidence of flares in an untreated population is unknown and a high incidence of disease is essential to demonstrate patient benefit from preventative treatment, a placebo regimen is crucial for this study. No active control group is included in the study because there is currently no drug approved for the prevention of GPP flares. In the Effisayil™ 2 study, treatment will be administered subcutaneously because patients will have clear or almost clear skin at randomization, meaning that different spesolimab exposure is expected to be required than is needed for treatment of a flare. In addition, because SC dosing is often preferred by patients, it has the potential to improve participant adherence [21]. In the Effisayil™ 1 study, an IV dose of 900 mg of spesolimab was shown to be effective in the treatment of GPP flares, with an

acceptable safety profile [15], and so was selected as the dose for administration if a patient experiences a GPP flare during the Effisayil™ 2 study. In addition, by treating patients with open-label IV 900-mg spesolimab, further data can be collected on the treatment of flares that will add to the evidence provided by the Effisayil™ 1 study.

Study Strengths and Limitations

Effisayil™ 2 is the first study to investigate the use of an antibody against the interleukin-36 receptor as treatment for the prevention of GPP flares, a key step for the efficacy assessment of spesolimab in an intermittently, repeatedly flaring disease. This will be the first and largest randomized, placebo-controlled study conducted in this population to date and will provide robust evidence on the efficacy of spesolimab in preventing the occurrence of GPP flares. Rollover of the study into an OLE will allow further examination of long-term use of spesolimab for the treatment of GPP. Recruitment for Effisayil™ 2 was completed at the time of writing, and common to studies into rare diseases, a challenge for this study was the recruitment of a sufficient number of participants. This challenge was minimized by the inclusion of multiple centers across a range of global regions, and the 3:1 active treatment to placebo allocation ratio providing a more favorable chance of receiving active treatment.

CONCLUSIONS

GPP is a disease in which there is a high unmet need for treatments that rapidly control and resolve disease flares, and prevent the occurrence and/or reoccurrence of flares. Effisayil™ 2 is the first placebo-controlled study in patients with GPP that focuses on flare prevention, through maintenance treatment with SC spesolimab. Efficacy and safety data from this study will provide valuable information on the use of maintenance spesolimab treatment in preventing GPP flares and delivering sustained symptom management.

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Compliance with Ethics Guidelines. The study will be conducted in compliance with the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Guideline for GCP, relevant Boehringer Ingelheim Standard Operating Procedures, the EU directive 2001/20/EC, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. The study is being conducted in 34 countries and across approximately 126 sites. Ethics committee approval is being gained at each site prior to study commencement. Boehringer Ingelheim, the study sponsor, will collate all the relevant site ethics approvals once the study has completed.

Data Availability. To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on [Vivli - Center for Global Clinical Research Data](#), and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit [Medical & Clinical Trials | Clinical Research | MyStudyWindow](#) for further information.

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