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ORIGINAL ARTICLE

Spesolimab improves patient-reported outcomes in patients with generalized pustular psoriasis: Results from the Effisayil 1 study

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Abstract

Background: Generalized pustular psoriasis (GPP) is a rare inflammatory skin disease with a considerable clinical burden. In the Effisayil™ 1 study, spesolimab, an anti-interleukin-36 receptor monoclonal antibody, demonstrated efficacy in treating GPP flares.

Objectives: To evaluate patient-reported outcomes (PROs) of patients with GPP who were treated with intravenous (IV) spesolimab 900 mg in the Effisayil™ 1 study.

Methods: Fifty-three patients presenting with a GPP flare were randomized (2:1) to receive a single dose of IV spesolimab 900 mg or placebo and were followed for 12 weeks. Four PROs (pain visual analogue scale [pain VAS]; Functional Assessment of Chronic Illness Therapy–Fatigue [FACIT–Fatigue]; Dermatology Life Quality Index [DLQI]; and Psoriasis Symptom Scale [PSS]) were assessed throughout the 12-week study. Minimal clinically important differences (MCIDs) were defined. All data are reported descriptively.

Results: In patients who received spesolimab, improvements from baseline (median [Q1, Q3]) were observed in pain VAS (−21.3 [−55.3, −3.1]), FACIT–Fatigue (7.0 [1.0, 20.0]), DLQI (−2.5 [−8.0, 1.0]) and PSS (−4.0 [−7.0, 0.0]) within 1 week of treatment. These improvements were sustained over 12 weeks and corresponded to the achievement of MCIDs at Week 1, which were also sustained over 12 weeks. Patients in the placebo arm experienced improvements in PROs and achievement of MCIDs after receipt of open-label spesolimab at Week 1.

Conclusions: Patients with a GPP flare treated with spesolimab achieved improvements in PROs by Week 1, which were sustained for 12 weeks, and achieved MCIDs as early as Week 1.

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening chronic inflammatory skin disease characterized by episodes of widespread eruption of sterile, macroscopic pustules.[1–7] Pustules can occur with or without systemic inflammation and symptoms such as pain and fatigue.[7–9] The severity of these symptoms may vary with each flare for an individual patient and may occur with typical psoriatic plaques.[3,4,8] The therapeutic management of GPP is a major challenge worldwide due to the considerable clinical burden associated with the disease.[2,4] At present, there are no standardized guidelines for the treatment of GPP, and there is a lack of double-blind, placebo-controlled trials including patients with GPP for disease management in the USA or Europe.[6,10,11] A few countries have approved biologics; however, these approvals are largely based on evidence from small studies.[6,10–18]

Unregulated interleukin (IL)-36 receptor (R) signalling leads to induction of downstream inflammatory cytokines that are implicated in GPP. Therefore, preventing inflammation through blocking IL-36R activation presents therapeutic potential in treating patients with GPP.[19–21] Recently, the Food and Drug Administration (FDA) approved the use of spesolimab, a humanized anti-IL-36R monoclonal antibody, specifically for the treatment of GPP flares.[22] Spesolimab is the first such agent to specifically target the IL-36 pathway.[1] Imsidolimab, another anti-IL-36R antibody, is also in development for the treatment of GPP.[23] The FDA approval of spesolimab was based on the results of the multicentre, randomized, double-blind, placebo-controlled study of spesolimab in patients presenting with a GPP flare (Effisayil™ 1 [NCT03782792]). The primary endpoint (assessed at the end of Week 1) was complete resolution of pustules as defined by a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0, achieved by 54% and 6% of patients in the spesolimab and placebo arms, respectively (one-sided $p < 0.001$). The key secondary endpoint was clear or almost clear skin as defined by a GPPGA total score of 0 or 1, achieved by 43% and 11% of patients, respectively (one-sided $p = 0.0118$). Spesolimab had an acceptable safety profile, with adverse event (AE) rates comparable between the spesolimab and placebo arms, although two serious AEs were reported by patients in the spesolimab arm during Week 1: drug hypersensitivity syndrome with systemic symptoms (considered implausible due to the time course of the AE) and arthritis.[1]

Patient-reported outcomes (PROs) are increasingly collected in clinical trials to provide unique information on the physical, functional and psychological impact of a therapy from the patient's perspective.[24] The PROs used previously to assess this impact in patients with plaque psoriasis include pain, fatigue, overall quality of life and cutaneous symptoms.[25] Although GPP is distinct from plaque psoriasis, owing to the nature of the items collected by the PRO scales in previous studies,[26–29] and the symptoms that patients with GPP experience (pain; itching; systemic symptoms such as malaise and fatigue; quality of life deterioration; impairment of work and daily activities),[4,7,8,30] there is a strong rationale for the use of these PROs to assess the impairments to patients' well-being in this rare disease. In addition, pain, fatigue and cutaneous symptoms are associated with flares, while quality of life is more useful for an overall assessment of the disease. Here, we report the effect of spesolimab on PROs in patients with a GPP flare in the Effisayil™ 1 study.

MATERIALS AND METHODS

Study design

The Effisayil™ 1 study design was previously described by Bachelez et al.[1]; the full study protocol is also available (Figure S1). Patients who presented with a GPP flare were randomized (2:1) to receive a single dose of intravenous (IV) spesolimab 900 mg or placebo at baseline and were followed for 12 weeks. Stratification of randomization was performed for Japanese versus non-Japanese race for operational purposes only. If disease worsening occurred during Week 1, patients were allowed to receive any other treatment for GPP at their physician's discretion, any time after their first dose of spesolimab or placebo at baseline and before Day 8. Patients with persistent symptoms (GPPGA pustulation subscore ≥2 and GPPGA total score ≥2, with higher scores indicating higher severity) and who did not receive any other treatment during Week 1 were eligible to receive open-label (OL) spesolimab on Day 8. Patients could receive another dose of OL spesolimab between Day 8 and Week 12 to treat new flares, which were defined by an increase of ≥2 in both GPPGA scores.

Patients

The study population has been described in detail by Bachelez et al.[1] Eligible patients were adults aged 18–75 years with a diagnosis of GPP prior to enrolment and presenting with a GPP flare at baseline. A GPP flare was defined as a GPPGA total score of ≥3, a GPPGA pustulation subscore of ≥2, and ≥5% of body surface area with erythema and the presence of pustules. Patients were excluded from participating in the trial if they had plaque psoriasis without pustules, or with pustules restricted to psoriatic plaques; drug-triggered acute generalized exanthematous pustulosis; an immediate life-threatening flare of GPP warranting intensive care treatment; or current treatment with methotrexate, cyclosporine, retinoids or other restricted medications.

Outcomes

Patients completed the following PRO questionnaires throughout the study: pain visual analogue scale (pain VAS), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue), Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Scale (PSS) (Figure 1).[26–29] All four PROs were measured at baseline, Day 8 and Weeks 2–4, 8 and 12, with PSS scores also being measured on Days 2 and 3. High total PRO scores indicate a large impairment or intense severity, except for FACIT–Fatigue, for which a higher score represents reduced fatigue. Minimal clinically important differences (MCIDs) for all four PRO scales have been defined in the literature and were used as guidance.[26,31–33] In this study, the MCIDs were defined relative to baseline as a 30-point decrease for pain VAS, a 4-point improvement for FACIT–Fatigue, a 4-point decrease for DLQI and a 2-point decrease for PSS.

Statistical analyses

All randomized patients were included in the analysis and two different types of statistical analyses were conducted. Data are presented for PROs for the spesolimab arm only (first dose and optional second dose at Day 8 for persistent flare symptoms; any use of other medication for GPP or use of spesolimab for a new flare was considered non-response)

because, consistent with the study design, most patients randomized to placebo received spesolimab at Day 8. As such, direct comparison between the spesolimab and placebo arms after Day 8 cannot be made. However, an intention-to-treat (ITT) analysis was also performed; this presents observed cases irrespective of any use of other treatment. Data are summarized descriptively.

Ethical considerations

The trial was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines, Regulation (EU [European Union]) No. 536/2014, the Japanese Good Clinical Practice regulations and applicable local regulations. The trial was approved by ethics committees of participating institutions and countries. All patients provided written informed consent.

RESULTS

Patients

At baseline, 35 patients received a single dose of IV spesolimab 900 mg and 18 patients received placebo. A total of 27 patients (spesolimab: 12 patients, placebo: 15 patients) received OL treatment with spesolimab on Day 8, and six patients (spesolimab: four patients, placebo: two patients) received treatment with spesolimab after Day 8 (Figure 2).

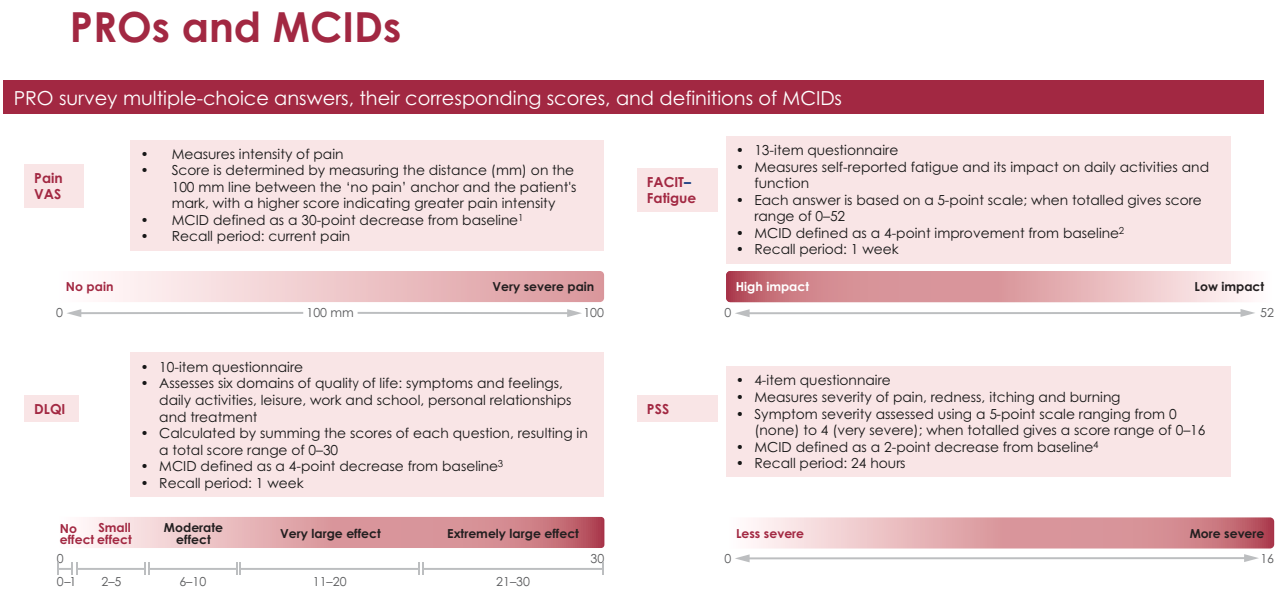

FIGURE 1 PRO survey multiple choice answers, their corresponding scores, and definitions of MCIDs. A visual representation of the PRO scales used to assess PRO outcomes throughout the study.[26,31–33] DLQI, Dermatology Life Quality Index; FACIT–Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; MCID, minimal clinically important difference; pain VAS, pain visual analogue scale; PRO, patient-reported outcome; PSS, Psoriasis Symptom Scale.

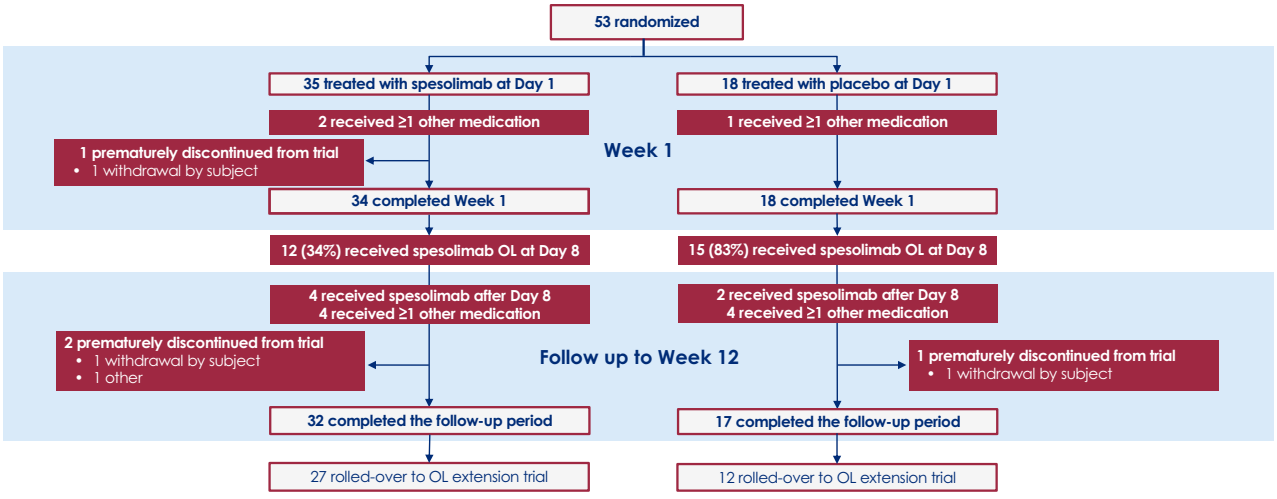

FIGURE 2 Patient disposition. OL, open-label. Figure reproduced with permission from the *New England Journal of Medicine*.[1]

Baseline demographics and clinical characteristics are described in Table S1. Median (Q1, Q3) baseline scores in the spesolimab group for pain VAS, FACIT–Fatigue, DLQI and PSS were 79.8 (70.5, 87.8), 14.0 (7.0, 28.0), 19.5 (16.0, 25.0) and 11.0 (9.0, 12.0), respectively. Similar scores were observed in the placebo group.

Absolute change in PRO scores from baseline to Week 12

Changes in PRO scores from baseline to Week 12 for patients randomized to spesolimab are shown in Figure 3a–d. Rapid improvements in pain VAS, FACIT–Fatigue, DLQI and PSS scores were observed, with median (Q1, Q3) values of −21.3 (−55.3, −3.1), 7.0 (1.0, 20.0), −2.5 (−8.0, 1.0) and −4.0 (−7.0, 0.0) at Week 1, respectively, and were sustained to Week 12. At Week 4, a significant correlation (Spearman's rank correlation coefficient) was observed between GPPGA total score and all PROs, except for FACIT–Fatigue (pain VAS: $p < 0.05$; DLQI: $p < 0.001$; and PSS: $p < 0.05$). The proportion of patients achieving a GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 also mirrored the improvements in PRO scores from baseline over time.

Absolute changes from baseline in PRO scores were also assessed in the ITT population (Figure S2A–D). There was a numerical trend for early separation between the spesolimab and placebo groups during the placebo-controlled period (Week 1), with clinically significant improvements observed in the spesolimab arm by Week 1. The spesolimab and placebo curves began to converge after Day 8. Similar improvements in PRO scores were observed in both arms by the end of the 12-week study.

Proportion of patients achieving clinically significant improvements (MCIDs) in PRO scores over time

The proportion of patients who achieved MCIDs was also assessed, according to the ITT principle (Figure S3A–D). This analysis showed a numerical difference between patients in the spesolimab and placebo groups; a higher proportion of patients in the former group achieved an MCID in PRO scores during Week 1. Patients in the placebo group demonstrated similar improvements after most received an optional IV dose of OL spesolimab 900 mg at Day 8.

DISCUSSION

In the Effisayil™ 1 study, treatment with spesolimab improved clinician-reported outcomes (GPPGA pustulation subscore of 0 [no visible pustules] and GPPGA total score of 0 or 1 [clear or almost clear skin]) in patients with a GPP flare, compared with placebo, at Week 1. Patients in the placebo arm experienced similar improvements in clinician-reported outcomes after receiving IV spesolimab at Day 8. Improvements in these outcomes were sustained in both treatment arms up to Week 12.[1] However, it is important for both clinicians and patients when interpreting clinical trial results to determine that a treatment provides benefits to PROs, which are a direct measure of the patient experience of the disease. Indeed, clinical trials that include PROs allow clinicians and patients to differentiate between treatments based on the experience of other patients in those trials and allow prescribers to understand the benefit–risk profile of a treatment.[34] In GPP, the use of these measures to assess patient-reported aspects of both flares and general disease course may allow the patient experience to be more fully captured.

Here, we demonstrated that in the Effisayil™ 1 study, patients who received spesolimab achieved clinically significant improvements from baseline in the PROs of pain, fatigue, overall quality of life and cutaneous symptoms. MCIDs have been defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management'[35] and therefore their achievement by patients in this study supports the use of spesolimab in the management of GPP. The specific MCIDs defined in this study also translate into a direct impact on the patient experience; for example, a 30-point reduction in pain VAS represents a pain severity reduction corresponding to what a patient would expect of an adequate analgesic.[33] The validation of these PRO scales in GPP is currently ongoing.

The clear separation of the spesolimab and placebo curves occurred early during the placebo-controlled period (Week 1), suggesting that spesolimab results in the rapid improvement of PROs, with considerable improvement in fatigue and pain. An overlay of GPPGA scores and PRO scores over time indicates that improvements in the former are mirrored by the latter; the GPPGA assesses the severity of pustules, erythema and scaling of GPP lesions,[2] and it would, therefore, be expected that a decrease in severity of these components would improve overall patient experience of the disease. When improvements in PROs were assessed according to the ITT principle, in which any use of other medication for GPP or OL spesolimab was included, consistent results were observed. Of note, once patients randomized to placebo received OL spesolimab at Day 8 ($n = 15$, 83%), PROs rapidly improved, further indicating a treatment benefit.

Limitations of this study include the brief randomized period of treatment; however, a challenge in designing trials for patients with this rare disease is the sporadic nature and severity of GPP flares, which require a rapid start of effective treatment. This was the rationale for allowing placebo patients to crossover at Week 1 if their flare symptoms persisted, and also for the presentation of results over time excluding use of spesolimab or other medications for GPP after Week 1. Hierarchical testing was performed at Week 4 in patients who received only a single dose of spesolimab at

baseline; however, consistent with the study design, many patients had received OL spesolimab or other medication before this point. This led to low numbers of patients, limiting interpretation and calculation of a treatment effect versus placebo at Week 1, whereby patients randomized to placebo exhibited gradual improvement in PRO scores

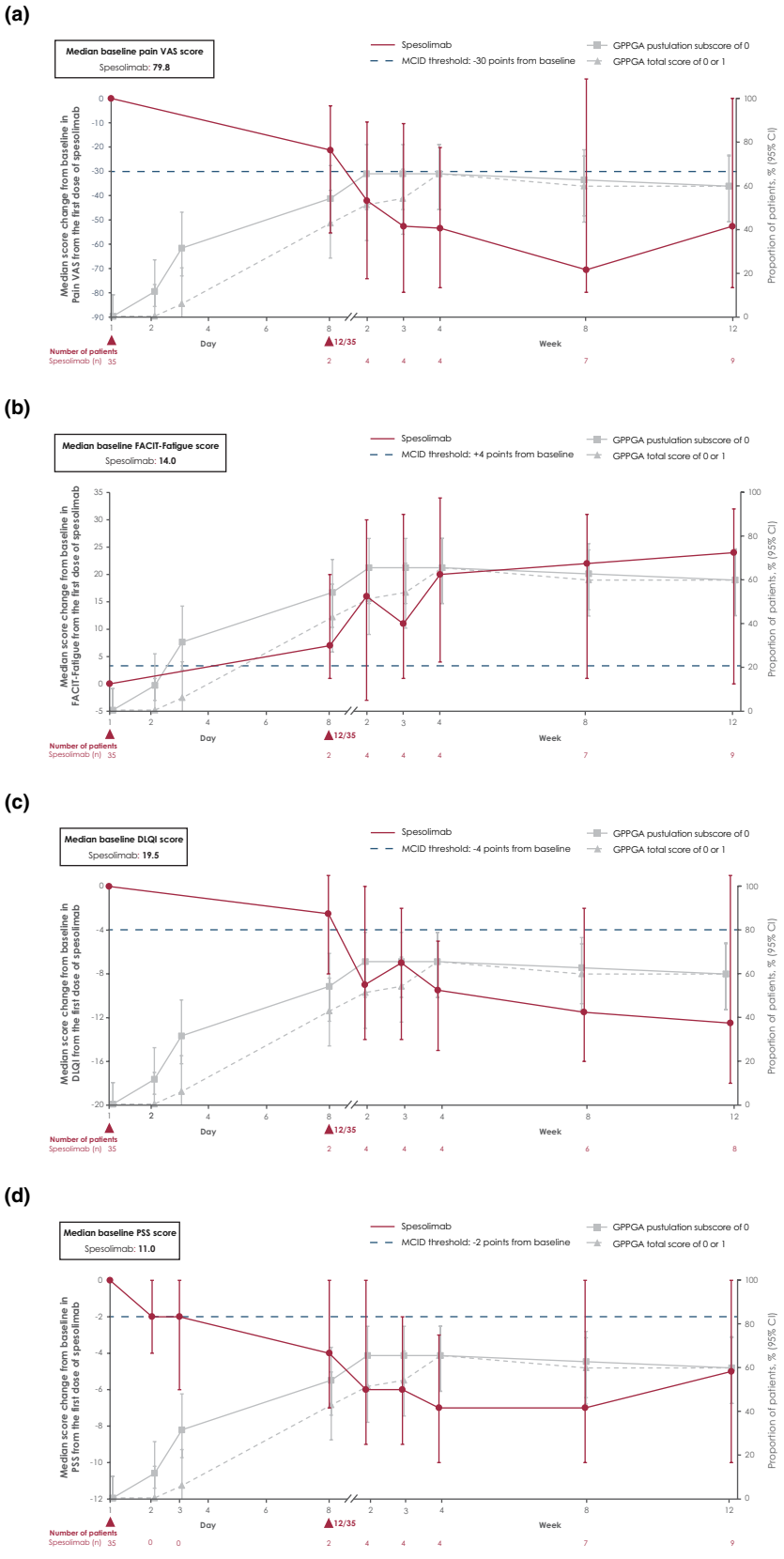

FIGURE 3 Absolute change from baseline in PRO scores over time in patients randomized to receive spesolimab on Day 1. (a) Pain VAS; (b) FACIT–Fatigue; (c) DLQI; (d) PSS. Treatment effect in patients who received up to two doses of spesolimab: Day 1 ($N = 35$) and optional dose at Day 8 ($n = 12$). The arrowhead indicates the days of intravenous spesolimab administration. Any use of other medication for GPP or use of spesolimab for the treatment of a new GPP flare were regarded as non-response for this analysis. The grey lines show the proportion of patients who achieved a GPPGA pustulation subscore of 0 and GPPGA total score of 0 or 1 over time. The dashed lines indicate PRO MCID threshold of 30 points for pain VAS, four points for FACIT–Fatigue and DLQI and two points for PSS.[26,31–33] CI, Confidence interval; DLQI, Dermatology Quality of Life Index; FACIT–Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IQR, Interquartile range; MCID, Minimal clinically important difference; pain VAS, pain visual analogue scale; PRO, patient-reported outcome; PSS, Psoriasis Symptom Scale. (a) and (c) have been reproduced with permission from the *New England Journal of Medicine*.[1]

when they had received OL spesolimab. Therefore, the main analysis presented—patients who received up to two doses of spesolimab (at baseline and at Day 8)—provides the most robust evidence for the effect of spesolimab in patients with a GPP flare. Although the sample size in this study was small, which was to be expected considering the rare nature of GPP, and despite the existence of a placebo effect, the proportion of patients who achieved MCIDs in all four PROs was high, indicating an overall treatment benefit.

In conclusion, spesolimab treatment resulted in clinically significant improvements (MCIDs) in patient-reported pain, fatigue, quality of life and cutaneous symptoms. These findings support the use of spesolimab for the treatment of patients with a GPP flare.

AUTHOR CONTRIBUTIONS

The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of this manuscript. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

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CONFLICT OF INTEREST

AAN declares being a consultant and advisor and/or receiving speaking fees and/or grants and/or serving as an investigator in clinical trials for AbbVie, Almirall, Amgen, Biomed, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Pierre Fabre Pharma, Regeneron, Sandoz, Sanofi and UCB. JCP declares paid activities as an advisor, speaker or consultant for Almirall, Boehringer Ingelheim, Janssen-Cilag, Novartis and Pfizer. AM declares receiving research grants, consulting fees and/or speaker's fees from AbbVie, Boehringer Ingelheim, Eisai, Eli Lilly, Janssen, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nichi-Iko, Nippon Kayaku, Novartis, Sun Pharmaceutical Industries, Taiho Pharmaceutical, Torii Pharmaceutical and Ushio. T-FT declares conducting clinical trials or paid consulting activities for AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, MSD, Novartis International, Pfizer and UCB. M-AV declares paid activities as an advisor, speaker or consultant for AbbVie, Almirall, Biogen Inc., Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen-Cilag, Medac and Novartis. LL, CT and MS are employees of Boehringer Ingelheim. MGL declares paid consulting activities for Aditum Bio, Almirall, AnaptysBio, Arcutis, Aristea, Arrive Technology, Avotres Therapeutics, Biomx, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, CorEvitas, Dermavant Sciences, Dr. Reddy's, Evelo, Evommune, Facilitate International Dermatologic Education, Forte, Foundation for Research and Education in Dermatology, Helsinn, LEO Pharma, Meiji, Mindera, Pfizer and Verrica. MGL also declares receiving research grants from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen, Ortho Dermatologics, Regeneron and UCB.

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfil 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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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