ORIGINAL ARTICLE

Rapid and sustained improvements in Generalized Pustular Psoriasis Physician Global Assessment scores with spesolimab for treatment of generalized pustular psoriasis flares in the randomized, placebo-controlled Effisayil 1 study

Boni E. Elewski, MD,[a] Mark G. Lebwohl, MD,[b] Milan J. Anadkat, MD,[c] Jonathan Barker, MD,[d] Kamran Ghoreschi, MD,[e] Shinichi Imafuku, MD,[f] Ulrich Mrowietz, MD,[g] Ling Li, MSc,[h] Manuel Quaresma, Lic,[i] Christian Thoma, MD,[j] and Hervé Bachelez, MD[k,l]

Background: Effisayil 1 was a randomized, placebo-controlled study of spesolimab, which is an anti-IL-36 receptor antibody, in patients presenting with a generalized pustular psoriasis flare.

Objective: To assess the effects of spesolimab over the 12-week study.

Methods: The primary endpoint of the study was Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 at week 1. Patients (N = 53) were randomized (2:1) to receive a single intravenous dose of 900 mg spesolimab or placebo on day 1. Patients could receive open-label spesolimab for persistent flare symptoms on day 8.

Results: Most patients receiving spesolimab achieved a GPPGA pustulation subscore of 0 (60.0%) and GPPGA total score of 0 or 1 (60.0%) by week 12. In patients randomized to placebo who received open-label spesolimab on day 8, the proportion with GPPGA pustulation subscore of 0 increased from 5.6% at day 8 to 83.3% at week 2. No factors predictive of spesolimab response were identified in patient demographics or clinical characteristics.

Limitations: The effect of initial randomization was not determined conventionally beyond week 1 due to patients receiving open-label spesolimab.

Conclusion: Rapid control of generalized pustular psoriasis flare symptoms with spesolimab was sustained over 12 weeks, further supporting its potential use as a therapeutic option for patients. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2023.02.040.)

Key words: GPP; GPPGA; IL-36; IL-36R; pustular psoriasis; spesolimab.

From the University of Alabama School of Medicine, Birmingham, Alabama[a]; Icahn School of Medicine at Mount Sinai, New York, New York[b]; Division of Dermatology, Washington University School of Medicine, St. Louis, Missouri[c]; St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom[d]; Department of Dermatology, Venereology and Allergology, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany[e]; Department of Dermatology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan[f]; Psoriasis-Center, Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Kiel, Germany[g]; Boehringer Ingelheim Investment Co, Ltd, Shanghai, China[h]; Boehringer Ingelheim International GmbH, Ingelheim, Germany[i]; Boehringer Ingelheim International GmbH, Biberach, Germany[j]; Service de Dermatologie, Assistance Publique—Hôpitaux de Paris Hôpital Saint-Louis, Paris, France[k]; and INSERM Unité 1163, Imagine Institute of Genetic Diseases, Université Paris Cité, Paris, France.[l]

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Correspondence to: Boni E. Elewski, MD, University of Alabama School of Medicine, 510 20th ST S STE 858, Birmingham, Alabama, 35233. E-mail: belewski@uabmc.edu.

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INTRODUCTION

Spesolimab, which is an anti-interleukin (IL)-36R monoclonal antibody, was shown to be effective for generalized pustular psoriasis (GPP) treatment in Effisayil 1 (NCT03782792), which was a global, multicenter, randomized, double-blind, placebo-controlled trial in patients with a GPP flare.[1] Primary analyses at week 1 showed that a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 was achieved by 54% of patients receiving spesolimab versus 6% receiving placebo (2-sided $P < .001$); a GPPGA total score of 0 or 1 was achieved by 43% and 11%, respectively (2-sided $P = .02$).[2] On the basis of the results of this study, spesolimab has been approved for the treatment of GPP flares in adults in the United States, Europe, Japan, and China.[3-6]

CAPSULE SUMMARY

- This analysis builds on primary analyses from Effisayil 1 in patients with a generalized pustular psoriasis flare, showing that rapid pustular clearance achieved 1 week after spesolimab is sustained for up to 12 weeks.
- This finding supports use of spesolimab as the first generalized pustular psoriasis-specific targeted therapeutic option.

We report the effects of spesolimab for treatment of GPP flares over the course of the 12-week Effisayil 1 study. We also determined the proportion of patients who achieved clinically significant improvements in GPPGA scores, compared the effects of single versus multiple doses of spesolimab, and investigated factors that may identify patients requiring 1 or 2 doses of spesolimab for flare treatment.

METHODS

Trial design and patient disposition

The Effisayil 1 study design has been published previously.[1,2] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by ethics committees of participating institutions and/or countries. All patients provided written informed consent. Patients presenting with a GPP flare were randomized (2:1) to receive a single intravenous dose of spesolimab 900 mg or placebo on day 1 (Supplementary Fig S1, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d).[1] Optional open-label (OL) spesolimab for persistent flare symptoms (GPPGA total score ≥2 and GPPGA pustulation subscore ≥2) was received on day 8 by 12 (34.3%) of 35 patients in the spesolimab arm and 15 (83.3%) of 18 in the placebo arm. Additional OL spesolimab for new flare (≥2-point increase in GPPGA total score and GPPGA pustulation subscore after achieving a clinical response [GPPGA 0 or 1]) treatment after day 8 was received by 4 patients in the spesolimab arm (2 received spesolimab on day 8) and 2 patients in the placebo arm (1 received spesolimab on day 8) (Supplementary Fig S2, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). At week 12, patients were eligible to enroll in a 5-year OL extension trial of spesolimab (Effisayil ON, NCT03886246). The patient disposition, including details of other GPP medications and OL spesolimab for a new flare, are provided in Supplementary Interactive Fig 1 (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d).

Analysis populations

Study outcomes are presented for 2 analysis populations. To assess the true effect of spesolimab treatment for GPP flares, outcomes were evaluated in patients who received up to 2 doses of spesolimab as follows: randomized treatment on day 1 plus optional OL spesolimab on day 8. Missing values, use of other GPP medication, or OL spesolimab for a new flare, were considered nonresponse. Intention-to-treat (ITT) analyses included observed values for all patients over time according to randomized treatment on day 1, regardless of any use of other GPP medication or OL spesolimab for a new flare.

Study assessments and exploratory analyses

GPPGA total score and pustulation, erythema, and scaling subscores were assessed on days 1 to 7 and weeks 1 to 4, 8, and 12. Minimal clinically important differences (MCIDs) in GPPGA pustulation subscore and GPPGA total score were defined as ≥2-point and ≥1-point changes, respectively.[7] Patients who achieved MCIDs were further classified by achievement of the primary (GPPGA pustulation score of 0; "no visible pustules") and key secondary endpoint (GPPGA total score of 0 or 1; "clear or almost clear skin") at week 1.

Patient demographics and clinical characteristics were assessed in patients randomized to the spesolimab arm who received 1 (day 1) or 2 doses (days 1 and 8). Patients who received 2 doses were further classified by response; responders achieved a GPPGA pustulation subscore of 0 1 week after the day 8 dose. Logistic regression analysis was performed to determine baseline characteristics

Abbreviations used:

CGI:	clinical global impression
GPP:	generalized pustular psoriasis
GPPGA:	Generalized Pustular Psoriasis Physician Global Assessment
IL:	Interleukin
ITT:	intention-to-treat
MCID:	minimally clinically important difference
OL:	open-label
PASI:	Psoriasis Area and Severity Index

that could identify patients who require 1 or 2 doses of spesolimab. Characteristics included were age, sex, race, weight, *IL36RN* mutation status, ongoing or history of plaque psoriasis, GPPGA pustulation subscore, and GPPGA total score. Characteristics associated with use of OL spesolimab for a new flare, or other medication for GPP, were also investigated.

RESULTS

GPPGA scores in patients randomized to spesolimab

Four (11.4%) of 35 patients randomized to spesolimab achieved a GPPGA pustulation subscore of 0 by day 2 and 11 (31.4%) patients by day 3. At week 1, 19 (54.3%), 15 (42.9%), 6 (17.1%), and 6 (17.1%) of 35 patients randomized to spesolimab achieved a GPPGA pustulation subscore of 0 or a GPPGA total score or erythema or scaling subscore of 0 or 1, respectively (Fig 1). At week 12, the corresponding values were 21 (60.0%), 21 (60.0%), 14 (40.0%), and 18 (51.4%) of 35. In patients initially randomized to spesolimab, a GPPGA pustulation subscore of 0 at week 12 was achieved by 15 (65.2%) of 23 patients who received a single dose, and 6 (50.0%) of 12 patients who received a second OL dose at week 1.

MCIDs in GPPGA pustulation subscore and GPPGA total score by primary and key secondary endpoints

Most patients (23/35 [65.7%]) who received spesolimab achieved the primary endpoint and MCID in GPPGA pustulation subscore or MCID only at week 1 (Fig 2); few patients (4/18 [22.2%]) who received placebo achieved these endpoints. Among patients who received spesolimab, 25 (71.4%) of 35 achieved the key secondary endpoint and MCID in GPPGA total score or MCID only (Fig 2); 7 (38.9%) of 18 patients randomized to the placebo achieved these endpoints.

ITT analysis of GPPGA scores through week 12

Images and GPPGA scores for 2 patients treated with spesolimab are shown in Supplementary Figure S3 (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). Rapid and sustained improvements in GPPGA scores were observed in both patients, regardless of their *IL36RN* mutation status. Individual patient data for GPPGA scores by the randomization arm are available in Supplementary Interactive Fig 2 (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). In patients randomized to spesolimab, 21 (61.8%) of 34 and 27 (84.4%) of 32 achieved a GPPGA pustulation subscore of 0 at weeks 1 and 12, respectively (Fig 3); 17 (50.0%) of 34 and 26 (81.3%) of 32 patients, respectively, achieved a GPPGA total score of 0 or 1 (Supplementary Fig S4, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). OL spesolimab at day 8 was received by 15 patients in the placebo arm. In these individuals, a marked increase in the proportion with a GPPGA pustulation subscore of 0 was observed, from 1 (5.6%) of 18 at week 1 to 15 (83.3%) of 18 at week 2 (Supplementary Fig S5, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d); a similar increase was observed for GPPGA total score of 0 or 1, from 3 (16.7%) of 18 patients at week 1 to 13 (72.2%) of 18 patients at week 2 (Supplementary Fig S5, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). The proportions of patients who achieved a GPPGA erythema or scaling subscore of 0 or 1 and breakdown of all GPPGA scores at each time point are shown in Supplementary Figures 5 to 7 (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d).

ITT analysis of MCIDs in GPPGA pustulation subscore and GPPGA total score over 12 weeks

MCIDs in GPPGA pustulation subscore or GPPGA total score were observed in 23 (67.6%) of 34 and 25 (73.5%) of 34 patients randomized to spesolimab, respectively, at week 1 and sustained in 31 (96.9%) of 32 and 32 (100%) of 32 patients, respectively, at week 12 (Supplementary Fig S8, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). In patients randomized to placebo who received OL spesolimab at day 8, a rapid increase in the proportion achieving MCIDs in the GPPGA pustulation subscore or GPPGA total score was observed, which increased from 4 (22.2%) of 18 patients at week 1 to 16 (88.9%) of 18 at week 2 (pustulation subscore), and from 7 (38.9%) of 18 patients at week 1 to 16 (88.9%) of 18 patients at week 2 (total score;

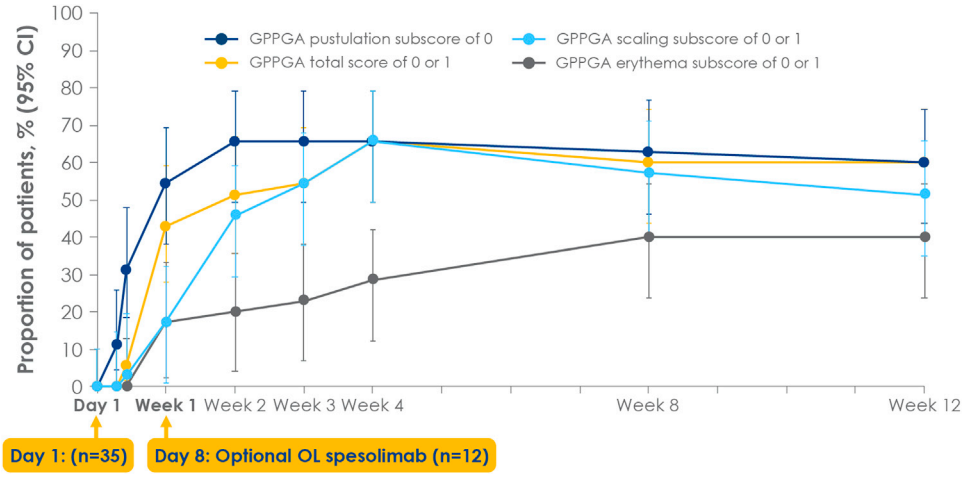

Fig 1. Proportion of patients randomized to spesolimab with a GPPGA pustulation subscore of 0 or GPPGA total, scaling, or erythema scores of 0 or 1 through week 12. Treatment effect in patients initially randomized to spesolimab who received up to 2 doses of spesolimab is as follows: day 1 (n = 35) and optional dose at Day 8 (n = 12). Missing values, any use of other medications for generalized pustular psoriasis, or use of spesolimab for the treatment of a new generalized pustular psoriasis flare were regarded as nonresponse for this analysis. *Arrowheads* indicate the days of intravenous spesolimab administration. *GPPGA*, Generalized Pustular Psoriasis Physician Global Assessment; *OL*, open-label.

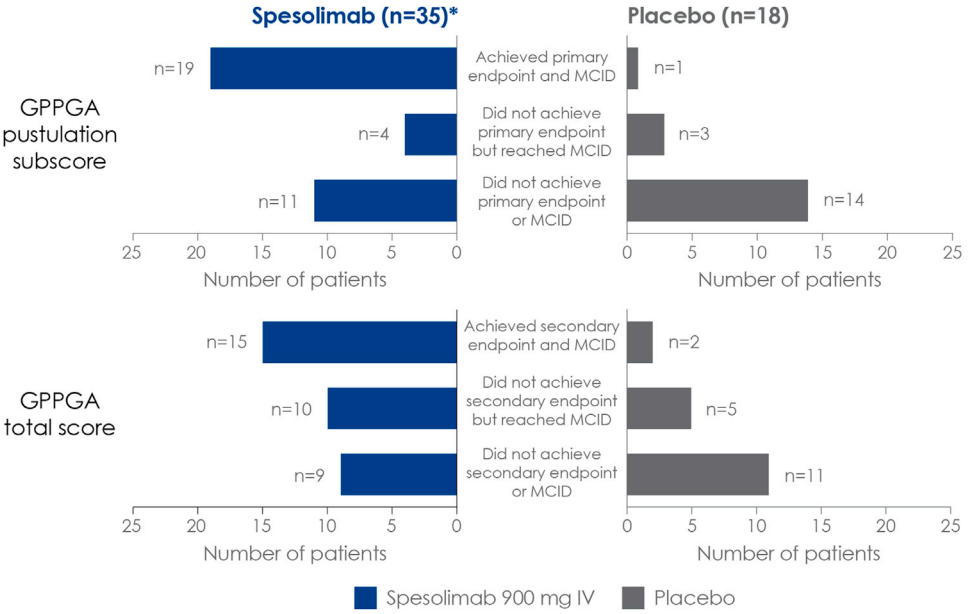

Fig 2. Number of patients who achieved MCIDs in GPPGA pustulation subscore (≥2 points) or GPPGA total score (≥1 point) by achievement of primary or secondary endpoint at week 1. Two patients in the spesolimab arm, and 1 patient in the placebo arm received other medication for GPP during the first week of the study. Missing values, any use of other medications for GPP, or use of spesolimab for the treatment of a new GPP flare were regarded as nonresponse for primary and key secondary analyses. *Asterisk* indicates 1 patient in the spesolimab arm who prematurely discontinued the trial and was not assessed at week 1. *GPP*, generalized pustular psoriasis; *GPPGA*, Generalized Pustular Psoriasis Physician Global Assessment; *IV*, intravenous; *MCID*, minimally clinically important difference.

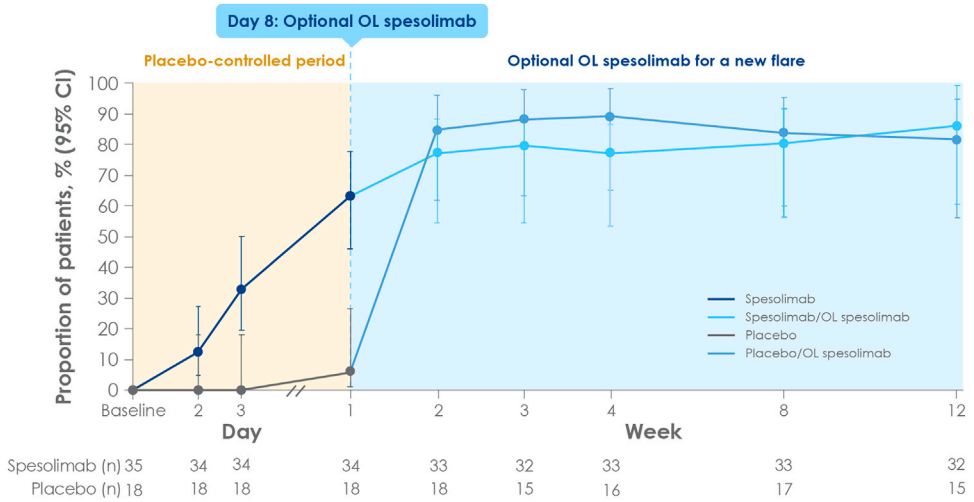

Fig 3. Proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment pustulation subscore of 0 through week 12: intention-to-treat analysis. Among 35 patients randomized to spesolimab, OL spesolimab was received by 12 patients at day 8 for persistent flare symptoms (Generalized Pustular Psoriasis Physician Global Assessment total score ≥2 and Generalized Pustular Psoriasis Physician Global Assessment pustulation subscore ≥2) and by 4 patients after day 8 for a new flare. Among 18 patients randomized to placebo, OL spesolimab was received by 15 patients at day 8 for persistent flare symptoms and by 2 patients after day 8 for a new flare. Intention-to-treat analysis population was defined as observed cases regardless of the use of any other medication for generalized pustular psoriasis or any additional dose of spesolimab. *OL*, open-label.

Supplementary Fig S8, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d); MCIDs were sustained in 15 (100%) of 15 patients at week 12.

Supplementary Figure S9 (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d) presents MCID data by randomized treatment and use of OL spesolimab at day 8. Results were similar for all treatment groups with ≥90% of patients achieving an MCID in GPPGA pustulation score (46 [97.9%] of 47 patients) and GPPGA total score (46 [97.9%] of 47 patients) at week 12.

Key characteristics of patients randomized to spesolimab

Mean time from first diagnosis of GPP to informed consent in patients randomized to spesolimab was 15.0 years (SD, 15.7). Baseline demographic and clinical characteristics for patients randomized to spesolimab, according to number of doses received and response, are shown in Table I and Supplementary Table SI (available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d). Baseline demographics, disease severity, or presence of systemic inflammation did not predict the number of required spesolimab doses. More patients with an *IL36RN* mutation received 1 dose of spesolimab (7/23 [30.4%]) compared with 2 doses (1/12 [8.3%]). In patients who received 2 doses, there was no difference in *IL36RN* mutation status between responders and nonresponders.

Patient characteristics associated with treatment response

Logistic regression analysis showed that no prognostic factor could estimate clinical outcomes that were independent of randomized treatment. Testing for interaction between baseline characteristics and treatment was not statistically significant ($P > .05$ for all). There was no strong predictor of differential treatment benefit from spesolimab compared with placebo that depended on patient characteristics.

Characteristics of patients who received other medication for GPP or OL spesolimab for a new flare

No factor was predictive of patients receiving other medication for GPP. Sex was the only baseline characteristic that was predictive of patients receiving OL spesolimab for a new flare (n = 6), as all were female (Table I); however, the small sample size limits interpretation. Among the 6 patients who had a new flare, 5 achieved a GPPGA pustulation subscore of 0 as follows: 2 of 2 patients in the placebo arm (1 received 1 dose, for new flare; 1 received 2 doses, day 8 and for new flare) and 3 of 4 patients in the spesolimab arm (2 received 3 doses, day 1, day 8, and for new flare; 1 received 2 doses,

Table I. Key demographic and clinical characteristics for patients randomized to spesolimab by number of doses for generalized pustular psoriasis flare treatment and achievement of a Generalized Pustular Psoriasis Physician Global Assessment pustulation subscore of 0 within 1 week of last dose (responder)*

			Spesolimab Two doses (days 1 and 8)				
	Spesolimab Total (n = 35)	Spesolimab single dose (day 1) (n = 23)	Responder† 1 week after day 8 dose (n = 5)	Nonresponder 1 week after day 8 dose (n = 7)	Total (n = 12)	Patients who experienced a new flare (n = 6)	Patients who received other medication (n = 15)
Age, ys, median (min, max)	41.0 (21, 69)	41.0 (21, 69)	45.0 (34, 58)	39.0 (28, 62)	42.0 (28, 62)	34.0 (28, 62)	36.0 (28, 69)
Sex, female, n (%)	21 (60.0)	15 (65.2)	2 (40.0)	4 (57.1)	6 (50.0)	6 (100.0)	11 (73.3)
GPPGA total score, n (%)							
3-4	35 (100)	23 (100)	5 (100)	7 (100)	12 (100)	6 (100)	15 (100)
GPPGA pustulation score, n (%)							
2	6 (17.1)	4 (17.4)	0	2 (28.6)	2 (16.7)	0	5 (33.3)
3-4	29 (82.9)	19 (82.6)	5 (100)	5 (71.4)	10 (83.3)	6 (100)	10 (66.7)
GPPASI total score, median (min, max)	27.4 (7.5, 54.2)	29.4 (8.6, 49.0)	31.6 (13.7, 47.8)	17.0 (7.5, 54.2)	18.0 (7.5, 54.2)	13.5 (9.9, 36.3)	15.5 (5.2, 54.2)
IL36RN mutation positive, n (%)	n = 29 8 (27.6)	n = 18 7 (38.9)	n = 4 0 (0)	n = 7 1 (14.3)	n = 11 1 (9.1)	n = 6 1 (16.7)	n = 13 1 (7.7)

GPPASI, Psoriasis Area and Severity Index for Generalized Pustular Psoriasis; *GPPGA*, Generalized Pustular Psoriasis Physician Global Assessment; max, maximum; min, minimum.
*Expanded listing of baseline demographics and characteristics provided in Supplementary Table S1, available via Mendeley at https://data.mendeley.com/datasets/nz35b7b26d.
†Responders were classified as patients who had achieved a GPPGA pustulation subscore of 0 1 week after administration of the second dose of spesolimab at day 8.

day 1 and for new flare). Among the 3 patients in the placebo arm who did not qualify for OL spesolimab on day 8, 1 had received other medication for GPP before day 8, and 2 had disease severity below the required threshold. Two of these 3 patients had spontaneous pustular clearance that was sustained to week 12.

DISCUSSION

In the Effisayil 1 study, in patients experiencing a GPP flare, a single infusion of the anti-IL-36R antibody spesolimab led to rapid pustular clearance (GPPGA pustulation subscore 0) and clear/almost clear skin (GPPGA total score 0 or 1) as early as 1 week after treatment.[2] Here, we show that some patients receiving spesolimab had complete pustular clearance within 24 hours and clear/almost clear skin within 48 hours. Furthermore, improvements observed after 1 week were sustained through week 12. The majority of patients initially randomized to placebo who received OL spesolimab at day 8 showed equally rapid and sustained pustular clearance and clear/almost clear skin. Most patients who received spesolimab achieved a MCID in both GPPGA pustulation and GPPGA total scores 1 week after treatment, and these changes were maintained over 12 weeks.

Availability of suitable patients with active disease to power randomized controlled trials is limited by the rarity of GPP, unpredictability of flares in relapsing forms of the disease, and sudden, self-limiting, episodic nature of flares.[8,9] To our knowledge, Effisayil 1 is the largest study and only randomized clinical trial to date in patients experiencing a GPP flare, which, therefore, allows comparison with natural history over the initial 1-week randomization period. Multinational study recruitment also means that results are applicable to populations beyond those seen in previous trials, which have assessed biologics for GPP treatment in predominantly Japanese patients.[10-13] Approval of biologics for GPP in Japan was largely on the basis of OL, single-arm clinical trials in <12 patients. Evidence generated from such trials is weak. Furthermore, these trials vary in time points for data collection, primary endpoints, and assessment of disease severity.[10,14,15] Secukinumab achieved a "very much improved" or "much improved" clinical global impression score in 83.3% of patients at week 16 (after 16 weeks of treatment), with some reductions in erythema and pustulation observed at week 1.[11] Similarly, guselkumab achieved clinical global impression scores of "very much improved," "much improved," or "minimally improved" in 77.8% of patients at week 16, with 50% achieving this by week 1,[16] and brodalumab achieved clinical global impression scores of "remission" or "improved" in 83.3% of patients at week 12.[12] On the basis of the Psoriasis Area and Severity Index (PASI), ixekizumab achieved PASI90 in 60.0% of patients by week 52 (after 12 weeks' treatment).[13] Clinical improvements achieved with spesolimab at week 1 and week 12 in the Effisayil 1 study, on the basis of GPPGA scores, compare favorably with efficacy reported at similar time points within each of these studies and have the key advantage of being a larger, randomized study on the basis of a GPP-specific tool that scores pustulation, which is the hallmark of GPP.

Although not a focus of this analysis, safety is key to understanding the risk-benefit balance of a treatment. Published data from Effisayil 1 shows that spesolimab has a safety profile similar to placebo,[2] and is consistent with other biologics.[17] The rate of adverse events at week 1 was 66% in the spesolimab group and 56% in the placebo group. At week 12, 82% of patients receiving spesolimab had an adverse event, but the time-adjusted incidence rate decreased from week 1 to 12.[2]

A strength of this study is data collection by physicians at multiple time points, which allowed detailed assessment throughout the study. GPPGA is a validated tool for measuring disease severity; it is sensitive and represents a reproducible and reliable endpoint for detecting meaningful within-patient changes in GPP severity.[18] MCIDs in the GPPGA pustulation subscore (≥2 points) and GPPGA total score (≥1 point) have been defined,[7] and the rapid and sustained increase in patients who achieved MCIDs in GPPGA scores following spesolimab highlights the fact that beneficial clinical outcomes were achieved in patients who failed to reach primary and key secondary endpoints.

Optional OL spesolimab at day 8 for persistent flare symptoms, or after day 8 for a new flare, were allowed to address the immediate safety needs of patients.[2] Given that most patients (15/18) initially assigned to placebo received OL spesolimab at day 8, a limitation of the study is that the effect of randomization groups of spesolimab versus placebo could not be determined beyond week 1 using conventional analyses. However, ITT analysis identified that even in patients who had a 1-week delay in treatment, spesolimab was efficacious in providing rapid flare control. Twelve of 35 patients randomized to spesolimab could also receive OL spesolimab at day 8, which introduced multiple dosing and limited direct comparison between treatment groups. These results indicate that some patients may require an additional dose of spesolimab to control GPP flare

symptoms; however, baseline characteristics and regression analysis did not reveal any factors that could predict response or identify patients who may require 1 or 2 doses of spesolimab. Therefore, clinical evaluation of patients 1 week after spesolimab treatment appears necessary to determine whether further treatment is required.

Together with the Effisayil 1 primary analyses,[2] these data indicate that spesolimab rapidly blocks the action of the IL-36 signaling pathway, which plays a central role in the pathogenesis of GPP,[19] and maintains this effect over time, further supporting its use as a therapeutic option for patients with a GPP flare. Although clinically meaningful improvements can be achieved in most patients with a single dose, an optional second dose may be needed in some patients. Evaluations of long-term administration of spesolimab (Effisayil ON) and use for flare prevention (Effisayil 2; NCT04399837) are ongoing.

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Conflicts of interest

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