Efficacy and safety of subcutaneous spesolimab for the prevention of generalised pustular psoriasis flares (Effisayil 2): an international, multicentre, randomised, placebo-controlled trial

Akimichi Morita, Bruce Strober, A David Burden, Siew Eng Choon, Milan J Anadkat, Slaheddine Marrakchi, Tsen-Fang Tsai, Kenneth B Gordon, Diamant Thaçi, Min Zheng, Na Hu, Thomas Haeufel, Christian Thoma, Mark G Lebwohl

Summary

Background Spesolimab is an anti-interleukin-36 receptor monoclonal antibody approved to treat generalised pustular psoriasis (GPP) flares. We aimed to assess the efficacy and safety of spesolimab for GPP flare prevention.

Methods This multicentre, randomised, placebo-controlled, phase 2b trial was done at 60 hospitals and clinics in 20 countries. Eligible study participants were aged between 12 and 75 years with a documented history of GPP as per the European Rare and Severe Psoriasis Expert Network criteria, with a history of at least two past GPP flares, and a GPP Physician Global Assessment (GPPGA) score of 0 or 1 at screening and random assignment. Patients were randomly assigned (1:1:1:1) to receive subcutaneous placebo, subcutaneous low-dose spesolimab (300 mg loading dose followed by 150 mg every 12 weeks), subcutaneous medium-dose spesolimab (600 mg loading dose followed by 300 mg every 12 weeks), or subcutaneous high-dose spesolimab (600 mg loading dose followed by 300 mg every 4 weeks) over 48 weeks. The primary objective was to demonstrate a non-flat dose-response curve on the primary endpoint, time to first GPP flare.

Findings From June 8, 2020, to Nov 23, 2022, 157 patients were screened, of whom 123 were randomly assigned. 92 were assigned to receive spesolimab (30 high dose, 31 medium dose, and 31 low dose) and 31 to placebo. All patients were either Asian (79 [64%] of 123) or White (44 [36%]). Patient groups were similar in sex distribution (76 [62%] female and 47 [38%] male), age (mean 40·4 years, SD 15·8), and GPP Physician Global Assessment score. A non-flat dose-response relationship was established on the primary endpoint. By week 48, 35 patients had GPP flares; seven (23%) of 31 patients in the low-dose spesolimab group, nine (29%) of 31 patients in the medium-dose spesolimab group, three (10%) of 30 patients in the high-dose spesolimab group, and 16 (52%) of 31 patients in the placebo group. High-dose spesolimab was significantly superior versus placebo on the primary outcome of time to GPP flare (hazard ratio [HR]=0·16, 95% CI 0·05–0·54; p=0·0005) endpoint. HRs were 0·35 (95% CI 0·14–0·86, nominal p=0·0057) in the low-dose spesolimab group and 0·47 (0·21–1·06, p=0·027) in the medium-dose spesolimab group. We established a non-flat dose-response relationship for spesolimab compared with placebo, with statistically significant p values for each predefined model (linear p=0·0022, emax1 p=0·0024, emax2 p=0·0023, and exponential p=0·0034). Infection rates were similar across treatment arms; there were no deaths and no hypersensitivity reactions leading to discontinuation.

Interpretation High-dose spesolimab was superior to placebo in GPP flare prevention, significantly reducing the risk of a GPP flare and flare occurrence over 48 weeks. Given the chronic nature of GPP, a treatment for flare prevention is a significant shift in the clinical approach, and could ultimately lead to improvements in patient morbidity and quality of life.

Funding Boehringer Ingelheim.

Lancet 2023; 402: 1541–51

Published **Online** September 19, 2023 https://doi.org/10.1016/S0140-6736(23)01378-8

See **Comment** page 1501

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (Prof A Morita MD); **Department of Dermatology, Yale University School of Medicine, New Haven, CT, USA** (B Strober MD); **Central Connecticut Dermatology, Cromwell, CT, USA** (B Strober); **School of Infection and Immunity, University of Glasgow, Glasgow, UK** (Prof A D Burden MD); **Department of Dermatology, Hospital Sultanah Aminah, and Clinical School Johor Bahru, Monash University Malaysia, Malaysia** (S E Choon MD); **Division of Dermatology, Washington University School of Medicine, St Louis, MO, USA** (Prof M J Anadkat MD); **Department of Dermatology, Hedi Chaker Hospital, University of Sfax, Sfax, Tunisia** (S Marrakchi MD); **Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan** (Prof T-F Tsai MD); **Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI, USA** (Prof K B Gordon MD); **Comprehensives Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany** (Prof D Thaçi MD); **Department of Dermatology, Second Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, Zhejiang, China** (Prof M Zheng MD); **Boehringer Ingelheim (China) Investment Co, Shanghai,**

Introduction

Generalised pustular psoriasis (GPP) is a chronic, rare, and potentially life-threatening skin condition characterised by widespread neutrophilic pustules, with a considerable patient burden.[1–3] The clinical course of GPP is highly unpredictable, with flares that can be triggered at any time; inciting factors include infections, pregnancy, stress, and medication withdrawal.[3,4]

Dysregulation of interleukin (IL)-36 signalling has a key role in GPP pathogenesis. Uncontrolled IL-36 expression by activated keratinocytes induces a self-perpetuating inflammatory cascade, during which the induction of chemokines (eg, CXCL1 and CXCL8) promotes neutrophil infiltration and the formation of epidermal pustules that are characteristic of GPP.[5–7] Indeed, loss-of-function mutations in the IL-36 receptor

China (N Hu PhD); **Boehringer Ingelheim International, Ingelheim, Germany** (T Haeufel MD); **Boehringer Ingelheim International, Biberach, Germany** (C Thoma MD); **Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof M G Lebwohl MD)

Correspondence to: Prof Mark G Lebwohl, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA **mark.lebwohl@mountsinai.org**

Research in context

Evidence before this study

Generalised pustular psoriasis (GPP) is a potentially life-threatening chronic skin disease with a mortality rate of 2–16%. Generalised pustular psoriasis has a highly unpredictable disease course; however, disease flares can be severe, often accompanied by systemic symptoms and requiring hospital admission in about half of cases. Spesolimab, a monoclonal anti-IL-36R antibody, has been approved for the treatment of GPP flares. There are currently no approved treatments for flare prevention in patients with this chronic, lifelong disease. We searched PubMed for papers published from database inception to April 14, 2023, using the search terms (generalised pustular psoriasis OR GPP) AND (flare) AND (prevention), with no language restrictions. Our search identified five publications, including a Delphi consensus paper, a survey of dermatologists, and a literature review. The literature search did not identify any studies or trials evaluating therapies for flare prevention. In the Delphi consensus study, almost all panellists (95–100%) agreed that the prevention of new flares and the sustained resolution of flare symptoms are key long-term treatment goals. Moreover, a survey of dermatologists in North America highlighted that GPP flare prevention was "often a challenge", with most patients continuing to experience chronic disease between flares. Dermatologists report that treatments for chronic GPP are often inadequate. A review article on GPP concluded that optimal treatment approaches should be able to prevent acute flares and disease recurrence; the need for data on long-term GPP treatments was also stressed. Overall, evidence before this study points toward a high unmet need for effective treatments for flare prevention and sustained disease control, with a favourable safety profile.

Added value of this study

This pivotal study is the first to systematically evaluate a treatment for GPP flare prevention, and is the largest multinational trial to date in patients with this rare disease. Our findings demonstrate the superiority of a high-dose subcutaneous spesolimab regimen (600 mg loading dose followed by 300 mg every 4 weeks) over placebo in preventing GPP flares over 48 weeks. Subcutaneous spesolimab had a favourable safety profile, with a similar incidence of patients with adverse events across spesolimab and placebo treatment arms.

Implications of all the available evidence

Existing evidence suggests that IL-36R inhibition is an effective treatment approach for GPP flares; however, treatment options for long-term flare prevention is an unmet clinical need. The results of this study reinforce existing clinical evidence for the key role of the IL-36 signalling axis in GPP pathogenesis, and support a new role for subcutaneous spesolimab as a therapy for flare prevention and improvement of long-term quality of life. Our findings are particularly pertinent given the potentially life-threatening nature of GPP flares, and the pressing need for effective long-term clinical management.

(IL-36R) antagonist gene *IL36RN* have been identified in 21–75% of patients with GPP.[8–11] Prevalence of *IL36RN* mutations in the GPP population can vary by geography and these mutations are most common in Asian populations.[12,13] The immunopathogenic responses in GPP are distinct from those in plaque psoriasis, which is largely driven by the IL-23/IL-17 signalling axis.[14,15] Supporting the pivotal role of IL-36 in GPP, intravenous administration of the anti-IL-36R monoclonal antibody spesolimab achieved rapid pustular clearance in patients experiencing a GPP flare,[16] leading to its approval for GPP flare treatment in the USA, Europe, Japan, and China.[17–20]

Nevertheless, effective treatments for GPP flare prevention are still needed. Long-term management of GPP should focus on disease control and should ultimately improve patients' health-related quality of life.[21,22] However, there are no approved therapies for GPP flare prevention, and no treatments have been systematically evaluated for this indication in a global randomised controlled trial.[23,24] Patients with GPP are prescribed a variety of maintenance therapies, which are then often discontinued, indicating ineffective long-term disease management.[25–27] We aimed to assess the use of spesolimab for flare prevention in patients with GPP.

See Online for appendix

Methods

Study design

We conducted this pivotal, multicentre, randomised, placebo-controlled, phase 2b trial at 60 hospitals and clinics across 20 countries. (A full list of trial investigators and study sites is given in the appendix [p 2]). The study was approved by ethics committees of participating institutions and countries.

Patients

Eligible study participants were aged between 12 and 75 years with a documented history of GPP as per the European Rare and Severe Psoriasis Expert Network criteria,[28] with a history of at least two past GPP flares, and a GPP Physician Global Assessment (GPPGA) score of 0 or 1 at screening and random assignment. Patients not on concomitant GPP treatment at randomisation must have had at least two moderate-to-severe flares in the past year, with at least one associated with fever, elevated C-reactive protein level, elevated white blood cell count, asthenia, or myalgia. Patients not receiving concomitant GPP treatment at random assignment but on concomitant GPP treatment until 12 weeks or less before random assignment must have had a history of flaring during treatment or following dose reduction or treatment discontinuation. Patients on concomitant GPP

treatment with retinoids, methotrexate, or cyclosporine were eligible for inclusion, but treatment had to be stopped at random assignment. These patients must have also had a history of flaring while on concomitant treatment for GPP or after dose reduction or discontinuation of concomitant medication. Details of inclusion and exclusion criteria and restricted medications are given in the appendix (pp 3–7). Patients self-reported their sex data from the options female or male. Important protocol deviations are provided in the appendix (p 8). Eligible patients were screened and recruited at the discretion of participating investigators. All patients provided written informed consent, and confidentiality agreements were in place between authors and Boehringer Ingelheim.

Randomisation and masking

Patients with a history of GPP were randomly assigned (1:1:1:1) to receive high-dose spesolimab, medium-dose spesolimab, low-dose spesolimab, or placebo. The three doses were selected to test a range of exposures to spesolimab and evaluate the dose-response relationship. Subjects and investigators were masked to dose and treatment group. Patients were randomly assigned by use of an interactive response technology system, and randomisation was stratified by a stratification factor (concomitant use of systemic GPP medications at randomisation [yes *vs* no]) and two blocking factors (region [Japan *vs* non-Japan] and population [adults *vs* adolescents]). Block randomisation ensured an even distribution of patients across the region and population groups; these blocking factors were not used as stratification factors for data analysis. Participants, hospital staff, investigators, and data managers were masked to treatment group. Placebo solution for injection was prepared to match spesolimab, and was presented in an identical, pre-filled syringe.

Procedures

Patients received either subcutaneous placebo loading dose followed by maintenance placebo every 4 weeks, subcutaneous spesolimab 300 mg loading dose followed by 150 mg every 12 weeks (low dose), subcutaneous spesolimab 600 mg loading dose followed by 300 mg every 12 weeks (medium dose), or subcutaneous spesolimab 600 mg loading dose followed by 300 mg every 4 weeks (high dose; appendix p 12). Patients received their last study treatment at week 44 and were followed up to week 48. Blood samples were collected at the visit at which they received their first loading dose, and genotyping was done centrally by the sponsor. Patients experiencing a GPP flare within the randomised treatment period (defined as a GPPGA pustulation subscore of ≥2 and an increase in the GPPGA score of ≥2) received treatment with 900 mg of open-label intravenous spesolimab. Patients with persistent flare symptoms 1 week after the first open-label treatment could receive an optional second intravenous 900 mg dose of spesolimab. After 12 weeks, patients with a response to open-label spesolimab could receive 300 mg of open-label subcutaneous spesolimab every 12 weeks as open-label maintenance treatment (appendix p 12) with the option to escalate to every 4 weeks. Patients who completed the trial to week 48 could also enter an open-label extension study of spesolimab in patients with GPP (NCT03886246). For those who did not agree or were not eligible to enter the open-label extension, there was a 16-week safety follow-up period. Full details of the Effisayil 2 trial design have been published previously.[29]

Outcomes

The primary endpoint was time to first GPP flare by week 48; the key secondary endpoint was the occurrence of at least one GPP flare by week 48 (measured as a binary outcome, ie, flare *vs* no flare). Other secondary endpoints included time to worsening (defined as an increase of four points from baseline for each score) of the Psoriasis Symptom Scale (PSS) and Dermatology Life Quality Index (DLQI) up to week 48, and the occurrence of adverse events by week 48.

The primary trial objective was to demonstrate a non-flat dose-response curve on the primary endpoint. If the study met the primary objective, the secondary objective would be analysed to assess the potential superiority of high-dose or medium-dose spesolimab over placebo, on the primary and key secondary endpoints. Adverse events were assessed by the investigator and recorded in the patient's case report form. The investigator reported serious adverse events (SAEs) using the sponsor SAE form within 24 h. On specific occasions, the investigator could inform the sponsor via telephone; however, this did not replace the requirement to complete and send the SAE form. All adverse events (serious and non-serious) were to be followed up until they had resolved, were assessed as chronic or stable, or no further information could be obtained. The investigator was to keep detailed records of all adverse events in the patient files. For the assessment of laboratory parameters, blood and urine samples were collected by the trial site at all visits (patients did not have to fast). Laboratory tests were done at a central laboratory, and reports were sent to the investigator for their evaluation. Findings that were judged as abnormal by the investigator could be reported as adverse events.

Statistical analysis

Based on multiplicity-adjusted success probability analyses, a sample size of 120 patients was selected so that a power of at least 90% could be achieved for at least one successful dose of spesolimab (high or medium dose) versus placebo on the primary and key secondary endpoints. For the primary objective, the dose-response relationship was assessed by use of a multiple comparison procedure with modelling techniques (MCPMod), using

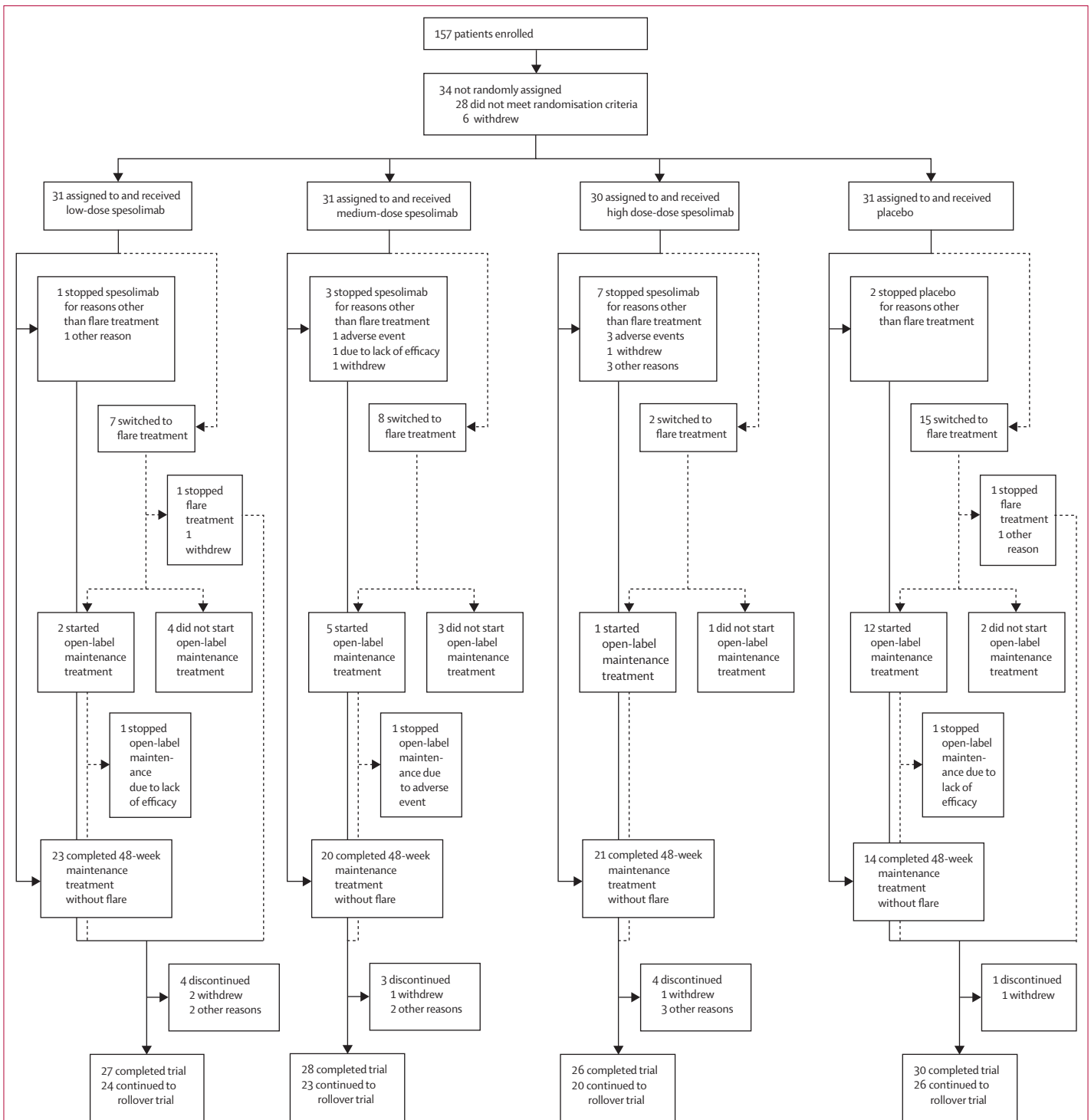

Figure 1: **Patient assignment and follow-up**
Patients who entered the rollover trial might not have received the first dose of spesolimab in that trial at the time of Effisayil 2 database lock. In the high-dose spesolimab group, seven patients discontinued treatment with spesolimab: three adverse events (breast cancer, worsening of psoriasis vulgaris, and pustular psoriasis), one patient withdrew, and three patients each had other reasons (could not comply with study visit, pregnancy, and use of other medication [acitretin] to treat chronic plaque psoriasis). No pattern with regard to the reason(s) for discontinuations was observed. A patient randomly assigned to the placebo group who accidentally received a single dose of spesolimab 150 mg on day 1 was assigned to the spesolimab low-dose group for the analyses of exposure and safety.

log hazard ratios [HRs] of each spesolimab dose versus placebo derived from a Cox regression model on the time to first GPP flare. MCPMod analyses were done with R (version 4.1.1) using the DoseFinding package.[30,31] Once a non-flat dose-response was established, formal statistical hypothesis testing was done on the superiority of high dose or medium dose versus placebo on the primary endpoint using a stratified log-rank test (overall one-sided α=0·025); multiplicity was controlled by the truncated Hochberg procedure (appendix p 13). If the test on the primary endpoint was successful for at least one dose group, the key secondary and other endpoints would be subsequently tested in a hierarchical manner. The key secondary endpoint was analysed using a Cochran-Mantel-Haenszel test. Analyses for all endpoints were stratified by the concomitant use of systemic GPP medications at random assignment. Any use of flare treatment with open-label intravenous spesolimab or other investigator-prescribed medication to treat GPP worsening was considered a GPP flare event; all reported p values are one-sided. For primary and secondary time-to-event endpoints, patients with missing data were censored. Missing data for patients who discontinued maintenance treatment were thoroughly reviewed; there were no observed trends regarding reasons for discontinuation. Missing data were censored assuming non-informative censoring. For the key secondary endpoint, missing data were imputed by a sequential regression multiple imputation method for patients with no flare by week 48.[32,33] The efficacy analyses included all randomly assigned patients; the safety analyses included all patients who were randomly assigned and received at least one treatment dose. The trial was done in accordance with the trial protocol, the International Council for Harmonisation Good Clinical Practice guidelines, Regulation number 536/2014 (EU), the Japanese Good Clinical Practice regulations, and applicable local regulations. This trial is registered with ClinicalTrials.gov, NCT04399837.

Role of the funding source

The funder of the study, Boehringer Ingelheim, designed the trial, analysed the data, provided spesolimab and placebo, and paid for professional writing assistance. The senior author wrote the manuscript first draft. Academic authors were not restricted by the sponsor in publishing trial results and were not paid for manuscript development.

Results

From June 8, 2020, to Nov 23, 2022, 157 patients were screened, of whom 123 were randomly assigned. Of these, 31 patients were assigned to receive placebo, 31 to receive low-dose spesolimab, 31 to receive medium-dose spesolimab, and 30 to receive high-dose spesolimab (figure 1 and table 1). At week 48, 30 patients in the placebo group, 27 patients in the low-dose spesolimab group, 28 patients in the medium-dose spesolimab group, and 26 patients in the high-dose spesolimab group completed the trial; a total of 93 patients were enrolled in the OLE trial (figure 1). Reasons for patient discontinuation from the trial are also detailed in figure 1; no pattern with respect to the reason(s) for discontinuation between treatment arms was observed.

All patients were either Asian (79 [64%] of 123) or White (44 [36%]). 76 (62%) patients were female and 47 (38%) were male. Mean age was 40·4 years (SD 15·8). Patient groups were similar in mean GPPGA score. The high-dose spesolimab group had higher mean Generalized Pustular Psoriasis Area and Severity Index (GPPASI 3·92; SD 4·42), PSS (5·3; 3·8), and DLQI (11·1; 6·9) scores at baseline relative to other treatment arms (GPPASI range 3·03 [SD 3·48] to

	Spesolimab			Placebo (n=31)
	Low (n=31)	Medium (n=31)	High (n=30)	
Sex				
Female	20 (65%)	20 (65%)	18 (60%)	18 (58%)
Male	11 (35%)	11 (35%)	12 (40%)	13 (42%)
Race				
Asian	20 (65%)	21 (68%)	21 (70%)	17 (55%)
White	11 (35%)	10 (32%)	9 (30%)	14 (45%)
Age, years	38·9 (16·5)	42·9 (16·7)	40·2 (16·4)	39·5 (14·0)
BMI, kg/m^2	26·9 (7·2)	27·4 (8·8)	25·6 (7·3)	26·9 (8·3)
GPPASI total score	3·03 (3·48)	3·12 (4·16)	3·92 (4·42)	3·11 (2·81)
GPPGA total score				
0	2 (6%)	8 (26%)	3 (10%)	4 (13%)
1	29 (94%)	23 (74%)	27 (90%)	27 (87%)
PSS total score	4·1 (3·8)	3·9 (2·9)	5·3 (3·8)	3·6 (2·9)
DLQI total score	7·6 (6·7)	6·6 (5·6)	11·1 (6·9)	7·2 (5·6)
IL36RN mutation				
Yes	7 (23%)	10 (32%)	7 (23%)	4 (13%)
No	17 (55%)	15 (48%)	19 (63%)	22 (71%)
Unknown*	7 (23%)	6 (19%)	4 (13%)	5 (16%)
Concurrent plaque psoriasis at baseline†				
Yes	10 (32%)	7 (23%)	7 (23%)	10 (32%)
No	21 (68%)	24 (77%)	23 (77%)	21 (68%)
Use of at least one systemic medication for GPP (discontinued before randomisation)	25 (81%)	23 (74%)	22 (73%)	22 (71%)
Historical use of at least one biologic therapy	5 (16%)	8 (26%)	6 (20%)	9 (29%)
Historical number of flares per year	2·7 (2·3)	1·9 (0·9)	2·4 (1·9)	2·4 (1·2)
Time since first diagnosis				
≤1 year	5 (16%)	4 (13%)	4 (13%)	3 (10%)
>1 to ≤5 years	6 (19%)	9 (29%)	9 (30%)	10 (32%)
>5 to ≤10 years	6 (19%)	8 (26%)	8 (27%)	7 (23%)
>10 years	14 (45%)	10 (32%)	9 (30%)	11 (35%)

Data are n (%) or mean (SD). DLQI=Dermatology Life Quality Index. GPP=generalised pustular psoriasis. GPPASI=Generalised Pustular Psoriasis Area and Severity Index. GPPGA=Generalised Pustular Psoriasis Physician Global Assessment. *IL36RN*=interleukin-36 receptor antagonist gene. PSS=Psoriasis Symptom Scale. **IL36RN* mutation status was unknown for patients from whom no blood sample was obtained. †The presence of concurrent plaque psoriasis was based on the investigator's clinical investigation at enrolment.

Table 1: **Patient demographics and baseline characteristics**

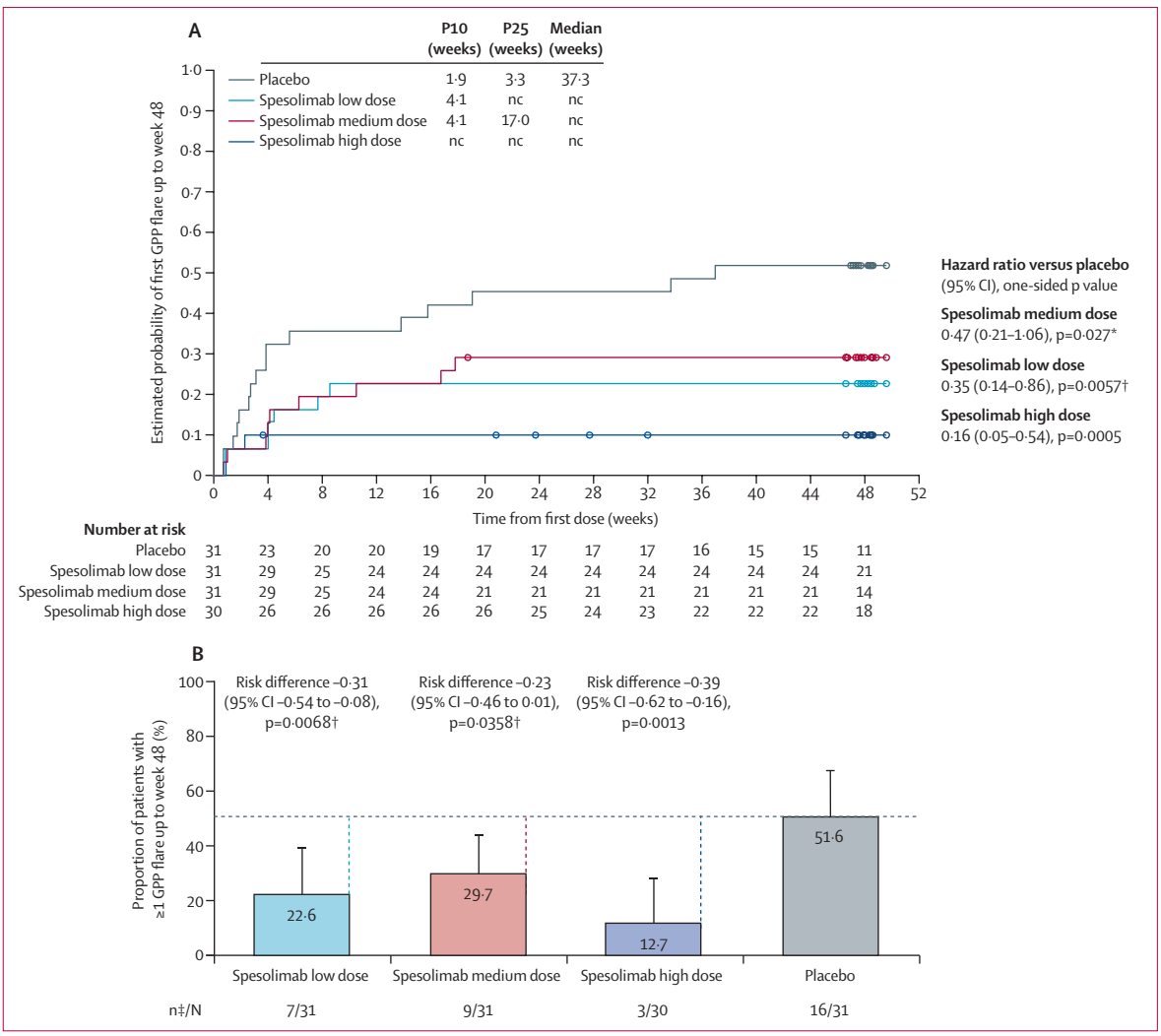

Figure 2: **Primary and key secondary endpoints**

(A) Kaplan–Meier plot showing the estimated probability of a first GPP flare over 48 weeks for all treatment groups. The use of medication with intravenous open-label spesolimab or other investigator-prescribed medication was considered to be a GPP flare. (B) Proportion of patients with at least one GPP flare up to week 48. The horizontal dashed line represents the proportion of patients with at least one GPP flare up to week 48 in the placebo group (51·6%). A multiple imputation method for binary endpoints with monotone missing assessments using sequential logistic regression method was used. The stratified Cochran-Mantel-Haenszel test was done for each dose of spesolimab versus placebo, stratified by use of systemic GPP medication at random assignment. GPP=generalised pustular psoriasis. nc=not calculable. P10=estimated probability of first GPP flare=0·1. P25=estimated probability of first GPP flare=0·25. *Not significant. †Not tested (statistical significance was not seen in previous families in the statistical testing hierarchy). ‡Before imputation.

3·12 [4·16], PSS range 3·6 [2·9] to 4·1 [3·8]; DLQI range, 6·6 [5·6] to 7·6 [6·7]; table 1). A smaller proportion of patients in the placebo group had an *IL36RN* mutation (four [13%] of 31) than in the spesolimab groups (seven [23%] of 31 in the low-dose group; ten [32%] of 31 in the medium-dose group; seven [23%] of 30 patients in the high-dose group).

By week 48, 35 patients had GPP flares; seven (23%) of 31 patients in the low-dose spesolimab group, nine (29%) of 31 patients in the medium-dose spesolimab group, three (10%) of 30 patients in the high-dose spesolimab group, and 16 (52%) of 31 patients in the placebo group (appendix p 10). For the primary outcome, we established a non-flat dose-response relationship for spesolimab compared with placebo, with statistically significant p values for each predefined model (linear p=0·0022, emax1 p=0·0024, emax2 p=0·0023, and exponential p=0·0034; appendix p 9).

For the secondary trial objective, high-dose spesolimab showed statistically significant improvement versus placebo on the primary endpoint, time to GPP flare (HR 0·16, 95% CI 0·05–0·54; p=0·0005, α=0·0125 available based on the truncated Hochberg procedure; appendix p 10). The estimated probability of developing a GPP flare began to diverge between the spesolimab and placebo treatment arms shortly after random

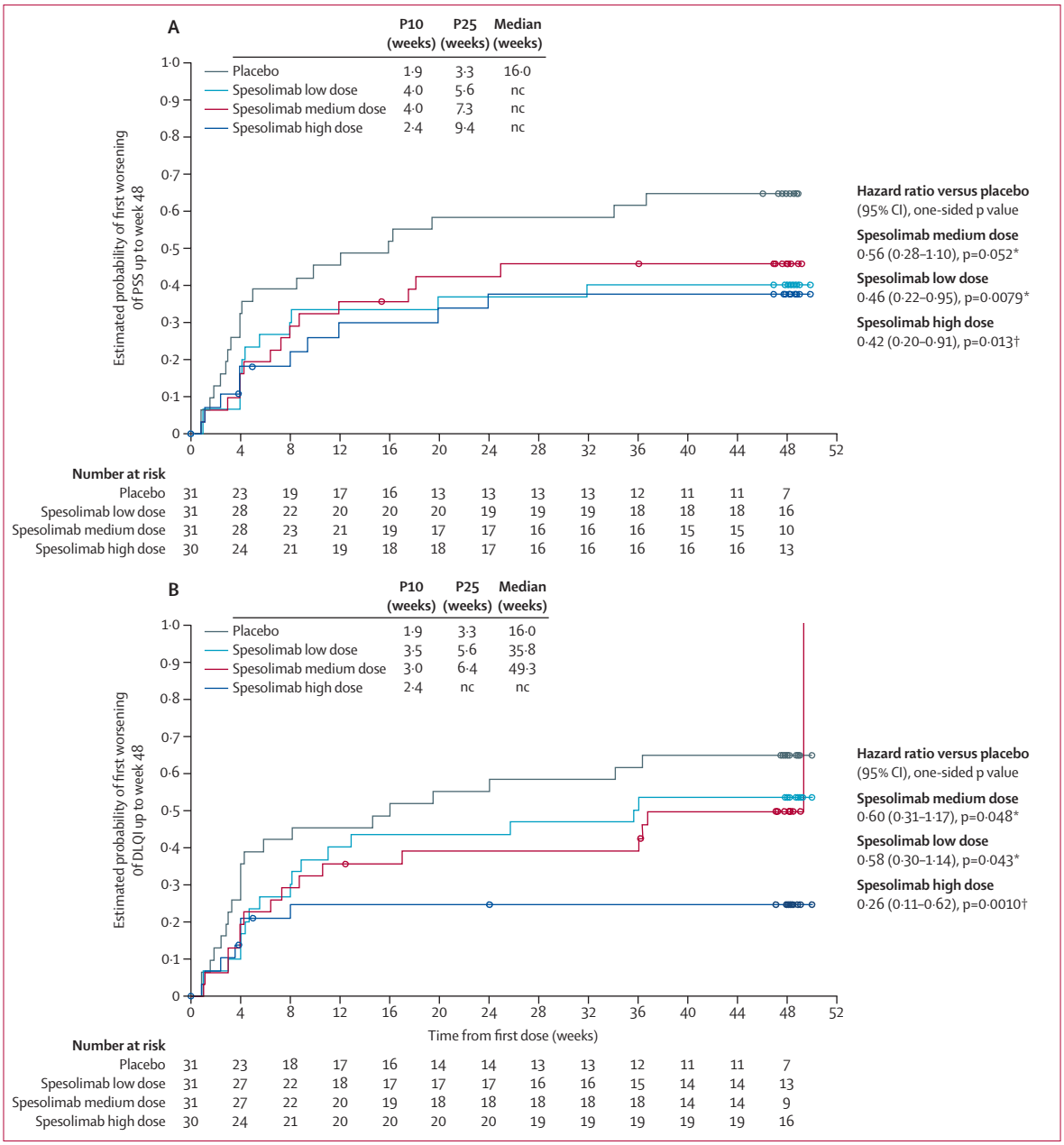

Figure 3: **Other secondary endpoints**
(A) Kaplan–Meier plot showing the estimated probability of a first worsening of PSS score. (B) Kaplan–Meier plot showing the estimated probability of a first worsening of DLQI score. For both scores, worsening was defined as a 4-point increase in total score from baseline. The use of intravenous open-label spesolimab or other investigator-prescribed medication was considered to be an event. DLQI=Dermatology Life Quality Index. nc=not calculable. P10=estimated probability of first GPP flare=0·1. P25=estimated probability of first GPP flare=0·25. PSS=Psoriasis Symptom Scale. *Not tested (statistical significance was not seen in previous families in the statistical testing hierarchy). †Not significant.

assignment and was sustained up to week 48 (figure 2A). There were no flares in the high-dose spesolimab group after the first 300 mg subcutaneous dose at week 4. The medium dose of spesolimab did not reach statistical significance versus placebo on the primary endpoint (p=0·027) as per the prespecified α of 0·019. Therefore, formal testing on subsequent secondary endpoints was done only for the high-dose group, with an allocated α of 0·0063 (appendix p 13). HRs were 0·35 (95% CI 0·14–0·86; nominal p=0·0057) in the low-dose spesolimab group and 0·47 (0·21–1·06; p=0·027) in the medium-dose spesolimab group (figure 2A and appendix p 10).

Primary endpoint data for patients with and without an *IL36RN* mutation are shown in the appendix (pp 16–18). For patients with an *IL36RN* mutation, zero patients in

	Spesolimab								Placebo (n=30)*	
	Low (n=32)		Medium (n=31)		High (n=30)		Total (n=93)		n (%)	Rate†
	n (%)	Rate†	n (%)	Rate†	n (%)	Rate†	n (%)	Rate†		
Any adverse event	29 (91%)	398·7	29 (94%)	411·0	26 (87%)	338·2	84 (90%)	381·5	26 (87%)	414·5
Severe adverse event: RCTC grade 3 or 4	6 (19%)	25·4	7 (23%)	31·6	5 (17%)	21·7	18 (19%)	26·2	7 (23%)	45·6
Investigator-defined drug-related adverse event	14 (44%)	86·7	11 (35%)	65·0	12 (40%)	76·2	37 (40%)	75·8	10 (33%)	74·9
Adverse event leading to discontinuation of study drug	0	0	2 (6%)	8·9	3 (10%)	12·9	5 (5·4%)	7·1	0	0
Serious adverse event‡	5 (16%)	21·2	1 (3%)	4·4	3 (10%)	12·8	9 (10%)	12·9	1 (3%)	5·8
Adverse events resulting in death	0	0	0	0	0	0	0	0	0	0
Most common adverse events§										
Skin and subcutaneous tissue disorders	17 (53%)	89·7	20 (65%)	127·4	13 (43%)	69·5	50 (54%)	93·7	22 (73%)	192·2
Pustular psoriasis	10 (31%)	41·9	10 (32%)	47·2	3 (10%)	12·7	23 (25%)	33·5	16 (53%)	95·8
Psoriasis	4 (13%)	18·0	5 (16%)	24·2	4 (13%)	18·0	13 (14%)	20·0	3 (10%)	19·9
Infections and infestations	12 (38%)	71·0	11 (35%)	64·1	8 (27%)	40·5	31 (33%)	57·6	10 (33%)	75·2
Upper respiratory tract infection	3 (9%)	12·8	6 (19%)	30·2	0	0	9 (10%)	13·4	4 (13%)	24·9
COVID-19	2 (6%)	8·4	1 (3%)	4·4	3 (10%)	13·8	6 (6%)	8·8	1 (3%)	5·9
Urinary tract infection	1 (3%)	4·1	0	0	4 (13%)	18·0	5 (5%)	7·2	0	0
General disorders and administration site conditions	9 (28%)	45·9	8 (26%)	43·6	8 (27%)	44·8	25 (27%)	44·8	3 (10%)	19·1
Injection-site erythema	4 (13%)	18·7	4 (13%)	19·3	5 (17%)	24·7	13 (14%)	20·8	1 (3%)	6·1
Investigations	9 (28%)	48·9	5 (16%)	24·3	5 (17%)	24·2	19 (20%)	31·8	6 (20%)	43·2
Blood creatine phosphokinase increased	4 (13%)	17·9	1 (3%)	4·4	0	0	5 (5%)	7·3	2 (7%)	12·1
Musculoskeletal and connective tissue disorders	5 (16%)	23·3	3 (10%)	14·5	5 (17%)	22·7	13 (14%)	20·3	3 (10%)	18·2
Arthralgia	4 (13%)	17·6	1 (3%)	4·6	3 (10%)	13·3	8 (9%)	11·9	1 (3%)	6·0

RCTC=Rheumatology Common Toxicity Criteria. *A patient randomly assigned to the placebo group who accidentally received a single dose of spesolimab 150 mg on day 1 was assigned to the spesolimab low-dose group for the analyses of exposure and safety. †Per 100 patient-years. ‡Serious adverse events in patients receiving spesolimab were hypertensive encephalopathy, encephalitis viral, pneumonia, skin bacterial infection, angioedema, drug eruption, palpitations, breast cancer, cholelithiasis, and pustular psoriasis. Of note, hypertensive encephalopathy was a differential diagnosis of viral encephalitis in the same patient. One patient receiving placebo had multiple sclerosis. §Most common adverse events are those occurring in at least 10% of patients in any trial group, by preferred term.

Table 2: **Summary of adverse events within the randomised treatment period up to the first dose of spesolimab**

the high-dose spesolimab group had a flare, compared with three (75%) of four patients in the placebo group (HR 0·04, 95% CI 0·00–1·15). For patients without an *IL36RN* mutation, three (16%) of 19 patients in the high-dose spesolimab group had a flare, compared with nine (41%) of 22 patients in the placebo group (0·41, 0·11–1·54).

Analysis of the key secondary endpoint revealed risk differences for the occurrence of a GPP flare compared with placebo over 48 weeks of –0·31 (95% CI –0·54 to –0·08, nominal p=0·0068) for low-dose spesolimab, –0·23 (–0·46 to 0·01, nominal p=0·036) for medium-dose spesolimab, and –0·39 (–0·62 to –0·16, p=0·0013) for high-dose spesolimab (figure 2B and appendix p 10). Using a one-sided α of 0·0063 (adjusted for multiplicity), high-dose spesolimab showed statistically significant improvement over placebo on the key secondary endpoint (p=0·0013).

Spesolimab reduced the risk of PSS worsening over 48 weeks compared with placebo, as demonstrated by HRs of 0·46 (95% CI 0·22–0·95, nominal p=0·0079) for the low-dose regimen, 0·56 (95% CI 0·28–1·10, nominal p=0·052) for the medium-dose regimen, and 0·42 (0·20–0·91, p=0·013) for the high-dose regimen (figure 3A and appendix p 11). A smaller proportion of patients in the low-dose (12 [39%] of 31), medium-dose (14 [45%] of 31), and high-dose (ten [33%] of 30) spesolimab groups reported a worsening of their PSS score compared with placebo (20 [65%] of 31; figure 3A and appendix p 11). High-dose spesolimab did not pass the significance threshold for superiority (α=0·0063) for time to worsening of PSS (p=0·013) and no further testing was done. Spesolimab reduced the risk of DLQI worsening over 48 weeks, with HRs versus placebo of 0·58 (95% CI 0·30–1·14, nominal p=0·043) for the low-dose group, 0·60 (0·31–1·17, nominal p=0·048) for the medium-dose group, and 0·26 (0·11–0·62, nominal p=0·0010) for the high-dose group (figure 3B and appendix p 11).

A similar proportion of patients receiving spesolimab (84 [90%] of 93) and placebo (26 [87%] of 30) experienced an adverse event; adverse event incidence was similar across spesolimab dose groups and did not follow a dose-dependent pattern (table 2). Patients receiving

spesolimab (total of all doses) and placebo had a similar incidence of severe adverse events (18 [19%] of 93 *vs* seven [23%] of 30) and investigator-defined drug-related adverse events (37 [40%] of 93 *vs* ten [33%] of 30). There were no adverse events resulting in death and adverse events were mostly non-serious and non-severe. The most common adverse events were pustular psoriasis (23 [25%] of 93 patients receiving spesolimab *vs* 16 [53%] of 30 patients receiving placebo), psoriasis (13 [14%] *vs* 3 [10%]), and injection-site erythema (13 [14%] *vs* one [3%]). Infection rates were similar across treatment groups. A greater proportion of patients receiving spesolimab experienced SAEs compared with those receiving placebo (nine [10%] of 93 *vs* one [3%] of 30); serious adverse events did not follow a dose-dependent pattern with spesolimab. SAEs reported in the high-dose spesolimab group were pustular psoriasis, breast cancer, and cholelithiasis (one patient each). There were no hypersensitivity reactions leading to treatment discontinuation.

Discussion

This is the first randomised, placebo-controlled trial to evaluate the efficacy and safety of a treatment for GPP flare prevention. Our findings support existing clinical evidence for the key role of IL-36 signalling in GPP pathogenesis.[16,34] Intravenous spesolimab has been shown to treat flares effectively.[16] This study is the first to support a new role for subcutaneous spesolimab as a prevention therapy for GPP flares. These findings are particularly pertinent given the chronic nature of the disease and that sustained pustular clearance is a key long-term goal for effective clinical management of patients with GPP.[21,22]

In this trial, a non-flat dose-response relationship was shown for three doses of spesolimab versus placebo on time to first GPP flare, achieving the primary trial objective. High-dose spesolimab was superior to placebo in preventing flares on the primary and key secondary endpoints. Statistical significance cannot be claimed for the remaining tests, although small nominal p values were observed for the reduced risk of quality of life deterioration. The enhanced efficacy in the high-dose group could indicate that sustained IL-36R inhibition requires maintenance of a high threshold level of spesolimab. We hypothesise that, because spesolimab works by blocking the IL-36R rather than the cytokine itself, a higher injection frequency (eg, every 4 weeks rather than every 12 weeks) might be required to ensure continual receptor inhibition and sustained downstream effects. A higher rate of treatment discontinuation was observed in the high-dose group compared with the low-dose and medium-dose groups; however, reasons (which included breast cancer, pregnancy, and patient withdrawal) were predominantly unrelated to spesolimab treatment. Overall, the safety profile of spesolimab was favourable;[16] the infection rate was similar across treatment arms, and there was no indication of increased rates with a higher dose. There were no adverse events resulting in death, and no hypersensitivity events leading to treatment discontinuation.

High-dose spesolimab was effective at preventing GPP flares in patients with and without *IL36RN* mutations, although the small sample sizes should be noted. These data suggest that there is clinical benefit to continuous spesolimab treatment for flare prevention, independent of *IL36RN* mutation status. Given the chronic and potentially life-threatening nature of the disease, and the high rate of patient hospital admission, there is a need for continuous systemic treatment for GPP flare prevention. The decision for treatment should be based on informed conversation between physician and patient. The ongoing 5-year OLE study will provide further data on long-term management of patients with GPP.

This study was limited by the small sample size. Although sample size is a common challenge in rare diseases, this trial is the largest study in patients with GPP to date, and effect sizes were large. As patients receiving placebo were treated with open-label spesolimab following a GPP flare, flare frequency over time could not be assessed; however, the use of rescue medication was crucial, given the potentially life-threatening nature of GPP flares. Although baseline GPPASI, PSS, and DLQI scores were higher in the high-dose spesolimab group, indicating marginally more severe disease at random assignment, large effect sizes suggest that this imbalance is unlikely to have affected results greatly. One limitation of this study is the high representation of Asian and European participants. The racial demographics in this study are probably due to both the epidemiology of GPP and the locations in which the trial was conducted. Studies have shown that there is a higher prevalence of GPP in Asia than in Europe, with specific disease mutations focused on certain geographies.[2,12] Of the 60 study sites that randomly assigned patients, most were in Asia and Europe, with fewer sites located in Africa (Tunisia) and North and South America. The feasibility of study sites in South Africa was considered, but no patients were recruited at these sites. This study might not have fully captured the diversity of patients worldwide, but it remains the largest multinational trial in patients with GPP.

High-dose spesolimab significantly reduced the risk of flare occurrence over 48 weeks, with a reassuring safety profile. A greater proportion of patients receiving high-dose spesolimab discontinued treatment, largely due to reasons unrelated to drug treatment. Although larger trials are challenging for a disease as rare as GPP, trials of longer duration, such as the ongoing 5-year OLE trial, will further investigate the long-term efficacy and safety of spesolimab.

Contributors

All authors have made substantial contributions to this study and agreed to publish this data. AM, NH, TH, CT, and MGL accessed and verified

the underlying data reported in the manuscript. AM, ADB, SEC, MJA, SM, T-FT, MZ, NH, TH, CT, and MGL contributed to the trial concept and design. AM, SEC, SM, T-FT, and MZ contributed to the conduct of the study. NH provided statistical expertise. MGL wrote the first draft of the manuscript. AM, BS, ADB, SEC, MJA, SM, T-FT, KBG, DT, MZ, NH, TH, CT, and MGL contributed to the data interpretation, and were involved in the development, critical appraisal, and approval of all versions of the manuscript.

Declaration of interests

AM reports consulting fees from AbbVie, Boehringer Ingelheim, Nichi-Iko, Nippon Kayaku, and Novartis; grant support from AbbVie, Eisai, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Sun Pharmaceutical Industries, Torii Pharmaceutical, and Taiho Pharmaceutical; and honoraria from AbbVie, Eli Lilly Japan, Eisai, Janssen, Kyowa Kirin, Maruho, Mitsubishi Tanabe, Novartis, Pfizer Japan, Sun Pharmaceutical Industries, Taiho Pharmaceutical, Torii Pharmaceutical, and UCB Japan; and declares advisory board participation for Bristol Myers Squibb, Eli Lilly Japan, GlaxoSmithKline, Kyowa Kirin, Pfizer Japan, and UCB Japan. BS reports consulting fees from AbbVie, Alamar, Almirall, Alumis, Amgen, Arcutis, Arena, Aristea, Asana, Bristol Myers Squibb, Boehringer Ingelheim, Connect Biopharma, Dermavant, Eli Lilly, Evelo Biosciences, Immunic Therapeutics Janssen, Kangpu Pharmaceuticals, LEO Pharma, Maruho, Meiji Seika Pharma, Mindera Health, Nimbus, Novartis, Pfizer, Protagonist, Regeneron, Sanofi-Genzyme, Sun Pharmaceutical Industries, UCB, Union Therapeutics, Ventyxbio, and vTv Therapeutics; has been a speaker for AbbVie, Arcutis, Dermavant, Eli Lilly, Incyte, Janssen, Regeneron, and Sanofi-Genzyme; is a scientific co-director (receiving a consulting fee) for the CorEvitas Psoriasis Registry; is an investigator for the CorEvitas Psoriasis Registry; has stock options in Connect Biopharma and Mindera Health; and is the editor-in-chief (receiving an honorarium) of the *Journal of Psoriasis and Psoriatic Arthritis*. ADB reports consulting fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, and UCB; honoraria from Almirall and Boehringer Ingelheim; and grant support from Boehringer Ingelheim, Bristol Myers Squibb, and Novartis. SEC reports consulting fees from AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, and Novartis; honoraria from AbbVie, Boehringer Ingelheim, Janssen, and Novartis; meeting attendance support from AbbVie, Boehringer Ingelheim, and Novartis; and leadership or fiduciary roles for the International Psoriasis Council and Malaysian Skin Foundation. MJA reports consulting fees from Boehringer Ingelheim, Eli Lilly, Innovaderm, and UCB; and a leadership or fiduciary role for the Association of Professors in Dermatology. SM declares no competing interests. T-FT reports consulting fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, and Sanofi; honoraria from AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Pfizer, and UCB; meeting attendance support from Pfizer; and declares advisory board participation for AbbVie, Boehringer Ingelheim, Eli Lilly, and Pfizer. KBG reports grant support from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, and UCB; and consulting fees from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly, Janssen, LEO Pharma, Moonlake, Novartis, Pfizer, Protagonist, and UCB. DT reports grant support from LEO Pharma and Novartis; consulting fees, honoraria, or advisory board participation from AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Novartis, and Pfizer; and a leadership or fiduciary role for the German Psoriasis Patients Association. MZ reports consulting fees from AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, LEO Pharma China, Novartis, Pfizer, and Xian-Janssen. NH, TH, and CT are employees of Boehringer Ingelheim. MGL is an employee of Mount Sinai and has received research funds from AbbVie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, LEO Pharma, Incyte, Janssen Research & Development, Ortho Dermatologics, Pfizer, Regeneron, and UCB; and is a consultant for Aditum Bio, Allergan, Almirall, AltruBio, AnaptysBio, Arcutis, Aristea Therapeutics, Avotres Therapeutics, BirchBioMed, BMD Skincare, Boehringer Ingelheim, Brickell Biotech, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Celltrion, CorEvitas, Dermavant Sciences, Dr Reddy, EMD Serono, EPI, Evelo Biosciences, Evommune, Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Helsinn, Incyte, Inozyme Pharma, Kyowa Kirin, LEO Pharma, Meiji Seika Pharma, Menlo, Mindera, Mitsubishi, Neuroderm, Pfizer, Seanergy, Strata, Theravance, Trevi, and Verrica.

Data sharing

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the International Committee of Medical Journal Editors (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 https://vivli.org, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete, and other criteria are met. Please visit https://www.mystudywindow.com/msw/datasharing for further information.

Acknowledgments

The study was supported and funded by Boehringer Ingelheim. We thank Hervé Bachelez, Professor of Dermatology at the Saint-Louis University Hospital in Paris, France, Sushmita Rajeswari, at Boehringer Ingelheim, and David Hall, at Boehringer Ingelheim, for their contributions to the trial conception and design, conduct of the trial, and analysis or interpretation of the data. The authors meet criteria for authorship as recommended by the ICMJE and 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. In the preparation of this manuscript, Isabella Goldsbrough Alves, of Hyperion, OPEN Health Communications, provided medical writing, editorial support, and formatting support, which were contracted and funded by Boehringer Ingelheim.

References

1 Reisner DV, Johnsson FD, Kotowsky N, Brunette S, Valdecantos W, Eyerich K. Impact of generalized pustular psoriasis from the perspective of people living with the condition: results of an online survey. *Am J Clin Dermatol* 2022; **23** (suppl 1)**:** 65–71.
2 Choon SE, Navarini AA, Pinter A. Clinical course and characteristics of generalized pustular psoriasis. *Am J Clin Dermatol* 2022; **23** (suppl 1)**:** 21–29.
3 Kharawala S, Golembesky AK, Bohn RL, Esser D. The clinical, humanistic, and economic burden of generalized pustular psoriasis: a structured review. *Expert Rev Clin Immunol* 2020; **16:** 239–52.
4 Kromer C, Loewe E, Schaarschmidt ML, et al. Drug survival in the treatment of generalized pustular psoriasis: a retrospective multicenter study. *Dermatol Ther* 2021; **34:** e14814.
5 Iznardo H, Vilarrasa E, López-Ferrer A, Puig L. Real-world drug survival of guselkumab, ixekizumab and secukinumab for psoriasis. *Br J Dermatol* 2021; **185:** 660–62.
6 Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Rev Clin Immunol* 2019; **15:** 907–19.
7 Marrakchi S, Puig L. Pathophysiology of generalized pustular psoriasis. *Am J Clin Dermatol* 2022; **23** (suppl 1)**:** 13–19.
8 Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol* 2019; **143:** 1021–26.
9 Hussain S, Berki DM, Choon SE, et al. IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. *J Allergy Clin Immunol* 2015; **135:** 1067–1070.e9.
10 Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011; **365:** 620–28.
11 Capon F. A viewpoint on the genetic determinants of generalised pustular psoriasis. *Exp Dermatol* 2023; **32:** 1188–93.
12 Wang TS, Chiu HY, Hong JB, Chan CC, Lin SJ, Tsai TF. Correlation of IL36RN mutation with different clinical features of pustular psoriasis in Chinese patients. *Arch Dermatol Res* 2016; **308:** 55–63.
13 Liu ZJ, Tian YT, Shi BY, Zhou Y, Jia XS. Association between mutation of interleukin 36 receptor antagonist and generalized pustular psoriasis: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99:** e23068.

14 Bachelez H, Barker J, Burden AD, Navarini AA, Krueger JG. Generalized pustular psoriasis is a disease distinct from psoriasis vulgaris: evidence and expert opinion. *Expert Rev Clin Immunol* 2022; **18:** 1033–47.

15 Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J Immunol* 2018; **201:** 1605–13.

16 Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. *N Engl J Med* 2021; **385:** 2431–40.

17 US Food and Drug Administration. US FDA approves first treatment option for generalized pustular psoriasis flares in adults. 2022. https://www.boehringer-ingelheim.com/human-health/skin-diseases/fda-approves-first-gpp-flare-treatment (accessed Sept 2, 2022).

18 Boehringer Ingelheim. European Commission approves SPEVIGO (spesolimab) for generalized pustular psoriasis flares. 2022. https://www.boehringer-ingelheim.com/human-health/skin-diseases/gpp/european-commission-approves-spevigo-spesolimab-generalized (accessed Jan 31, 2023).

19 Boehringer Ingelheim. First-ever treatment aimed at alleviating acute symptoms in pustular psoriasis [media release]. 2022. https://www.boehringer-ingelheim.jp (accessed Jan 1, 2023).

20 Boehringer Ingelheim. The spesolimab injection approved for marketing. 2022. https://www.ccfdie.org/en/gzdt/webinfo/2022/12/1668877790372263.htm (accessed Feb 28, 2023).

21 Krueger J, Puig L, Thaçi D. Treatment options and goals for patients with generalized pustular psoriasis. *Am J Clin Dermatol* 2022; **23** (suppl 1)**:** 51–64.

22 Puig L, Choon SE, Gottlieb AB, et al. Generalized pustular psoriasis: a global Delphi consensus on clinical course, diagnosis, treatment goals and disease management. *J Eur Acad Dermatol Venereol* 2023; **37:** 737–52.

23 Fujita H, Terui T, Hayama K, et al. Japanese guidelines for the management and treatment of generalized pustular psoriasis: the new pathogenesis and treatment of GPP. *J Dermatol* 2018; **45:** 1235–70.

24 Robinson A, Van Voorhees AS, Hsu S, et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* 2012; **67:** 279–88.

25 Feldman S, Gao R, Bohn RL, et al. Biologic treatment adherence and persistence in patients with generalized pustular psoriasis: a real-world, claims-based study. World Congress of Dermatology; July 3–8, 2023.

26 Feldman S, Gao R, Bohn RL, et al. Treatment patterns among patients with generalized pustular psoriasis. 31st European Academy of Dermatology and Venereology Congress; Sept 7–10, 2022. Abstr 253.

27 Burden AD, Okubo Y, Zheng M, et al. Efficacy of spesolimab for the treatment of generalized pustular psoriasis flares across pre-specified patient subgroups in the Effisayil 1 study. *Exp Dermatol* 2023; **00:** 1–5.

28 Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol* 2017; **31:** 1792–99.

29 Morita A, Choon SE, Bachelez H, et al. Design of Effisayil 2: a randomized, double-blind, placebo-controlled study of spesolimab in preventing flares in patients with generalized pustular psoriasis. *Dermatol Ther (Heidelb)* 2023; **13:** 347–59.

30 Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. *J Biopharm Stat* 2006; **16:** 639–56.

31 Pinheiro J, Bornkamp B, Glimm E, Bretz F. Model-based dose finding under model uncertainty using general parametric models. *Stat Med* 2014; **33:** 1646–61.

32 Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons Inc, 1987.

33 Raghunathan TE, Lepkowski J, Van Hoewyk MJ, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol* 2001; **27:** 85–96.

34 Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. *N Engl J Med* 2019; **380:** 981–83.