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References: 1. Adtralza® SPC. **2.** Duggan S. Drugs 2021;81(14):1657–1663. **3.** Bieber T. Allergy 2020;75:54–62.

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CONCISE COMMUNICATION

Experimental Dermatology WILEY

Efficacy of spesolimab for the treatment of generalized pustular psoriasis flares across pre-specified patient subgroups in the Effisayil 1 study

A. D. Burden[1] | Y. Okubo[2] | M. Zheng[3] | D. Thaçi[4] | P. van de Kerkhof[5] | N. Hu[6] | M. Quaresma[7] | C. Thoma[8] | S. E. Choon[9]

[1]School of Infection and Immunity, University of Glasgow, Glasgow, UK

[2]Department of Dermatology, Tokyo Medical University, Tokyo, Japan

[3]Department of Dermatology, Second Affiliated Hospital, Zhejiang University, School of Medicine, Hangzhou, Zhejiang, China

[4]Institute and Comprehensive Center for Inflammation Medicine, University of Lübeck, Lübeck, Germany

[5]Department of Dermatology, Radboud University, Nijmegen, The Netherlands

[6]Boehringer Ingelheim (China) Investment Co., Ltd, Shanghai, China

[7]Boehringer Ingelheim International GmbH, Ingelheim, Germany

[8]Boehringer Ingelheim International GmbH, Biberach, Germany

[9]Department of Dermatology, Hospital Sultanah Aminah, Clinical School Johor Bahru, Monash University Malaysia, Subang Jaya, Malaysia

Correspondence
A. D. Burden, School of Infection and Immunity, University of Glasgow, Glasgow, UK.
Email: david.burden@glasgow.ac.uk

Funding information
Boehringer Ingelheim

Abstract

Effisayil 1 was a multicentre, randomized, double-blind, placebo-controlled study of the anti-interleukin (IL)-36 receptor monoclonal antibody, spesolimab, in patients presenting with a generalized pustular psoriasis (GPP) flare. Previously published data from this study revealed that within 1 week, rapid pustular and skin clearance were observed in patients receiving spesolimab versus placebo. In this pre-specified subgroup analysis, the efficacy of spesolimab was evaluated according to patient demographic and clinical characteristics at baseline in patients receiving spesolimab ($n = 35$) or placebo ($n = 18$) on Day 1. Efficacy was by assessed by achievement of primary endpoint (Generalized Pustular Psoriasis Physician Global Assessment [GPPGA] pustulation subscore of 0 at Week 1) and key secondary endpoint (GPPGA total score of 0 or 1 at Week 1). Safety was assessed at Week 1. Spesolimab was found to be efficacious and had a consistent and favourable safety profile in patients presenting with a GPP flare, regardless of patient demographics and clinical characteristics at baseline.

KEYWORDS
autoinflammatory disorders, clinical trial, psoriasis

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1 | BACKGROUND

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening skin disease characterized by recurrent flares of widespread sterile pustules, with or without systemic inflammation.[1,2] Associated with a considerable clinical burden (e.g. pain, fever, fatigue and comorbidities), GPP can greatly affect a patient's quality of life.[3,4] The clinical course of GPP is heterogeneous: It can be a relapsing disease with recurrent flares or a persistent disease with intermittent flares. Moreover, the severity of symptoms may vary by flare within individuals.[1,2] There is limited evidence regarding the efficacy and safety of current therapies, and new treatments are needed.[5]

Spesolimab, an anti-interleukin (IL)-36 receptor monoclonal antibody, was recently approved for use to treat GPP flares in adults, in the USA,[6] Europe,[7] Japan[8] and China.[9] Effisayil 1 (NCT03782792) was a multicentre, randomized, double-blind, placebo-controlled study of single-dose spesolimab (900 mg intravenously) in 53 patients presenting with a GPP flare.[10] Within 1 week, rapid pustular and skin clearance were observed in patients receiving spesolimab versus placebo: 19/35 (54.3%) versus 1/18 (5.6%), respectively, achieved the primary endpoint of a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (risk difference, 48.7%; 95% confidence interval [CI] 21.5–67.2, $p < 0.001$) and 15/35 (42.9%) versus 2/18 (11.1%), respectively, achieved the key secondary endpoint of a GPPGA total score of 0 or 1 (risk difference, 31.7%, 95% CI: 2.2–52.7, $p = 0.0118$).[10] At Week 1, 23/35 (65.7%) versus 10/18 (55.6%) patients receiving spesolimab versus placebo, respectively, experienced adverse events (AEs; severe AEs in 2/35 [5.7%] vs 1/18 [5.6%] patients, respectively).

Spesolimab is therefore proven an effective treatment for treating GPP flares, but its efficacy and safety in different subpopulations is not well characterized. The present pre-specified subgroup analysis from Effisayil 1 provides insight into the actions of spesolimab according to patient demographics and clinical characteristics at baseline.

2 | EXPERIMENTAL DESIGN

2.1 | Trial design and patient disposition

The Effisayil 1 study design has been published previously.[10,11] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines; the trial protocol was approved by ethics committees in 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 (IV) dose of spesolimab 900 mg ($n = 35$) or placebo ($n = 18$) on Day 1.[11]

Efficacy and safety were evaluated at Week 1 in patients who received single-dose spesolimab (900 mg IV) versus placebo on Day 1 in pre-specified patient subgroups that had ≥5 patients in

TABLE 1 Baseline demographics and clinical characteristics (spesolimab vs placebo).

	Spesolimab ($n = 35$)	Placebo ($n = 18$)
Age, mean (SD), years	43.2 (12.1)	42.6 (8.4)
Sex, *n* (%)		
Female	21 (60.0)	15 (83.3)
Male	14 (40.0)	3 (16.7)
Race, *n* (%)		
Asian	16 (45.7)	13 (72.2)
White	19 (54.3)	5 (27.8)
BMI, kg/m^2, mean (SD)	27.4 (7.6)	26.3 (9.6)
BMI categories, *n* (%)		
$<25\,kg/m^2$	15 (42.9)	9 (50.0)
25 to $<30\,kg/m^2$	10 (28.6)	6 (33.3)
$\geq 30\,kg/m^2$	10 (28.6)	3 (16.7)
Presence of plaque psoriasis, *n* (%)		
No	29 (82.9)	15 (83.3)
Yes	6 (17.1)	3 (16.7)
IL36RN mutation positive[a], *n* (%)		
No	21 (60.0)	11 (61.1)
Yes	8 (22.9)	6 (33.3)
GPPGA total score, *n* (%)		
3 (moderate)	28 (80.0)	15 (83.3)
4 (severe)	7 (20.0)	3 (16.7)
GPPGA pustulation subscore, *n* (%)		
2 (mild)	6 (17.1)	5 (27.8)
3 (moderate)	16 (45.7)	7 (38.9)
4 (severe)	13 (37.1)	6 (33.3)
GPPASI total score, mean (SD)	27.8 (13.4)	24.1 (15.2)
JDA GPP severity index, *n* (%)		
Mild	9 (25.7)	5 (27.8)
Moderate	19 (54.3)	8 (44.4)
Severe	4 (11.4)	4 (22.2)
Missing	3 (8.6)	1 (5.6)
Medication for GPP prior to randomization, *n* (%)[b]	18 (51.4)	9 (50.0)
Clobetasol propionate	5 (14.3)	1 (5.6)
Acitretin	4 (11.4)	1 (5.6)
Cyclosporin	2 (5.7)	3 (16.7)
Betamethasone valerate	2 (5.7)	2 (11.1)
Methotrexate	1 (2.9)	3 (16.7)
Betamethasone dipropionate	1 (2.9)	2 (11.1)
Betamethasone calcipotriol	2 (5.7)	1 (5.6)
Emulsifying wax; paraffin, liquid, white soft paraffin	1 (2.9)	2 (11.1)

Abbreviations: BMI, body mass index; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment, JDA, Japanese Dermatological Association; SD, standard deviation.

[a]Genotyping data were available for 46 patients. DNA sequencing was not performed in seven patients. Patients who were homozygous or heterozygous for an *IL36RN* mutation were considered to be positive.

[b]Background medication for GPP in ≥3 patients of the overall population (see Table S1. 'Medication for GPP prior to randomization' for full list).

≥2 categories. Subgroups included: sex (male/female), race (Asian/White), body mass index (BMI; <25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2), presence of plaque psoriasis at baseline (no/yes), *IL36RN* mutation status (no/yes), GPPGA total score (3/4), GPPGA pustulation subscore (<4/4), GPPASI total score (below or above median at baseline; ≤27.2, >27.2), Japanese Dermatological Association (JDA) GPP severity index (mild/moderate or severe) and background medication for GPP before randomization (no/yes). Efficacy was assessed in these subgroups by achievement of the primary endpoint (GPPGA pustulation subscore of 0 at Week 1) and key secondary endpoint (GPPGA total score of 0 or 1 at Week 1). Missing values or any use of other medication for GPP within the first week of the trial were regarded as non-response for the analysis of these endpoints.

2.2 | Statistical analysis

Descriptive statistics (including mean and standard deviation [SD]) were generated for all demographic data and clinical characteristics. Risk difference between spesolimab versus placebo in subgroups was performed, with 95% CIs calculated using the method of Chan and Zhang.[12] Subgroup analysis by age category was not performed as only two patients were aged ≥65 years. Patients who were homozygous or heterozygous for an *IL36RN* mutation were considered to be positive.

3 | RESULTS

In the placebo arm, there were more female and Asian patients than in the spesolimab arm (83% vs 60% respectively, and 72% vs 46%, respectively); aside from these, clinical characteristics across the subgroups were generally balanced between study arms (Table 1). The most common background medications used for GPP before randomization in patients assigned to spesolimab and placebo, respectively, included clobetasol propionate (14.3% and 5.6%), cyclosporin (5.7% and 16.7%) and methotrexate (2.9% and 16.7%), which were to be discontinued at randomization (i.e. when patients experienced a GPP flare despite receiving these treatments; see Table S1.).

At Week 1, the overall risk difference for spesolimab versus placebo for a GPPGA pustulation subscore of 0 was 0.487 (95% confidence interval [CI] 0.215–0.672), and for a GPPGA total score of 0 or 1, it was 0.317 (95% CI 0.022–0.527). For the primary endpoint (Figure 1A) and key secondary endpoint (Figure 1B), the efficacy of spesolimab was consistent across all the patient subgroups analysed, with most risk differences lying within the overall 95% CI. The subgroups lying on or above the upper 95% CI limit had small group sizes, which limited statistical analysis: Four patients receiving spesolimab and four receiving placebo with severe JDA GPP severity index at baseline, and eight patients receiving spesolimab and six receiving placebo with *IL36RN* mutations. Regardless of the limited

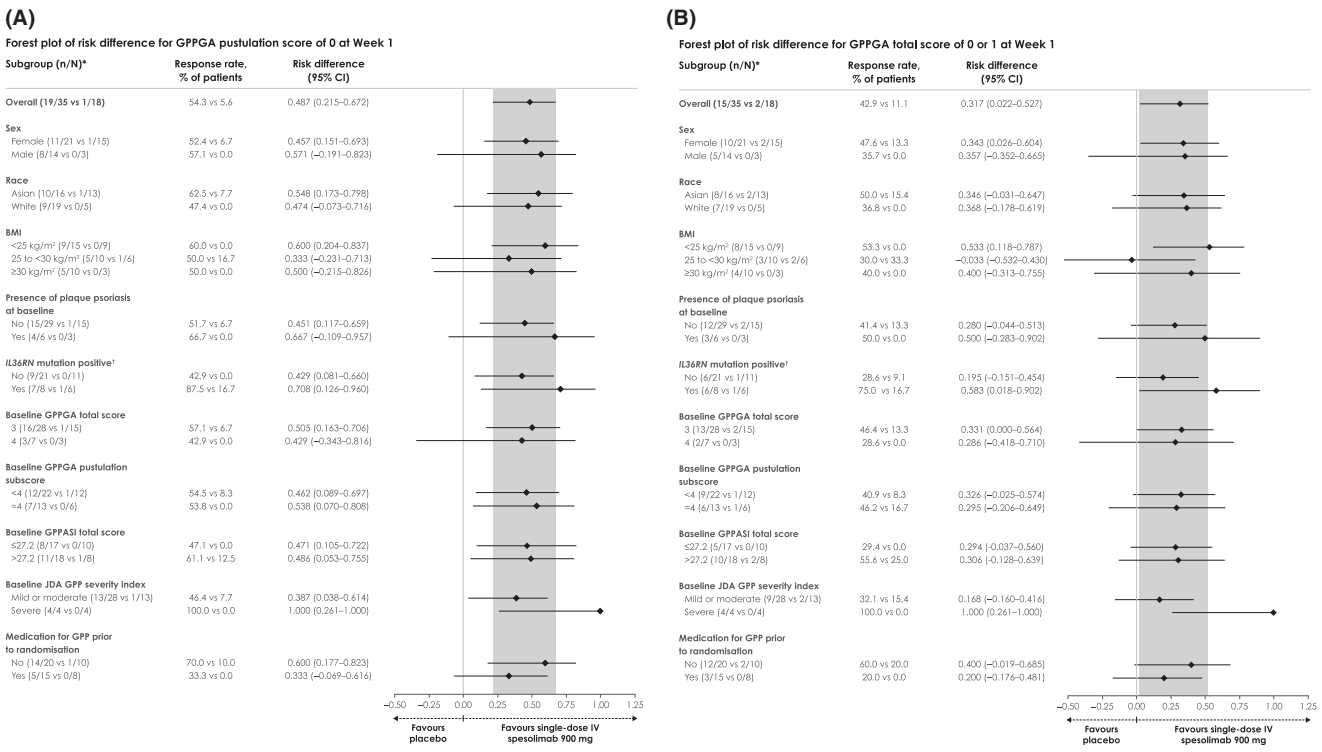

FIGURE 1 Subgroup analysis of (A) GPPGA pustulation subscore of 0 at Week 1 and (B) GPPGA total score of 0 or 1 at Week 1 (spesolimab vs placebo). 95% CIs were calculated using the method of Chan and Zhang.[12] *Single-dose IV spesolimab 900 mg vs placebo; subgroup analysis by age was not performed as only two patients were aged ≥65 years; †Patients who were homozygous or heterozygous for an *IL36RN* mutation were considered to be positive. BMI, body mass index; CI, confidence interval; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; JDA, Japanese Dermatological Association.

sample sizes, treatment effects were observed in all pre-specified subgroups in a positive trend, with a large overlap in CIs. Up to Week 1, similar proportions of patients across subgroups experienced AEs, and few reported severe AEs, with differences possibly due to small group sizes for some subgroups (Table S2.). Images and corresponding GPPGA scores for two patients, with and without *IL36RN* mutations, before and after treatment with spesolimab are shown in Figure S1.

4 | CONCLUSIONS AND PERSPECTIVES

The efficacy (pustular and skin clearance) and safety of spesolimab compared with placebo were consistent across all pre-specified subgroups that were analysed, and estimates of spesolimab treatment effect in each patient subgroup were generally similar to those in the overall population for both the primary endpoint and key secondary endpoint.[10] However, several subgroups had very few patients, thereby limiting the strength of statistical analyses, and patients aged <18 years or >75 years were excluded from the study. Furthermore, analysis was limited to the achievement of study endpoints at Week 1, with no long-term assessment of subgroups regarding the maintenance of treatment response.

GPP is a rare disorder and is more prevalent in women, and in certain geographies.[13] As noted in the primary Effisayil 1 study,[10] at trial initiation prevalence estimates indicated that GPP was five times more common in Asia than in Europe and the USA. Therefore, an unavoidable limitation of this subgroup analysis is that we see more Asian patients, less White patients and no Black patients in this study.

In conclusion, spesolimab is efficacious and has a consistent and favourable safety profile in patients presenting with a GPP flare, regardless of baseline sex, race, BMI, GPPGA total score, GPPGA pustulation subscore, GPPASI total score, JDA GPP severity index, presence of plaque psoriasis at baseline, background medication before randomization and *IL36RN* mutation status.

AUTHOR CONTRIBUTIONS

ADB, YO, MZ, NH, CT and SEC contributed to the design of the trial. NH provided statistical expertise. All authors were involved in the analysis and/or interpretation of the data and contributed to drafting the manuscript and critically revised and commented on its previous versions and the final version. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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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: 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 Medical & Clinical Trials | Clinical Research | MyStudyWindow: https://www.mystudywindow.com/msw/datasharing for further information.

ORCID

A. D. Burden https://orcid.org/0000-0001-7395-9931

Y. Okubo https://orcid.org/0000-0002-9526-1259
D. Thaçi https://orcid.org/0000-0001-8513-550X
P. van de Kerkhof https://orcid.org/0000-0003-0084-3131
C. Thoma https://orcid.org/0000-0002-0967-2028
S. E. Choon https://orcid.org/0000-0002-7796-5746

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SUPPORTING INFORMATION

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

Figure S1.
Table S1.
Table S2.

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