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Effisayil™ 1: A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and tolerability of spesolimab in patients with a generalized pustular psoriasis flare

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Background

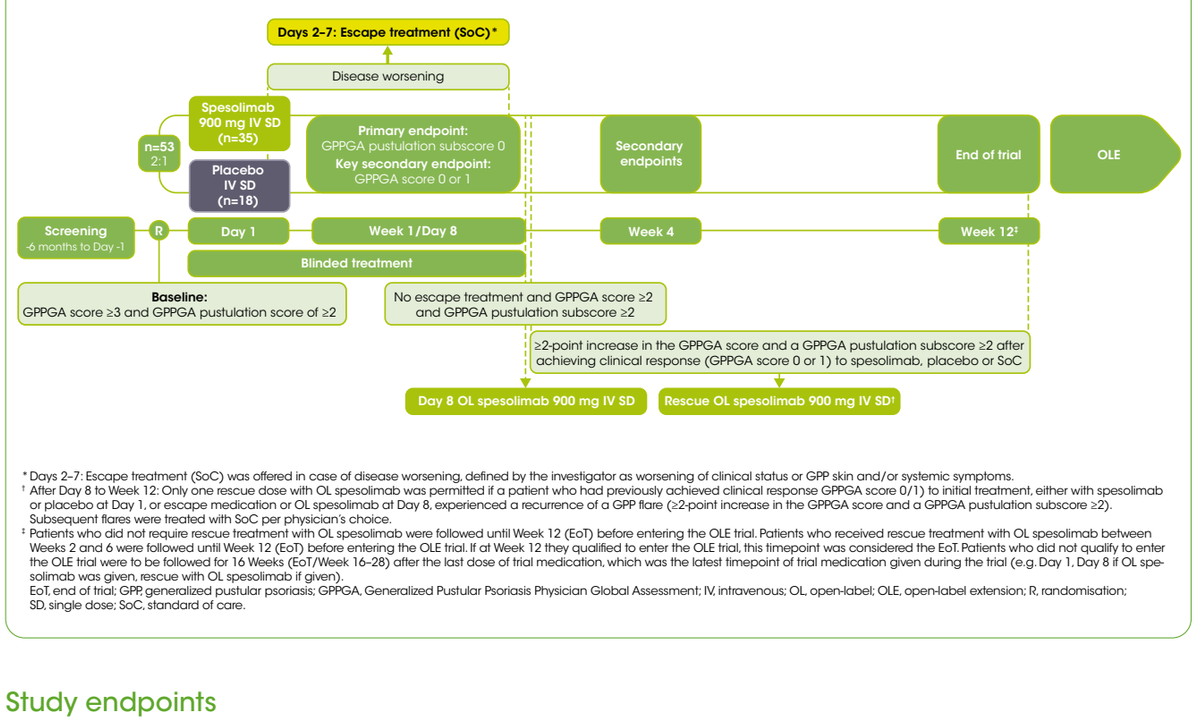
- Generalized pustular psoriasis (GPP) is a rare, neutrophilic, autoinflammatory skin disease characterised by abrupt episodes of widespread sterile, macroscopic pustules that can occur with or without systemic inflammation[1,2]
- GPP flares can be life-threatening and are typically accompanied by systemic symptoms, such as pain, fever, malaise and fatigue, having a high clinical burden and severely impacting patient quality of life[2,3]
- Dysregulation of the interleukin (IL)-36 pathway is central to the pathogenesis of GPP[4]
- Here, we report results from the Phase II Effisayil™ 1 study, investigating, for the first time, the efficacy and safety of spesolimab versus placebo within 1 week and the sustained effects of spesolimab, a humanised anti-IL-36R monoclonal antibody, in patients presenting with a GPP flare

Methods and analysis

Study design

- This global, Phase II, multicentre, randomised, double-blind, placebo-controlled trial (Effisayil™ 1) was conducted between February 2019 and January 2021, at 37 sites in 12 countries (ClinicalTrials.gov identifier: NCT03782792)
- Eligible patients (aged 18–75 years) with GPP (defined by the European Rare And Severe Psoriasis Expert Network [ERASPEN][1] at screening) and presenting with a flare of moderate-to-severe intensity (a Generalized Pustular Psoriasis Physician Global Assessment [GPPGA] score ≥3 [moderate], new appearance or worsening of pustules, a GPPGA pustulation subscore ≥2 and ≥5% body surface area with erythema and the presence of pustules) were randomly assigned (2:1) to receive a single intravenous (IV) dose of 900 mg spesolimab or placebo on Day 1 and followed for 12 weeks (**Figure 1**)
  - On Day 8, patients were eligible to receive an open-label, single IV dose of 900 mg spesolimab if they had a GPPGA score ≥2 and GPPGA pustulation subscore ≥2 at Week 1
  - Patients who achieved clinical improvement and completed the trial without flare symptoms were eligible to enter the 5-year open-label extension trial (ClinicalTrials.gov identifier: NCT03886246)

Figure 1. Effisayil™ 1 study design



* Days 2–7: Escape treatment (SoC) was offered in case of disease worsening, defined by the investigator as worsening of clinical status or GPP skin and/or systemic symptoms.
† After Day 8 to Week 12: Only one rescue dose with OL spesolimab was permitted if a patient who had previously achieved clinical response GPPGA score 0/1) to initial treatment, either with spesolimab or placebo at Day 1, or escape medication or OL spesolimab at Day 8, experienced a recurrence of a GPP flare (≥2-point increase in the GPPGA score and a GPPGA pustulation subscore ≥2). Subsequent flares were treated with SoC per physician's choice.
‡ Patients who did not require rescue treatment with OL spesolimab were followed until Week 12 (EoT) before entering the OLE trial. Patients who received rescue treatment with OL spesolimab between Weeks 2 and 6 were followed until Week 12 (EoT) before entering the OLE trial. If at Week 12 they qualified to enter the OLE trial, this timepoint was considered the EoT. Patients who did not qualify to enter the OLE trial were to be followed for 16 Weeks (EoT/Week 16–28) after the last dose of trial medication, which was the latest timepoint of trial medication given during the trial (e.g. Day 1, Day 8 if OL spesolimab was given, rescue with OL spesolimab if given).
EoT, end of trial; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; OL, open-label; OLE, open-label extension; R, randomisation; SD, single dose; SoC, standard of care.

Study endpoints

- The primary endpoint was a GPPGA pustulation subscore of 0 (pustular clearance) at Week 1; the key secondary endpoint was a GPPGA total score of 0 or 1 (clear or almost clear skin) at Week 1
  - The GPPGA is a clinician assessment of overall GPP severity based on a modified Physician Global Assessment (PGA)[5]; Erythema, pustules and scaling of all psoriatic lesions are scored from 0 (least severe) to 4 (most severe)
- Secondary endpoints at Week 4 included a >75% improvement in Generalized Pustular Psoriasis Area and Severity Index (GPPASI 75), and change from baseline in pain visual analogue scale (VAS), Psoriasis Symptom Scale (PSS) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores
- Safety endpoints at Week 1 and through 12 weeks included the occurrence of treatment-emergent adverse events (AEs) and serious AEs (SAEs)

Statistical analyses

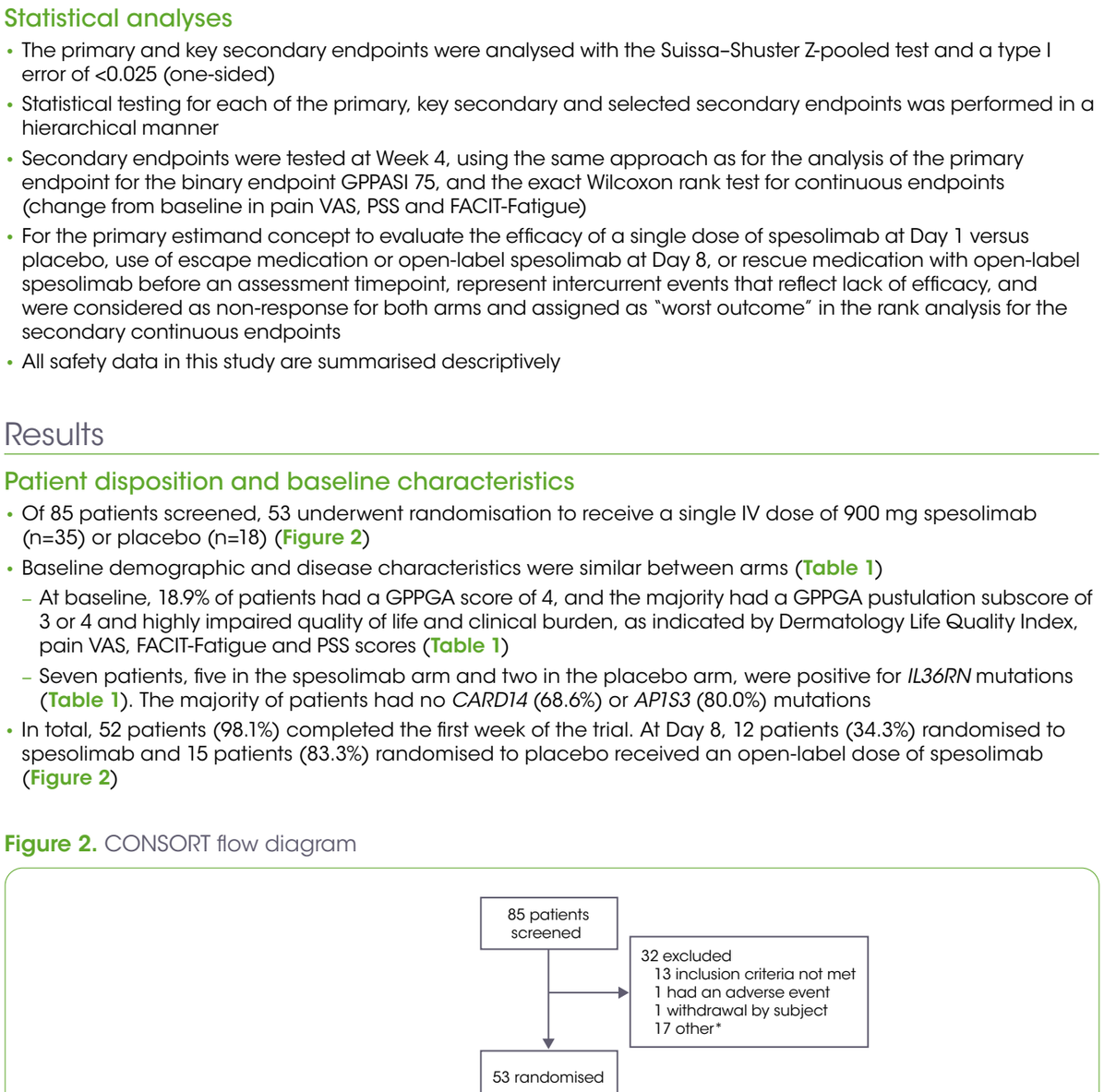
- The primary and key secondary endpoints were analysed with the Suissa–Shuster Z-pooled test and a type I error of <0.025 (one-sided)
- Statistical testing for each of the primary, key secondary and selected secondary endpoints was performed in a hierarchical manner
- Secondary endpoints were tested at Week 4, using the same approach as for the analysis of the primary endpoint for the binary endpoint GPPASI 75, and the exact Wilcoxon rank test for continuous endpoints (change from baseline in pain VAS, PSS and FACIT-Fatigue)
- For the primary estimand concept to evaluate the efficacy of a single dose of spesolimab at Day 1 versus placebo, use of escape medication or open-label spesolimab at Day 8, or rescue medication with open-label spesolimab before an assessment timepoint, represent intercurrent events that reflect lack of efficacy, and were considered as non-response for both arms and assigned as "worst outcome" in the rank analysis for the secondary continuous endpoints
- All safety data in this study are summarised descriptively

Results

Patient disposition and baseline characteristics

- Of 85 patients screened, 53 underwent randomisation to receive a single IV dose of 900 mg spesolimab (n=35) or placebo (n=18) (**Figure 2**)
- Baseline demographic and disease characteristics were similar between arms (**Table 1**)
  - At baseline, 18.9% of patients had a GPPGA score of 4, and the majority had a GPPGA pustulation subscore of 3 or 4 and highly impaired quality of life and clinical burden, as indicated by Dermatology Life Quality Index, pain VAS, FACIT-Fatigue and PSS scores (**Table 1**)
  - Seven patients, five in the spesolimab arm and two in the placebo arm, were positive for *IL36RN* mutations (**Table 1**). The majority of patients had no *CARD14* (68.6%) or *AP1S3* (80.0%) mutations
- In total, 52 patients (98.1%) completed the first week of the trial. At Day 8, 12 patients (34.3%) randomised to spesolimab and 15 patients (83.3%) randomised to placebo received an open-label dose of spesolimab (**Figure 2**)

Figure 2. CONSORT flow diagram



* Exclusion by other included trial completion, global recruitment target achieved and patients who did not present with a flare within the 6-month screening period.
† Patients were blinded to randomised treatment, but could be eligible to an open-label dose of spesolimab at Day 8.
‡ Patients who did not continue in the OLE trial were to be followed for 16 weeks after the last dose of trial medication, which was the latest timepoint of trial medication given during the trial (e.g. Day 1, Day 8 if open-label spesolimab was given, rescue with open-label spesolimab if given).
OLE, open-label extension; SoC, standard of care.

Table 1. Baseline demographics and disease characteristics

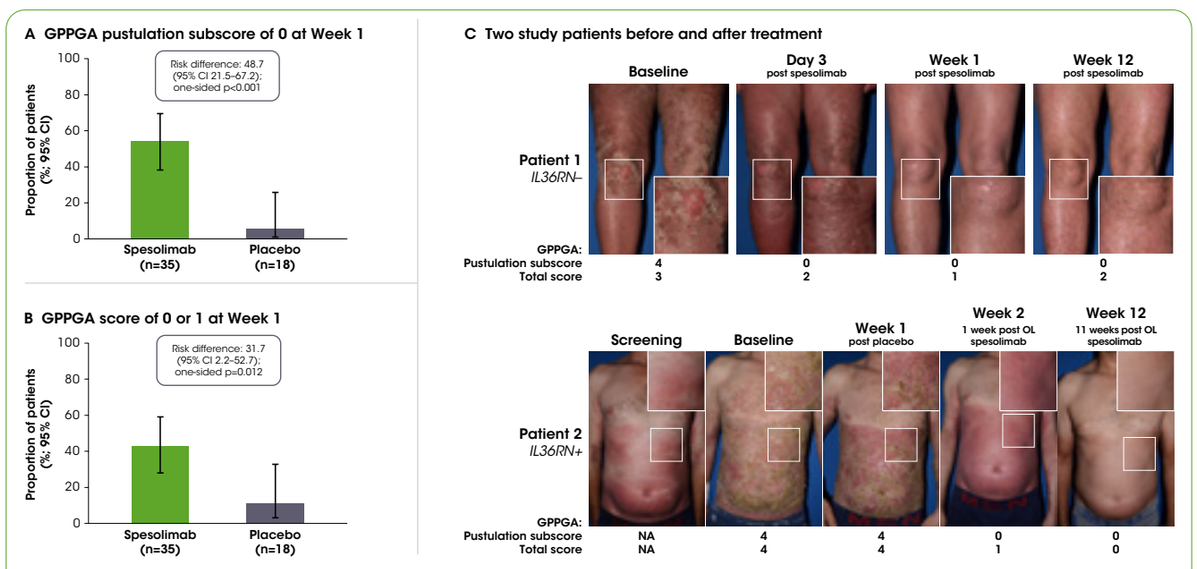
Characteristic	Spesolimab (n=35)	Placebo (n=18)	Total (N=53)
Mean age (SD), years	43.2 (12.1)	42.6 (8.4)	43.0 (10.9)
Mean weight (SD), kg	73.7 (24.0)	68.8 (26.6)	72.0 (24.7)
Female, n (%)	21 (60.0)	15 (83.3)	36 (67.9)
Asian race,* n (%)	16 (45.7)	13 (72.2)	29 (54.7)
White race,* n (%)	19 (54.3)	5 (27.8)	24 (45.3)
Baseline CRP, n (%)†			
≥3 mg/L and <70 mg/L	20 (58.8)	12 (66.7)	32 (61.5)
≥70 mg/L	11 (31.4)	4 (22.2)	15 (28.3)
GPPGA total score, n (%)			
3	28 (80.0)	15 (83.3)	43 (81.1)
4	7 (20.0)	3 (16.7)	10 (18.9)
GPPGA pustulation subscore, n (%)			
2	6 (17.1)	5 (27.8)	11 (20.8)
3	16 (45.7)	7 (38.9)	23 (43.4)
4	13 (37.1)	6 (33.3)	19 (35.8)
Median GPPASI total score (IQR)	27.4 (15.5–36.8)	20.9 (12.0–32.0)	27.2 (15.4–36.1)
IL36RN mutation, n (%)			
Yes	5 (14.3)	2 (11.1)	7 (13.2)
No	24 (68.6)	12 (66.7)	36 (67.9)
Median DLQI score (IQR)	19.5 (16.0–25.0)	19.5 (14.0–24.0)	19.5 (15.5–25.0)
Median PSS score (IQR)	11.0 (9.0–12.0)	10.5 (9.0–11.0)	11.0 (9.0–12.0)
Median pain VAS score (IQR)	79.8 (70.5–87.8)	70.0 (50.0–89.4)	77.9 (60.6–87.8)
Median FACIT-Fatigue (IQR)	14.0 (7.0–28.0)	18.0 (6.0–33.0)	15.0 (7.0–28.0)

*Race was reported by the patient.
†A total of 52 patients were included; five patients had missing values at baseline.
CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; FACIT, Functional Assessment of Chronic Illness Therapy; GPPASI, Generalized Pustular Psoriasis Area and Severity Index; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IQR, interquartile range; PSS, Psoriasis Symptom Scale; SD, standard deviation; VAS, visual analogue scale.

Primary and secondary efficacy endpoints

- At Week 1, 19 patients (54.3%) receiving spesolimab versus one patient (5.6%) receiving placebo achieved a GPPGA pustulation subscore of 0; (risk difference: 48.7%; 95% confidence interval [CI] 21.5–67.2; one-sided p<0.001) (**Figure 3A**)
- A GPPGA score of 0 or 1 at Week 1 was achieved by 15 patients (42.9%) receiving spesolimab versus two patients (11.1%) receiving placebo (risk difference: 31.7%; 95% CI 2.2–52.7; one-sided p=0.012) (**Figure 3B**)
- Clinical responses were observed regardless of *IL36RN* mutation status (**Figure 3C**)

Figure 3. Primary and key secondary efficacy outcomes



A. Primary endpoint, GPPGA pustulation subscore of 0 at Week 1. **B.** Key secondary endpoint, GPPGA total score of 0 or 1. **C.** Photographic examples of improvements for two patients with GPP; the images were taken at screening, baseline (before treatment) and at each visit thereafter: one patient was *IL36RN* mutation negative and was randomised to spesolimab (Patient 1, upper row) and the other was *IL36RN* mutation positive and was randomised to placebo (Patient 2, bottom row).
CI, confidence interval; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Global Assessment; NA, not applicable; OL, open-label.

- At Week 4, 16 patients (45.7%) randomised to spesolimab achieved a GPPASI 75 versus two patients (11.1%) randomised to placebo (risk difference: 34.6%; 95% CI 5.8–55.4; one-sided p=0.008)
  - Patient-reported outcomes including, pain VAS, PSS and FACIT-Fatigue were also significantly improved with spesolimab versus placebo at Week 4
- In patients who received up to two doses of spesolimab, improvements in clinical and patient-reported outcomes were maintained through 12 weeks

Safety

- After 1 week, AEs were reported in 65.7% of patients with spesolimab and 55.6% with placebo. SAEs were reported in 5.7% of patients in the spesolimab arm and no patients in the placebo arm (**Table 2**)
- At Week 12, 82.4% of patients randomised to spesolimab, including those who received a second spesolimab dose at Day 8 and those initially randomised to placebo, had an AE; 11.8% had an SAE (**Table 2**)
  - Symptoms observed in two patients receiving spesolimab were reported as drug reactions with eosinophilia and systemic symptoms, with RegiSCAR scores[5] ≤3 and in close temporal relationship to the reported GPP flares, which was 2 days after treatment in one case. In the other case, similar cutaneous symptoms reoccurred after re-administration with spiramycin, suggesting spiramycin as an alternative explanation. Both patients recovered
- After one week, infections were reported in 17.1% and 5.6% of patients in the spesolimab and placebo arms, respectively. All infections were mild to moderate in intensity

Table 2. AE summary*

n (%) [rate/100 patient-years]	Week 1		Week 12†
	Spesolimab (n=35)	Placebo (n=18)	Spesolimab (n=51)
Any AE	23 (65.7) [5874.7]	10 (55.6) [4623.4]	42 (82.4) [981.5]
Severe AE (RCTC grade 3 or 4)	2 (5.7) [309.5]	1 (5.6) [304.4]	5 (9.8) [40.9]
Investigator-defined drug-related AE	10 (28.6) [1747.6]	5 (27.8) [1773.1]	28 (54.9) [353.5]
Serious AE	2 (5.7) [309.5]	0	6 (11.8) [49.7]
Death	0	0	0
AE leading to treatment discontinuation	0	0	0
Common AE‡			
Pyrexia	2 (5.7) [313.5]	4 (22.2) [1404.8]	5 (9.8) [41.3]
Dizziness	0	2 (11.1) [619.1]	0

* All AEs occurring between start of treatment and end of the residual effect period (16 weeks after the last dose of trial) were considered "treatment-emergent". AEs were coded using the Medical Dictionary for Drug Regulatory Activities version 23.1. and AE severity was graded according to the RCTC version 2.0 safety analysis set. Pustular psoriasis was excluded as an AE from this safety analysis.
†Dataset at Week 12 includes patients randomised to spesolimab who received up to three doses of spesolimab, including 12 patients who received open-label spesolimab at Day 8. All AEs in the residual effect period are included but censored at the day rescue treatment with spesolimab was administered.
‡Common AEs are reported in ≥10% of patients in any treatment group.
AE, adverse event; RCTC, Rheumatology Common Toxicity Criteria.

Discussion

- Effisayil™ 1 is the first randomised, placebo-controlled study in patients with GPP
- Spesolimab treatment of GPP flares was associated with rapid pustular and skin clearance within 1 week, which were sustained during the 12-week study duration
- Pustular and skin clearance were accompanied by clinically significant improvements in quality of life and symptoms, such as pain, psoriasis symptoms and fatigue
- The overall safety profile for spesolimab was acceptable, with overall AE rates generally comparable between spesolimab and placebo groups
- Long-term administration of spesolimab is being evaluated with a subcutaneous formulation in an ongoing 5-year open-label extension study (ClinicalTrials.gov identifier: NCT03886246) and for the prevention of flares in the Effisayil™ 2 study (ClinicalTrials.gov identifier: NCT04399837)

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