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Effect of the presence or absence of genetic mutations on spesolimab efficacy in patients with generalized pustular psoriasis (GPP)

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Spesolimab achieved rapid and sustained pustular and skin clearance in patients with and without an *IL36RN* mutation; the safety profile for spesolimab was also similar regardless of mutation status

PURPOSE

To explore whether patients with or without an *IL36RN* mutation, or any genetic mutation (*IL36RN*, *CARD14*, or *AP1S3*), had the same treatment effect with spesolimab versus placebo.

INTRODUCTION

- GPP is a rare and potentially life-threatening skin disease, with flares characterised by the eruption of neutrophilic pustules, with or without systemic inflammation[1,2]
- GPP is associated with homozygous and heterozygous loss-of-function mutations in the *IL36RN* gene, encoding the interleukin-36 receptor (IL-36R) antagonist, found in:
  - 21–24% of overall GPP cases worldwide[3,4]
  - Up to 82% of cases without plaque psoriasis[5,6]
- Other mutations associated with GPP are *CARD14* and *AP1S3* (~11% and ~3% of cases, respectively)[4]
- The Effisayil 1 study (NCT03782792) evaluated the efficacy and safety of the anti-IL-36R monoclonal antibody spesolimab in patients with a GPP flare[7,8]

CONCLUSIONS

- Patients treated with spesolimab achieved rapid and sustained pustular and skin clearance, regardless of mutation status
- Among patients randomised to placebo, improvements in GPPGA scores were seen in patients with and without an *IL36RN* mutation after OL spesolimab treatment
- A high proportion of patients with an *IL36RN* mutation achieved the primary endpoint
- The safety profile of spesolimab was similar in patients with and without an *IL36RN* mutation
- Our findings support the use of spesolimab as a treatment for patients with GPP irrespective of *IL36RN* mutation status

METHODS

- In the Effisayil 1 study, 53 patients received a single 900 mg IV dose of spesolimab or placebo on Day 1, and an optional dose of open-label spesolimab for persistent flare symptoms on Day 8[7]
- GPPGA scores were assessed on Days 2–3, and Weeks 1–4, 8 and 12
  - Primary and key secondary endpoints were defined as a GPPGA pustulation score of 0, and a GPPGA total score of 0 or 1, respectively, at Week 1
- Targeted DNA resequencing was performed to determine patients' mutational status for *IL36RN, CARD14,* and *AP1S3*
- In this subgroup analysis, efficacy and safety of spesolimab was evaluated in patients by the presence or absence of an *IL36RN* mutation
  - As analyses for any mutation (*IL36RN, CARD14,* or *AP1S3*) only included 4 additional patients, we present data for the *IL36RN* mutation subgroup only; similar results were observed for the any mutation subgroup analysis

RESULTS

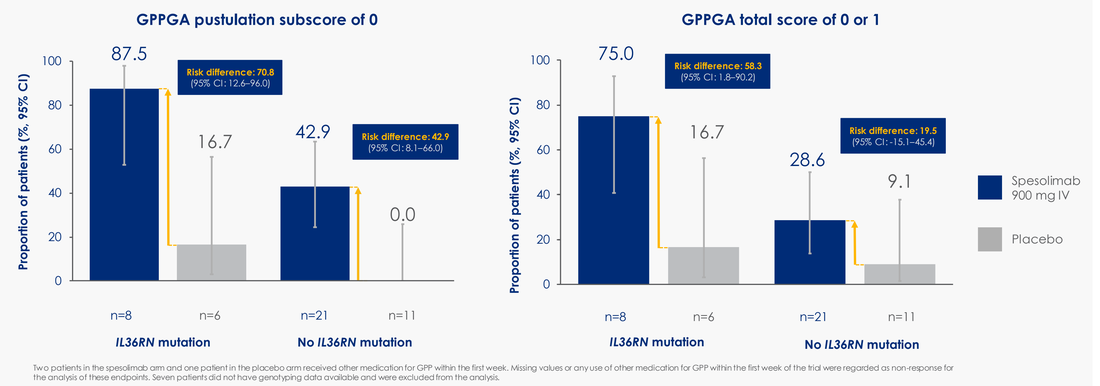
Baseline demographics and clinical characteristics

Characteristic	No *IL36RN* mutation (n=32)	*IL36RN* mutation (n=14)	No *IL36RN*, *CARD14*, or *AP1S3* mutation (n=28)	*IL36RN*, *CARD14*, or *AP1S3* mutation (n=18)
Mean age (SD), years	42.0 (9.8)	46.6 (10.4)	41.9 (9.8)	45.8 (10.2)
Mean age at onset of GPP (SD), years	33.6 (15.9)	21.1 (17.2)	NA	NA
Sex, n (%)				
Male	10 (31.3)	3 (21.4)	8 (28.6)	5 (27.8)
Female	22 (68.6)	11 (78.6)	20 (71.4)	13 (72.2)
Mean BMI (SD), kg/m²	27.7 (9.2)	25.4 (5.6)	28 (9.7)	25 (5.2)
Race, n (%)				
Asian	18 (56.3)	7 (50.0)	18 (64.3)	7 (38.9)
White	14 (43.8)	7 (50.0)	10 (35.7)	11 (61.1)
Presence of *IL36RN* mutation, n (%)	0	14 (100.0)	0	14 (77.8)
Presence of *AP1S3* mutation, n (%)	0	1 (7.1)	0	1 (5.6)
Presence of *CARD14* mutation, n (%)	4 (12.5)	1 (7.1)	0	5 (27.8)
GPPGA total score, n (%)				
3	27 (84.4)	10 (71.4)	24 (85.7)	13 (72.2)
4	5 (15.6)	4 (28.6)	4 (14.3)	5 (27.8)
GPPGA pustulation subscore, n (%)				
2	6 (18.8)	3 (21.4)	5 (17.9)	4 (22.2)
3	15 (46.9)	5 (35.7)	14 (50.0)	6 (33.3)
4	11 (34.4)	6 (42.9)	9 (32.1)	8 (44.4)
GPPASI total score, median (range)	20.1 (5.2–54.2)	28.4 (6.6–68.8)	18.9 (5.2–54.2)	29.5 (6.6–68.8)
Hospitalised for current flare, n (%)	12 (37.5)	7 (50.0)	8 (28.6)	11 (61.1)

Data for each subgroup include both treatment arms.
Of 53 patients enrolled, 46 had genotyping data available. Of the 14 patients with an *IL36RN* mutation, 10 had a homozygous mutation and 4 had a heterozygous mutation.

Patients with a genetic mutation had an earlier age at onset of GPP, higher GPPGA and GPPASI total scores at baseline and were more likely to be hospitalised for their current flare

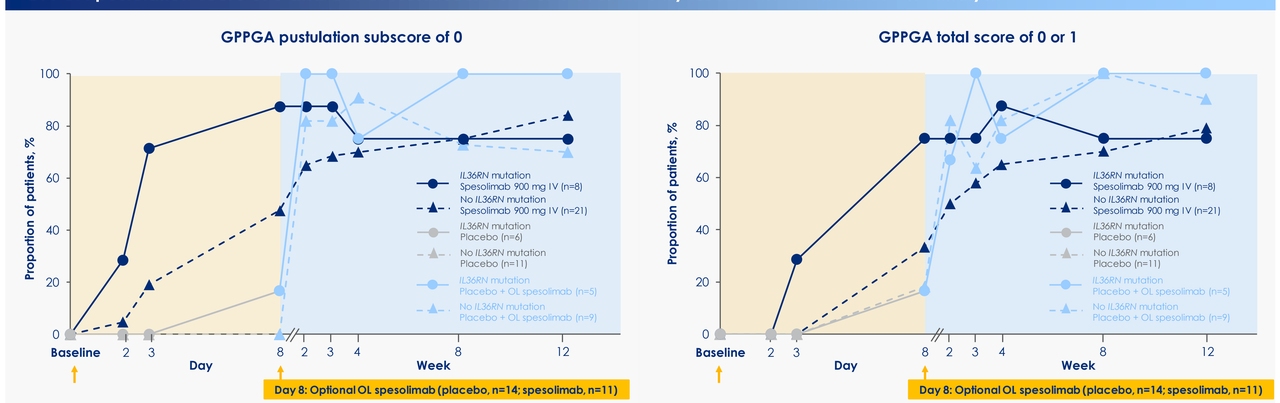
Proportion of patients who achieved the primary and key secondary endpoint by *IL36RN* mutation status at Week 1



Two patients in the spesolimab arm and one patient in the placebo arm received other medication for GPP within the first week. 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. Seven patients did not have genotyping data available and were excluded from the analysis.

Although based on a small sample size, a high proportion of patients with an *IL36RN* mutation met the primary (7 of 8 patients) and key secondary endpoints (6 of 8 patients)

GPPGA pustulation score of 0 and GPPGA total score of 0 or 1 over time by *IL36RN* mutation status – ITT analysis*



*ITT: observed cases regardless of use of any other medication for GPP or any additional dose of spesolimab. Among 29 patients randomised to spesolimab, OL spesolimab was received by 11 patients at Day 8 due to persistent flare symptoms and by 4 patients after Day 8 due to a new flare. Among 17 patients randomised to placebo, OL spesolimab was received by 14 patients at Day 8 due to persistent flare symptoms and by 2 patients after Day 8 due to a new flare. Two patients in the spesolimab arm and one patient in the placebo arm received other medication for GPP within the first week.

Patients treated with spesolimab had sustained pustular clearance and clear/almost clear skin over 12 weeks, regardless of *IL36RN* mutation status; following treatment with OL spesolimab at Day 8, similar treatment effects were observed in patients in the placebo arm, regardless of *IL36RN* mutation status

Safety at Week 1 according to *IL36RN* mutation status

Parameter, n (%)	No *IL36RN* mutation		*IL36RN* mutation	
	Spesolimab (n=21)	Placebo (n=11)	Spesolimab (n=8)	Placebo (n=6)
Patients with any AE	13 (61.9)	5 (45.5)	5 (62.5)	4 (66.7)
Patients with severe AEs*	1 (4.8)	1 (9.1)	1 (12.5)	0
Patients with investigator-defined drug-related AE	5 (23.8)	1 (9.1)	1 (12.5)	3 (50.0)
Patients with serious AEs	1 (4.8)	0	1 (12.5)	0
Common AEs†				
Pyrexia	1 (4.8)	1 (9.1)	0	2 (33.3)
Headache	3 (14.3)	0	0	1 (16.7)
Dizziness	0	2 (18.2)	0	0
Anaemia	1 (4.8)	0	0	1 (16.7)
Myalgia	1 (4.8)	0	0	1 (16.7)
Pain in extremity	1 (4.8)	0	0	1 (16.7)
Asthenia	0	0	1 (12.5)	1 (16.7)
Streptococcal infection	0	0	0	1 (16.7)
Erythropenia	0	0	0	1 (16.7)
Decreased appetite	0	0	0	1 (16.7)
Hypotension	0	0	0	1 (16.7)
Cough	0	0	0	1 (16.7)
Allergic dermatitis	0	0	0	1 (16.7)

*Severe AEs were defined as those with a Rheumatology Common Toxicity Criteria (RCTC) grade 3 or 4. †Common AEs were those occurring in ≥15% of patients in any subgroup. With regard to serious adverse events, of the patients with no *IL36RN* mutation, 1 patient in the spesolimab arm had a urinary tract infection, drug-induced liver injury, and a drug reaction with eosinophilia and systemic symptoms. Of the patients with an *IL36RN* mutation, 1 patient in the spesolimab arm had arthritis.

A similar proportion of patients in each subgroup and treatment arm reported AEs; the most commonly reported AEs were pyrexia and headache

Abbreviations

AE, adverse event; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DLQI, dermatology life quality index; FACIT, functional assessment of chronic illness therapy; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; GPPASI, Generalized Pustular Psoriasis Area and Severity Index; ICU, intensive care unit; ITT, intention-to-treat; IV, intravenous; JDA, Japanese Dermatological Association; NA, not assessed; OL, open label; PsO, psoriasis; PSS, psoriasis symptom scale; US, United States; VAS, visual analogue scale; WBC, white blood cells.

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