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Characterisation of the immunogenicity of spesolimab in patients with a generalized pustular psoriasis (GPP) flare

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Treatment with spesolimab led to the development of ADAs with a maximum titre of >4000 in a limited proportion of patients. Efficacy and safety of spesolimab were similar regardless of the presence of ADAs

PURPOSE

To investigate the immunogenicity of spesolimab and its impact on PKs, efficacy and safety in patients with a GPP flare.

INTRODUCTION

- Spesolimab is a humanised IgG1 mAb that blocks agonists binding to IL-36R, preventing downstream activation of pro-inflammatory cytokines, which drive pathogenesis in GPP[1]
- The efficacy of spesolimab in achieving rapid and sustained pustular and skin clearance has been demonstrated in patients presenting with a GPP flare in the pivotal Effisayil™ 1 study:[2]
  - The primary endpoint (GPPGA pustulation subscore of 0 at Week 1) was achieved by 54% of patients receiving spesolimab vs 6% receiving placebo (two-sided p<0.001)
  - The key secondary endpoint (GPPGA total score of 0 or 1 at Week 1) was achieved by 43% of patients receiving spesolimab vs 11% receiving placebo (two-sided p=0.02)
- While inhibition of IL-36 signalling by spesolimab was expected to rapidly downregulate innate responses,[1,3] the immunogenicity profile of spesolimab remains largely unknown

CONCLUSIONS

- Data from spesolimab-treated patients across three clinical trials provide evidence that:
  - NAbs were associated with ADA titre; all positive ADAs with titre >4000 were also neutralising
  - The impact of ADAs on the PKs of spesolimab (trough concentrations of plasma spesolimab) was also dependent on titre
    - ADA titres <4000 had no apparent impact on spesolimab exposure
  - Spesolimab efficacy was generally similar irrespective of the presence of ADAs/NAbs
    - Patients who achieved a GPPGA pustulation subscore of 0 or GPPGA total score of 0 or 1 maintained the treatment effect over time
  - There was no apparent correlation between the presence of ADAs/NAbs and hypersensitivity events

METHODS

- Plasma samples were analysed from three spesolimab clinical trials:
  - ***Trial 1*** (Proof of concept; NCT02978690)[4]
    - Seven patients received IV spesolimab 10 mg/kg
  - ***Trial 2*** (Effisayil™ 1; NCT03782792)[2]
    - 53 patients were randomised to receive IV spesolimab 900 mg or placebo on Day 1, with optional OL spesolimab on Day 8 for persistent flare symptoms
    - 51 patients received at least one dose of spesolimab during the study
  - ***Trial 3*** (5-year Effisayil™ ON; NCT03886246)[5]
    - At the end of Trial 2, eligible patients could enrol in Trial 3; patients received SC spesolimab 300 mg Q12W or Q6W for flare prevention
    - Interim data are reported (N=39; January 2021)
- Hypersensitivity events were defined as any event from narrow SMQs: "Anaphylactic reaction", "Angioedema", and "Hypersensitivity"
- In Trials 2 and 3, patients could receive additional OL IV spesolimab 900 mg for a new flare
- All patients included in these analyses were ADA-negative at baseline

RESULTS

ADA/NAb response in patients with GPP after spesolimab treatment

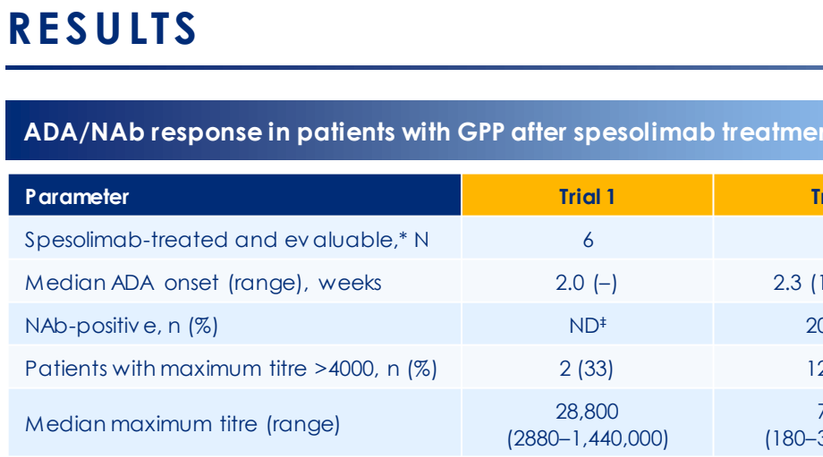
Parameter	Trial 1	Trial 2	Trial 3
Spesolimab-treated and evaluable,* N	6	50	36†
Median ADA onset (range), weeks	2.0 (–)	2.3 (1.0–11.7)	7.6 (2.0–61.3)
NAb-positive, n (%)	ND‡	20 (40)	17 (47)
Patients with maximum titre >4000, n (%)	2 (33)	12 (24)	10 (28)
Median maximum titre (range)	28,800 (2880–1,440,000)	7200 (180–3,600,000)	2880 (180–17,300,000)
Median time of maximum titre (range), weeks	ND§ (2–12)	11.7 (2.0–16.7)	20.3 (2.0–61.3)

*Evaluable refers to patients who had a baseline immunogenicity assessment and at least one post-baseline value. †One patient only received placebo during Trial 2 before receiving SC spesolimab treatment in Trial 3. ‡NAbs were not determined in Trial 1. §Median not determined as data limited to three patients.

After IV spesolimab treatment, 24–33% of patients had an ADA titre >4000; 30% of females had a maximum titre >4000 compared with 12% of males

Impact of immunogenicity on spesolimab PKs

Plasma concentration–time profiles for patients who received one or two doses of spesolimab in Trial 2, including patients who received spesolimab for a new flare



Grey, light blue and dark blue circles represent ADA-negative, ADA-positive/NAb-negative and ADA-positive/NAb-positive status, respectively. Circle size reflects the titre value for ADA-positive/NAb-positive: the higher the titre, the larger the circle. All spesolimab concentrations below the LLOQ have been assigned the value of 10 µg/L (1/2 of LLOQ) for the purpose of visualisation.

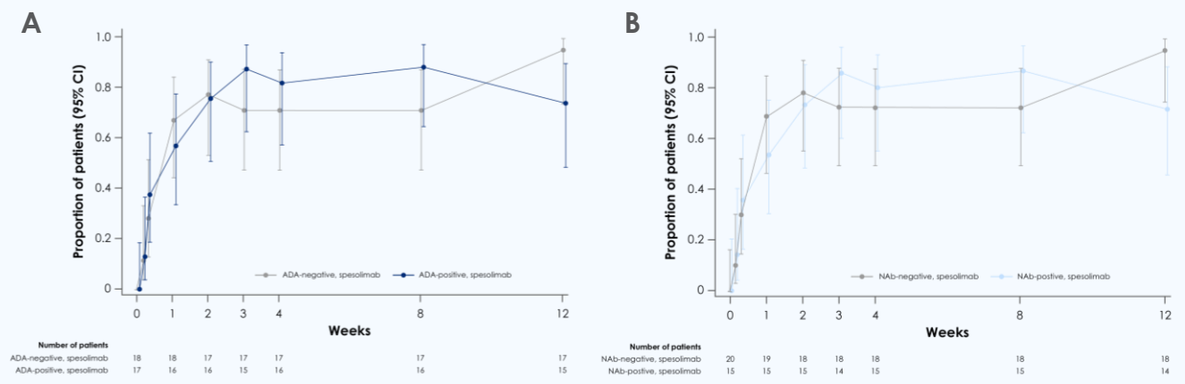
PK parameters for IV spesolimab 900 mg

PK parameter	gMean (gCV [%])	
	ADA-negative/ ADA titre <4000 n=25	ADA titre >4000 n=7
AU $C_{0-\infty}$ (µg day/mL)*	4240 (34.5)	2230 (48.8)
$t_{1/2}$ (days)	23.7 (21.9)	4.9 (78.1)
CL (L/day)*	0.21 (35.7)	0.40 (48.1)
V_{ss} (L)	7.4 (27.7)	6.0 (18.7)

*AU C was slightly underestimated and CL was slightly overestimated because plasma samples were not collected at the end of infusion. The earliest sample was 3 days or 1 week after dosing.

In Trial 2, there was no apparent impact on spesolimab PKs in patients with ADA titres <4000. However, in patients with ADA titres >4000, plasma spesolimab concentrations were greatly reduced. In ADA-positive vs ADA-negative patients, terminal $t_{1/2}$ was shorter and more variable, CL was higher and AUC was lower, with higher inter-patient variability

Proportion of patients with a GPPGA pustulation subscore of 0 over time by (A) ADA or (B) NAb status, in patients randomised to spesolimab

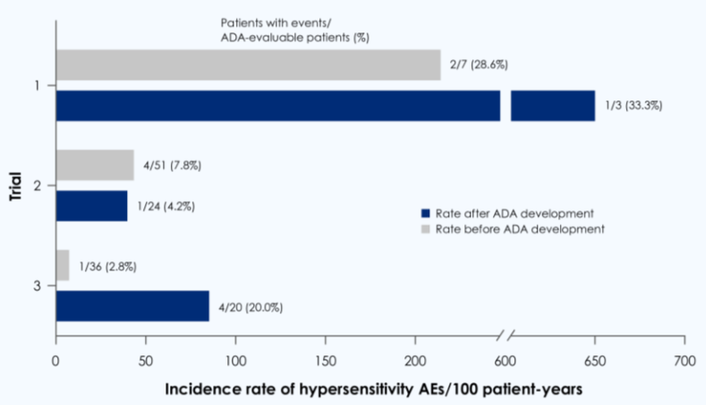


Data are from the randomised set. The denominator for percentages and proportions is the number of patients with observed data at the corresponding time point. The 95% CIs were calculated using the Wilson method. ITT analysis population: observed cases regardless of the use of other medication for GPP, OL spesolimab use at Day 8 or additional OL spesolimab for a new flare are included.

In Trial 2, the proportion of patients with a GPPGA pustulation subscore of 0 over time was similar for ADA-negative vs ADA-positive patients, and for NAb-negative vs NAb-positive patients; results were similar for evaluation of GPPGA total score of 0 or 1 over time

- In Trial 3, the impact of ADAs on efficacy upon retreatment after Week 12 has not been fully determined, as 77% (30/39) of patients did not have a new flare. Of the 9/39 patients who reported a flare up to the cut-off date for the analysis, seven were ADA-positive and two were ADA-negative

Incidence of hypersensitivity events in patients with GPP after spesolimab treatment*



*Due to the short trial duration (and therefore small denominator), incidence rates had a lower precision in some trials. "Before ADA development" refers to the time period prior to detecting an antibody developed by a patient's immune system specifically against spesolimab.

- **In all three trials, the overall number of hypersensitivity events was low (3–5 patients; 9.8–42.9%)**
- **In Trials 1 and 3, the incidence of hypersensitivity events was lower before ADAs were recorded as having developed in patients, as opposed to after. However, a review of the timing of events and titre indicated the events were unlikely to be related to ADA development**
- **In Trial 2, the incidence of hypersensitivity events was similar before and after ADA development, with no increase in the number of patients who received OL spesolimab at Day 8 or for a new flare**
- **There was no indication for any clinically relevant (severe or life-threatening) immediate hypersensitivity reactions such as anaphylactic reactions**
  - **There was no indication that the two serious AEs reported as DRESS in Trial 2 were related to ADA/NAb development**
- **In Trial 3, most patients were already pre-treated with spesolimab from Trial 2, and approximately half were already ADA-positive at trial start**

Abbreviations

ADA, anti-drug antibody; AE, adverse event; $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; CI, confidence interval; CL, clearance; DRESS, drug reaction with eosinophilia and systemic symptoms; gCV, geometric coefficient of variation; gMean, geometric mean; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; Ig, immunoglobulin; IL-36/R, interleukin-36/receptor; ITT, intention-to-treat; IV, intravenous; LLOQ, lower limit of quantification; mAb, monoclonal antibody; NE, not estimable; NAb, neutralising antibody; ND, not determined; OL, open-label; ON, open-label extension study; PK, pharmacokinetic; Q6W, every 6 weeks; Q12W, every 12 weeks; SC, subcutaneous; SMQs, Standardised MedDRA Queries; $t_{1/2}$, half-life; V_{ss}, apparent volume of distribution at steady state.

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