Expected spesolimab plasma exposure following intravenous and subcutaneous dosing in patients with generalized pustular psoriasis

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Simulation of PK parameters can guide clinicians on dosing and route of administration of spesolimab for patients with GPP in clinical practice

AIM

- To simulate the PK of IV vs SC doses of spesolimab to compare drug exposure profiles and support dosing recommendations in patients with GPP

INTRODUCTION

- GPP is a rare, chronic, and potentially life-threatening inflammatory skin disease characterized by episodic flares of widespread pustular eruptions and erythema
- Spesolimab is a first-in-class anti–interleukin-36 receptor monoclonal antibody approved to treat GPP flares in adults via IV infusion in the US,[1] and many other countries
- A population PK model was developed using clinical PK data collected in patients treated with spesolimab to simulate the plasma drug exposure levels over time in patients following administration of IV spesolimab vs SC spesolimab

METHODS

- A population PK model was developed using individual-level PK, ADA, and covariate data from 18 studies in which patients were treated with IV or SC spesolimab[2]
- The mathematical model quantified the PK of spesolimab following IV and SC administration, including the effect of patient-specific factors on PK (e.g. body weight, disease state, ADA titer)
- The resulting population PK model was used to simulate concentration–time profiles over 12 weeks (84 days) of various IV and SC doses:
  - IV spesolimab 300 mg and 900 mg administered over 90 minutes, as 1 dose or 900 mg as 2 doses (1 week apart), and
  - SC spesolimab 300 mg, 600 mg, 900 mg, and 2250 mg injections, as 1 dose or as 2 doses (1 week apart)
- For each dose, C_{max}, T_{max}, and AUC over 14 and 84 days were summarized

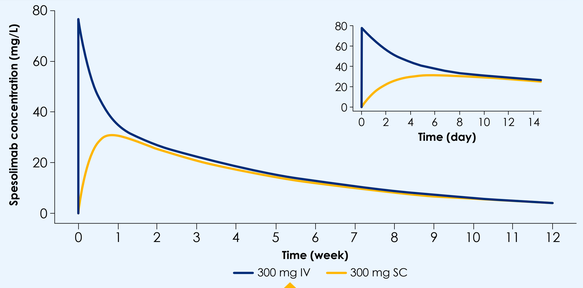
CONCLUSIONS

- PK data from this simulation suggest that treatment with IV and SC spesolimab can result in differences in drug exposure in clinical practice
- Significantly higher C_{max} and more rapid T_{max} was observed for the IV vs SC doses of spesolimab
- To match the C_{max} of the 900 mg IV dose, a SC dose 2.5× greater (2250 mg, equivalent to 15 injections of the 150 mg SC pre-filled syringe) would be required
- The immediate and high bioavailability of IV spesolimab compared with SC spesolimab are supportive of the use of IV spesolimab in acute GPP flare treatment and SC spesolimab in maintenance dosing strategies for prevention

RESULTS

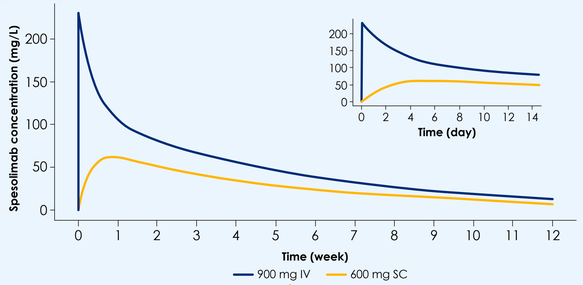
- Spesolimab plasma concentration–time course for varying doses of SC and IV were simulated from the PK model for a typical GPP subject, assuming body weight of 75 kg, ADA negative, SC injection into the abdomen, and reference values for all other covariates. The simulations are presented below (**Figures 1–4**)

Figure 1. Model-predicted concentration–time profiles of 300 mg IV vs 300 mg SC spesolimab



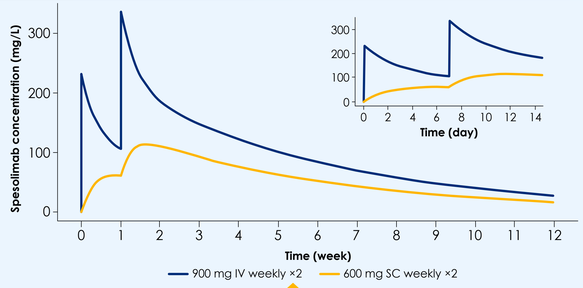
The simulated C_{max} was approximately 2.5-fold greater with 300 mg IV vs 300 mg SC spesolimab. The T_{max} was at the end of the 90-minute infusion for IV spesolimab vs approximately 1 week after dosing for SC spesolimab

Figure 2. Model-predicted concentration–time profiles of 900 mg IV vs 600 mg SC spesolimab



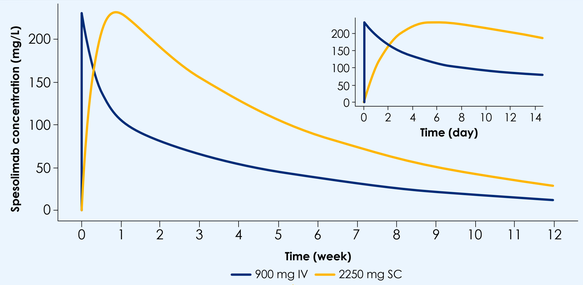
The simulated C_{max} was approximately 3.7-fold greater with 900 mg IV vs 600 mg SC spesolimab. The T_{max} was at the end of the 90-minute infusion for IV spesolimab vs approximately 1 week after dosing for SC spesolimab

Figure 3. Model-predicted concentration–time profiles of 900 mg IV ×2 vs 600 mg SC ×2 spesolimab



When administered as a 2-dose regimen, exposure increased due to accumulation. However, the C_{max} was still approximately 3-fold greater with IV vs SC dosing after the second dose. Similarly, the T_{max} occurred approximately 1 week after each dose of SC compared with immediately after the end of each 90-minute IV infusion

Figure 4. Model-predicted concentration–time profiles of 900 mg IV vs 2250 mg SC spesolimab



A SC dose of 2250 mg was required to attain a target C_{max} equivalent to that of 900 mg IV spesolimab. With the SC dose, T_{max} was delayed 1 week and AUC was almost twice as large; most importantly, a SC injection of this size is not clinically feasible (equivalent to 15 injections of the 150 mg SC pre-filled syringe)

Summary exposure metrics after single IV or SC dose in patients with GP

Dose (mg)	C_{max} (mg/L)	T_{max} (day)	AUC (mg/L*day) 14-day	AUC (mg/L*day) 84-day
IV				
300	77.1	0.07	557	1400
900	231	0.07	1670	4230
IV weekly ×2				
900	337	7.07	2710	8370
SC				
2250	232	6.09	2750	8710
300	30.9	6.08	367	1150
600	61.8	6.09	734	2310
900	92.8	6.09	1100	3470
SC weekly ×2				
600	115	11.9	1070	4580

Simulated spesolimab exposures demonstrated that the C_{max} and AUC of the single-dose 900 mg IV route of administration consistently exceeded that of all feasible single doses of SC spesolimab. A similar trend was observed for the IV and SC 2-dose regimens. Slow absorption is expected with the SC formulation, with T_{max} attained immediately following 90-minute infusion for single IV doses vs approximately 1 week after SC injection

Abbreviations

ADA, anti-drug antibody; AUC, area under the curve; C_{max}, peak plasma concentration; GPP, generalized pustular psoriasis; IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; T_{max}, time to peak plasma concentration

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2. Boehringer Ingelheim. Data on File: Modeling and simulation report: population pharmacokinetics and exposure-response of spesolimab in Generalized Pustular Psoriasis. 2023;c41839684-01.

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