Pharmacokinetics, safety, and tolerability of intravenous spesolimab, an anti-interleukin 36 receptor monoclonal antibody, in healthy male subjects

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Spesolimab exhibited target-mediated drug disposition (TMDD) after single-dose (SD) administration and demonstrated linear pharmacokinetics (PK) from 0.3 to 20 mg/kg. Single- and multiple-dose (MD) spesolimab up to 20 mg/kg were well tolerated in healthy male subjects

BACKGROUND

- Dysregulation of interleukin (IL)-36 receptor (IL-36R) signaling promotes infiltration of neutrophils into the epidermis, leading to the formation of sterile pustules[1]
- The IL-36 pathway is key to the pathogenesis of inflammatory diseases such as generalized pustular psoriasis (GPP);[1–5] there are currently no approved therapies for GPP flares
- Spesolimab (BI 655130) is a selective, humanized antibody against IL-36R, preventing activation of IL-36R by IL36α, IL36β, or IL36γ, and inhibiting downstream pro-inflammatory signaling[5]
- Binding of spesolimab to IL-36R modulates the activation of downstream effector, pro-inflammatory cytokines that are implicated in GPP, including tumor necrosis factor α, IL-17, IL-23, IL-1β, and IL-8[5]
- Here we present data from two Phase I placebo-controlled studies that evaluated the PK, safety, and tolerability of single or multiple rising doses of spesolimab administered as an intravenous (IV) infusion to healthy male subjects

METHODS

Study design

- **Study 1** (NCT02525679) was a single-blind, partially randomized, single-rising-dose study
  - Randomized 3:1 to ten dose-escalation cohorts (0.001–10 mg/kg spesolimab) with 8 subjects per cohort
    - An unplanned cohort was introduced to accommodate 3 subjects who were wrongly dosed (0.05 mg/kg instead of 0.1 mg/kg); 6 subjects received spesolimab as planned within the 0.001, 0.003, 0.01, 0.03, 1, 3, and 6 mg/kg dose groups, 5 subjects within the 0.1 mg/kg dose group, and 4 subjects within each of the 0.3 and 10 mg/kg dose groups
  - Spesolimab was administered as an IV infusion over 30 minutes on Day 1
- **Study 2** (NCT02852824) comprised two parts:
  - **Part 1:** Double-blind, randomized 3:1 to four MD escalation cohorts (3–20 mg/kg spesolimab), with 8 subjects per cohort receiving single IV doses on Days 1, 8, 15, and 22
  - **Part 2:** Single-blind, partially randomized 3:1 to one SD cohort (20 mg/kg) with 8 subjects
  - Spesolimab was administered as an IV infusion over 30 minutes for the 3 and 6 mg/kg MD cohorts, over 60 minutes for the 10 mg/kg MD and 20 mg/kg SD cohorts, and over 90 minutes for the 20 mg/kg MD cohort
- All subjects were observed for 48 hours following administration of spesolimab/placebo and before being discharged from the study site
- Cohorts in both studies were assessed consecutively in ascending order of dose, with at least 14 days between cohorts; the decision to escalate to the next dose cohort was based on assessment of safety and tolerability

Subjects

- Studies planned to enroll healthy male subjects aged 18–45 years (Study 1) and 18–50 years (Study 2) with a body mass index (BMI) 18.5–29.9 kg/m^2

For detailed methodologies of the PK and safety assessment please click on the icon.

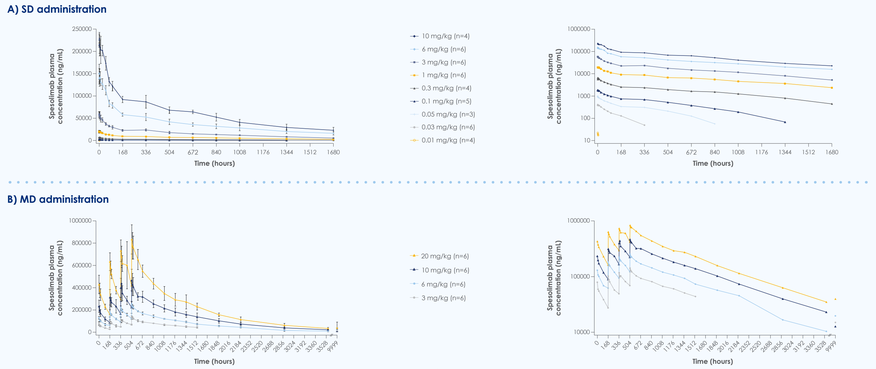
RESULTS

Subject disposition and baseline characteristics

- **Study 1:** 78 male subjects enrolled and completed the study, with all 78 included in the PK analysis set (PKAS)
  - All subjects were white, except for one American Indian or Alaska Native (1.3%) and one Asian subject (1.3%). Most subjects were of non-Hispanic/Latino origin (98.7%)
  - Mean (standard deviation) age of the subjects was 33.1 (7.7) years (range 19–46) and mean (standard deviation) BMI was 24.8 (2.8) kg/m^2 (range 19.2–30.2; two subjects had a BMI that exceeded the upper limit of the target range by <2%, but this was considered irrelevant for interpretation of the study results)
- **Study 2:** 40 male subjects were enrolled and treated, 37 completed the study (one subject from the MD placebo cohort withdrew consent after receiving all four planned doses; two subjects in the spesolimab 20 mg/kg MD cohort discontinued treatment because of AEs, one after the first dose and one during the third infusion). All 30 subjects who received spesolimab were included in the PKAS
  - All subjects were white, except for one who was of Hispanic/Latino origin (2.5%; 20 mg/kg MD spesolimab)
  - Mean (standard deviation) age of the subjects was 36.3 (8.1) years (range 23–50) and mean (standard deviation) BMI was 24.6 (2.6) kg/m^2 (range 20.2–29.9)
- Within each study, treatment groups were similar with respect to demographic and baseline characteristics

Pharmacokinetics

Mean (± standard deviation) spesolimab plasma concentration–time profiles following SD or MD administration to healthy male subjects



Spesolimab exhibited TMDD after SD administration and an approximate linear dose-exposure response after MD administration

Summary of spesolimab PK parameters following SD administration (Study 1 and Study 2)

Parameter (unit)	Spesolimab SD									
	Study 1									Study 2
	0.01 mg/kg (n=4)	0.03 mg/kg (n=6)	0.05 mg/kg (n=3)	0.1 mg/kg (n=5)	0.3 mg/kg (n=4)	1 mg/kg (n=6)	3 mg/kg (n=6)	6 mg/kg (n=6)	10 mg/kg (n=4)	20 mg/kg (n=6)
C_{max} (µg/mL)	0.023 (33.5)	0.413 (21.2)	0.998 (15.7)	1.96 (11.9)	6.63 (3.3)	20.3 (13.6)	60.6 (7.2)	153 (12.7)	235 (2.8)	490 (29.0)
AUC_{inf} (µg•day/mL)	0.023 (125)	2.35 (23.9)	13.0 (6.6)	27.7 (16.6)	127 (6.1)	563 (26.2)	1260 (6.8)	3380 (15.6)	5080 (18.9)	10500 (19.2)
$t_{½}$ (day)	0.787 (150)	4.97 (17.3)	19.2 (23.0)	15.6 (24.0)	20.4 (11.9)	33.5 (55.4)	25.8 (13.3)	33.9 (18.7)	29.3 (26.3)	35.2 (15.2)
CL (L/day)	35.3 (130)	0.973 (12.3)	0.329 (17.9)	0.283 (10.8)	0.187 (8.8)	0.147 (38.4)	0.193 (8.2)	0.157 (16.7)	0.155 (8.5)	0.163 (17.7)
V_z (L)	40.1 (35.7)	6.83 (17.8)	8.52 (10.2)	6.28 (19.9)	6.02 (4.5)	7.13 (21.6)	7.32 (13.3)	7.20 (17.5)	6.26 (19.8)	7.84 (17.6)

Data shown as geometric mean (geometric coefficient of variation %).

Following a SD administration, spesolimab exhibited a more than dose-proportional increase in AUC at lower doses but increased linearly with 0.3 to 20 mg/kg. In the linear range, $t_{½}$ was 20.4–35.2 days and systemic clearance was 0.147–0.193 L/day

Summary of selected spesolimab PK parameters following MD administration (Study 2)

Dose	Parameter (unit)	Spesolimab MD (Study 2)			
		3 mg/kg (n=6)	6 mg/kg (n=6)	10 mg/kg (n=4)	20 mg/kg (n=6)
First dose	C_{max} (µg/mL)	77.9 (19.4)	130 (8.5)	229 (22.9)	422 (18.5)
	$AUC_{τ}$ (µg•day/mL)	298 (9.3)	552 (10.4)	923 (17.3)	1770 (12.5)
Fourth dose	C_{max} (µg/mL)	141 (4.3)	253 (8.7)	467 (21.4)	826 (15.8)*
	$AUC_{τ}$ (µg•day/mL)	760 (4.2)	1390 (4.6)	2500 (16.7)	4660 (12.9)*
	$t_{½}$ (day)	33.5 (15.7)	26.5 (27.1)	32.4 (10.6)	31.9 (12.9)*
	$R_{A,AUC}$	2.55 (8.6)	2.51 (7.0)	2.71 (5.2)	2.52 (11.6)*
	$R_{A,Cmax}$	1.81 (18.3)	1.95 (7.1)	2.04 (5.6)	1.83 (10.8)*

Data shown as geometric mean (geometric coefficient of variation %). *n=4.

Following MD administration, steady state was not reached for any treatment groups. Accumulation ratios ($R_{A,AUC}$ and $R_{A,CMAX}$) gradually increased after once-weekly doses for all dose groups, indicating accumulation of spesolimab; accumulation ratios after 4 weeks of dosing were similar for all treatment groups

Immunogenicity

- Positive ADA responses following SD or MD administration occurred during the terminal phase of the spesolimab concentration–time profile, when the exposure was low or depleted. Overall, formation of ADAs had minimal impact on the plasma concentration of spesolimab and no AEs of hypersensitivity reactions were reported
  - **Study 1:** In total, 6 spesolimab-treated subjects (10%) had treatment-induced or boosted ADA
  - **Study 2:** In total, 17% and 4% of treated subjects had treatment-induced ADA in the SD and MD part, respectively

Safety

- No relevant changes were observed in safety laboratory tests, vital signs, or ECGs. Assessments of local tolerability revealed no relevant issues

Summary of treatment-emergent adverse events (TEAEs)

n (%)	Study 1		Study 2			
	Placebo SD (n=20)	Total spesolimab SD (n=58)	Placebo SD (n=2)	Spesolimab 20 mg/kg SD (n=6)	Placebo MD (n=8)	Total spesolimab MD (n=24)
Any TEAE	13 (65.0)	36 (62.1)	2 (100.0)	4 (66.7)	8 (100.0)	22 (91.7)
Any serious TEAE	0	0	0	0	0	0
Any severe TEAE	0	0	0	0	0	0
TEAE leading to discontinuation	0	0	0	0	0	2 (8.3)
Investigator-defined, drug-related TEAEs	3 (15.0)	8 (13.8)	0	2 (33.3)	4 (50.0)	13 (54.2)
Any TEAE*						
Nasopharyngitis	3 (15.0)	12 (20.7)	2 (100.0)	2 (33.3)	1 (12.5)	10 (41.7)
Headache	3 (15.0)	5 (8.6)	0	1 (16.7)	2 (25.0)	10 (41.7)
Injection-site erythema	0	1 (1.7)	0	3 (50.0)	2 (25.0)	5 (20.8)
Injection-site hematoma	0	2 (3.4)	0	0	2 (25.0)	4 (16.7)
Nausea	0	2 (3.4)	0	0	0	4 (16.7)
Injection-site reaction	0	2 (3.4)	1 (50.0)	0	1 (12.5)	3 (12.5)
Injection-site bruising	0	0	0	0	0	3 (12.5)
Diarrhea	2 (10.0)	2 (3.4)	0	0	0	3 (12.5)
Fatigue	0	2 (3.4)	0	0	3 (37.5)	3 (12.5)
Paresthesia	0	0	0	0	0	3 (12.5)
Influenza-like illness	2 (10.0)	4 (6.9)	0	0	0	1 (4.2)

*Table shows TEAEs by preferred term that were reported by more than two subjects in any treatment group.

The overall incidence of TEAEs was comparable between spesolimab and placebo groups, and all were of mild or moderate intensity. The most frequently reported TEAEs following SD and MD spesolimab administration were nasopharyngitis and headache. TEAEs leading to discontinuation were mild pyrexia (associated with dyspnea, headache, back pain, oropharyngeal pain, and fatigue) and a mild potential infusion-related reaction (associated with anxiety, dizziness, dyspnea, headache, and paresthesia) following MD administration of spesolimab 20 mg/kg

CONCLUSIONS

- Spesolimab exhibited TMDD at lower doses (0.01 to 0.3 mg/kg) and demonstrated linear PK from 0.3 to 20 mg/kg
- Steady state was not attained after the fourth dose due to the long $t_{½}$ (20.4–35.2 days)
- The incidence of ADAs ranged from 4–17% following SD or MD administration of spesolimab. Formation of ADAs had minimal impact on PK. There was no association between ADA formation and hypersensitivity
- SDs and MDs of spesolimab up to 20 mg/kg were well tolerated in healthy male subjects

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