Poster 682

A phase 1, first-in-human, single ascending-dose study with a novel antibody to the human thymic stromal lymphopoietin receptor

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KEY FINDINGS

UPB-101 displayed favorable safety and tolerability following single-dose administration in healthy participants.

Simulations for repeated SC administration of UPB-101 show that dosing intervals of ≥ 84 days (12 weeks) are predicted to maintain UPB-101 serum concentration above the estimated therapeutic threshold.

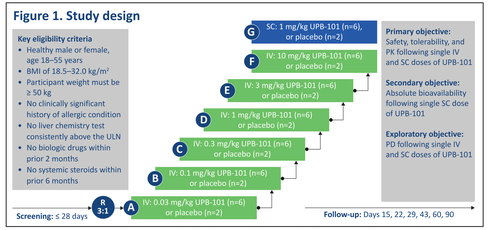
INTRODUCTION

- Up to 10% of patients with asthma have severe disease, and a subset of these remain uncontrolled, despite treatment[1]
- Thymic stromal lymphopoietin (TSLP) is an upstream alarmin that acts on multiple immune cell lineages[1]
  - Targeting TLSP affects multiple downstream signaling pathways and has proven effective in the treatment of patients with severe asthma[1,2]
- UPB-101 (formerly known as ASP7622) is a novel recombinant fully human IgG1 monoclonal antibody that targets the TSLP receptor
  - Preclinical data suggest a 4- to 5-fold increased potency for UPB-101 compared with tezepelumab, which targets the TSLP ligand[3]
  - The estimated therapeutic threshold of UPB-101 is 1.0 µg/mL (above this concentration the target is saturated)[4]
- This phase 1, randomized, double-blinded, placebo-controlled, single dose-escalation study evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of both intravenous (IV) and subcutaneous administration of UPB-101 in healthy male and female participants

METHODS

- The study design and objectives are shown in **Figure 1**

Figure 1. Study design



BMI, body mass index; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; R, randomization; SC, subcutaneous; ULN, upper limit of normal.

Assessments

- Safety and tolerability: adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, and anti-drug antibody (ADA) monitoring
- Blood samples were taken for PK and PD assessments

RESULTS

Participant disposition and characteristics

- A total of 56 participants were randomized; all completed the study per protocol, except for 1 participant each in cohorts D and G, who were lost to follow-up from days 8 and 161, respectively
- The mean age of participants enrolled in each cohort ranged from 30.7 to 40.0 years, and the majority were Black/African American (**Table 1**)

Table 1. Participant demographics and baseline characteristics

Characteristic	Placebo, IV (n=12)	UPB-101, IV (each n=6)							Cohort G Placebo, SC (n=2)	Cohort G UPB-101, SC 1 mg/kg (n=6)
		Cohort A 0.03 mg/kg	Cohort B 0.1 mg/kg	Cohort C 0.3 mg/kg	Cohort D 1 mg/kg	Cohort E 3 mg/kg	Cohort F 10 mg/kg	Total (n=36)		
Age (years), mean (SD)	34.8 (7.4)	40.0 (12.0)	30.7 (8.0)	34.7 (11.1)	37.2 (9.2)	34.2 (7.8)	32.8 (8.0)	34.9 (9.3)	34.0 (8.5)	35.2 (12.6)
Race, n (%) White Black/AA Other[a]	2 (16.7) 10 (83.3) 0	1 (16.7) 5 (83.3) 0	0 6 (100) 0	1 (16.7) 4 (66.7) 1 (16.7)	1 (16.7) 5 (83.3) 0	1 (16.7) 5 (83.3) 0	0 5 (83.3) 1 (16.7)	4 (11.1) 30 (83.3) 2 (5.6)	1 (50.0) 1 (50.0) 0 (0)	2 (33.3) 3 (50.0) 1 (16.7)
Male, n (%)	4 (33.3)	3 (50.0)	5 (83.3)	3 (50.0)	3 (50.0)	3 (50.0)	1 (16.7)	3 (50.0)	18 (50.0)	2 (100)	0 (0)
BMI (kg/m²), mean (SD)	26.6 (4.1)	26.5 (4.5)	26.4 (3.1)	29.4 (1.4)	26.0 (4.0)	27.3 (4.6)	26.1 (4.2)	26.9 (3.7)	26.3 (3.2)	24.7 (4.6)
Baseline eosinophils (cells/µL), median (range)	89 (28–647)	98 (42–130)	86 (62–189)	184 (89–492)	155 (52–214)	90 (78–406)	255 (88–441)	112 (42–492)	121 (71–171)	104 (61–371)

[a]Other denotes Asian, Native Hawaiian or Other Pacific Islander, and Other per disclosure.
AA, African American; BMI, body mass index; IV, intravenous; SC, subcutaneous; SD, standard deviation.

RESULTS

Safety and tolerability

- Treatment-emergent adverse events (TEAEs) were reported by 21/42 and 3/14 participants who received UPB-101 or placebo, respectively (**Table 2**)
  - The majority of TEAEs were mild in severity, and there was no clinically relevant increase in the frequency of TEAEs with increasing dose
- Less than half of all reported TEAEs were considered by the investigator to be related to the study drug
- One participant who received 1 mg/kg UPB-101 IV had a serious TEAE of nephrolithiasis, which was considered not related to the study drug by the investigator; no drug-related serious TEAEs occurred during the study in any participants
- The most frequently reported TEAEs were headache and dysmenorrhea

Table 2. Incidence of TEAEs[a] by cohort (safety analysis set)

Parameter	Placebo, IV (n=12)	UPB-101, IV (each n=6)							Cohort G Placebo, SC (n=2)	Cohort G UPB-101, SC 1 mg/kg (n=6)
		Cohort A 0.03 mg/kg	Cohort B 0.1 mg/kg	Cohort C 0.3 mg/kg	Cohort D 1 mg/kg	Cohort E 3 mg/kg	Cohort F 10 mg/kg	Total (n=36)		
Any TEAE, n (%); event	3 (25.0); 16	3 (50); 5	4 (66.7); 6	2 (33.3); 2	3 (50.0); 4	3 (50.0); 7	1 (16.7); 1	16 (44.4); 25	0	5 (83.3); 7
Mild event (% of TEAEs)	15 (94.0)	5 (100)	2 (33.0)	1 (50.0)	2 (50.0)	4 (57.0)	1 (100)	15 (60.0)	0	6 (86.0)
Moderate event (% of TEAEs)	1 (6.0)	0	4 (67.0)	1 (50.0)	0	3 (43.0)	0	8 (32.0)	0	1 (14.0)
Severe event (% of TEAEs)	0	0	0	0	2 (50.0)	0	0	2 (8.0)	0	0
Drug-related TEAE[b], n (%); event	2 (16.7); 7	1 (16.7); 1	3 (50.0); 3	0	0	1 (16.7); 3	0	5 (13.9); 7	0	3 (50.0); 3
Serious TEAE[c], n (%); event	0	0	0	0	1 (16.7); 1	0	0	1 (2.8); 1	0	0
Nephrolithiasis, n (%); event	0	0	0	0	1 (16.7); 1	0	0	1 (2.8); 1	0	0

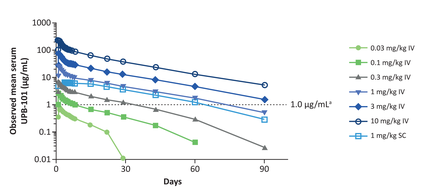
[a]Defined as any adverse event that started or worsened in severity after dose of study drug through end-of-study. [b]Possible or probable, as assessed by the investigator or records where relationship was missing. [c]Included serious adverse events upgraded by the sponsor based on review of the sponsor's list of Always Serious terms, if any upgrade was done. IV, intravenous; SC, subcutaneous; SOC, System Organ Class (per MedDRA v18.1); TEAE, treatment-emergent adverse event.

- No clinically relevant trends in clinical laboratory analyses (hematology, biochemistry, urinalysis), vital signs, physical assessments, or ECGs were detected, and no injection site reactions were reported after the subcutaneous (SC) dose
- ADAs were detected in 13 participants dosed with UPB-101. Titers were low (≤ 128), and the presence of ADAs did not significantly impact the serum PK profile in these individuals

Pharmacokinetics

- Following IV infusion, there was a linear and dose-proportional increase in C_{max} and AUC over the 0.1–10 mg/kg dose range. The mean terminal half-life was ~20 days for the 1, 3, and 10 mg/kg dose groups (**Figure 2**)
  - There was evidence of more rapid elimination of UPB-101 at serum concentrations below ~1 µg/mL, which may be attributed to target-mediated drug disposition
- Absolute bioavailability after a SC dose of 1 mg/kg UPB-101 was ~70%

Figure 2. Single dose PK profiles

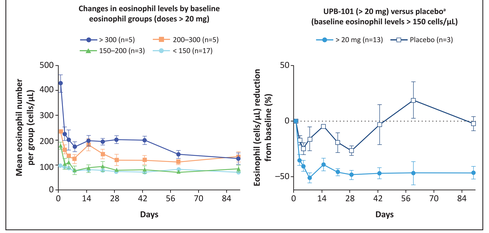


[a]Projected therapeutic threshold.

Pharmacodynamics

- A *post-hoc* analysis revealed a post-treatment decrease of blood eosinophil levels in participants with > 150 cells/µL at baseline. This reduction occurred within 2–4 weeks post-dose and was maintained for ≥ 13 weeks (**Figure 3**) at doses ≥ 0.3 mg/kg (i.e., doses > 20 mg, assuming a 70 kg participant)

Figure 3. *Post-hoc* analysis showing changes in baseline eosinophil levels in healthy participants following a single dose of UPB-101 (IV or SC) or placebo

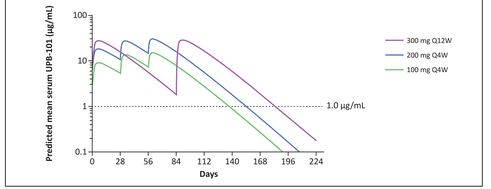


[a]One participant receiving placebo was excluded due to very high baseline eosinophil levels (646 cells/µL).

Predicted exposure after repeated SC administration

- A PK model fitted to the single dose SC PK data was used to predict the PK profiles after repeated SC administration of UPB-101 at different dose levels and different dosing intervals
  - The anticipated therapeutic threshold concentration is predicted to be maintained at feasible SC doses with a ≥ 84-day (12-week) dosing interval (**Figure 4**)

Figure 4. Simulated PK profiles for serum UPB-101 after repeated SC administration



[a]Projected therapeutic threshold. Q4W, every 4 weeks; Q12W, every 12 weeks.

CONCLUSIONS

- Single-dose administration of UPB-101 presented a favorable safety and tolerability profile in healthy participants
- UPB-101 showed evidence of target-mediated drug disposition, with linear and dose-proportional PK at concentrations exceeding the anticipated therapeutic threshold
- UPB-101 has advanced to phase 1b development based on SC dosing in patients with asthma

REFERENCES

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DISCLOSURES

Aaron Deykin is a full-time employee of and owns equity in Upstream Bio.
Chaim M. Brickman was a full-time employee of Upstream Bio, and now serves as a full-time consultant for them, and owns equity in Upstream Bio.
Peter Lloyd has received consultancy fees from Upstream Bio.
Oren M. Becker is a co-founder of Upstream Bio, serves as a consultant for them, and owns equity in Upstream Bio.

ACKNOWLEDGMENTS

This study was funded and conducted by Astellas Pharma. Upstream Bio purchased the study drug in Q4 of 2021. Writing assistance was provided by Luciana Gardner, MSc, and Lisa Jolly, PhD, of Parexel International, and was funded by Upstream Bio.