A multiple ascending dose study with verekitug, a novel antibody to the human thymic stromal lymphopoietin receptor, in adults with asthma

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KEY FINDINGS

- Verekitug, a first-in-class, fully human IgG1 monoclonal antibody targeting the thymic stromal lymphopoietin receptor (TSLPR), was studied in adults with asthma and found to be safe and well tolerated after multiple subcutaneous (SC) administrations
- High potency was observed as reflected by complete target engagement (TSLPR occupancy), and reductions in fractional exhaled nitric oxide (FeNO) and blood eosinophil levels that were rapid, substantial, and sustained for up to 24 weeks after last dose
- Data support dosing every 24 weeks for the treatment of severe asthma

BACKGROUND

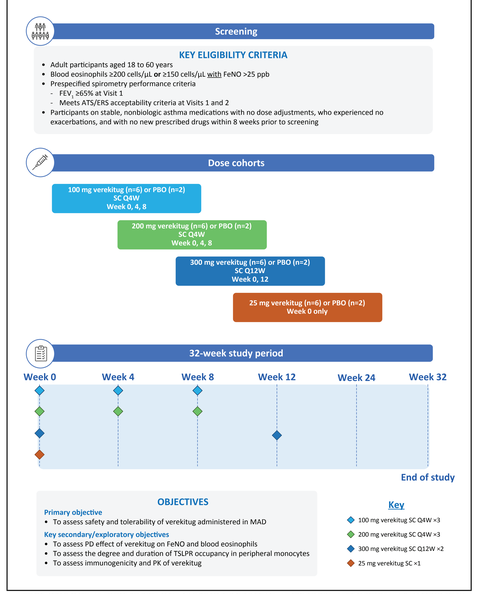
- Thymic stromal lymphopoietin (TSLP) is an epithelial cell–derived cytokine that acts through the TSLP receptor (TSLPR) as an upstream initiator and mediator of the inflammatory cascade[1-3]
- Inhibition of TSLP signaling using an anti-TSLP monoclonal antibody (mAb) is a clinically validated therapeutic approach for severe asthma[4]
- Verekitug (previously UPB-101 and ASP7266) is a novel, fully human anti–TSLPR IgG1 monoclonal antibody. It is the only anti–TSLPR in development as a potential therapy for severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)[5,6]
- In vitro assays demonstrate verekitug has superior potency (90% maximal inhibitory concentration) compared with tezepelumab, an anti-TSLP (ligand) antibody[5]
- Verekitug demonstrated a favorable safety and tolerability profile, low immunogenicity, and predictable pharmacokinetics (PK) in a phase 1 study in healthy volunteers[6]
- Here we present data from a 32-week multiple ascending dose (MAD) study to assess the safety, tolerability, PK, immunogenicity, and pharmacodynamics (PD) of verekitug in participants with asthma

METHODS

Study design

- This phase 1, multicenter, randomized, double-blind, placebo-controlled study enrolled participants with mild to moderate asthma and blood eosinophils ≥200 cells/µL or ≥150 cells/µL with FeNO >25 parts per billion (ppb) (NCT05448651; **Figure 1**)
- Four dosing cohorts, each with 6 participants receiving verekitug and 2 participants receiving placebo, were enrolled: 100 mg every 4 weeks (Q4W), total 3 doses (×3); 200 mg Q4W ×3; 300 mg Q12W ×2; 25 mg ×1
- Participants were observed for 32 weeks following randomization. Interim data from all participants to at least 24 weeks observation are reported here

Figure 1. Dose Cohorts and Study Design



ATS, American Thoracic Society; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; MAD, multiple ascending dose; PBO, placebo; PD, pharmacodynamic; PK, pharmacokinetics; Q4W, every 4 weeks; Q12W, every 12 weeks; SC, subcutaneous; TSLPR, thymic stromal lymphopoietin receptor.

Assessments

- Adverse events (AEs) and injection site reactions were collected up to 32 weeks
- FeNO was assessed from baseline up to 32 weeks
- Blood samples were collected for PK, anti-drug antibody (ADA), and PD assessments from baseline up to 32 weeks
- Population PK/PD modeling was conducted using PK, FeNO, and blood eosinophil data

RESULTS

Participant disposition and baseline characteristics

- A total of 32 participants were randomized, and all completed the study
- Baseline demographics and disease characteristics are presented in **Table 1**
  - Sixty-six percent of participants (range from 50% to 83% among cohorts) reported using inhaled corticosteroids
  - Mean baseline FeNO levels in the overall study population was 53.5 ppb (SE: 7.6)
  - Mean baseline blood eosinophil counts in the overall study population was 302.9 cells/µL (SE: 21.3)

Table 1. Demographics and Baseline Asthma Characteristics

	Verekitug 100 mg Q4W (n=6)	Verekitug 200 mg Q4W (n=6)	Verekitug 300 mg Q12W (n=6)	Verekitug 25 mg × 1 dose (n=6)	Placebo[a] (n=8)	Overall (N=32)
Age, mean year (SD)	35.7 (10.3)	37.7 (8.8)	32.7 (9.5)	48.0 (5.3)	37.0 (11.4)	38.1 (10.2)
Sex, n (%)						
Male	1 (17)	2 (33)	4 (67)	4 (67)	5 (63)	16 (50)
Female	5 (83)	4 (67)	2 (33)	2 (33)	3 (38)	16 (50)
BMI, mean kg/m^2 (SD)	26.6 (3.2)	25.2 (2.1)	25.2 (2.8)	27.7 (2.5)	25.6 (3.1)	26.0 (2.8)
Using any inhaled corticosteroid, n (%)	3 (50)	4 (67)	3 (50)	5 (83)	6 (75)	21 (66)
FEV_1, % predicted, mean (SE)	89.8 (6.7)	89.7 (5.7)	98.1 (7.6)	87.3 (4.9)	89.0 (5.3)	90.7 (2.6)
FeNO, mean ppb (SE)	54.3 (8.5)	75.0 (26.4)	62.0 (22.5)	50.5 (16.6)	32.8 (8.1)	53.5 (7.6)
Blood eosinophils, mean cells/µL (SE)	335.8 (55.8)	316.7 (37.4)	229.5 (30.9)	412.7 (59.2)	240.5 (26.4)	302.9 (21.3)

[a]Data from the placebo groups in all cohorts were pooled for analysis.
BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; Q4W, every 4 weeks; Q12W, every 12 weeks.

Safety and tolerability

- Treatment-emergent adverse events (TEAEs) were reported by 21/24 and 7/8 participants (88% for each group) receiving verekitug or placebo, respectively (**Table 2**)
  - 51/57 TEAEs were deemed unrelated to verekitug
  - All TEAEs were mild or moderate in severity. No serious adverse events (SAEs) were reported
- No TEAEs led to withdrawal from study or discontinuation of study drug
- The most common TEAE reported during the duration of the study was headache (n=8/32 [25%])
- Solicited reports of injection site reactions (n=11/32 [34%]) were self-limited and generally mild to moderate

Table 2. Summary Over 32 Weeks

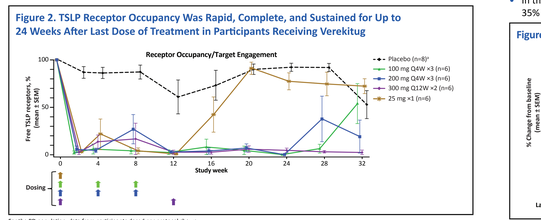
	Verekitug 100 mg Q4W (n=6)	Verekitug 200 mg Q4W (n=6)	Verekitug 300 mg Q12W (n=6)	Verekitug 25 mg × 1 dose (n=6)	Placebo[a] (n=8)	Overall (N=32)
Number of TEAEs, n	19	17	12	9	25	82
Number of study drug–related TEAEs,[b] n	2	1	3	0	1	7
Participants with any TEAE, n (%)	5 (83)	6 (100)	6 (100)	4 (67)	7 (88)	28 (88)
Mild, n (%)	1 (17)	4 (67)	5 (83)	0	3 (38)	13 (41)
Moderate, n (%)	4 (67)	2 (33)	1 (17)	4 (67)	4 (50)	15 (47)
Severe, n (%)	0	0	0	0	0	0
Participants with any study drug–related TEAE,[b] n (%)	1 (17)	1 (17)	2 (33)	0	1 (13)	5 (16)

[a]Data from the placebo groups in all cohorts were pooled for analysis.
[b]Study drug–related TEAEs include any that were deemed possibly, probably, or definitely related to study drug by the investigator.
Q4W, every 4 weeks; Q12W, every 12 weeks; TEAE, treatment-emergent adverse event.

TSLPR occupancy and pharmacodynamics

- 100% TSLPR occupancy by verekitug (as measured by flow cytometry in peripheral monocytes) was observed for all cohorts within 2 weeks after first dose
- Verekitug doses ≥100 mg led to sustained TSLPR occupancy for up to 24 weeks after last dose (**Figure 2**)

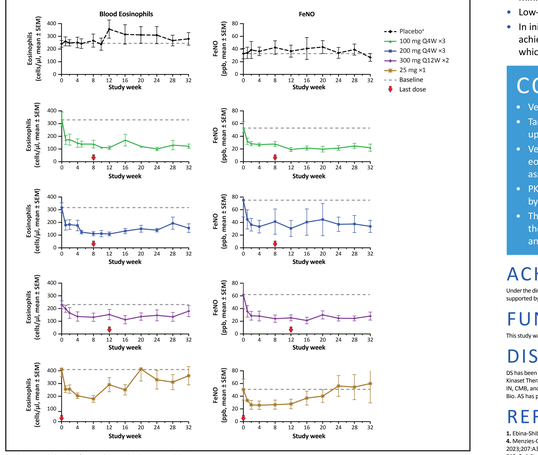
Figure 2. TSLP Receptor Occupancy Was Rapid, Complete, and Sustained for Up to 24 Weeks After Last Dose of Treatment in Participants Receiving Verekitug



For the PD population, data from participants dosed per protocol shown.
[a]Data from the placebo groups in all cohorts were pooled for analysis.
PD, pharmacodynamic; Q4W, every 4 weeks; Q12W, every 12 weeks; TSLP, thymic stromal lymphopoietin.

- Blood eosinophil and FeNO levels were substantially reduced after the first dose, and these reductions were sustained for up to 24 weeks after the last dose in cohorts receiving ≥100 mg verekitug (**Figure 3**)

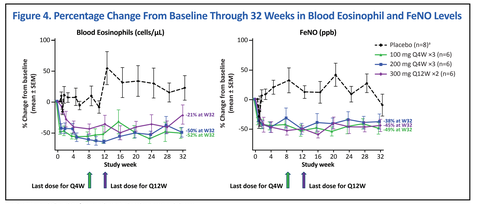
Figure 3. Reduction in Blood Eosinophil and FeNO Levels Was Rapid, Substantial, and Sustained for Up to 24 Weeks After Last Dose in Cohorts Receiving ≥100 mg Dose Verekitug



For the PD population, data from participants dosed per protocol shown.
Additional time points included for the 25 mg cohort are not shown.
[a]Data from the placebo groups in all cohorts were pooled for analysis.
FeNO, fractional exhaled nitric oxide; PD, pharmacodynamic; Q4W, every 4 weeks; Q12W, every 12 weeks.

- In cohorts receiving ≥100 mg, verekitug resulted in 21%-52% and 38%-49% mean reduction from baseline in blood eosinophils and FeNO, respectively, at 32 weeks (**Figure 4**)
  - At comparable baseline values,[7] these changes in absolute eosinophil count and FeNO after treatment with verekitug are numerically greater than those reported for an anti-TSLP ligand antibody
- In the cohort receiving a 25-mg single dose verekitug, a 26% reduction in blood eosinophils and a 35% reduction in FeNO at 12 weeks were observed

Figure 4. Percentage Change From Baseline Through 32 Weeks in Blood Eosinophil and FeNO Levels



For the PD population, data from participants dosed per protocol shown.
[a]Data from the placebo groups in all cohorts were pooled for analysis.
FeNO, fractional exhaled nitric oxide; PD, pharmacodynamic; Q4W, every 4 weeks; Q12W, every 12 weeks.

Pharmacokinetics and immunogenicity

- After SC administration, there was a slightly greater than dose-proportional increase in verekitug exposure as measured by C_{max} and AUC_{inf}
- Verekitug had a linear elimination phase with a half-life of ~20 days
- Minimal accumulation of verekitug was noted following multiple doses administered Q12W
- Low-titer ADA signal was observed without clinically meaningful impact on PK, PD, or safety
- In initial population PK/PD modeling, verekitug demonstrated high potency with an E_{max} (maximal achievable effect) of ~43.5% and ~40.3% suppression of FeNO and blood eosinophil count, respectively, which is greater than those reported for an anti-TSLP ligand antibody[8]

CONCLUSIONS

- Verekitug was safe and well tolerated at all dose levels
- Target engagement (TSLPR occupancy) and reductions in FeNO and blood eosinophil levels were sustained up to 24 weeks after the last dose in groups receiving multiple doses of 100 mg or more of verekitug
- Verekitug is a potent inhibitor of TSLP signaling as indicated by the observation that FeNO and blood eosinophil levels were rapidly and more substantially suppressed compared with historical data associated with an anti-TSLP ligand mAb[3]
- PK after SC administration were slightly greater than dose-proportional and were not meaningfully impacted by ADA development
- The clinical efficacy and safety of verekitug is currently being studied in two phase 2 studies for the treatment of severe asthma and CRSwNP in dosing intervals of up to 24 weeks (NCT06164704 and NCT06196879)[9,10]

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DISCLOSURES

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