32-Week data from a multiple ascending-dose trial with verekitug, a novel investigational antibody to the human TSLP receptor (TSLPR) in adults with asthma

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KEY FINDINGS

Verekitug, to our knowledge, is the only agent currently in development targeting TSLPR, and **was generally well tolerated in patients with asthma** following multiple doses and 32 weeks of observation

The multiple-dose regimens in this trial resulted in **rapid PD effects sustained for up to 24 weeks after last dose,** including
- Complete TSLPR occupancy
- Substantial reductions in blood eosinophils and FeNO (≈50% from baseline)
- Lower circulating IL-5

PK/PD modeling suggests **substantially higher potency of verekitug** as assessed by FeNO E_{max} and EC_{90} compared with published values for tezepelumab

Verekitug administered as 100 mg **Q12W** and/or 400 mg **Q24W**, both predicted to maintain trough concentrations above FeNO EC_{90} levels for >95% of the dosing interval, **is under development as a novel therapy for severe asthma, CRSwNP, and other indications**[7,8]

INTRODUCTION

- 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]
  - Disrupting this pathway by binding the TSLP ligand has proven beneficial to patients with asthma, regardless of phenotype, as indicated by clinical outcomes and key biomarkers (e.g., fractional exhaled nitric oxide (FeNO) and elevated blood eosinophils)[2,4]
- Verekitug (previously referred to as UPB-101 and ASP7266) is an investigational, novel, highly potent, recombinant, fully human monoclonal antibody targeting a TSLPR[5]
  - In vitro assays demonstrated verekitug has superior potency as expressed by IC_{90} (90% maximal inhibitory concentration) compared to previously published data evaluating tezepelumab, an anti-TSLP (ligand) antibody[5]
  - Verekitug demonstrated a generally favorable safety and tolerability profile, low immunogenicity, and predictable pharmacokinetics (PK) in a Phase 1 trial in healthy volunteers[6]
  - To our knowledge, verekitug is the only anti-TSLPR in development as a potential therapy for severe asthma and chronic rhinosinusitis with nasal polyps (CRSwNP)[5,7,8]
- Here we present data from a 32-week multiple ascending-dose (MAD) trial to assess the safety, tolerability, PK, immunogenicity, and pharmacodynamics (PD) of verekitug in participants with asthma

METHODS

Verekitug Phase 1b Trial in Patients With Mild to Moderate Asthma

32-Week Double-Blind, Placebo-Controlled, Multiple Ascending-Dose Trial

Enrolled participants with mild to moderate asthma **and** blood eosinophils ≥200 cells/µL or ≥150 cells/µL with FeNO >25 ppb[9]

TRIAL DESIGN[9]

Key eligibility criteria
- Adult participants aged 18 to 60 years
- Blood eosinophils ≥200 cells/µL **or** ≥150 cells/µL with FeNO >25 ppb
- Participants on stable, nonbiologic asthma medications with no dose adjustments, who experienced no exacerbations, and with no new prescribed drugs within 8 weeks prior to screening

Dose cohorts
- 100 mg verekitug (n=6) or PBO (n=2) SC Q4W Week 0, 4, and 8
- 200 mg verekitug (n=6) or PBO (n=2) SC Q4W Week 0, 4, and 8
- 300 mg verekitug (n=6) or PBO (n=2) SC Q12W Week 0 and 12
- 25 mg verekitug (n=6) or PBO (n=2) SC Single dose, Week 0

TRIAL OBJECTIVES

Objectives

PRIMARY OBJECTIVE
- To assess safety and tolerability of verekitug administered in MAD

KEY SECONDARY/EXPLORATORY OBJECTIVES
- To assess PD effect of verekitug on blood eosinophils and FeNO
- To assess the degree and duration of TSLPR occupancy in peripheral monocytes
- To assess immunogenicity and PK of verekitug

FeNO, fractional exhaled nitric oxide; MAD, multiple ascending-dose; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; ppb, parts per billion; Q4W, every 4 weeks; Q12W, every 12 weeks; SC, subcutaneous; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

RESULTS

Demographics and Baseline Characteristics

	Verekitug 100 mg Q4W ×3 (n=6)	Verekitug 200 mg Q4W ×3 (n=6)	Verekitug 300 mg Q12W ×2 (n=6)	Verekitug 25 mg ×1 (n=6)	Placebo (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/m² (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)

BMI, body mass index; cells/µL, cells per microliter; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ppb, parts per billion; Q4W, every 4 weeks; Q12W, every 12 weeks.

- Enrolled mild to moderate asthma population consistent with expected demographics of target population
- Majority were using inhaled corticosteroids
- Type 2 (T2) inflammatory phenotype[a]
- Baseline forced expiratory volume in 1 second (FEV_1) in normal range[b]
- Some heterogeneity across dosing groups as expected due to cohort design

[a]Markers of T2 inflammation include blood eosinophils ≥150/µL, and/or FeNO ≥20 ppb.[4]
[b]FEV_1% predicted values >80%.[10]

MAD Trial Treatment-Emergent Adverse Events Were Mild or Moderate

>90% of TEAEs in the trial were assessed by investigators as unrelated to study drug

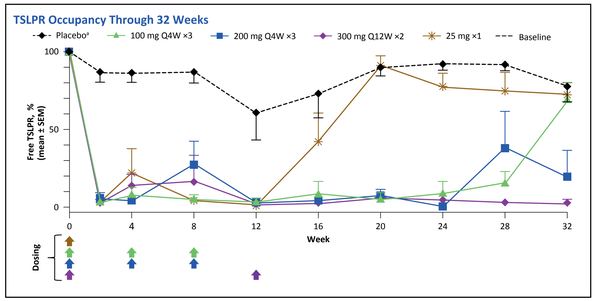
	Verekitug 100 mg Q4W ×3 (n=6)	Verekitug 200 mg Q4W ×3 (n=6)	Verekitug 300 mg Q12W ×2 (n=6)	Verekitug 25 mg ×1 (n=6)	Placebo (n=8)	Overall (N=32)
Number of TEAEs	19	17	12	9	25	82
Number of related TEAEs	2	1	3	0	1	7
Participants with any TEAE, n (%)	5 (83)	6 (100)	6 (100)	4 (67)	7 (88)	28 (88)
Mild, n (%)	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 related TEAE, n (%)	1 (17)	1 (17)	2 (33)	0	1 (13)	5 (16)
Participants with any serious TEAE, n	0	0	0	0	0	0
Participants with any TEAE leading to withdrawal, n	0	0	0	0	0	0
Participants with any TEAE leading to discontinuation of IMP, n	0	0	0	0	0	0

IMP, investigational medicinal product; MAD, multiple ascending-dose; Q4W, every 4 weeks; Q12W, every 12 weeks; TEAE, treatment-emergent adverse event.

- All treatment-emergent adverse events (TEAEs) were mild or moderate in severity
- No serious TEAEs
- No TEAEs leading to withdrawal from trial or discontinuation of study drug
- Most common TEAE was headache
- Injection site reactions self-limited and mild to moderate in severity
- No systemic allergic or immunologic TEAEs were reported
- No change in lung function or asthma symptoms

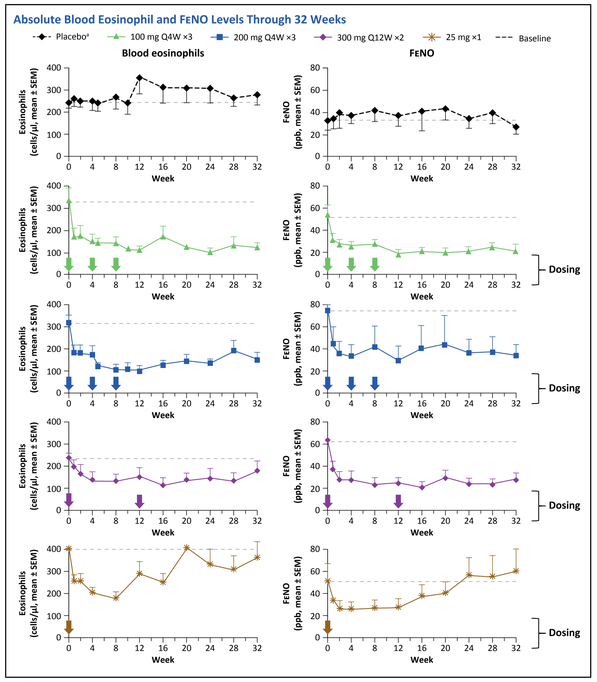
32-Week Data Showed Receptor Saturation and Sustained PD Effects of Verekitug for Up to 24 Weeks After Last Dose

TSLPR Occupancy Through 32 Weeks



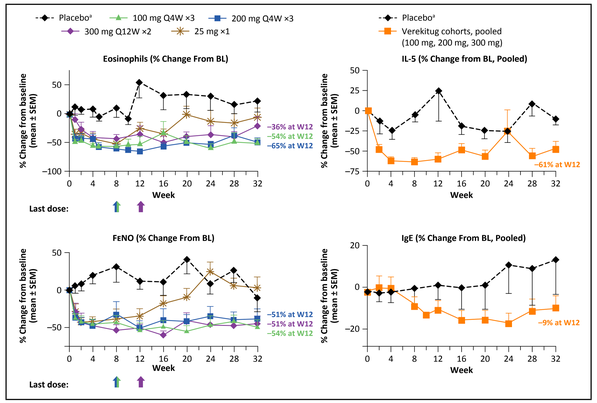
For the PD population, data from participants dosed per protocol shown.
Receptor occupancy was measured as percentage of free TSLPR relative to baseline in CD14+ monocytes/macrophages in whole blood.
[a]Data from the placebo groups in all cohorts were pooled for analysis.
PD, pharmacodynamics; Q4W, every 4 weeks; Q12W, every 12 weeks; SEM, standard error of the mean; TSLPR, thymic stromal lymphopoietin receptor.

Absolute Blood Eosinophil and FeNO Levels Through 32 Weeks



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, pharmacodynamics; ppb, parts per billion; Q4W, every 4 weeks; Q12W, every 12 weeks; SEM, standard error of the mean.

Verekitug Produced Rapid, Substantial, and Sustained Reductions in Blood Eosinophils, FeNO, and IL-5 and Gradual Reductions in IgE

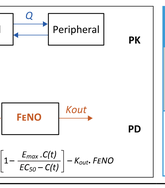


[a]Data from patients dosed per protocol shown.
BL, baseline; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; Q4W, every 4 weeks; Q12W, every 12 weeks; SEM, standard error mean; W12, week 12.

Verekitug Has High Potency in Asthma Patients as Estimated by PK/PD Modeling

- Impact on FeNO estimated to be substantially greater than that published for tezepelumab

Verekitug FeNO PK/PD Model Parameters Relative to Previously Reported Tezepelumab Data



Verekitug				Tezepelumab[11,a]			
E_{max} (reduction from BL)	EC_{50} (µg/mL)	EC_{80} (µg/mL)	EC_{90} (µg/mL)	E_{max} (reduction from BL)	EC_{50} (µg/mL)	EC_{80} (µg/mL)	EC_{90} (µg/mL)
43.5% (95% CI: 36.6-50.4)	0.008	0.03	0.07	27.8% (95% CI: 23.1-32.2)	2.5	10	22.5

BL, baseline; CL, clearance; EC_{50}, concentration at 50% of E_{max}; EC_{80}, concentration at 80% of E_{max}; EC_{90}, concentration at 90% of E_{max}; E_{max}, maximal effective concentration; FeNO, fractional exhaled nitric oxide; K, rate constant; PD, pharmacodynamics, PK, pharmacokinetics, Q, inter-compartmental clearance; Q12W, every 12 weeks, Q24W, every 24 weeks.
[a]A direct response model was used to describe the relationship between FeNO and exposure to tezepelumab.

- ≈1.5 times greater maximal reduction in PD (FeNO) based on third-party data evaluating tezepelumab
- Substantial estimated difference in potency (EC_{50} and EC_{90}) between verekitug and tezepelumab
- PK/PD modeling predicts 100 mg Q12W and 400 mg Q24W to maintain trough serum levels above EC_{90} levels for >95% of the dosing interval

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DISCLOSURES

AD, AK, SB, SS, and AS are employees of Upstream Bio, Inc. PL, IN, CMB, and OMB are consultants for Upstream Bio, Inc. AS, AK, SB, CMB, and OMB have received stock options from Upstream Bio, Inc.
AD and OMB have leadership or fiduciary roles with Upstream Bio, Inc. AS was employed by Amgen. DS has been a consultant for Upstream Bio, Inc., Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GlaxoSmithKline, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pulmatrix, Sanofi, Synairgen, Teva, Theravance Biopharma, and Verona Pharma.

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