OA5553

VALIANT: a phase 2 trial of the efficacy and safety of verekitug, a thymic stromal lymphopoietin (TSLP) receptor antagonist, for severe asthma

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KEY FINDINGS

Verekitug is a novel, unmodified, high-potency, fully human monoclonal antibody antagonist to the receptor for TSLP, and the only known TSLP receptor antagonist antibody in clinical development

In participants with severe asthma on standard background therapy, verekitug every 12 weeks or every 24 weeks led to statistically significant, clinically meaningful reductions in asthma exacerbations, with early and sustained improvements in lung function and asthma symptoms

Verekitug was well tolerated, with a safety profile comparable with placebo, and no new safety concerns identified

Verekitug, with extended dosing intervals of every 12 or 24 weeks, has the potential to improve outcomes in patients with severe asthma

INTRODUCTION

- Verekitug is a novel, unmodified, fully human monoclonal antibody antagonist to the receptor for TSLP, and the only known TSLP receptor antagonist antibody in clinical development[1–6]
- Low circulating verekitug concentrations are sufficient to saturate TSLP receptors and abrogate TSLP signaling, thus enabling extended dosing intervals[2–4]
- The phase 2 VIBRANT trial demonstrated statistically significant and durable reductions in nasal polyp score and symptom burden in patients with chronic rhinosinusitis with nasal polyps[5]
- Here, we report results of VALIANT, a phase 2, randomized, placebo-controlled, dose-ranging trial evaluating the efficacy and safety of verekitug in adults with uncontrolled, severe asthma

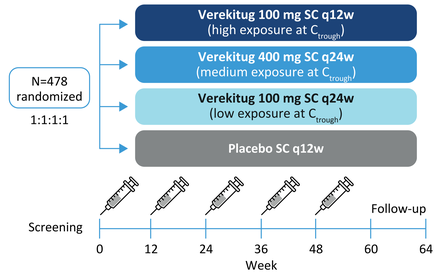
METHODS

- VALIANT (NCT06196879) is a multicenter, randomized, placebo-controlled phase 2 trial with up to 60-week treatment period, assessing efficacy and safety of verekitug vs placebo in patients with severe asthma (**Figure 1**)

METHODS

Figure 1. Study design

Key inclusion criteria
Aged 18–80 years
Physician-diagnosed asthma for ≥ 12 months
Pre-BD FEV_1 ≥ 30% and ≤ 80% predicted with evidence of BD reversibility
Treatment with medium/high-dose ICS ≥ 3 months
Documented history of asthma exacerbation(s) in past 12 months as defined by any of: ≥ 2 events requiring SCS ≥ 1 event requiring inpatient care ≥ 24 hours ≥ 1 event requiring SCS + FeNO ≥ 50 ppb
ACQ-6 ≥ 1.5



Variable treatment period design: Minimum 24 weeks, maximum 60 weeks

Endpoints	
Primary	Annualized asthma exacerbation rate (AAER) from baseline up to week 60 (90% power to detect ≥ 50% reduction vs placebo)
Key secondary endpoints *(study not powered for secondary endpoints)*	• Change from baseline to week 60: – Pre-BD FEV_1 – FeNO – ACQ-6 • Prespecified 24-week estimate for all secondary endpoints

ACQ-6, Asthma Control Questionnaire-6; BD, bronchodilator; FeNO, fractionated exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; ppb, parts per billion; q*w, every * weeks; SC, subcutaneous; SCS, systemic corticosteroids.

RESULTS

Disposition and treatment follow-up

- A total of 478 participants were randomized (verekitug 100 mg q12w, n=121; verekitug 400 mg q24w, n=118; verekitug 100 mg q24w, n=120; placebo, n=119)
  - VALIANT trial design specified a variable treatment period of 24–60 weeks
  - ~15% reached 60 weeks of treatment; 91% received 3 or more doses of study intervention
  - Treatment duration was similar across arms, at a median of ~37 weeks

RESULTS

Baseline characteristics

- Baseline characteristics were generally balanced across arms (**Table 1**)

Primary endpoint – AAER

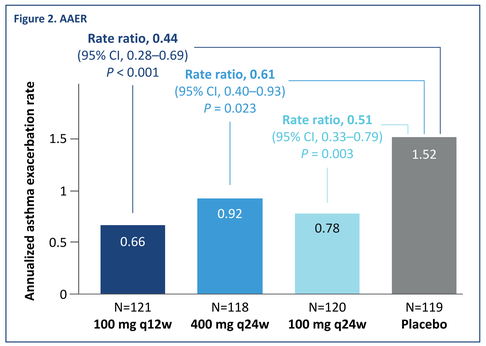
- Asthma exacerbations were significantly reduced with verekitug (**Figure 2**)

Table 1. Baseline characteristics

		Verekitug 100 mg q12w N=121	Verekitug 400 mg q24w N=118	Verekitug 100 mg q24w N=120	Placebo N=119
Age, mean (SD), years		54.6 (12.2)	53.8 (11.7)	51.7 (15.4)	54.0 (13.1)
Race, n (%)	White	91 (75.2)	90 (76.3)	90 (75.0)	93 (78.2)
	Black/African American	13 (10.7)	12 (10.2)	15 (12.5)	8 (6.7)
	Other	17 (14.1)	16 (13.6)	15 (12.5)	18 (15.1)
Region, n (%)	North America	32 (26.4)	29 (24.6)	33 (27.5)	38 (31.9)
	Western Europe	17 (14.0)	13 (11.0)	15 (12.5)	19 (16.0)
	Central/Eastern Europe	35 (28.9)	38 (32.2)	41 (34.2)	33 (27.7)
	Rest of the world[a]	37 (30.6)	38 (32.2)	31 (25.8)	29 (24.4)
Dose of inhaled glucocorticoids, n (%)	Medium	63 (52.1)	62 (52.5)	59 (49.2)	61 (51.3)
	High[b]	58 (47.9)	56 (47.5)	61 (50.8)	58 (48.7)
Historical asthma exacerbations, n (%)	≥ 2 ER visits + SCS ≥ 3 days	99 (81.8)	96 (81.4)	96 (80.0)	100 (84.0)
	≥ 1 hospitalization	14 (11.6)	16 (13.6)	20 (16.7)	11 (9.2)
Asthma duration, mean (SD), years		27.2 (17.0)	22.0 (17.0)	24.2 (15.3)	26.8 (17.6)
Prebronchodilator FEV_1, mL, mean (SD)		1802 (620)	1831 (590)	1878 (623)	1873 (644)
Baseline FeNO, mean (SD), ppb		41.9 (44.8)	39.3 (46.5)	32.7 (28.8)	37.9 (37.2)
Baseline ACQ-6 score, mean		2.72 (0.66)	2.54 (0.57)	2.67 (0.67)	2.65 (0.67)
Blood eosinophil count, cells/μL	Median	290	270	260	250
	(min, max)	(30, 1850)	(30, 3090)	(30, 2720)	(30, 2090)

[a]Includes Latin America, Asia-Pacific, and South Africa. [b]Medium-dose ICS without oral corticosteroid; high-dose ICS and/or oral corticosteroids.
ER, emergency room; SD, standard deviation.

Figure 2. AAER



CI, confidence interval.

Key secondary endpoints

- Verekitug led to meaningful improvements in secondary endpoints at week 24 that were generally sustained to week 60 (**Table 2**)
- Verekitug improvements were observed as early as week 2 across secondary outcomes

Subgroup analysis

- Subgroup analysis demonstrated an 87% AAER reduction among participants with high blood eosinophil counts and robust FEV_1 improvement across most subgroups with the 100 mg q12w dose vs placebo (**Figure 3**)

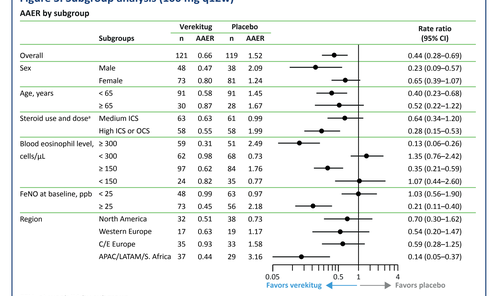
Table 2. Key secondary endpoints

Change from baseline	Endpoint	Verekitug 100 mg q12w N=121	Verekitug 400 mg q24w N=118	Verekitug 100 mg q24w N=120
Week 24	**Pre-BD FEV_1**	N=108	N=108	N=105
	LSM diff vs PBO (95% CI), mL	**99** (9–189)	**157** (67–248)	**47** (−44 to 137)
	Nominal *P* value	0.0317	0.0007	0.3102
	ACQ-6	N=114	N=111	N=112
	LSM diff vs PBO (95% CI)	**−0.21** (−0.43 to 0.01)	**−0.34** (−0.57 to −0.12)	**−0.23** (−0.45 to −0.01)
	Nominal *P* value	0.0651	0.0027	0.0447
	FeNO	N=113	N=109	N=111
	LSM diff vs PBO (95% CI), ppb	**−13.7** (−18.6 to −8.8)	**−12.2** (−17.2 to −7.3)	**−7.5** (−12.4 to −2.6)
	Nominal *P* value	< 0.0001	< 0.0001	0.0028
Week 60	**Pre-BD FEV_1**	N=19	N=18	N=17
	LSM diff vs PBO (95% CI), mL	**150** (−45 to 346)	**140** (−59 to 339)	**85** (−116 to 287)
	Nominal *P* value	0.1309	0.1674	0.4057
	ACQ-6	N=19	N=19	N=17
	LSM diff vs PBO (95% CI)	**0.06** (−0.42 to 0.55)	**−0.21** (−0.70 to 0.28)	**−0.24** (−0.74 to 0.26)
	Nominal *P* value	0.8000	0.3928	0.3541
	FeNO	N=19	N=18	N=17
	LSM diff vs PBO (95% CI), ppb	**−20.4** (−31.5 to −9.4)	**−26.3** (−37.6 to −15.0)	**−17.0** (−28.4 to −5.6)
	Nominal *P* value	0.0003	< 0.0001	0.0036

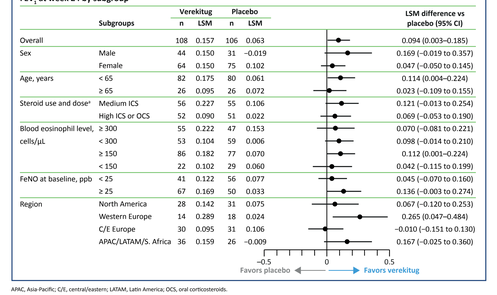
Diff, difference; LSM, least squares mean; PBO, placebo.

Figure 3. Subgroup analysis (100 mg q12w)

AAER by subgroup



FEV_1 at week 24 by subgroup



APAC, Asia-Pacific; C/E, central/eastern; LATAM, Latin America; OCS, oral corticosteroids.

Safety

- Verekitug was well tolerated, with a similar safety profile to placebo (**Table 3**)
- The most common TEAEs were nasopharyngitis, urinary tract infections, headache, and bronchitis
- Injection site reactions were similar across verekitug groups and placebo, and of mild severity with no grade 3 or higher event
- Antidrug antibodies were detected in 50%–60% of participants and had no impact on safety findings, pharmacodynamics, or efficacy

Table 3. Safety summary

	Verekitug 100 mg q12w N=121	Verekitug 400 mg q24w N=118	Verekitug 100 mg q24w N=119	Placebo N=119
Any TEAE	75 (62.0)	69 (58.5)	74 (62.2)	78 (65.5)
TEAE related to study treatment[a]	10 (8.3)	4 (3.4)	9 (7.6)	8 (6.7)
Any serious TEAEs	5 (4.1)	8 (6.8)	6 (5.0)	10 (8.4)
Any serious TEAEs related to study treatment[a]	0	1 (0.8)	0	0
TEAEs with outcome of death	0	0	0	0
Grade ≥ 3 TEAEs	8 (6.6)	13 (11.0)	10 (8.4)	10 (8.4)
TEAEs leading to study discontinuation/interruption	4 (3.3)	1 (0.8)	4 (3.4)	2 (1.7)
TEAEs of special interest[b]	2 (1.7)	0	1 (0.8)	2 (1.7)
Most common TEAEs (≥ 5%)[c]				
Nasopharyngitis	13 (10.7)	9 (7.6)	9 (7.6)	12 (10.1)
Urinary tract infections	7 (5.8)	7 (5.9)	6 (5.0)	6 (5.0)
Headache	8 (6.6)	3 (2.5)	8 (6.7)	6 (5.0)
Bronchitis	9 (7.4)	8 (6.8)	2 (1.7)	3 (2.5)
Upper respiratory tract infection	3 (2.5)	5 (4.2)	6 (5.0)	7 (5.9)
Influenza	4 (3.3)	3 (2.5)	5 (4.2)	8 (6.7)
Asthma	3 (2.5)	3 (2.5)	6 (5.0)	7 (5.9)
Back pain	6 (5.0)	3 (2.5)	2 (1.7)	4 (3.4)

[a]Adverse events assessed by the investigator as related to study treatment or adverse events with missing relationship to study treatment. [b]Adverse events associated with the drug class. [c]Adverse events were coded according to the preferred terms of the Medical Dictionary for Regulatory Activities, version 28.0.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Verekitug every 12 or 24 weeks led to statistically significant, clinically meaningful reductions in asthma exacerbations
- Verekitug improved secondary outcomes of FEV_1, ACQ-6, and FeNO, with improvements observed as early as week 2 in all regimens
- AAER reductions were up to 87% and up to 65% among participants with blood eosinophil counts ≥ 300 cells/μL and ≥ 150 cells/μL, respectively
  - While improvements in FEV_1 were observed in participants with lower blood eosinophil counts, no reductions in AAER were observed in this subgroup
- Verekitug was well tolerated, with a safety profile comparable with placebo, and no new safety concerns identified
- A phase 3 trial is planned to confirm the efficacy and safety of verekitug

ACKNOWLEDGMENTS

We would like to thank all trial participants, their families and caregivers, as well as investigators and site staff. Under the direction of the authors, medical writing assistance was provided by Lewis Cawkwell, PhD, of Parexel International, and supported by Upstream Bio, Inc.

FUNDING AND DISCLOSURES

This study was funded by Upstream Bio, Inc., Waltham, MA, USA.
M.E. Wechsler has received grants or contracts from AstraZeneca, GlaxoSmithKline, and Sanofi/Regeneron; consulting fees from AbbVie, Allakos, Amgen, Apogee, Areteia Therapeutics, Arrowhead Pharmaceuticals, AstraZeneca, Avalo Therapeutics, Belenos Bio, Cellidex, Connect Biopharma, CytoReason, Eli Lilly, Enveda, Equillium, General Medicines, Gilead, GlaxoSmithKline, Jasper, Kinaset, Kymera, Merck, myBiometry, Pharming, Phylaxis, Pfizer, Pulmatrix, Rapt Therapeutics, Recludix Pharma, Regeneron, Roche/Genentech, Sanofi/Genzyme, Sentien, Sound Biologics, Spiro Medical, Tetherex Pharmaceuticals, Uniquity Bio, Upstream Bio, Verona Pharma, and Zura Bio; speaker fees from AstraZeneca, GlaxoSmithKline, Amgen, and Sanofi/Regeneron; participated on a data safety monitoring board or advisory board for Sentien; and has stock or stock options in Upstream Bio.

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