Top-line Results for the Phase 2 VALIANT Trial in Severe Asthma

February 11, 2026

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Agenda

Introduction	Rand Sutherland, MD Chief Executive Officer
VALIANT Phase 2 Top-line Results	Aaron Deykin, MD Chief Medical Officer and Head of R&D
Path Forward	Rand Sutherland, MD
Analyst Q&A	Rand Sutherland, MD Aaron Deykin, MD

UpstreamBIO™

Phase 2 VALIANT study met primary endpoint in reduction of AAER

Statistically significant and clinically meaningful reductions in AAER with verekitug dosed for up to 60 weeks **at 100mg every 12 weeks and 400mg every 24 weeks**

Both verekitug doses also delivered clinically meaningful improvements in lung function (FEV_1) and exhaled nitric oxide (FeNO)

100mg q12w

- **56%** reduction in **AAER** (p<0.0003)
- **122mL** improvement in **FEV_1**
- **20.4ppb*** reduction in **FeNO**

43.5% * reduction vs baseline

400mg q24w

- **39%** reduction in **AAER** (p<0.02)
- **139mL** improvement in **FEV_1**
- **26.3ppb*** reduction in **FeNO**

44.9% * reduction vs baseline

Verekitug was generally well tolerated, with a safety profile consistent with prior studies

AAER, annualized asthma exacerbation rates

* Placebo-corrected

About Upstream Bio

Clinical-stage immunology company focused on severe respiratory diseases

Developing the only known clinical-stage antagonist of the TSLP receptor

→ Verekitug's pharmacology is unique and characterized by rapid, complete and sustained occupancy of the TSLP receptor for up to 24 weeks after the last dose

Studying verekitug across multiple indications with high unmet need

→ All trials randomized and placebo-controlled, with registration-enabling endpoints

- VALIANT: Ph 2 trial in severe asthma – Reporting out positive top-line results today
  - VALOUR, long-term extension study – Currently enrolling eligible participants who completed VALIANT
- VIBRANT: Ph 2 trial in CRSwNP – Reported positive top-line results in September 2025
- VENTURE: Ph 2 trial in COPD – Currently enrolling and enrollment >60% complete

Addressing significant commercial opportunities

→ Severe asthma and COPD markets are expanding and expected to drive a $35B+ global biologics market by 2033

Cash, cash equivalents and short-term investments of ~$341.5M as of Dec 31, 2025[1] expected to fund planned operations through 2027

TSLP, thymic stromal lymphopoietin; CRSwNP, chronic rhinosinusitis with nasal polyps; COPD, chronic obstructive pulmonary disease.

[1] Preliminary, unaudited and subject to change.

Large and growing commercial opportunity in core indications, with asthma and COPD alone expected to be a $35B+ global biologics market in 2033

Severe Asthma

2023: $7.5B[2]
2032e: $12.6B[2]

~1.3M
Biologic eligible severe asthma patients in the US[1]

~80% of biologic sales are in the US[2]

<25%
of eligible patients with severe asthma are currently estimated to receive biologic therapies[3]

>$12.5B
In 2033, peak global sales for all approved biologics in severe asthma are estimated to be at least $12.5 billion[2]

$3B
Tezspire is projected to reach peak global annual sales of over $3B for severe asthma alone in 2032,[2] and achieved more than 20% of new to brand share of prescriptions in the US in its first commercial year[4]

CRSwNP

2025: >$1.5B[5,6*]

- → Biologics to treat CRSwNP have been available for only ~6 years, now with 4 approved treatment options
- → Use of biologics is growing rapidly, with >20% increases in number of claims, prescribing HCPs, and patients receiving biologics to manage CRSwNP[4]
- → Current global biologics sales in CRSwNP alone estimated to be $1.5B+ annually[5,6]
- → ~300K+ biologic eligible CRSwNP patients in the US[1], with significant potential for growth as the proportion of eligible patients taking a biologic increases and novel biologics enter the market

COPD

2033e: $23B[2]

- → Currently ~1.1M severe COPD patients in the US, expected to be ~3.5M globally by 2033[2]; ~70% of 2033 biologic sales are expected to be in the US[2]
- → Currently only 2 biologics are approved for the treatment of COPD
- → If approved in this indication, Tezspire is projected to reach global annual sales of over $5B for COPD alone in 2033[2]

UpstreamBIO™

[1] Upstream Bio Analysis 2025 [2] Datamonitor [3] IQVIA Claims Data (Unique Asthma Pts on Biologics FY '24, Pt Growth Rate '20-'24) [4] Amgen Investor Presentation May 2024 [5] Symphony Claims Data (June '24 – May '25) [6] Manufacturer Sales and Pricing Disclosures

valiant
Asthma study

Phase 2 VALIANT Trial in Severe Asthma

Aaron Deykin, MD
Chief Medical Officer and Head of R&D

VALIANT phase 2 trial design

Enrolled 478 patients with severe asthma across 15 countries[1-3]

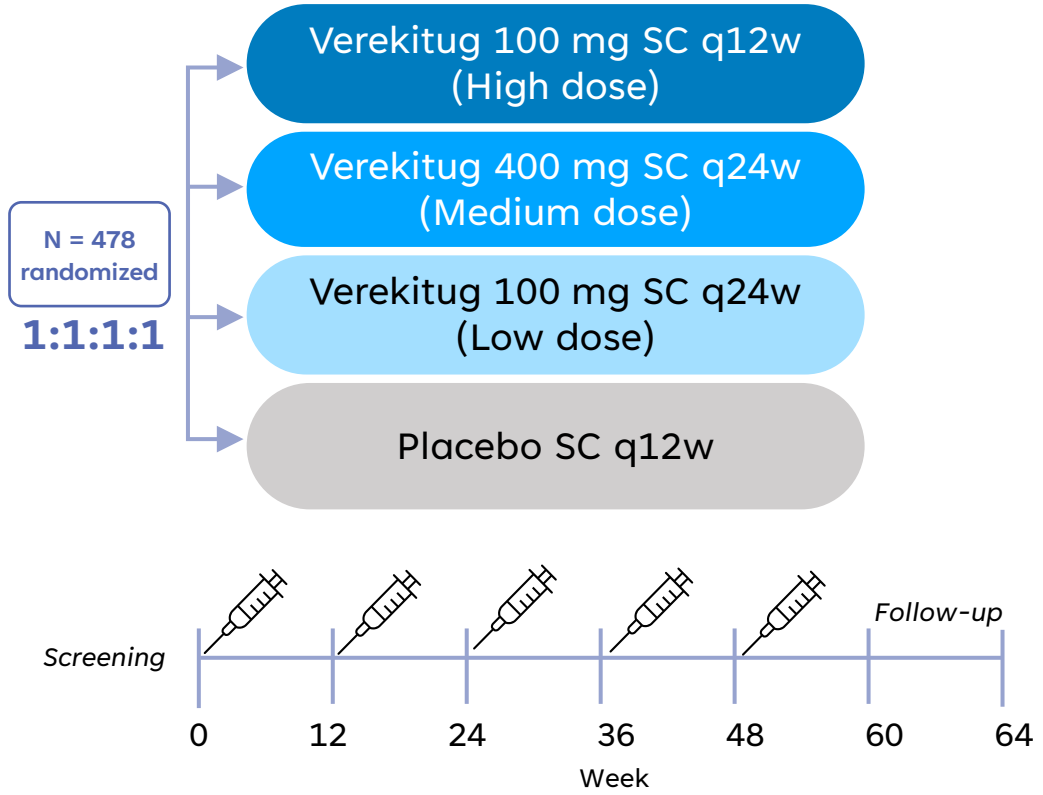
Global, randomized, placebo-controlled phase 2 trial with up to 60-week treatment period (NCT06196879)

Key inclusion criteria:

- Aged 18–80 years
- Physician-diagnosed asthma for at least 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 req. SCS
  - ≥ 1 event req. inpatient care ≥ 24 hrs
  - ≥ 1 event req. SCS + FeNO ≥ 50 ppb
- ACQ-6 ≥1.5

Variable Treatment Period Design:

Min 24 weeks - Max 60 weeks



Primary endpoint:

- Annualized Asthma Exacerbation Rate (AAER) from baseline up to Week 60

90% power to detect ≥50% reduction vs placebo

Secondary endpoints:

(Study not powered for secondary endpoints)

- Change from baseline to week 60
  - Pre-BD FEV_1
  - FeNO
  - ACQ-6

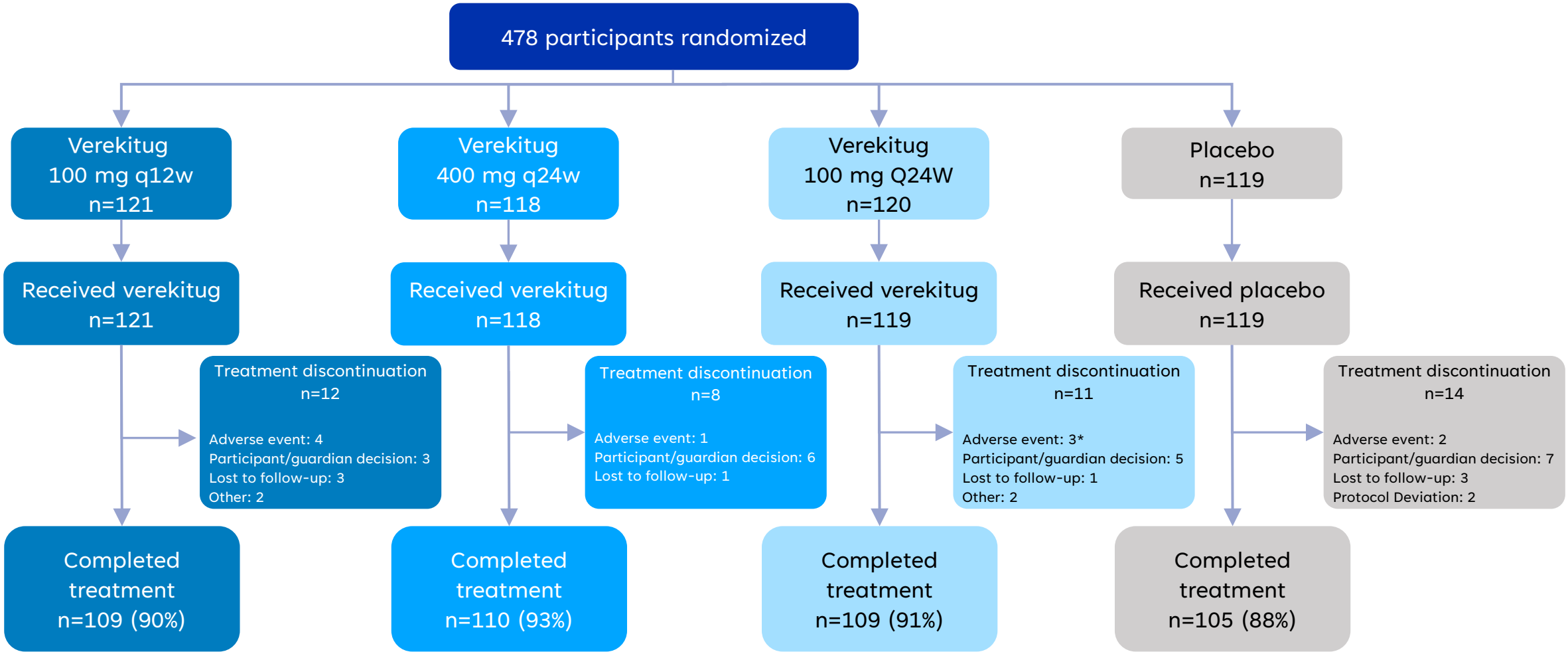
Pre-specified 24-week estimate for all secondary endpoints

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

1. Data on file. Table 14.1.1.1. 2. NCT06196879. https://clinicaltrials.gov/study/NCT06196879. 3. VALIANT Study Protocol V4.0.

VALIANT ITT population disposition

433 (91%) of participants completed treatment



*Including one participant who was not dosed due to AE.
AE, adverse event; ITT, intent-to-treat; q×w, every × weeks.
Data on file. Table 14.1.1.1.

Baseline characteristics were balanced across treatment groups

Reflect an uncontrolled, severe asthma population

		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[1]		54.6 (12.15)	53.8 (11.74)	51.7 (15.37)	54.0 (13.06)
Female sex, n (%)[1]		73 (60.3)	79 (66.9)	72 (60.0)	81 (68.1)
Race, n (%)[1]	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 (%)[1]	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†	37 (30.6)	38 (32.2)	31 (25.8)	29 (24.4)
Asthma duration, mean (SD), years[2]		27.2 (16.98)	22.0 (17.03)	24.2 (15.28)	26.8 (17.55)
ICS use, n (%)[2]	Medium / high dose*	63 (52.1) / 58 (47.9)	62 (52.5) / 56 (47.5)	59 (49.2) / 61 (50.8)	61 (51.3) / 58 (48.7)
Prebronchodilator FEV_1, liter, mean (SD)[2]		1.69 (0.58)	1.75 (0.58)	1.84 (0.60)	1.77 (0.59)
Baseline FeNO, mean ppb (SD)[2]		41.9 (44.79)	39.3 (46.47)	32.7 (28.80)	37.9 (37.20)
Baseline ACQ-6 score, mean[3]		2.72 (0.655)	2.54 (0.573)	2.67 (0.674)	2.65 (0.674)
Blood eosinophil count, cells/µL[2]	Median (min-max)	290 (30, 1850)	270 (30, 3090)	260 (30, 2720)	250 (30, 2090)

*Median dose inhaled corticosteroids without oral corticosteroid; high dose ICS and/or oral corticosteroids; †Includes Latin America, Asia-Pacific and South Africa. FeNO, fractionated exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; q×w, every × weeks; SD, standard deviation.
1. Data on file. Table 14.1.3.1. 2. Data on file. Table 14.1.3.2.1. 3. Data on file. Table 14.2.2.4.2.

Verekitug was generally well tolerated across treatment groups

	Verekitug 100 mg q12w N=121	Verekitug 400 mg q24w N=118	Verekitug 100 mg q24w N=119	Placebo N=119
AE category, % of participants[1]				
Any TEAE	62.0	58.5	62.2	65.5
Any grade 3-5 TEAEs	6.6	11.0	8.4	8.4
Any TEAEs with outcome of death	0	0	0	0
Any serious TEAEs	4.1	6.8	5.0	8.4
Any TEAEs leading to study drug discontinuation/interruption	3.3	0.8	3.4	1.7
Most common TEAE, any grade (≥5% in any cohort)[2]				
Nasopharyngitis	10.7	7.6	7.6	10.1
Bronchitis	7.4	6.8	1.7	2.5
Headache	6.6	2.5	6.7	5.0
Urinary tract infection	5.8	5.9	5.0	5.0
Back pain	5.0	2.5	1.7	3.4
Influenza	3.3	2.5	4.2	6.7
Asthma	2.5	2.5	5.0	5.9
Upper respiratory tract infection	2.5	4.2	5.0	5.9
Immunogenicity[3]				
ADA positive*	60.3	50.8	60.5	--

- Overall incidence of TEAEs was similar across treatment groups
- Serious TEAEs were similar across treatment groups
- ADAs did not impact safety

*Numbers are treatment-induced and treatment-boosted ADA.
Safety follow-up is ongoing.
ADA, anti-drug antibody; AE, adverse event; q×w, every × weeks; TEAE, treatment-emergent adverse event.
1. Data on File. Table 14.3.1.1. 2. Data on File. Table 14.3.1.2. 3. Data on File. Table 14.2.3.16.3.

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valiant Asthma study

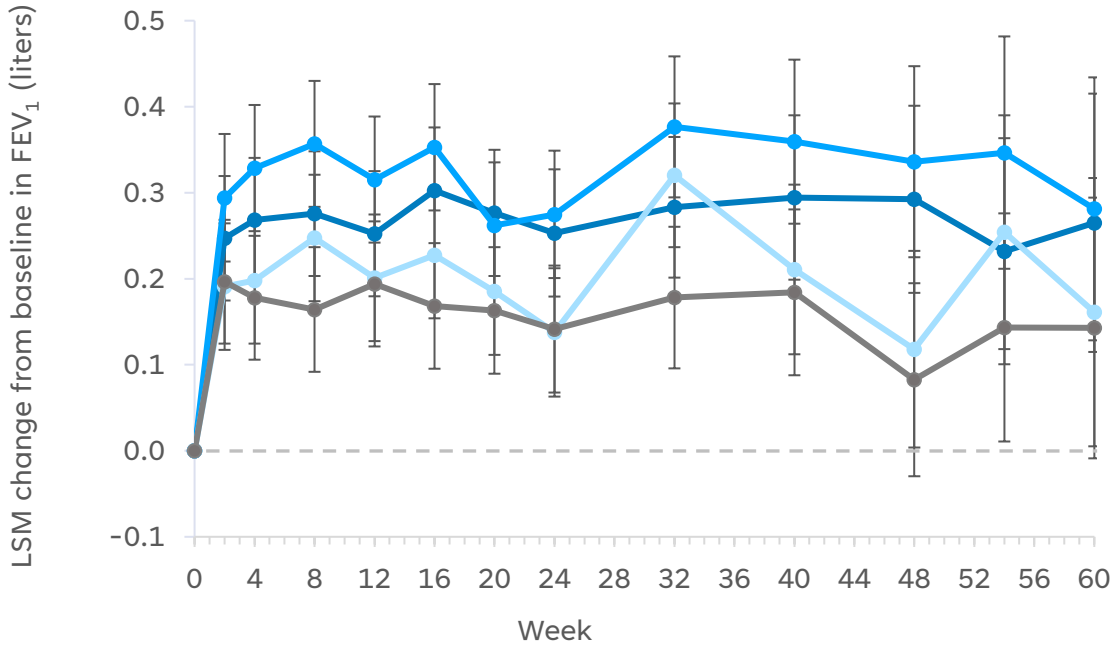
Verekitug led to statistically significant improvements in AAER at 60 weeks with both q12w and q24w regimens

		Verekitug 100 mg q12w n=121	Verekitug 400 mg q24w n=118	Verekitug 100 mg q24w n=120	Placebo n=119
Primary endpoint	**AAER over 60 weeks (95% CI)[1*]**	0.66 (0.47, 0.94)	0.92 (0.67, 1.27)	0.78 (0.55, 1.08)	1.52 (1.13, 2.03)
	Rate ratio vs placebo (95% CI) *P* value	**0.44** (0.28, 0.69) **0.0003**	**0.61** (0.40, 0.93) **0.0227**	**0.51** (0.33, 0.79) **0.0028**	–
Secondary endpoints[†]	**Prebronchodilator FEV_1 (mL) change from baseline at 60 weeks, LSM (95% CI)[2]**	265 (115, 415)	281 (128, 434)	161 (5, 317)	143 (-9, 294)
	LSM difference vs placebo (95% CI) Nominal *P* value	**122 (-90, 335)** 0.2589	**139 (-76, 353)** 0.2047	**18 (-198, 235)** 0.8678	–
	FeNO (ppb) change from baseline at 60 weeks, LSM (95% CI)[3]	-17.4 (-25.2, -9.6)	-23.3 (-31.4, -15.1)	-13.9 (-22.2, -5.6)	3.1 (-4.8, 11.0)
	LSM difference vs placebo (95% CI) Nominal *P* value	**-20.4 (-31.5, -9.4)** 0.0003	**-26.3 (-37.6, -15.0)** <0.0001	**-17.0 (-28.4, -5.6)** 0.0036	–
	ACQ-6 change from baseline at 60 weeks, LSM (95% CI)[4]	-1.04 (-1.39, -0.70)	-1.32 (-1.67, -0.96)	-1.34 (-1.71, -0.97)	-1.10 (-1.45, -0.76)
	LSM difference vs placebo (95% CI) Nominal *P* value	**0.06 (-0.42, 0.55)** 0.8000	**-0.21 (-0.70, 0.28)** 0.3928	**-0.24 (-0.74, 0.26)** 0.3541	–

*AAER, Rate Ratio, 95% confidence intervals, and p-values are from a negative binomial regression model with number of asthma exacerbations as the dependent variable and fixed effects for study treatment, region, baseline steroid use as randomized, and baseline eosinophil level as randomized.
†Secondary endpoints were not powered for statistical significance.
ACQ-6, Asthma Control Questionnaire; AAER, annual asthma exacerbation rate; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LSM, least squares mean; ppb, parts per billion; q×w, every × weeks
1. Data on File. Table 14.2.1.1.1. 2. Data on File. Table 14.2.2.2.1.3. 3. Data on File. Table 14.2.2.3.2. 4. Data on File. Table 14.2.2.4.2.

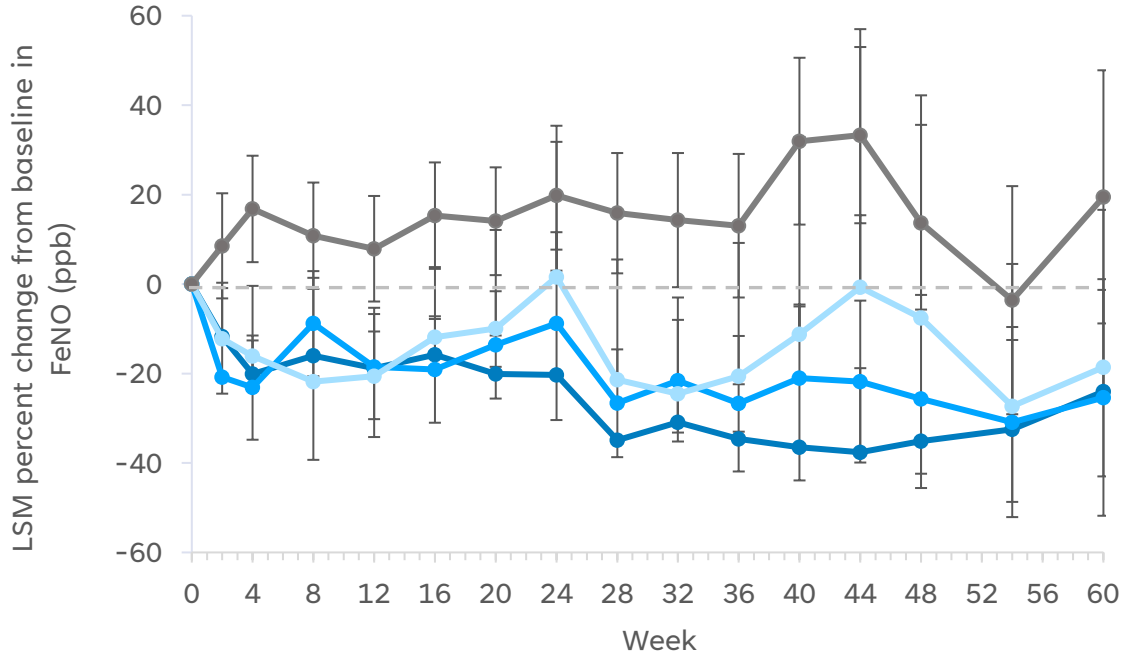
Verekitug 100 mg q12w and 400 mg q24w doses led to numerical improvements in lung function and FeNO as early as week 2 and sustained over 60 weeks

FEV_1 over 60 weeks[1]



No. of participants												
Verekitug 100 mg q12w	118	114	111	110	106	109	106	66	43	35	21	18
Verekitug 400 mg q24w	117	110	111	111	110	114	107	67	44	32	20	18
Verekitug 100 mg q24w	116	110	110	109	112	109	103	62	40	31	21	17
Placebo	119	113	110	110	109	105	106	64	43	32	22	18

FeNO over 60 weeks[2]



No. of participants															
Verekitug 100 mg q12w	121	118	117	114	108	115	113	78	69	64	47	40	38	23	19
Verekitug 400 mg q24w	118	115	115	112	109	112	109	82	66	60	46	38	34	21	18
Verekitug 100 mg q24w	119	115	115	113	113	113	111	84	66	62	42	35	31	21	17
Placebo	119	109	110	113	110	108	108	83	67	60	43	40	32	23	19

Secondary endpoints were not powered for statistical significance.
FeNO, fractionated exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LSM, least squares mean; ppb, parts per billion; q×w, every × weeks.
1. Data on file. Table 14.2.2.2.1.3. 2. Data on file. Table 14.2.2.3.5.

Verekitug led to clinically meaningful improvements in all secondary endpoints and biomarkers at 24 weeks

		Verekitug 100 mg q12w n=121	Verekitug 400 mg q24w n=118	Verekitug 100 mg q24w n=120	Placebo n=119
Secondary endpoints	**Prebronchodilator FEV_1 (ml) change from baseline at 24 weeks, LSM (95% CI)[1]**	253 (179, 327)	275 (201, 349)	138 (63, 212)	142 (68, 215)
	LSM difference vs placebo (95% CI) Nominal *P* value	**112** (8, 216) **0.0350**	**133** (30, 237) **0.0119**	**-4** (-101, 100) **0.9419**	–
	FeNO (ppb) change from baseline at 24 weeks, LSM (95% CI)[2]	-15.9 (-19.3, -12.4)	-14.4 (-17.9, -10.9)	-9.7 (-13.1, -6.2)	-2.2 (-5.7, 1.3)
	LSM difference vs placebo (95% CI) Nominal *P* value	**-13.7** (-18.6, -8.8) **<0.0001**	**-12.2** (-17.2, -7.3) **<0.0001**	**-7.5** (-12.4, -2.6) **0.0028**	–
	ACQ-6 change from baseline at 24 weeks, LSM (95% CI)[3]	-1.12 (-1.28, -0.97)	-1.26 (-1.41, -1.10)	-1.14 (-1.30, -0.98)	-0.91 (-1.07, -0.75)
	LSM difference vs placebo (95% CI) Nominal *P* value	-0.21 (-0.43, 0.01) **0.0651**	-0.34 (-0.57, -0.12) **0.0027**	-0.23 (-0.45, -0.01) **0.0447**	–

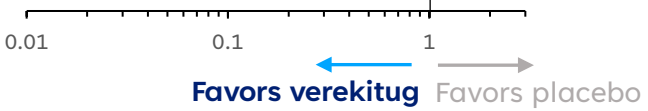
P values for secondary endpoints are nominal and not adjusted for multiple comparisons.
ACQ-6, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LSM, least squares mean; ppb, parts per billion; q×w, every × weeks
1. Data on File. Table 14.2.2.2.1.3. 2. Data on File. Table 14.2.2.3.2. 3. Data on File. Table 14.2.2.4.2.

Verekitug 100 mg q12w demonstrated clinical effect in AAER and FEV_1 in most subgroups

Results were similar in the 400 mg q24w and 100 mg q24w dose cohorts

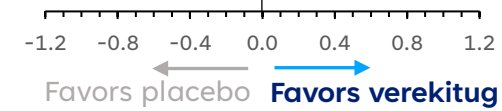
AAER by subgroup[1]

Subgroups		Verekitug n	Verekitug AAER	Placebo n	Placebo AAER	Rate ratio (95% CI)
Overall		**121**	**0.66**	**119**	**1.52**	0.44 (0.28, 0.69)
Age, years	< 65	91	0.58	91	1.45	0.40 (0.23, 0.68)
	≥ 65	30	0.87	28	1.67	0.52 (0.22, 1.22)
Sex	Male	48	0.47	38	2.09	0.23 (0.09, 0.57)
	Female	73	0.80	81	1.24	0.65 (0.39, 1.07)
Region	North America	32	0.51	38	0.73	0.70 (0.30, 1.62)
	Western Europe	17	0.63	19	1.17	0.54 (0.20, 1.47)
	Central/Eastern Europe	35	0.93	33	1.58	0.59 (0.28, 1.25)
	Rest of World	37	0.44	29	3.16	0.14 (0.05, 0.37)
Steroid use and dose	Medium ICS without OCS	63	0.63	61	0.99	0.64 (0.34, 1.20)
	High ICS and/or OCS	58	0.55	58	1.99	0.28 (0.15, 0.53)
Blood eosinophil level, cells/µL	< 300	62	0.98	68	0.73	1.35 (0.76, 2.42)
	≥ 300	59	0.31	51	2.49	0.13 (0.06, 0.26)
FeNo at baseline, ppb	< 25	48	0.99	63	0.97	1.03 (0.56, 1.90)
	≥ 25	73	0.45	56	2.18	0.21 (0.11, 0.40)



FEV_1 by subgroup[2]

Subgroups		Verekitug n	Verekitug LSM	Placebo n	Placebo LSM	LSM difference vs placebo (95% CI)
Overall		**18**	**0.265**	**18**	**0.143**	0.122 (-0.090, 0.335)
Age, years	< 65	14	0.288	13	0.144	0.145 (-0.114, 0.403)
	≥ 65	4	0.159	5	0.164	-0.006 (-0.332, 0.320)
Sex	Male	8	0.300	8	0.122	0.178 (-0.207, 0.562)
	Female	10	0.257	10	0.144	0.113 (-0.136, 0.362)
Region	North America	10	0.296	13	0.141	0.155 (-0.161, 0.471)
	Western Europe	2	0.483	2	0.383	0.101 (-0.441, 0.642)
	Central/Eastern Europe	4	0.072	2	0.328	-0.256 (-0.710, 0.198)
	Rest of World	2	0.327	1	0.186	0.142 (-0.649, 0.932)
Steroid use and dose	Medium ICS without OCS	11	0.247	12	0.145	0.102 (-0.187, 0.390)
	High ICS and/or OCS	7	0.311	6	0.131	0.180 (-0.146, 0.506)
Blood eosinophil level, cells/µL	< 300	7	0.166	10	0.027	0.140 (-0.144, 0.423)
	≥ 300	11	0.364	8	0.313	0.051 (-0.278, 0.380)
FeNo at baseline, ppb	< 25	4	0.096	4	0.015	0.082 (-0.274, 0.437)
	≥ 25	14	0.319	14	0.182	0.137 (-0.142, 0.415)



AAER, annualized asthma exacerbation rate; FEV_1, forced expiratory volume in 1 second; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroid; ppb, parts per billion; LSM, least square mean; q24w, every 24 weeks.
1. Data on File. Figure 14.2.1.1.4.2. 2. Figure 14.2.2.2.1.6.

Phase 2 VALIANT study met primary endpoint in reduction of AAER

Statistically significant and clinically meaningful reductions in AAER with verekitug dosed for up to 60 weeks **at 100mg every 12 weeks and 400mg every 24 weeks**

Both verekitug doses also delivered clinically meaningful improvements in lung function (FEV_1) and exhaled nitric oxide (FeNO)

100mg q12w

- **56%** reduction in **AAER** (p<0.0003)
- **122mL** improvement in **FEV_1**
- **20.4ppb*** reduction in **FeNO**

43.5% * reduction vs baseline

400mg q24w

- **39%** reduction in **AAER** (p<0.02)
- **139mL** improvement in **FEV_1**
- **26.3ppb*** reduction in **FeNO**

44.9% * reduction vs baseline

Verekitug was generally well tolerated, with a safety profile consistent with prior studies

AAER, annualized asthma exacerbation rates

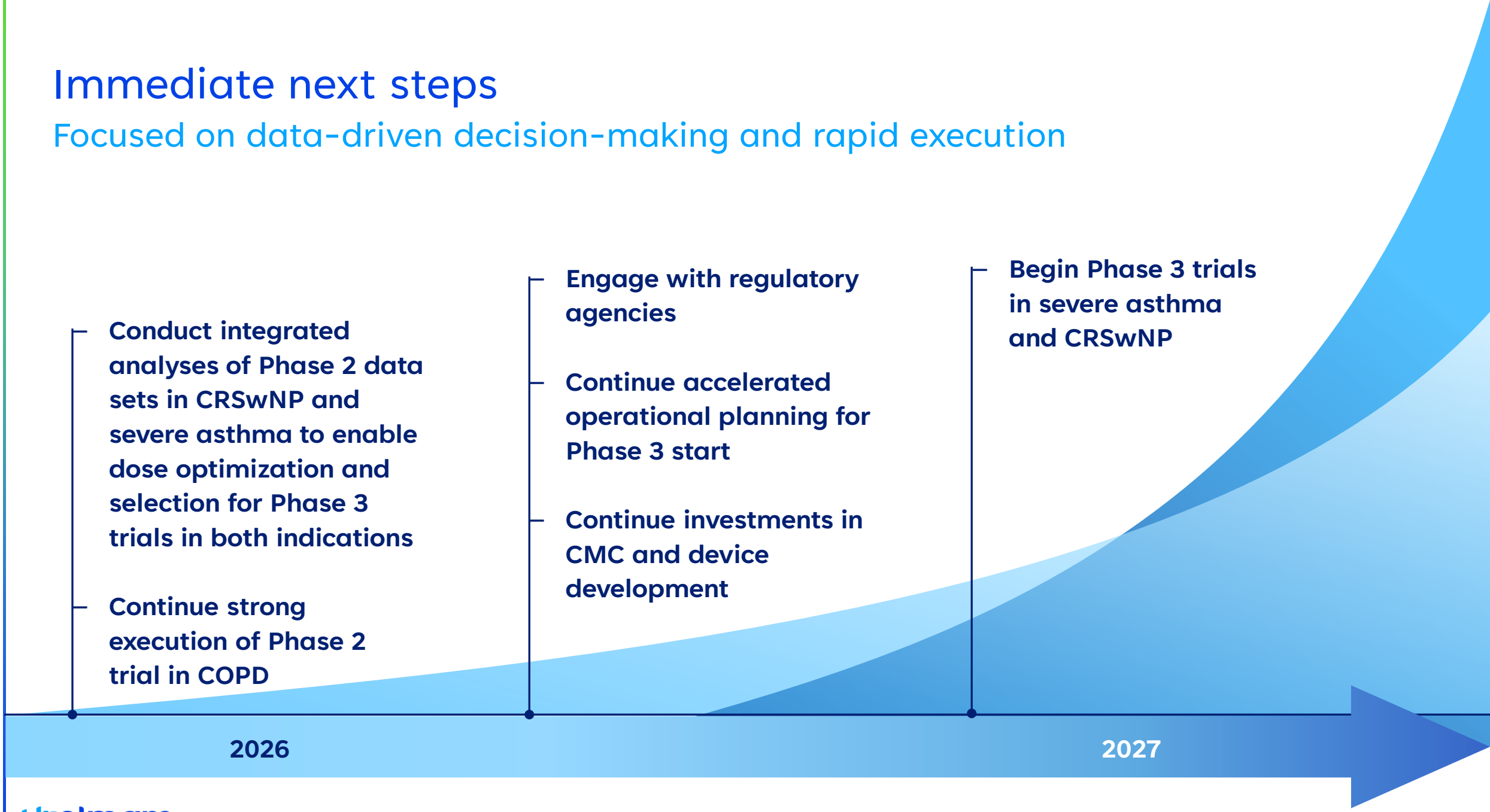
* Placebo-corrected

Path Forward

Rand Sutherland, MD
Chief Executive Officer

Immediate next steps

Focused on data-driven decision-making and rapid execution



Thank you
Q&A