



Corporate Presentation

September 8, 2026

Disclaimer

This presentation contains “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, each as amended. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “continue,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “predict,” “project,” “seeks,” “should,” “target,” “will” and variations of these words or similar expressions. Any statements in this presentation that are not statements of historical fact may be deemed to be forward-looking statements. These forward-looking statements include, without limitation, express or implied statements regarding: the clinical development of verekitug for the treatment of severe asthma, CRSwNP and COPD, including our plans to initiate Phase 3 clinical trials in severe asthma and CRSwNP in the first quarter of 2027 and the timing, progress and results of ongoing and planned clinical trials; our expectations regarding the differentiation, safety, efficacy, tolerability, or extended dosing interval of verekitug and the potential for verekitug to deliver best-in-class efficacy; the potential to develop verekitug for quarterly at-home administration for patients with severe asthma and CRSwNP, irrespective of biomarker status; expectations regarding interactions with regulatory authorities, including our Phase 3 clinical development plans in severe asthma and CRSwNP and the outcomes of any such interactions; and the potential of the endpoints of our clinical trials to produce data that could support submissions for product approval and the timing of such submissions; the potential for U.S. approval and launch of verekitug as early as 2030; expectations for the size and growth potential of the market for verekitug and our ability to serve that market; additional potential indications for verekitug; and our expected cash runway through 2027. Forward-looking statements are based on our current expectations and are described in “Risk Factors,” in our Annual Report on Form 10-K and most recent Quarterly Report on Form 10-Q, as well as discussions of potential risks, subject to risks, uncertainties and assumptions that could negatively affect our business, operating results, financial condition and stock value. Factors that could cause actual results to differ materially from those currently anticipated include: risks relating to our ability to advance verekitug through clinical development; the results of preclinical studies, or clinical studies not being predictive of future results in connection with future studies; the initiation, timing, progress and results of clinical trials; our ability to fund our development activities and achieve development goals; our research and development activities; our ability to execute on our strategy for verekitug including obtaining the requisite regulatory approvals on the expected timeline, if at all; uncertainties relating to preclinical and clinical development activities; our dependence on third parties to conduct clinical trials, manufacture verekitug and develop and commercialize our product candidates, if approved; our ability to attract, integrate and retain key personnel; risks related to the company’s financial condition and need for substantial additional funds in order to complete development activities and commercialize a product candidate, if approved; risks related to regulatory developments and approval processes of the U.S. Food and Drug Administration and comparable foreign regulatory authorities, including any additional interactions with the U.S. Food and Drug Administration regarding the sufficiency of our Phase 3 development plans; risks related to establishing and maintaining our intellectual property protections; and risks related to the competitive landscape for verekitug; ; and other risks uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. 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About Upstream Bio

Clinical-stage company developing treatments for severe inflammatory respiratory diseases

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

- Verekitug's pharmacology is unique and characterized by high-potency inhibition of TSLP signaling
- Focused on multiple indications with high unmet need:
 - Completed Phase 2 trials in severe asthma and CRSwNP
 - Ongoing Phase 2 trial in COPD; Enrollment in VENTURE completed, with data expected in H2 2027

Addressing significant commercial opportunities

- Severe asthma and COPD markets expected to drive a \$35B+ global biologics market by 2033

Pursuing Phase 3 development strategy designed to deliver best-in-class efficacy with convenient quarterly at-home injection in broad patient populations

One pivotal Phase 3 trial for each indication

Total of ~1,500 patients across both trials

400mg dosed quarterly

Selected to target best-in-class efficacy with quarterly at-home administration

Broad population

Trials designed to evaluate broad patient populations without restriction based on baseline biomarkers

Existing capital is expected to fund planned operations through 2027

Leadership team

Deep experience and complementary areas of expertise

EXECUTIVE TEAM



Rand Sutherland, MD

Chief Executive Officer



Aaron Deykin, MD

Chief Medical Officer & Head of R&D



Mike Gray

Chief Financial Officer & Chief Operating Officer



Allison Ambrose

General Counsel



Lisa Fiering

SVP, People & Culture



Adam Houghton, PhD

Chief Business Officer



Stacy Price

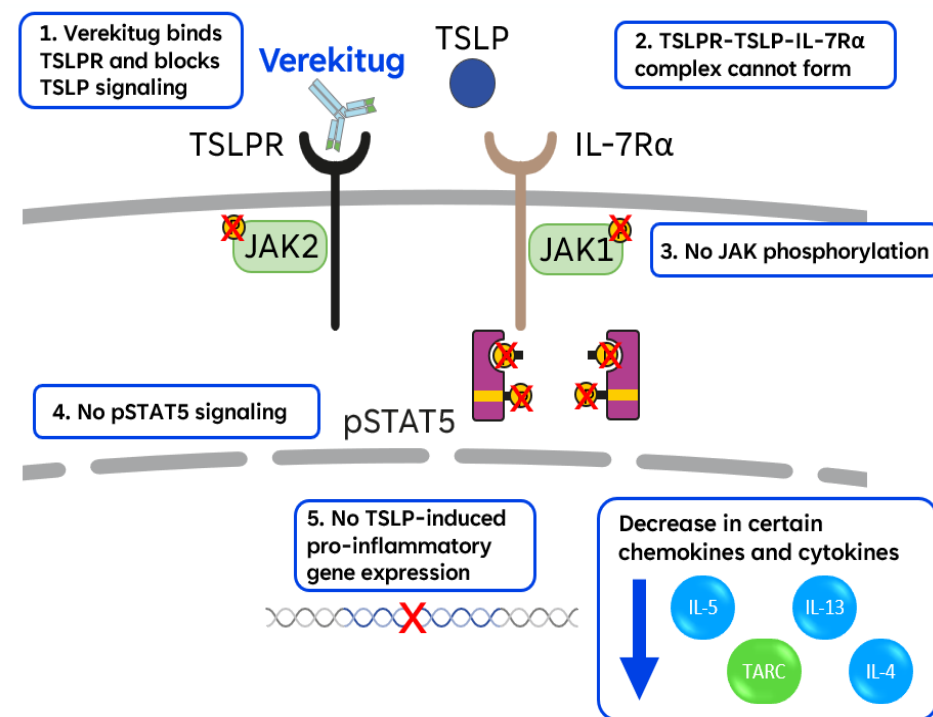
Chief Technology Officer



About verekitug

- Verekitug is the only known clinical-stage antagonist of the TSLP receptor
- Fully-human IgG1 antibody, discovered by Astellas/Regeneron and acquired by Upstream Bio
- Verekitug's potency is approximately 300-fold greater than that of tezepelumab, which may support both robust efficacy and extended interval dosing
- Comprehensive dataset from ~500 participants treated with verekitug across Phase 1 & 2 trials
- Demonstrated strong clinical benefit and favorable safety profile with every 12-week dosing in both severe asthma and CRSwNP

Mechanism of verekitug inhibition of TSLP signaling^{1,2,3}



Multiple upcoming milestones anticipated in 2027

INDICATIONS		DEVELOPMENT				NEXT ANTICIPATED MILESTONES
		PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	
Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)						Phase 3 Initiation Q1 2027*
Severe Asthma						Phase 3 Initiation Q1 2027*
						Data Expected H2 2027†
Chronic Obstructive Pulmonary Disease (COPD)						Enrollment Completed & Data Expected H2 2027*

* Anticipated timing

† VALOUR is a Phase 2 long-term safety and efficacy study of verekitug in eligible participants with severe asthma who completed the Phase 2 VALIANT study.

Market Research Overview

Prioritizing a high-efficacy quarterly regimen to maximize verekitug's potential commercial value

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: \$7.5B²
2032e: \$12.6B²

~1.3M

Biologic eligible severe asthma patients in the US¹

~80% of biologic sales are in the US²

<25%

of eligible patients with severe asthma are currently estimated to receive biologic therapies^{1,3}

>\$12.5B

Projected global sales for all approved biologics in severe asthma by 2033²

>\$3B

Tezspire is projected to reach global annual sales of over \$3B for severe asthma alone in 2032²

CRSwNP

2025: >\$1.5B^{5,6}

~300K

Biologic eligible CRSwNP patients in the US¹

>\$1.5B

Current global biologics sales in CRSwNP alone estimated to be \$1.5B+ annually^{5,6}

>\$600M

Tezspire is projected to reach global annual sales of over \$600M for CRSwNP by early 2030s⁷

COPD

2033e: \$23B²

~1.1M

COPD patients inadequately controlled on triple-therapy in the US²

~3.5M

Projected COPD patients inadequately controlled on triple-therapy in the US by 2033²

~70%

of 2033 COPD biologic sales are expected to be in the US²

>\$5B

Tezspire is projected to reach global annual sales of over \$5B for COPD alone in 2033², if approved in this indication

Optimizing development strategy to address patient needs and maximize potential commercial value

Prioritizing verekitug development strategy to deliver potential best-in-class efficacy with quarterly dosing, consistent with market research that shows:

Efficacy differentiation is the primary driver of treatment decisions and commercial success*

The majority of dosing convenience value is captured with quarterly administration*

These findings are consistent across multiple waves of qualitative and quantitative market research conducted with HCPs, patients, and payers*

Market research shows efficacy is the primary driver for decision-making among HCPs in both asthma and CRSwNP

Importance of Product Attributes for Asthma and CRSwNP		
% HCPs ranking attribute as the <u>top 3 most important</u> when selecting biologics for asthma & CRSwNP patients		
Product Attributes	Asthma <i>i.e., AAER, FEV₁, and symptomology</i>	CRSwNP <i>i.e., reduction NPS and improvement in NCS</i>
Efficacy	100%	100%
Safety	28%	21%
Dosing frequency	14%	5%

Market research shows HCPs are not willing to trade off safety or efficacy for extended dosing interval

For instance, ~70% of HCPs reported that they would switch their asthma patients to another biologic if they observed waning efficacy of a q24w drug

Phase 2 Clinical Data Overview in Severe Asthma and CRSwNP

Phase 3 strategy designed to maximize verekitug's potential commercial value by targeting best-in-class efficacy with at-home quarterly dosing

Target product profile

Deliver potential **best-in-class efficacy with quarterly dosing** in both severe asthma and CRSwNP

Strategy supported by strong clinical data package and comprehensive market research in both indications

Single 400 mg subcutaneous injection

Convenient quarterly dosing regimen

High and low-eosinophil populations

Planned self-administration via autoinjector at launch

Parallel Phase 3 trials in severe asthma & CRSwNP

Verekitug's profile supports potential for best-in-class efficacy & quarterly dosing in severe asthma and CRSwNP

5 clinical studies completed to date with
~500 participants dosed with verekitug

1

Phase 2 trials delivered efficacy outcomes meeting or exceeding approved biologics in both severe asthma and CRSwNP dosed every 12 weeks*

2

Favorable safety profile, consistent across clinical development program

3

Potential to deliver best-in-class efficacy in severe asthma and CRSwNP with a single high-dose quarterly injection

4

Phase 2 trials demonstrate positive treatment effects in high and low eosinophil subgroups in severe asthma and CRSwNP

5

Well-characterized immunogenicity profile has no meaningful impact on safety or efficacy

*No head-to-head trials have been conducted. Comparisons based on published data.

Results for Phase 2 VIBRANT study in CRSwNP

Verekitug dosed every 12 weeks, treatment period 24 weeks

Phase 2 VIBRANT

100 mg q12w
vs placebo

Met primary endpoint, with NPS reduction of -1.8 ($p < 0.0001$)

Met key secondary endpoints,
including NCS reduction of -0.8 ($p = 0.0003^*$) and 76% reduction in
need for surgery/steroids ($p = 0.03^*$)

Generally well tolerated, no SAEs observed

Observed clinical benefit at 12-week dosing interval
supports potential utility in severe asthma
and other Type 2 inflammatory diseases

*Nominal p values

NPS, nasal polyp score; NCS, nasal congestion score; q12w, every 12 weeks; SAEs, serious adverse events.

Top-line data reported Sept 2025.

Data presented at AAAAI in March 2026 of new analyses incorporating a worst-observation carried-forward (WOCF) statistical approach to adjust for concomitant rescue therapy use, including nasal polyp surgery, systemic corticosteroids, or escalation of background treatments, demonstrated NPS reduction of -1.95 ($p < 0.0001$) and NCS reduction of -0.96 ($p < 0.0001$).

Results for Phase 2 VALIANT study in severe asthma

Verekitug dosed every 12 weeks, treatment period up to 60 weeks

Statistically significant and clinically meaningful reductions in AAER for up to 60 weeks

Clinically meaningful improvements in lung function (FEV₁) and exhaled nitric oxide (FeNO)

56% reduction in AAER (p<0.0003)
150mL^{1,2} improvement in FEV₁
43.5%^{1,2} reduction vs baseline in FeNO
0.21 point^{1,3} reduction in ACQ-6

Generally well tolerated, with a safety profile consistent with prior studies

Phase 2 VALIANT

100 mg q12w
vs placebo
dataset

Consistent and favorable safety profile across both Phase 2 trials



- Overall incidence of AEs was similar across treatment groups
- TEAEs related to study treatment occurred more frequently in placebo
- No SAEs reported
- Most common TEAEs in study population ($\geq 5\%$) were consistent with CRSwNP symptoms, which occurred frequently in the placebo group



- Overall incidence of TEAEs was similar across treatment groups
- Serious TEAEs were similar across treatment groups

Adverse Event Category, n, subjects (%) ²	Verekitug (n=40)	Placebo (n=40)
Any treatment-emergent adverse events (TEAE)	27 (67.5)	26 (65.0)
Any TEAEs related to study treatment	1 (2.5)	3 (7.5)
Any serious TEAEs	0	0
Any serious TEAEs related to study treatment	0	0
Any TEAEs with outcome of death	0	0
Any TEAEs leading to study drug discontinuation	0 (0.0)	1 (2.5)

TEAE, by Preferred Term, n, subject (%)	Verekitug	Placebo
Upper respiratory tract infections	3 (7.5)	6 (15)
Sinusitis	2 (5)	3 (7.5)
Nasopharyngitis	2 (5)	3 (7.5)
Nasal polyps	0	5 (12.5)
Headache	2 (5)	2 (5)

AE category, % of participants ⁴	Verekitug 100 mg q12w N=121	Verekitug 400 mg q24w N=118	Verekitug 100 mg q24w N=119	Placebo N=119
Any TEAE	62.0	59.5	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 ($\geq 5\%$ in any cohort)⁵				
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

*Safety follow-up is ongoing.

AE, adverse event; q×w, every × weeks; TEAE, treatment-emergent adverse event. SAEs, serious adverse events.

1. Top-line data reported Sept 2025. 2. Data on file. 14.3.1.2.

3. Top-line data reported Feb 2026. 4. Data on File. Table 14.3.1.15. 5. Data on File. Table 14.3.1.3.

In CRSwNP, verekitug led to significant and clinically meaningful improvements in NPS and all key secondary endpoints

		Verekitug	Placebo	Treatment difference
Primary Endpoint	NPS change from baseline*	-2.1 (0.26)	-0.3 (0.27)	-1.8 (-2.51, -1.03) p<0.0001
Key Secondary Endpoints	NCS change from baseline*	-1.5 (0.14)	-0.8 (0.14)	-0.8 (-1.17, -0.37) p=0.0003 [†]
	LMK change from baseline*	-9.0 (0.8)	-1.0 (0.8)	-8.0 (-10.2, -5.9) p<0.0001 [†]
	TSS change from baseline*	-10.1 (0.94)	-5.8 (0.95)	-4.3 (-6.94, -1.65) p=0.0018 [†]
	DSS change from baseline*	-1.5 (0.15)	-0.6 (0.16)	-0.9 (-1.29, -0.42) p=0.0002 [†]
	% requiring sinus surgery and/or SCS	7.3%	25.0%	76% reduction** p=0.03 [†]

*Change from baseline is least square (LS) mean (standard error) and treatment difference is LS mean difference vs placebo (95% confidence interval)

**Risk reduction vs placebo

[†]p values for secondary endpoints are nominal and not adjusted for multiple comparisons.

LMK, Lund-Mackay; TSS, total symptom score; DSS, difficulty with smell score; SCS, systemic corticosteroids.

NPS range: 0–8; NCS range: 0–3 over 2 weeks; LMK CT score (0–24); TSS range: 0–24; 8 symptoms over 2 weeks; DSS range: 0–3 over 2 weeks.

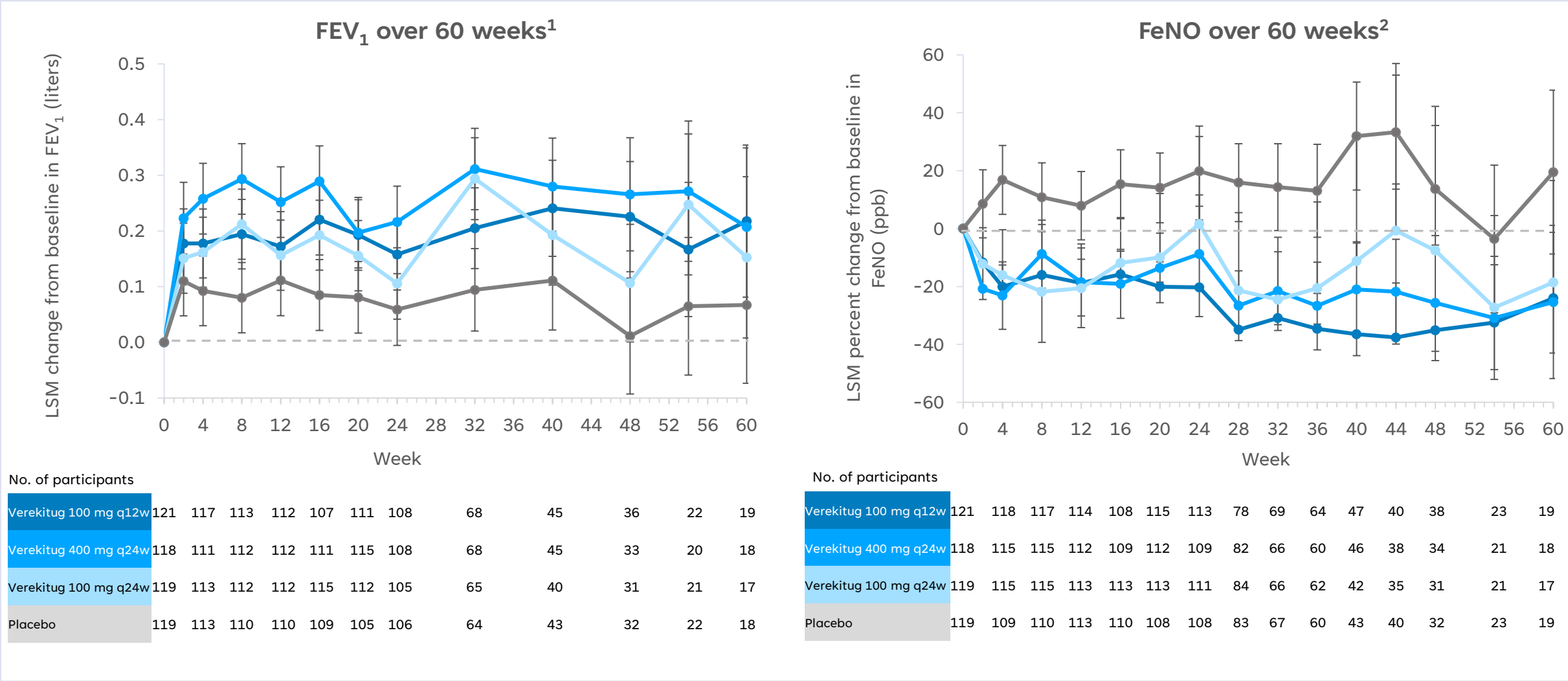
Top-line data reported Sept 2025. Data on file: Tables 14.2.1.1.1, 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.2.9.1, 14.2.2.4.1

In severe asthma, verekitug led to meaningful improvements in primary and secondary endpoints at week 24 that were generally sustained to week 60

Timing	Endpoint	Verekitug 100 mg q12w (high exposure at C _{trough})	Verekitug 400 mg q24w (medium exposure at C _{trough})	Verekitug 100 mg q24w (low exposure at C _{trough})
Baseline through week 60	AAER* Rate ratio vs placebo (95% CI) P value	N=121 0.44 (0.28, 0.69) 0.0003	N=118 0.61 (0.40, 0.93) 0.0227	N=120 0.51 (0.33, 0.79) 0.0028
Change from baseline to week 24*	Pre-BD FEV₁ LSM difference vs placebo mL (95% CI) P value	N=108 99 (9, 189) 0.0317	N=108 157 (67–248) 0.0007	N=105 47 (–44 to 137) 0.3102
	ACQ-6 LSM difference vs placebo (95% CI) P value	N=114 -0.21 (–0.43, 0.01) 0.0651	N=111 -0.34 (–0.57, –0.12) 0.0027	N=112 -0.23 (–0.45, –0.01) 0.0447
Change from baseline to week 60*	Pre-BD FEV₁ LSM difference vs placebo mL (95% CI) P value	N=19 150 (–45 to 346) 0.1309	N=18 140 (–59 to 339) 0.1674	N=17 85 (–116 to 287) 0.4057
	ACQ-6 LSM difference vs placebo (95% CI) P value	N=19 0.06 (–0.42, 0.55) 0.8000	N=19 -0.21 (–0.70, 0.28) 0.3928	N=17 -0.24 (–0.74, 0.26) 0.3541

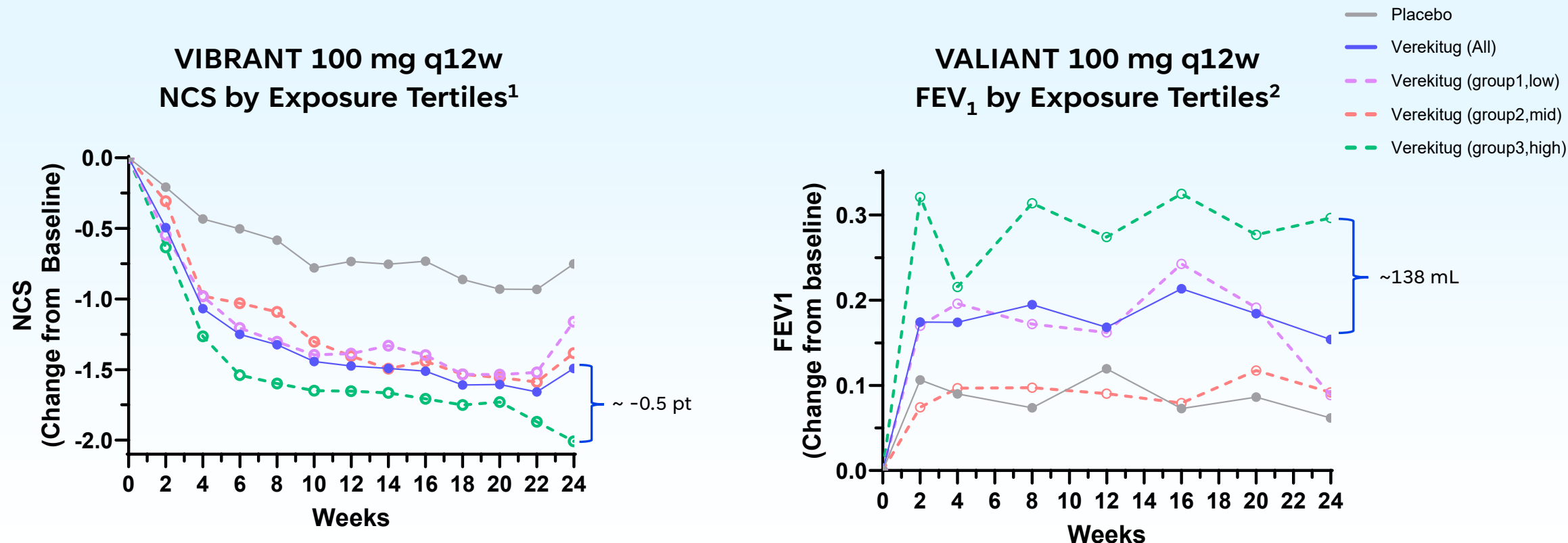
*AAER, Rate Ratio, 95% confidence intervals, and p-values are from a negative binomial regression model with number of asthma exacerbations as the dependent variable and fixed effects for study treatment, region, baseline steroid use as randomized, and baseline eosinophil level as randomized.
Final top-line data presented at ERS, Sept 2026.
Table 14.2.1.1.1; Table 14.2.2.1.3; 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



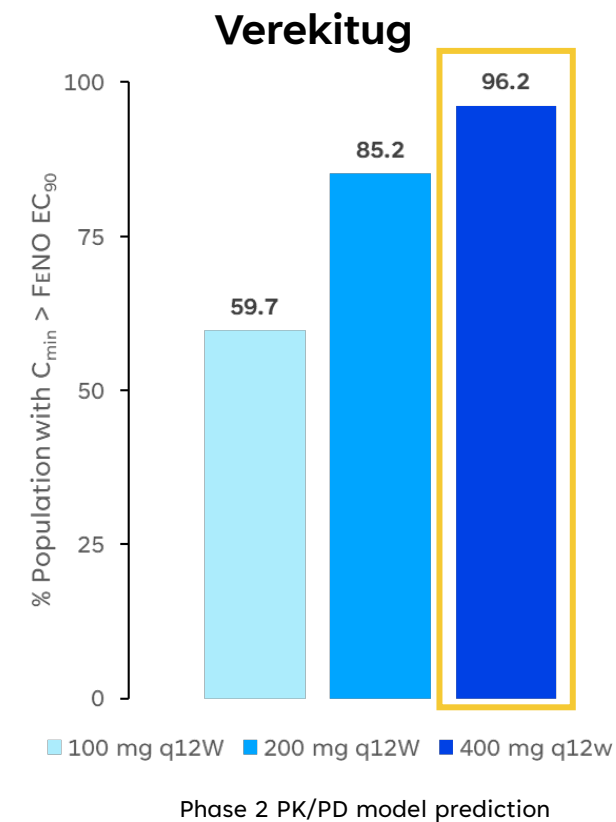
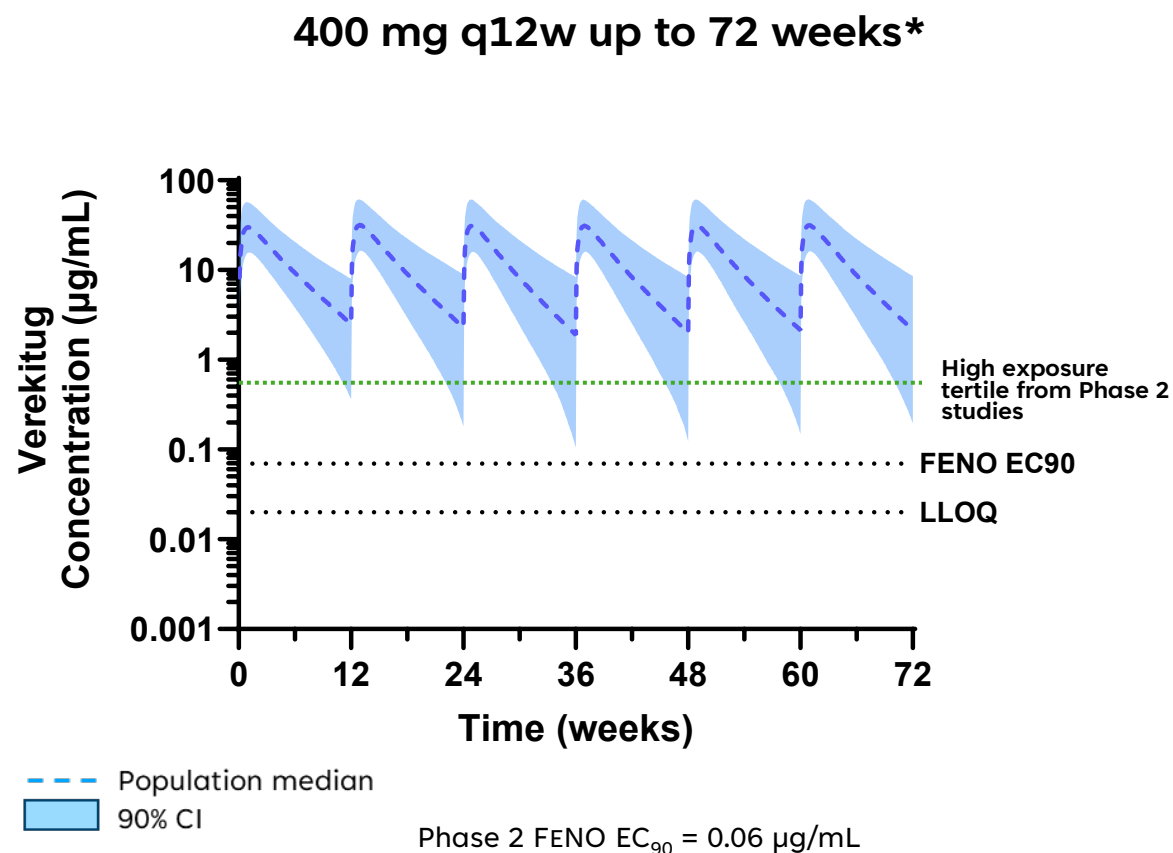
Secondary endpoints were not powered for statistical significance.
FeNO, fractionated exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; LSM, least squares mean; ppb, parts per billion; q×w, every × weeks.
Based on final top-line data presented at ERS, Sept 2026. 1. Data on file. Table 14.2.2.1.3. 2. Data on file. Table 14.2.2.3.5.

In both CRSwNP and severe asthma, patients with highest verekitug exposures experienced the greatest clinical benefit

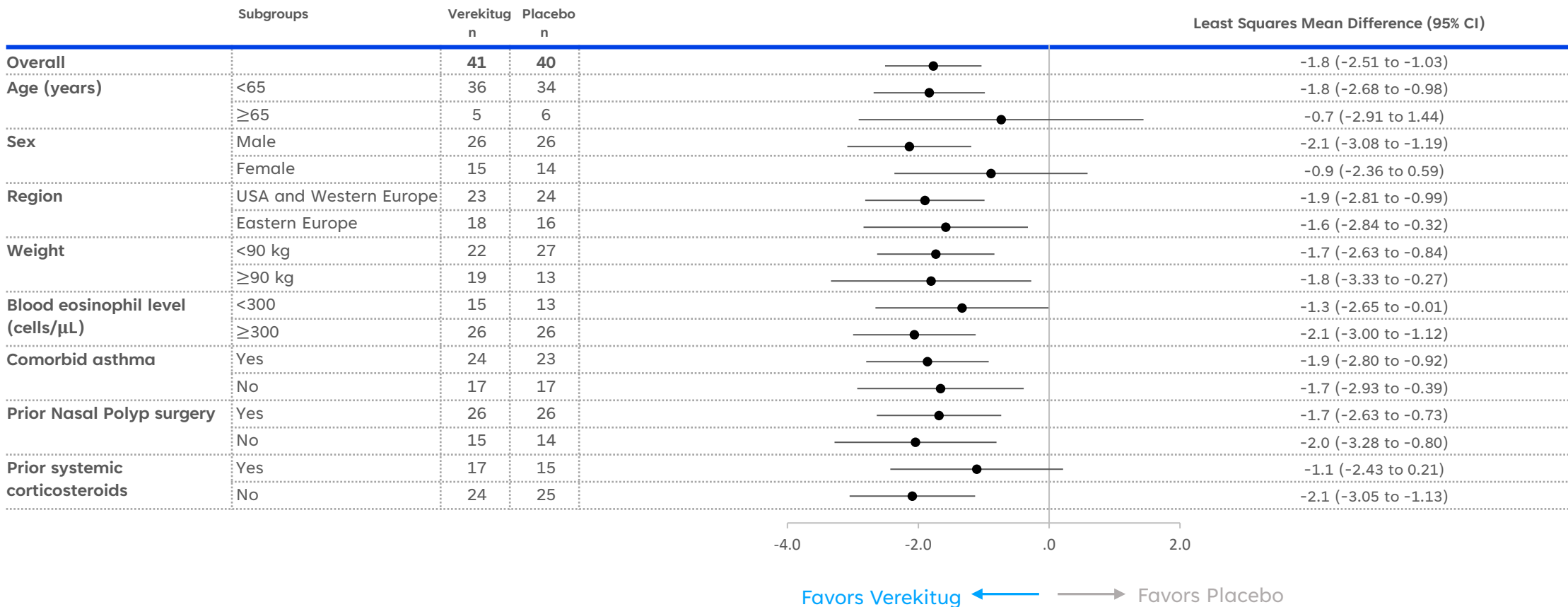


Data presented as mean
NCS, Nasal Congestion Score; FEV₁, Forced Expiratory Volume in 1 second; q12w, every 12 weeks.
1. Based on top-line data reported Sept 2025. 2. Based on final top-line data presented at ERS, Sept 2026.

Modeling of data through Phase 2 predicts that 400 mg q12w could optimize proportion of patients achieving maximally therapeutic levels

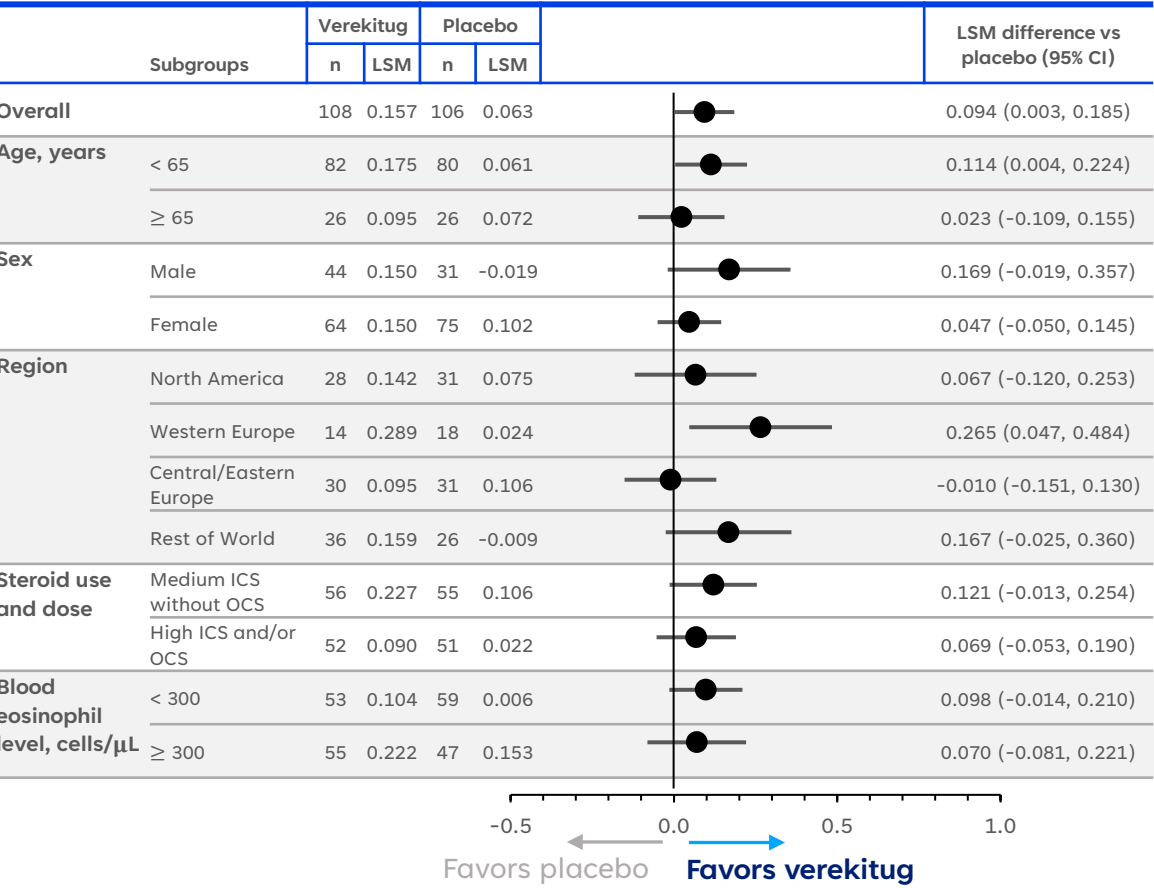


Verekitug demonstrated clinical effect in NPS across all subgroups analyzed in the VIBRANT study

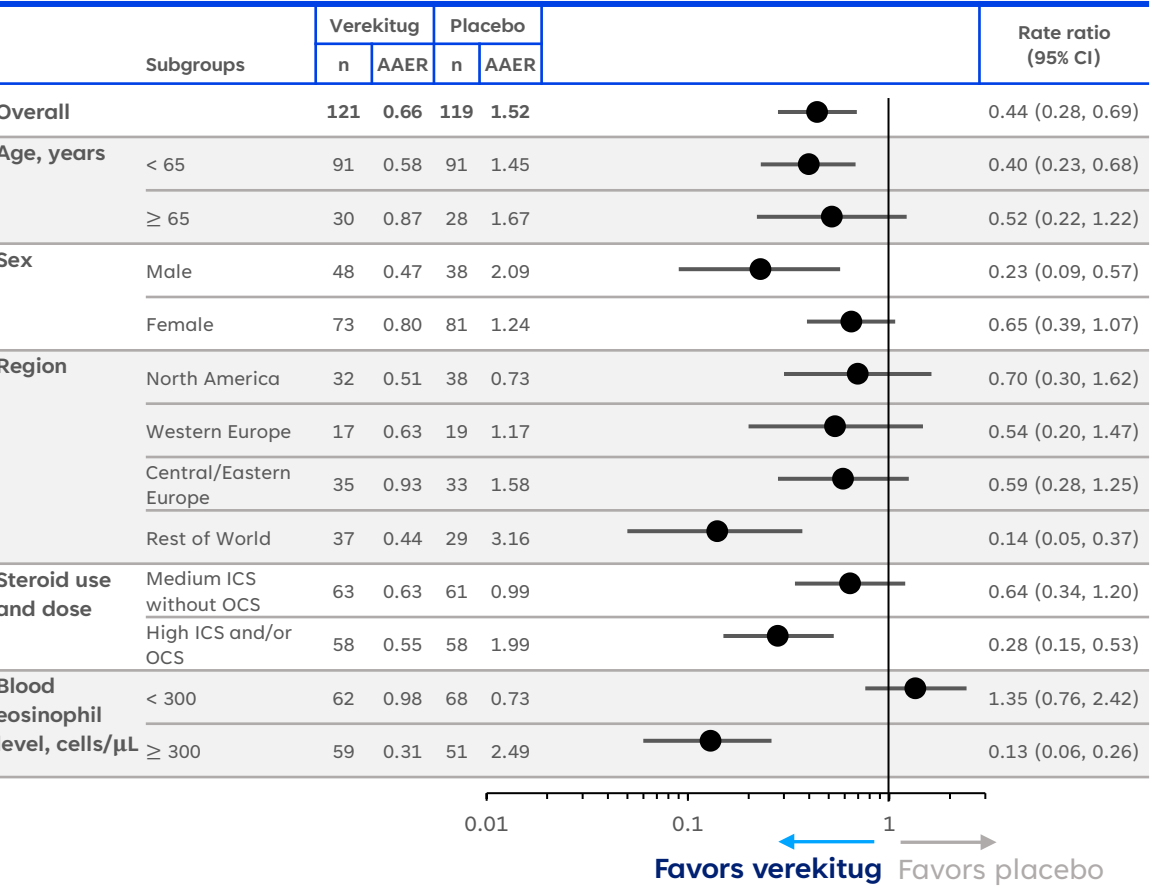


Analysis of VALIANT data supports evaluation in broad populations in Phase 3

FEV₁ (L) by subgroup^{1,2}

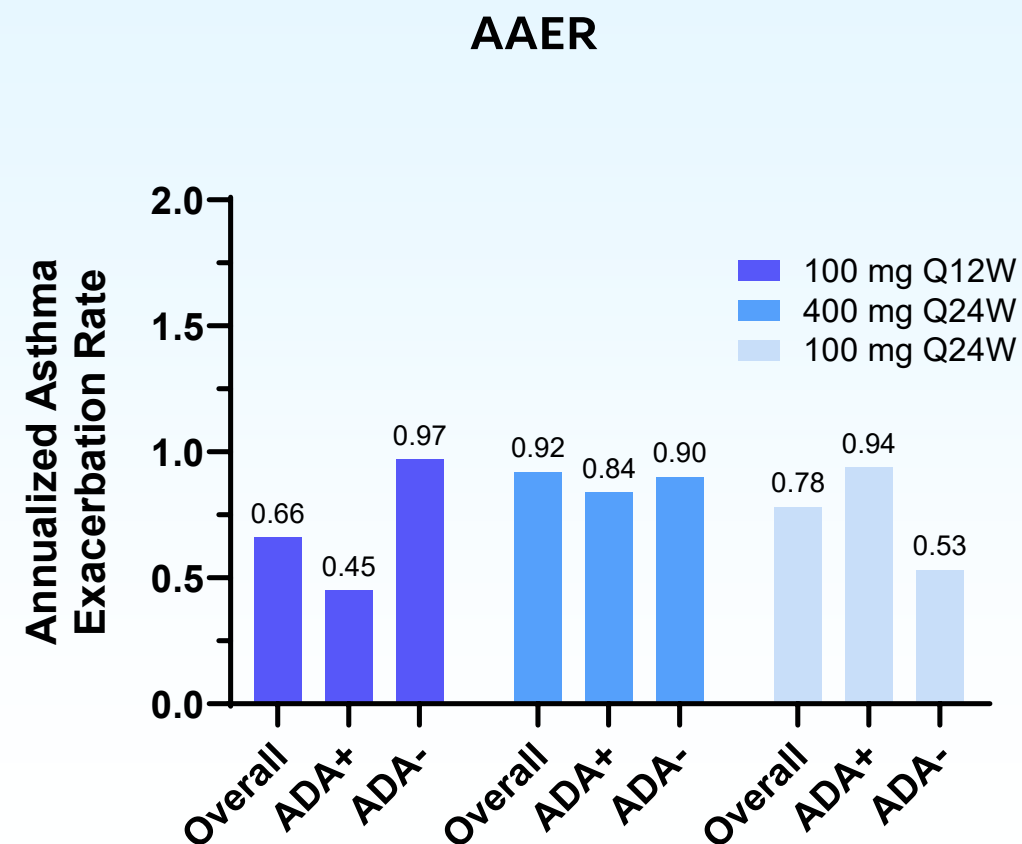
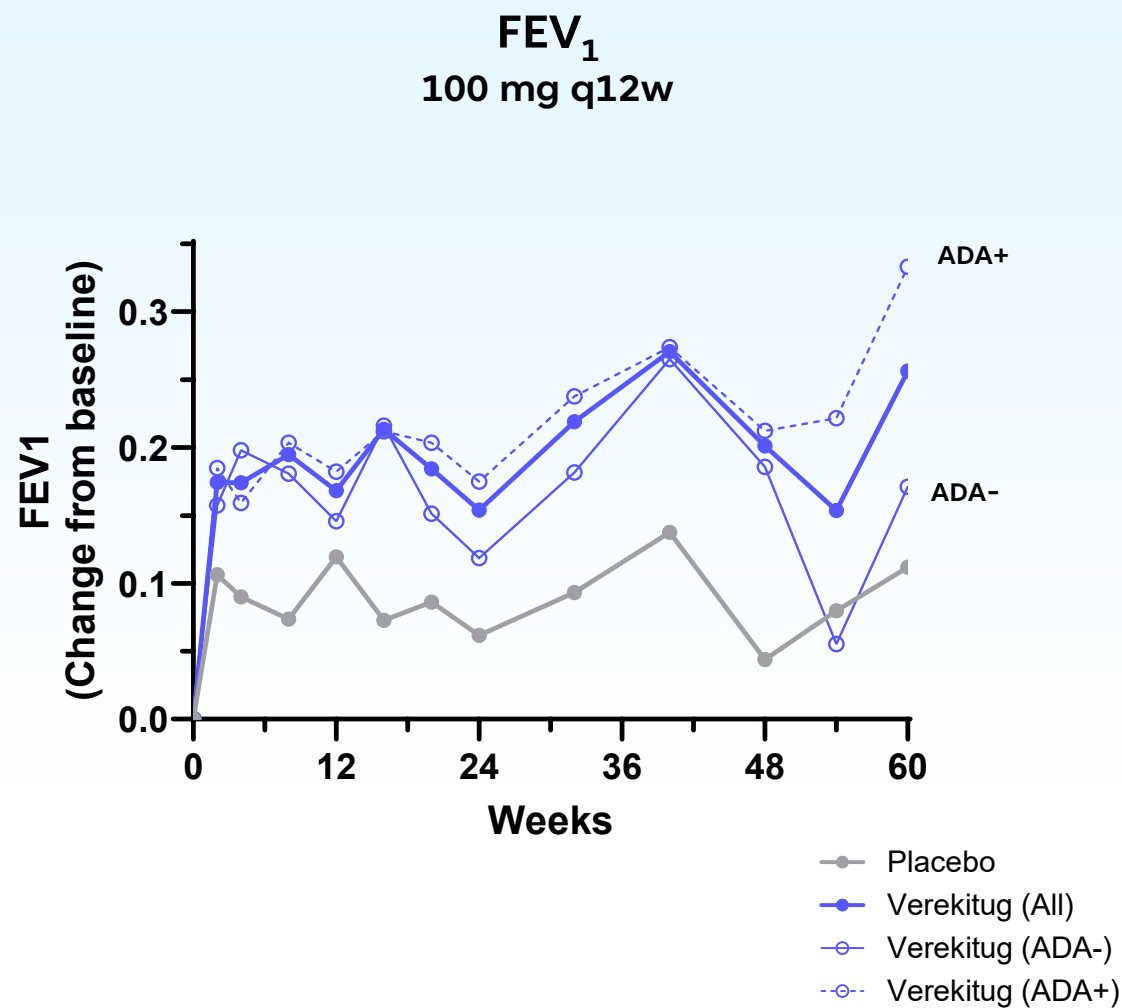


AAER by subgroup^{3,4}



AAER, annualized asthma exacerbation rate; FEV₁, 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. Final top-line data presented at ERS, Sept 2026. 1. Figure 14.2.2.2.1.7. 2. At 24 weeks using data up to Week 24. 3. Data on File. Figure 14.2.1.1.4.2. 4. Over 60 weeks.

No meaningful impact of immunogenicity on AAER or FEV₁ in VALIANT



Based on final top-line data presented at ERS, Sept 2026. Data on file: Table 14.2.1.1.5

Looking Ahead

Focused on disciplined execution

2026

Q1 2027

H2 2027

Completed productive End-of-Phase 2 interactions with FDA

Initiation of Phase 3 trials in severe asthma and CRSwNP expected

Data from Phase 2 trial in COPD expected

Continue accelerated operational planning for Phase 3 start in severe asthma and CRSwNP

Data from severe asthma LTE expected

Continue ongoing Phase 2 trial in COPD

Ongoing investments in CMC and device development