



# Corporate Presentation

April 2026

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# About Upstream Bio

Clinical-stage immunology company focused on severe 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

Addressing significant commercial opportunities

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

Pursuing Phase 3 development strategy in both severe asthma and CRSwNP designed to deliver best-in-class efficacy with a single quarterly at-home injection in broad patient populations

- Robust clinical data and comprehensive market research provide a clear path to maximize the potential commercial value of verekitug
- The Company plans to:
  - Engage with regulators later this year
  - Initiate Phase 3 trials in severe asthma and CRSwNP in Q1 2027

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



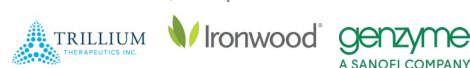
**Allison Ambrose**

General Counsel



**Lisa Fiering**

SVP, People & Culture



**Adam Houghton, PhD**

Chief Business Officer



**Stacy Price**

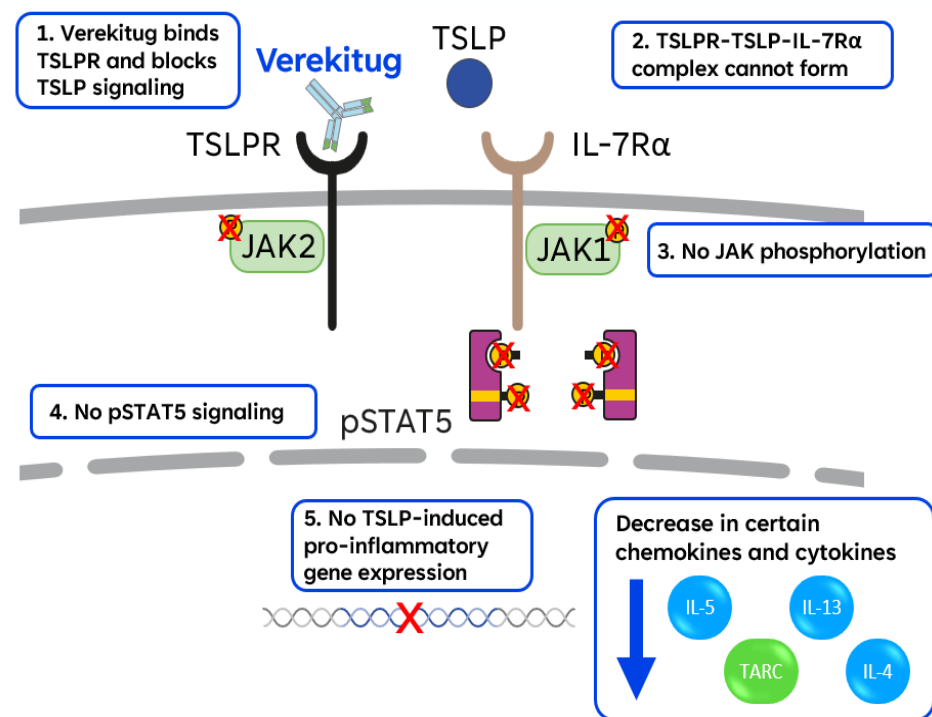
Chief Technology Officer



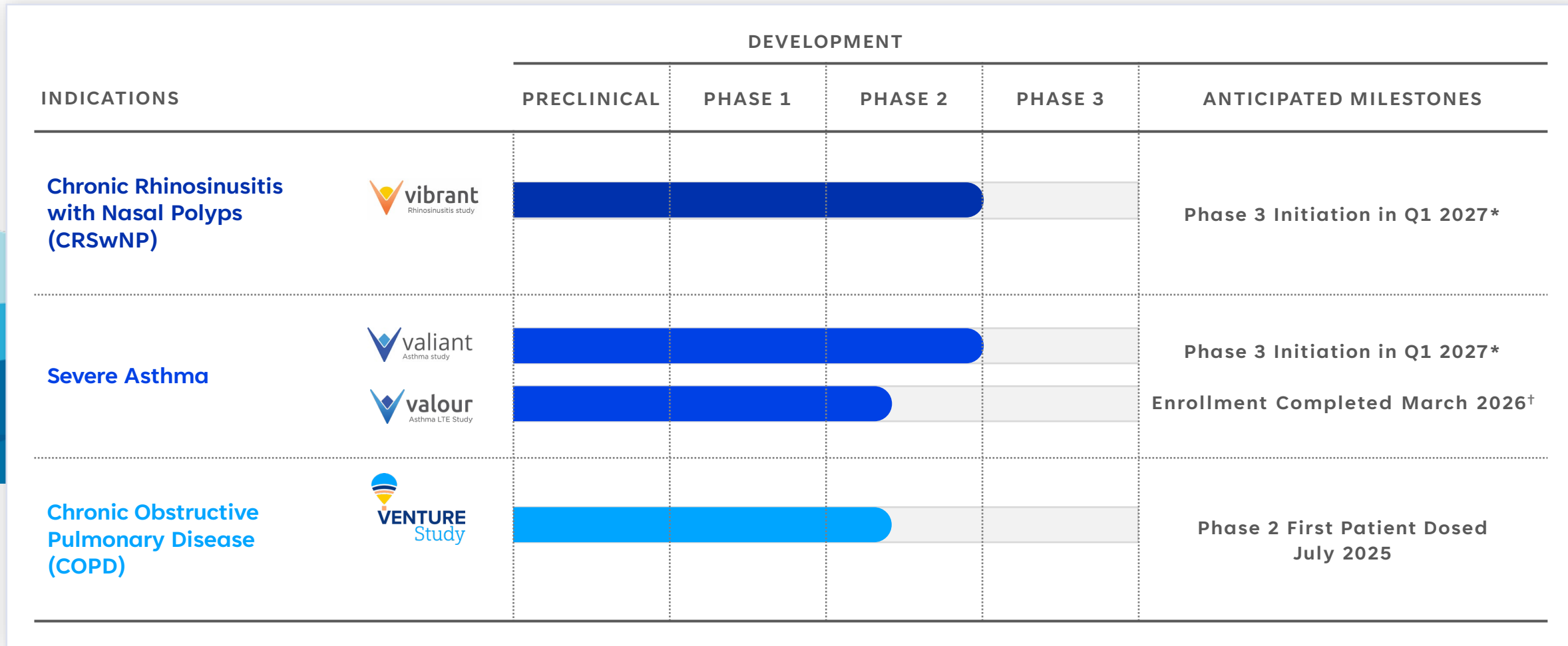
# About verekitug

- 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, enabling 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 with every 12-week dosing in both severe asthma and CRWNP

## Mechanism of verekitug inhibition of TSLP signaling<sup>1,2,3</sup>



# Developing verekitug in TSLP-driven severe respiratory diseases



\* Phase 3 preparations ongoing in both CRSwNP and severe asthma

† 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.

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

## Target product profile

Deliver **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 high-dose injection, up to 400 mg\*

Convenient quarterly dosing regimen

High and low-eosinophil populations

Self-administration via autoinjector at launch

Parallel Phase 3 trials in severe asthma & CRSwNP

# Market Research Overview

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

<p><b>Severe Asthma</b></p> <p>2023: \$7.5B<sup>2</sup> 2032e: \$12.6B<sup>2</sup></p>	<p><b>~1.3M</b></p> <p>Biologic eligible severe asthma patients in the US<sup>1</sup></p> <p><b>~80%</b> of biologic sales are in the US<sup>2</sup></p>	<p><b>&lt;25%</b></p> <p>of eligible patients with severe asthma are currently estimated to receive biologic therapies<sup>1,3</sup></p>	<p><b>&gt;\$12.5B</b></p> <p>Projected global sales for all approved biologics in severe asthma by 2033<sup>2</sup></p>	<p><b>&gt;\$3B</b></p> <p>Tezspire is projected to reach global annual sales of over \$3B for severe asthma alone in 2032<sup>2</sup></p>
<p><b>CRSwNP</b></p> <p>2025: &gt;\$1.5B<sup>5,6</sup></p>	<p><b>~300K</b></p> <p>Biologic eligible CRSwNP patients in the US<sup>1</sup></p>	<p><b>&gt;\$1.5B</b></p> <p>Current global biologics sales in CRSwNP alone estimated to be \$1.5B+ annually<sup>5,6</sup></p>	<p><b>&gt;\$600M</b></p> <p>Tezspire is projected to reach global annual sales of over \$600M for CRSwNP by early 2030s<sup>7</sup></p>	
<p><b>COPD</b></p> <p>2033e: \$23B<sup>2</sup></p>	<p><b>~1.1M</b></p> <p>COPD patients inadequately controlled on triple-therapy in the US<sup>2</sup></p>	<p><b>~3.5M</b></p> <p>Projected COPD patients inadequately controlled on triple-therapy in the US by 2033<sup>2</sup></p>	<p><b>~70%</b></p> <p>of 2033 COPD biologic sales are expected to be in the US<sup>2</sup></p>	<p><b>&gt;\$5B</b></p> <p>Tezspire is projected to reach global annual sales of over \$5B for COPD alone in 2033<sup>2</sup>, if approved in this indication</p>

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# Targeting best-in-class efficacy with quarterly at-home dosing to address patient needs and maximize commercial value



**Efficacy differentiation is the primary driver of clinical impact and commercial success**

Market research to date shows:

- Physician treatment decisions in asthma and CRSwNP primarily driven by efficacy
- Physicians unwilling to trade off reductions in efficacy for extended dosing intervals
- Strong efficacy must be delivered as a component of extended-dosing regimens



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

Market research to date shows:

- Most of the benefit from improved dosing frequency is achieved by moving from every 2- or 4-week to quarterly dosing
- Incremental increases in product value with less frequent dosing are modest and eroded by even minor losses in efficacy

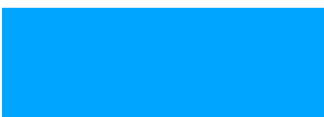







**Prioritizing verkitug development strategy to deliver best-in-class efficacy with quarterly dosing**

- In Phase 2 trials in both severe asthma and CRSwNP, quarterly dosing delivered efficacy outcomes that met or exceeded available biologics
- A high-dose quarterly regimen is predicted to deliver the optimal combination of efficacy and convenience

*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, FEV<sub>1</sub>, 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

# 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 with 100 mg 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

# Top-line 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

# Top-line 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 (FEV<sub>1</sub>) and exhaled nitric oxide (FeNO)

56% reduction in AAER (p<0.0003)  
122mL<sup>1</sup> improvement in FEV<sub>1</sub>  
20.4ppb<sup>1</sup> reduction in FeNO  
43.5%<sup>1</sup> reduction vs baseline  
0.21 point<sup>1,2</sup> 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 (%) <sup>3</sup>	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 <sup>1</sup>	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
<b>Most common TEAE, any grade (<math>\geq 5\%</math> in any cohort)<sup>2</sup></b>				
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 $\times$ w, every  $\times$  weeks; TEAE, treatment-emergent adverse event. SAEs, serious adverse events.

1. Data on File. Table 14.3.1.1. 2. Data on File. Table 14.3.1.2. 3. Data on file. 14.3.1.2..

# 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 with 100 mg 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

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

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

\*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

<sup>†</sup>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.

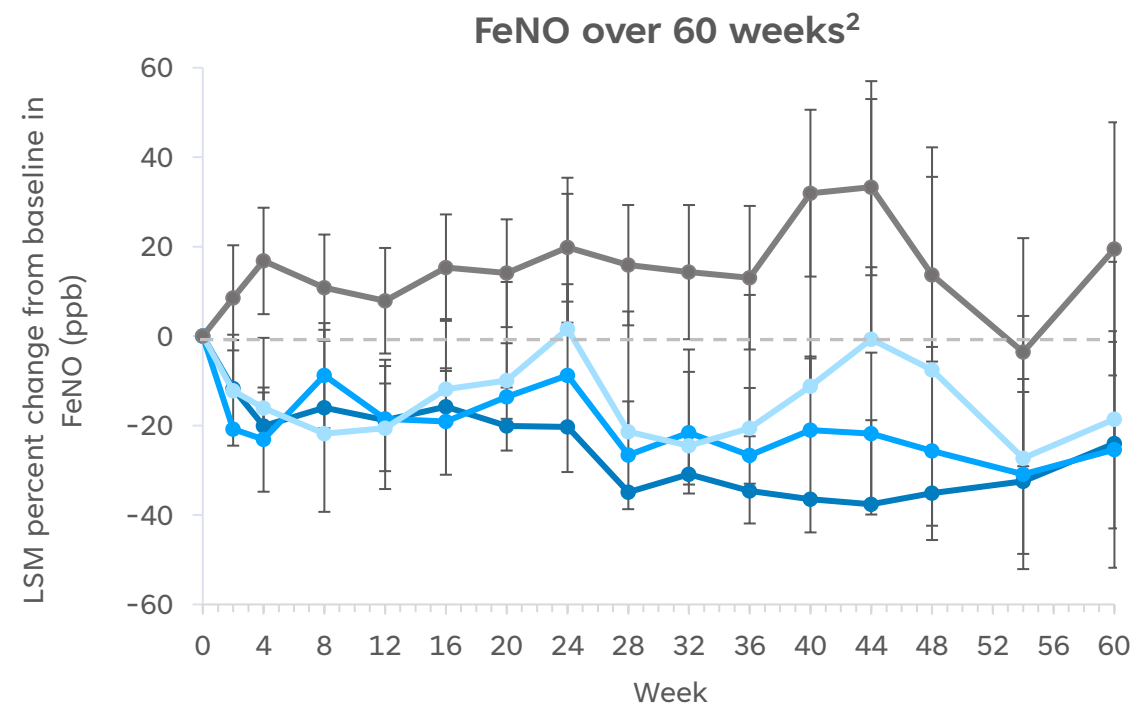
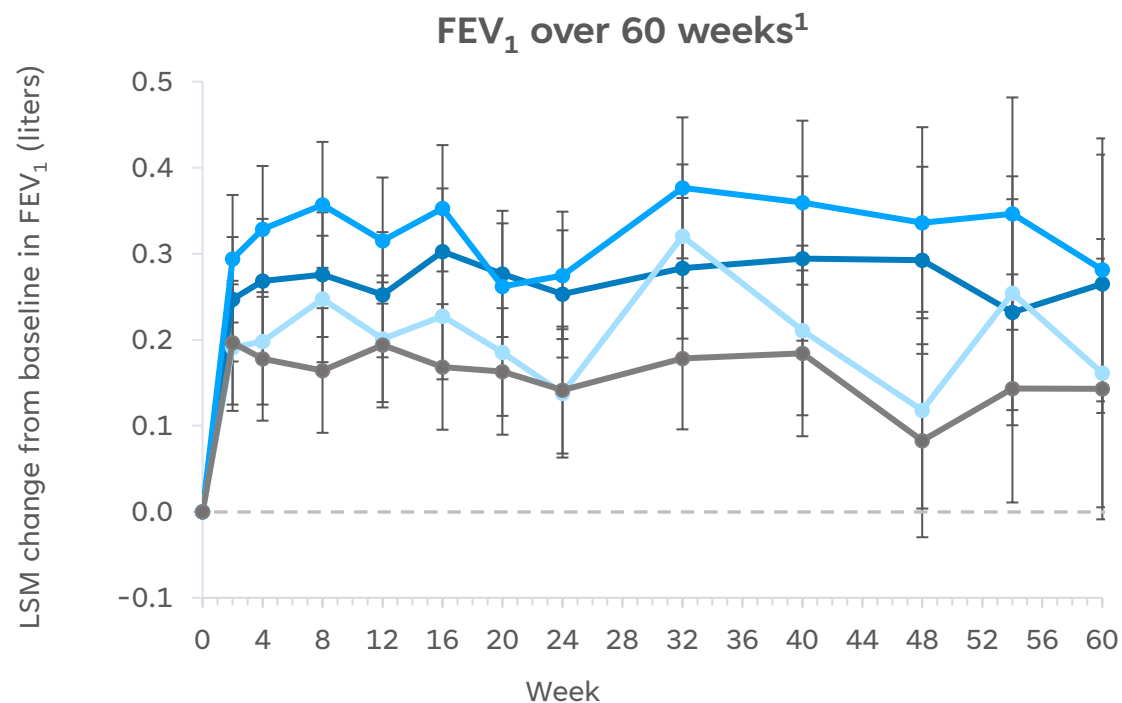
Data on file: Tables 14.2.1.1.1, 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1, 14.2.2.9.1, 14.2.2.4.1

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	Verekitug 400 mg q24w	Verekitug 100 mg q24w
Baseline through week 60	<b>AAER*</b> Rate ratio vs placebo (95% CI) P value	N=121 <b>0.44</b> (0.28, 0.69) <b>0.0003</b>	N=118 <b>0.61</b> (0.40, 0.93) <b>0.0227</b>	N=120 <b>0.51</b> (0.33, 0.79) <b>0.0028</b>
	<b>Pre-BD FEV<sub>1</sub></b> LSM difference vs placebo mL (95% CI) P value	N=106 <b>112</b> (8, 216) <b>0.0350</b>	N=107 <b>133</b> (30, 237) <b>0.0119</b>	N=103 <b>-4</b> (-108, 100) <b>0.9419</b>
Change from baseline to week 24*	<b>ACQ-6</b> LSM difference vs placebo (95% CI) P value	N=114 <b>-0.21</b> (-0.43, 0.01) <b>0.0651</b>	N=111 <b>-0.34</b> (-0.57, -0.12) <b>0.0027</b>	N=112 <b>-0.23</b> (-0.45, -0.01) <b>0.0447</b>
	<b>Pre-BD FEV<sub>1</sub></b> LSM difference vs placebo mL (95% CI) P value	N=18 <b>122</b> (-90, 335) 0.2589	N=18 <b>139</b> (-76, 353) 0.2047	N=17 <b>18</b> (-198, 235) 0.8678
Change from baseline to week 60*	<b>ACQ-6</b> LSM difference vs placebo (95% CI) P value	N=19 <b>0.06</b> (-0.42, 0.55) 0.8000	N=19 <b>-0.21</b> (-0.70, 0.28) 0.3928	N=17 <b>-0.24</b> (-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.  
Data on File. Table 14.2.1.1.1; Table 14.2.2.2.1.3; Table 14.2.2.3.2; 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



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

No. of participants

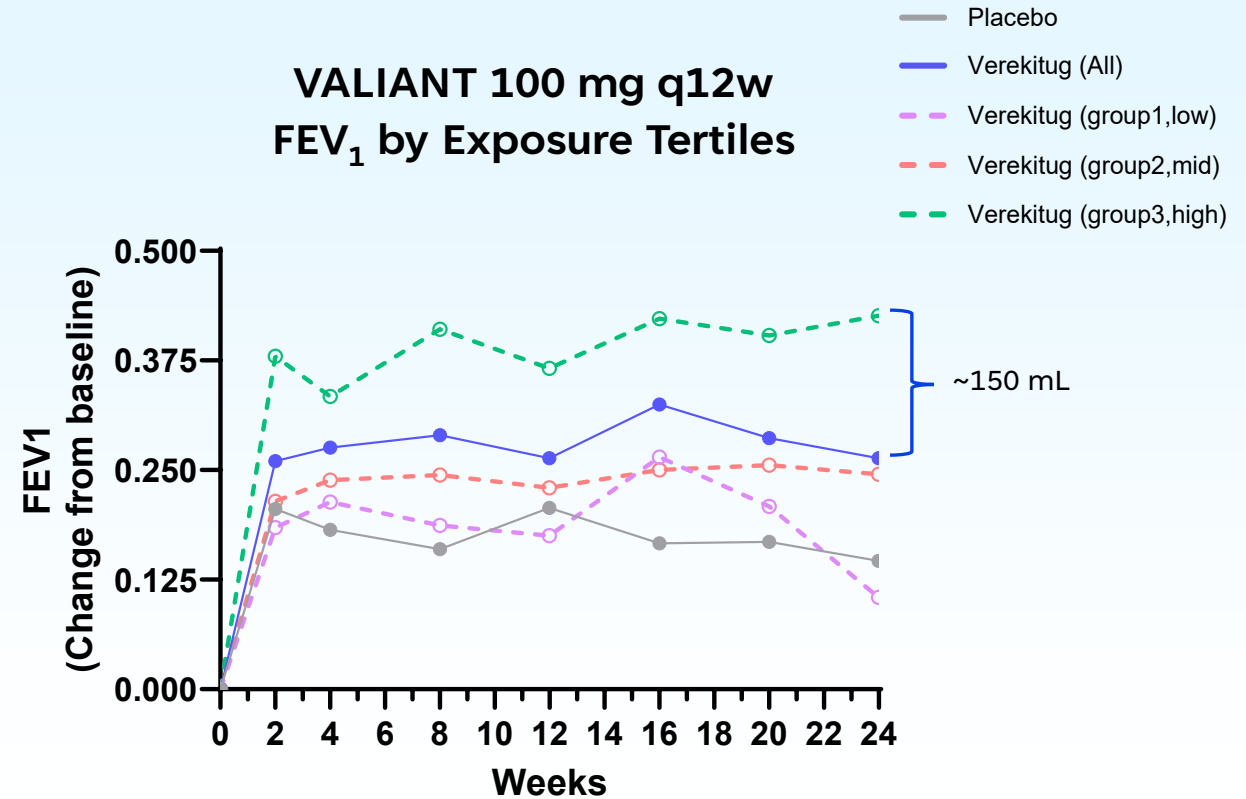
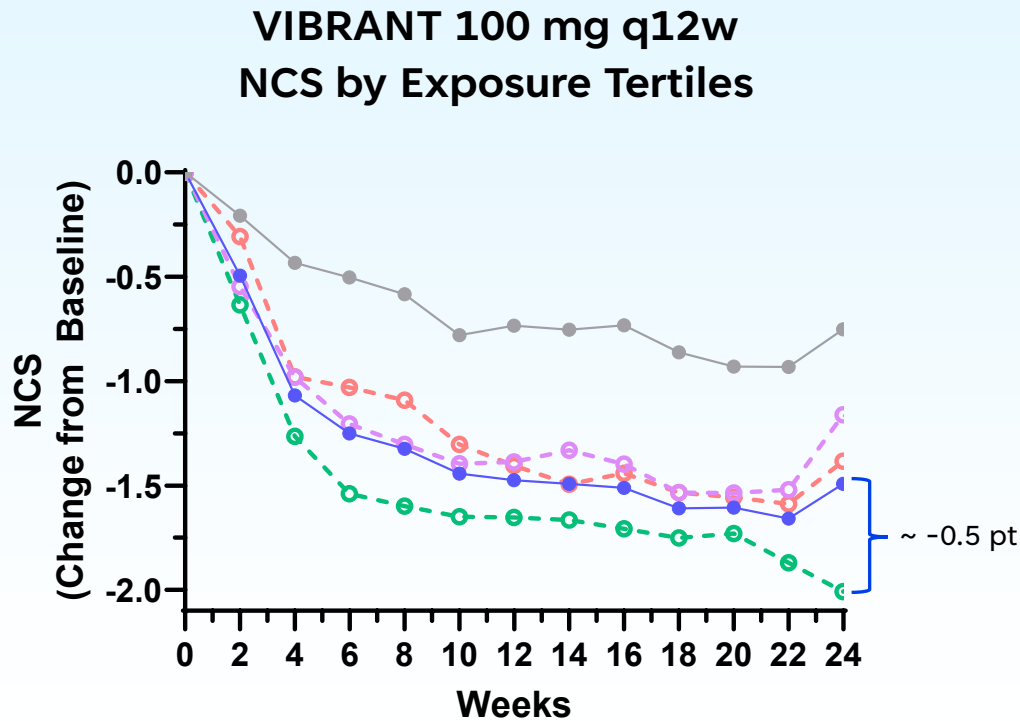
Verekitug 100 mg q12w	121	118	117	114	108	115	113	78	69	64	47	40	38	23	19
Verekitug 400 mg q24w	118	115	115	112	109	112	109	82	66	60	46	38	34	21	18
Verekitug 100 mg q24w	119	115	115	113	113	113	111	84	66	62	42	35	31	21	17
Placebo	119	109	110	113	110	108	108	83	67	60	43	40	32	23	19

Secondary endpoints were not powered for statistical significance.

FeNO, fractionated exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; LSM, least squares mean; ppb, parts per billion; q $\times$ w, every  $\times$  weeks.

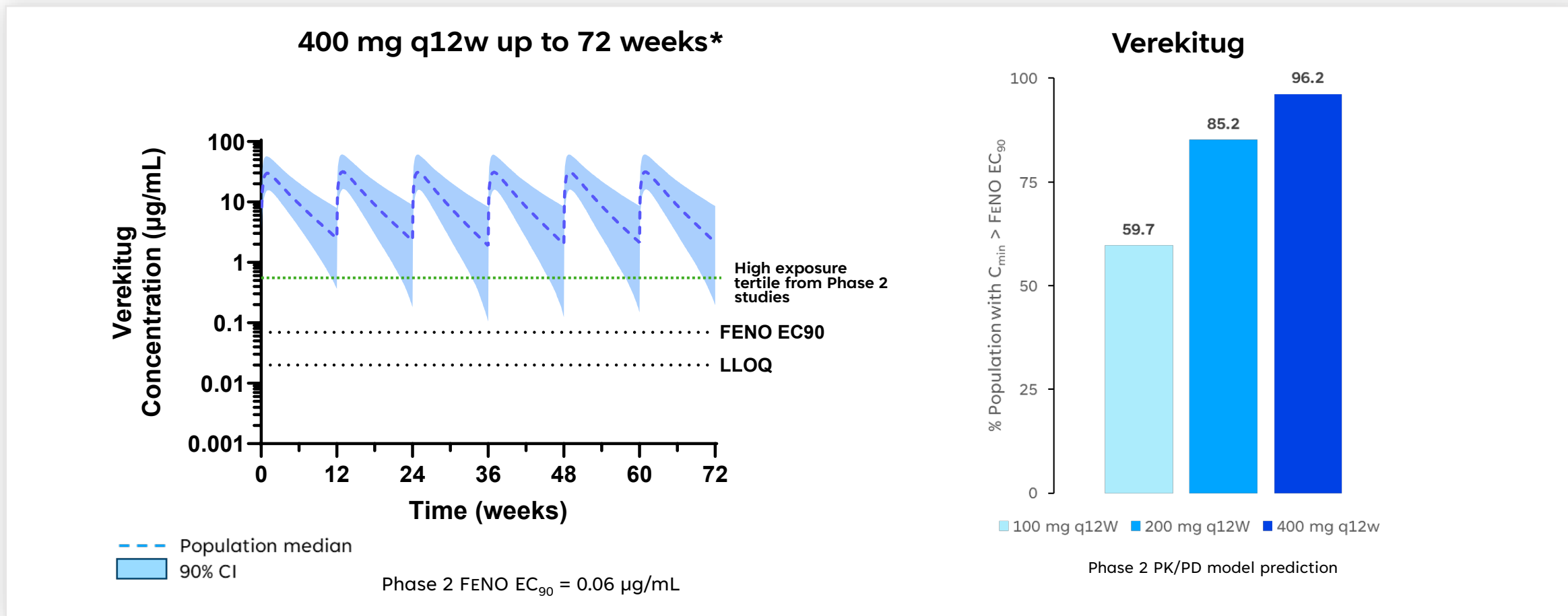
1. Data on file. Table 14.2.2.2.1.3. 2. Data on file. Table 14.2.2.3.5.

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



# Modeling of Phase 2 data predicts that increasing quarterly dose above 100 mg will further increase exposure over the FENO EC<sub>90</sub>

Exposure over verekitug FENO EC<sub>90</sub> predicted to be greater than that of tezepelumab's approved dose over its FENO EC<sub>90</sub>



# 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 with 100 mg 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

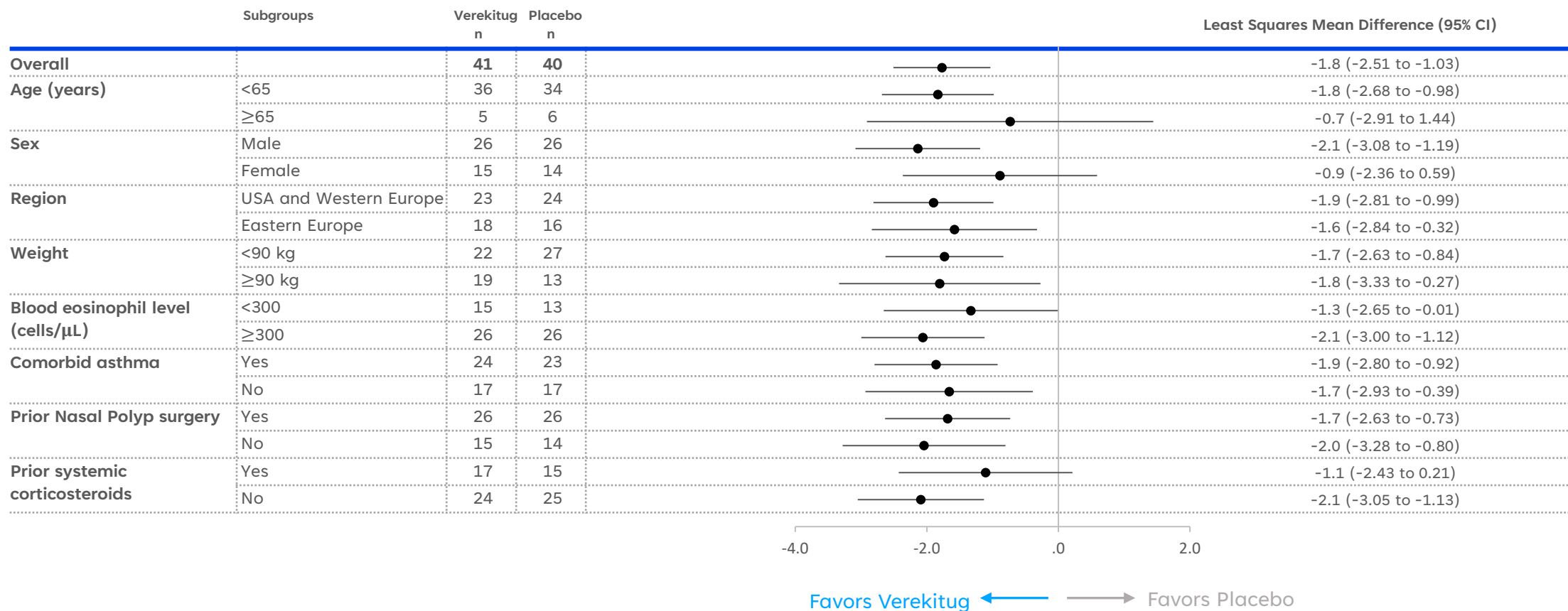
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**Phase 2 trials demonstrate positive treatment effects in high and low eosinophil subgroups in severe asthma and CRSwNP**

5

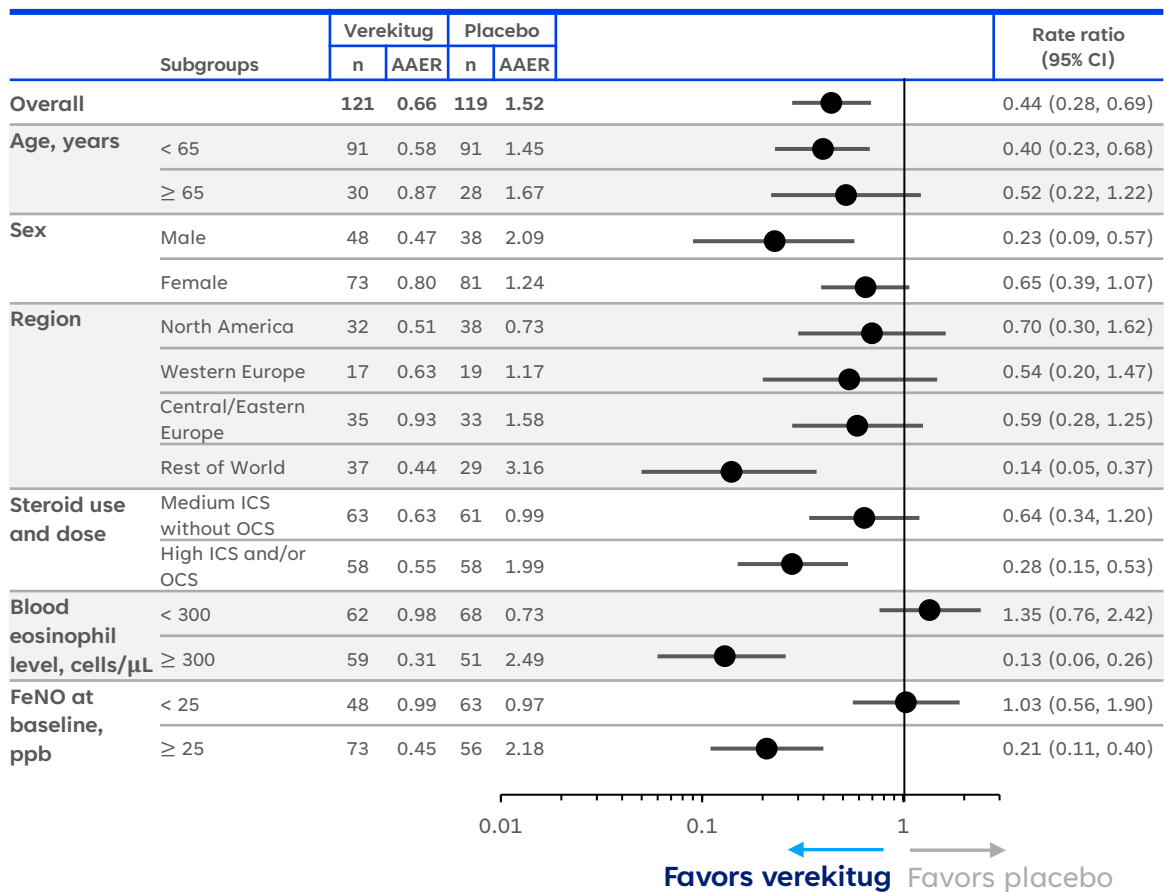
Well-characterized immunogenicity profile has no meaningful impact on safety or efficacy

# Verekitug demonstrated clinical effect in NPS across all subgroups

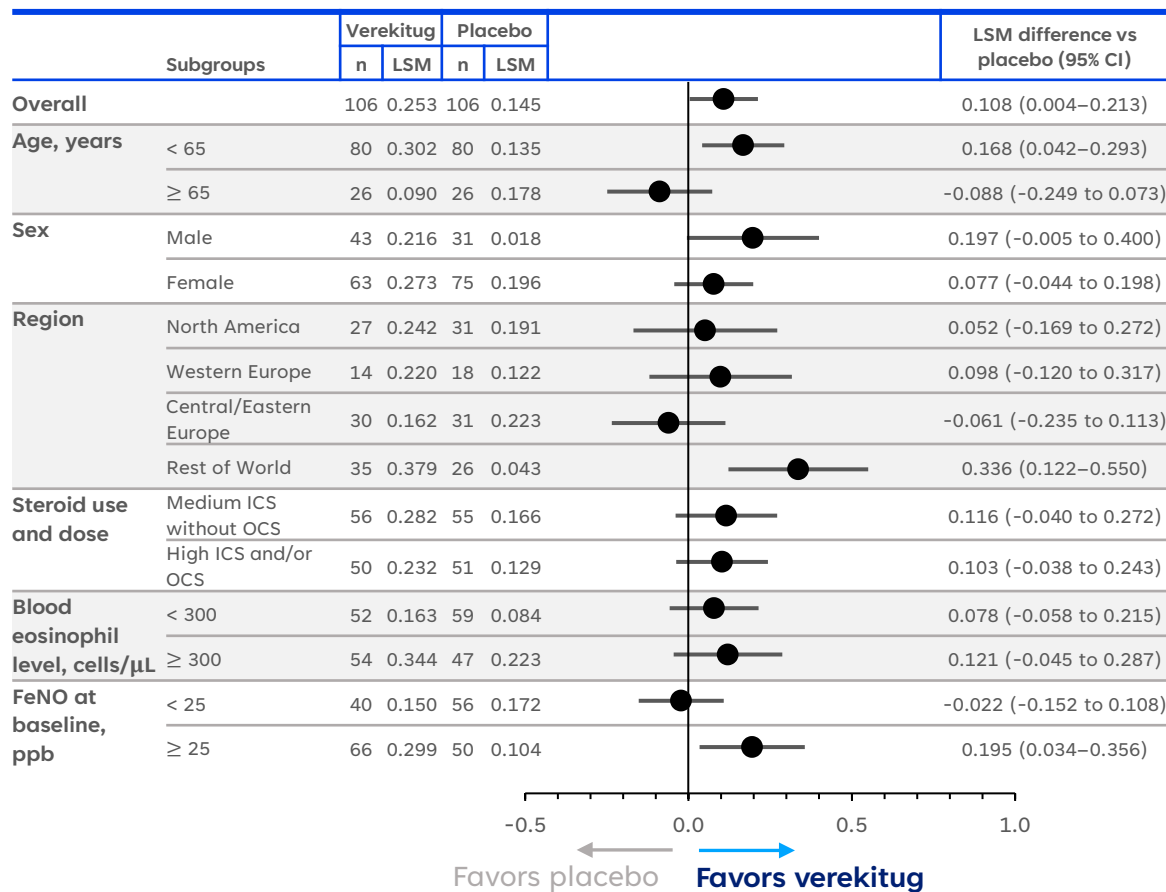


# Analysis of VALIANT data supports evaluation in broad populations in Phase 3, driven by FEV<sub>1</sub> data and very low placebo AAER

## AAER by subgroup<sup>1,2</sup>



## FEV<sub>1</sub> by subgroup<sup>3,4</sup>



AAER, annualized asthma exacerbation rate; FEV<sub>1</sub>, 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.

1. Data on File. Figure 14.2.1.1.4.2. 2. At 60 weeks 3. Figure 14.2.2.2.1.7. 4. At 24 weeks

# Verekitug Phase 2 data support efficacy in broad populations in both severe asthma and CRSwNP

- Positive treatment responses in both high and low eosinophil subgroups in severe asthma and CRSwNP reinforce verekitug's continued development in a broad population of patients in both indications, as observed in:
  - NPS subgroup analyses in CRSwNP
  - FEV<sub>1</sub> subgroup analyses in severe asthma
    - In VALIANT, a very low placebo AAER of 0.73 in the low eosinophil group limited ability to detect therapeutic effect of verekitug in that subgroup
- Preclinical and clinical studies of TSLP biology have identified effects that extend beyond Type 2 inflammation alone, with strong evidence of clinical efficacy in patients independent of eosinophilic phenotype

# 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 with 100 mg 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

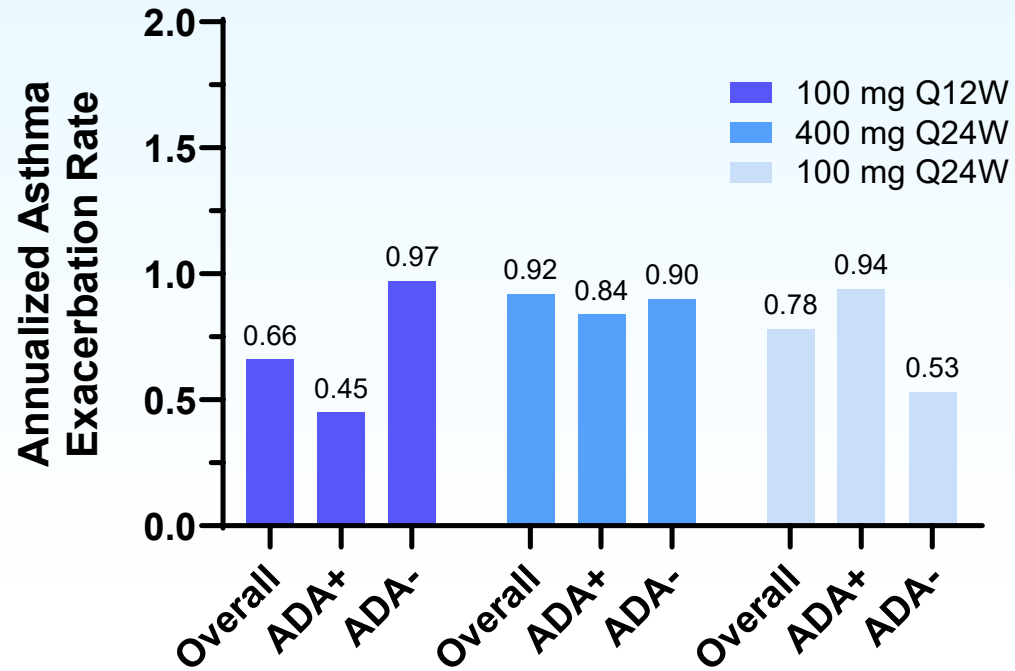
Phase 2 trials demonstrate positive treatment effects in high and low eosinophil subgroups in severe asthma and CRSwNP

5

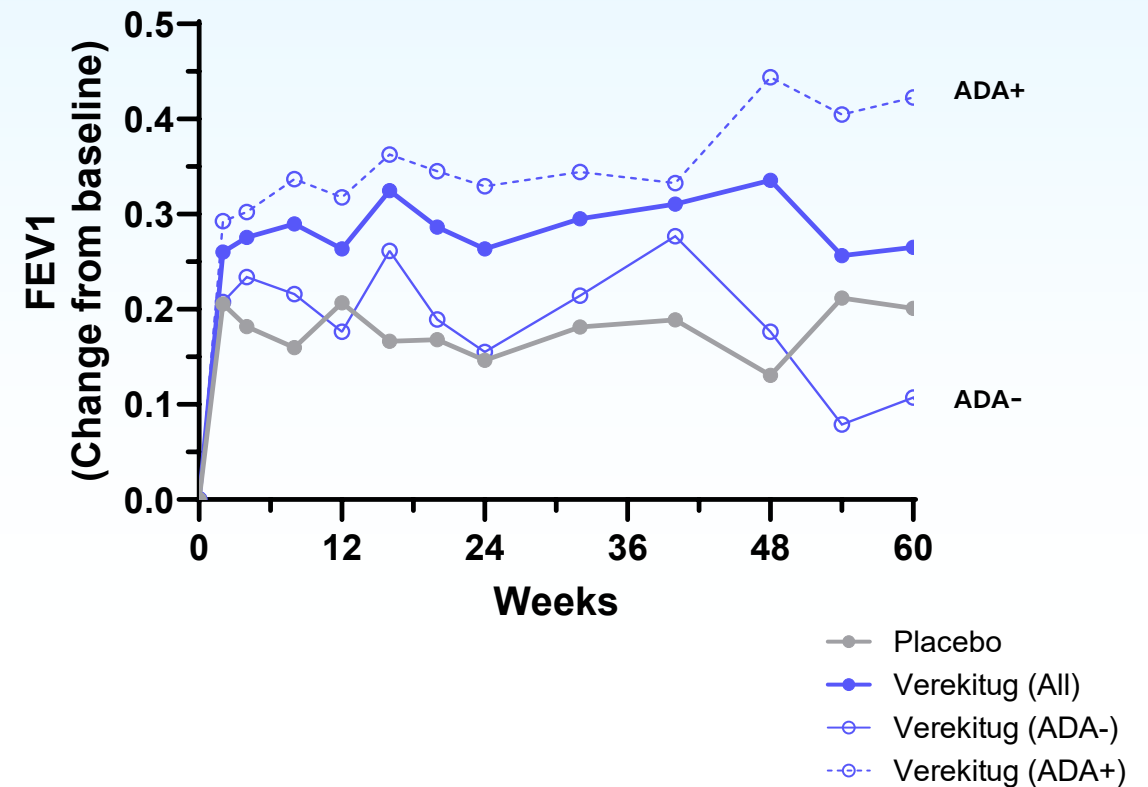
**Well-characterized immunogenicity profile has no meaningful impact on safety or efficacy**

# No meaningful impact of immunogenicity on AAER or FEV<sub>1</sub> in VALIANT

## AAER



## FEV<sub>1</sub> 100 mg q12w



# Conclusion

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

## Target product profile

Deliver **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 high-dose injection, up to 400 mg\*

Convenient quarterly dosing regimen

High and low-eosinophil populations

Self-administration via autoinjector at launch

Parallel Phase 3 trials in severe asthma & CRSwNP

# Focused execution toward Phase 3 initiation in severe asthma and CRSwNP



Conduct integrated analyses of Phase 2 data sets in CRSwNP and severe asthma to enable dose optimization and selection for Phase 3 trials in both indications

Engage with regulatory agencies

Continue accelerated operational planning for Phase 3 start

Ongoing investments in CMC and device development

Initiate dosing in Phase 3 trials in severe asthma and CRSwNP

2026

Q1 2027