



Phase 2 VIBRANT Top-line Results in CRSwNP

September 2, 2025

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Agenda

Introduction

Rand Sutherland, MD

Chief Executive Officer

VIBRANT Phase 2 Top-line Results

Aaron Deykin, MD

Chief Medical Officer and Head of R&D

Looking Ahead

Rand Sutherland, MD

Chief Executive Officer

Analyst Q&A

Rand Sutherland, MD

Chief Executive Officer

Aaron Deykin, MD

Chief Medical Officer and Head of R&D

Top-line results for Phase 2 VIBRANT study of verekitug in CRSwNP

Study drug 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 ($p < 0.0001$)

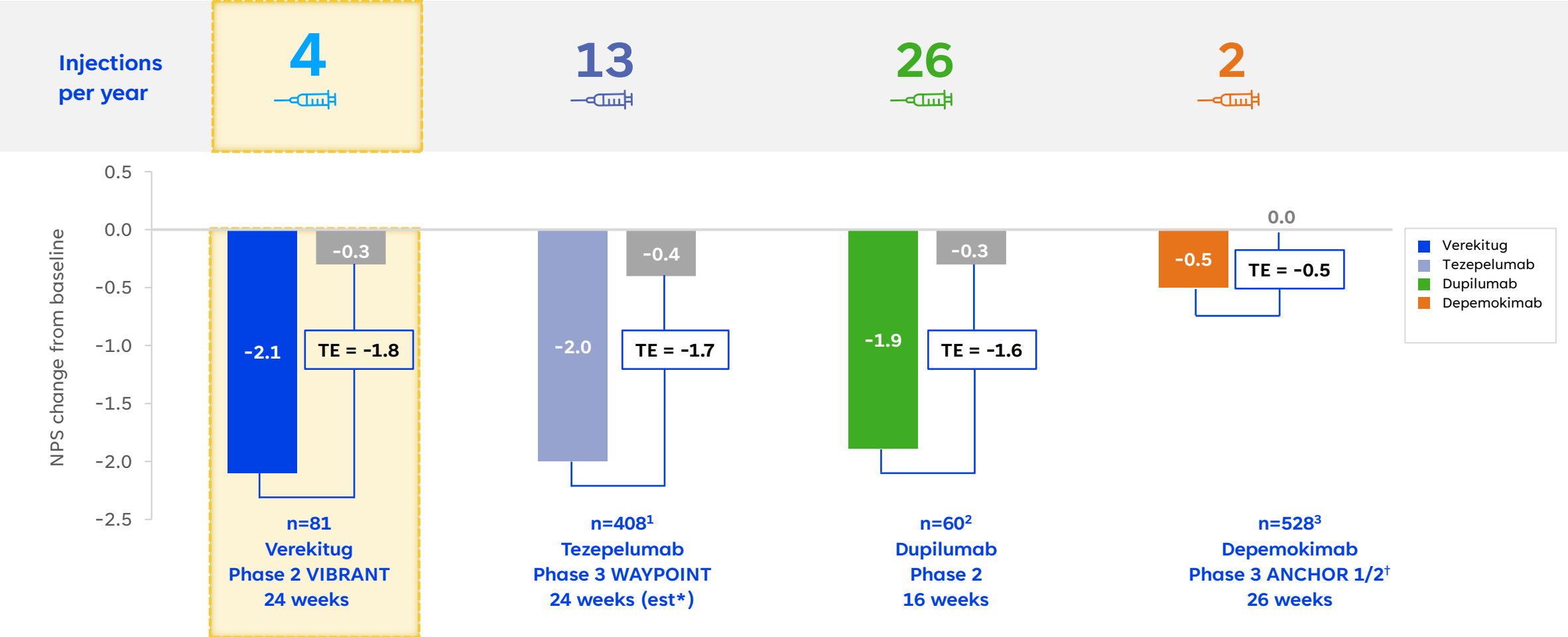
Met key secondary endpoints,
including NCS reduction of -0.8 ($p = 0.0003^*$) and 76% reduction in
need for surgery/steroids ($p = 0.03^*$)

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
CRSwNP, chronic rhinosinusitis with nasal polyps; NPS, Nasal Polyp Score;
NCS, Nasal Congestion Score; Q12W, every 12 weeks; SAEs, serious adverse events.

Verekitug dosed every 12 weeks delivered clinical activity at week 24 similar to tezepelumab dosed every 4 weeks



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TE, Placebo-adjusted treatment effect.
1. Lipworth B, et al *N Engl J Med*, (2025). 2. Bachert C, et al *JAMA*, (2016). 3. Gevaert P, et al *Lancet*, (2025).

About Upstream Bio

Clinical-stage
immunology company
focused on severe
respiratory diseases

Developing the only known antagonist of the TSLP receptor

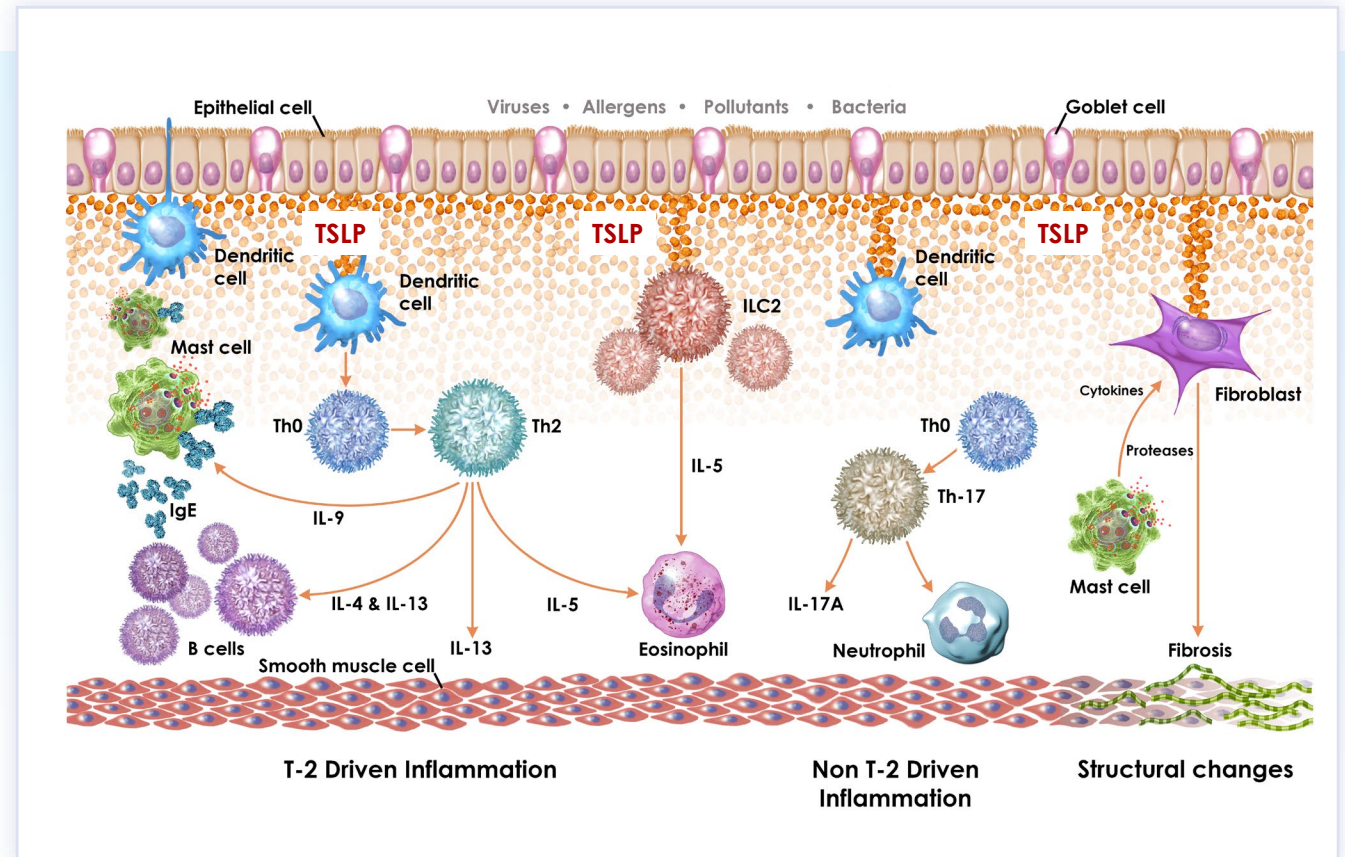
- Verekitug's pharmacology is unique and characterized by rapid, complete and sustained occupancy of the TSLP receptor, for up to 24 weeks after the last dose

Studying verekitug across multiple indications with high unmet need

- VIBRANT, our phase 2 trial in CRSwNP, now complete and reporting today
- VALIANT, our phase 2 trial in severe asthma, on track to report top-line data in Q1 2026
- VENTURE, our phase 2 trial in COPD, currently enrolling
- All trials randomized and placebo-controlled, with registrational endpoints
- TSLP biology supports expansion into other therapeutic areas, including dermatology and GI

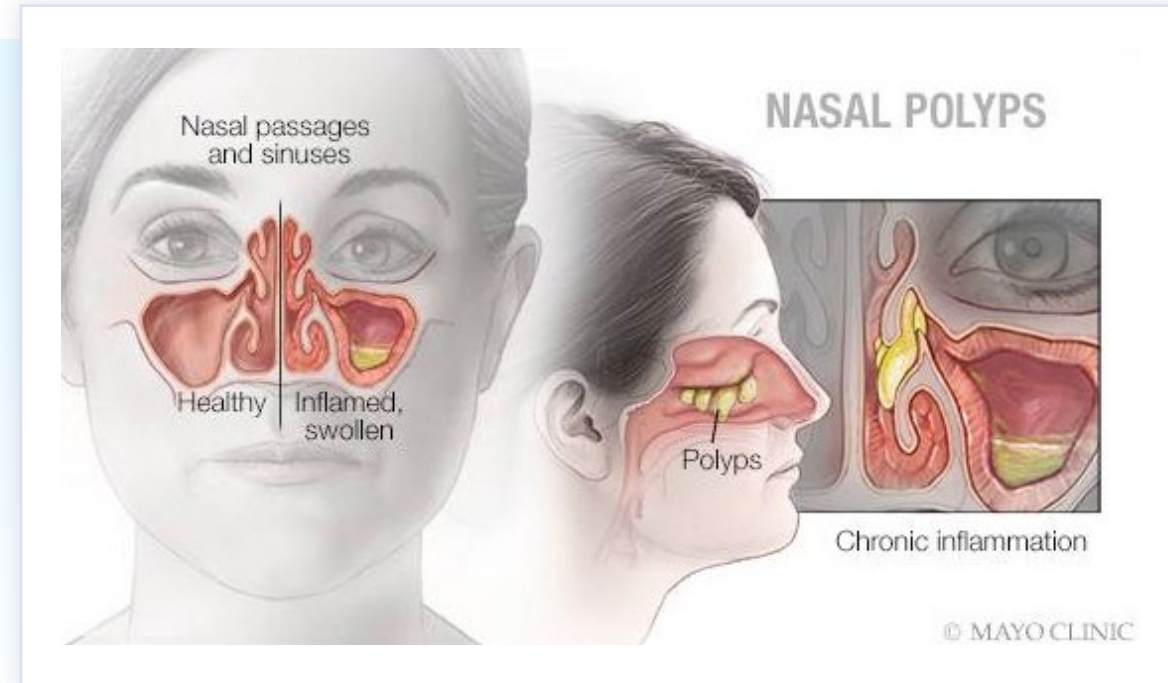
Verekitug blocks TSLP receptor assembly and potently reduces TSLP-driven inflammation

- Inhibition of TSLP signaling reduces type 2 and non-type 2 inflammation, as well as fibrotic responses
- Verekitug blocks the formation of the heterodimeric TSLP receptor and reduces key disease-associated biomarkers
- Verekitug's potency is approximately 300-fold greater than that of tezepelumab
- Upstream Bio's clinical programs are designed to evaluate the impact of verekitug's high potency on both dosing interval and efficacy in CRSwNP, severe asthma and COPD



CRSwNP: A TSLP-driven disease with substantial unmet need

- CRSwNP is a chronic inflammatory disease of the upper airway, marked by nasal and sinus inflammation and the presence of nasal polyps
- Severe disease significantly impacts quality of life, often necessitating surgery and systemic steroid therapy²
- TSLP is a key driver of inflammation in CRSwNP
- Up to 70% of patients will have comorbid asthma³
- Current biologics sales in CRSwNP alone estimated to exceed \$1B globally^{4,5}



1. Mayo Clinic. (2025). 2. Bachert et al *J Asthma Allergy*, (2021). 3. Bachert et al *J Allergy Clin Immunol Pract*, (2023).
4. Symphony Claims Data (June '24 – May '25). 5. Manufacturer Sales and Pricing Disclosures



Phase 2 VIBRANT Trial in Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

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

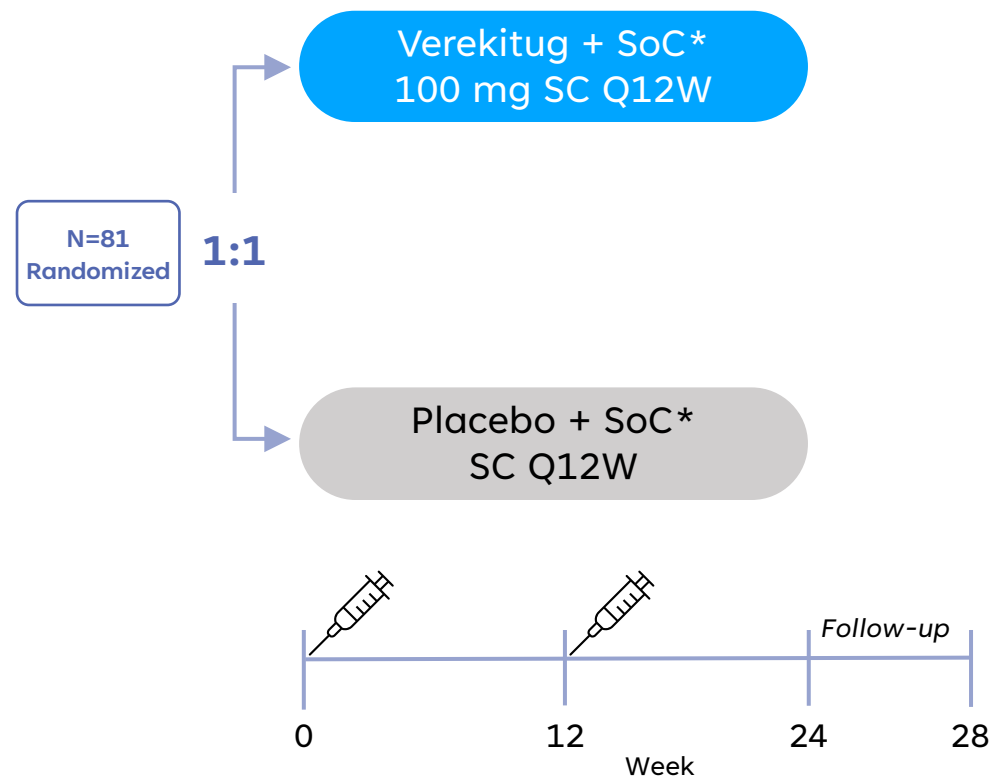
VIBRANT Phase 2 trial design

Enrolled 81 patients with CRSwNP in the US and Europe

Randomized, double-blind, placebo-controlled Phase 2 study with a 24-week treatment period (NCT06164704)

Key inclusion criteria:

- History of nasal polyp (NP) surgery OR NP exacerbation requiring systemic steroids in past 24 months
- Endoscopic nasal polyp score (NPS) ≥ 5
- Nasal congestion score (NCS) ≥ 2 over 14 days
- CRSwNP symptoms for ≥ 8 weeks
- Stable standard of care treatment for CRSwNP for ≥ 30 days



Primary endpoint:

Change in NPS
(from baseline to week 24)

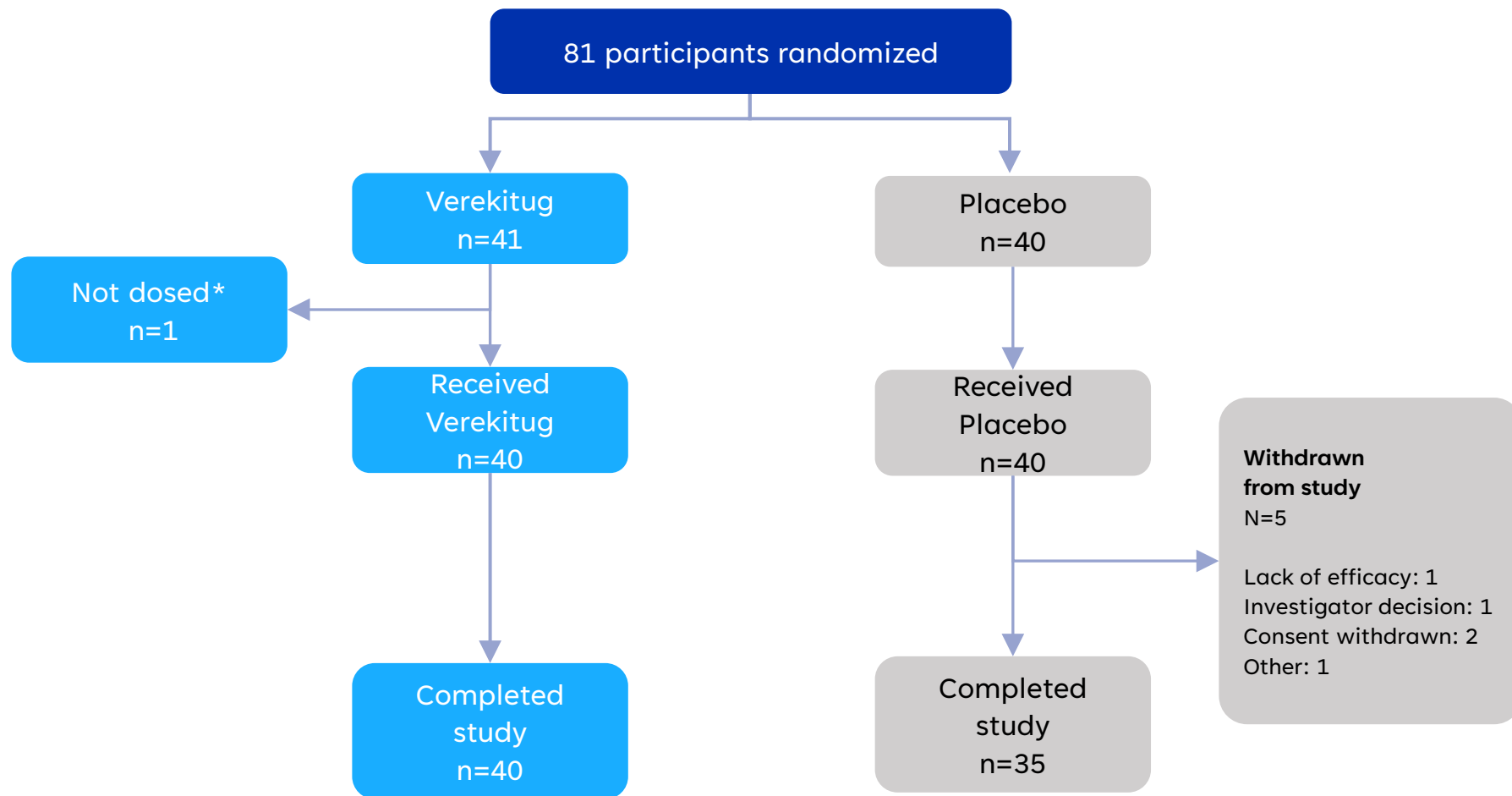
Key secondary endpoints:

- ☐ Change from baseline to week 24
 - NCS
 - Sinus opacification (Lund-Mackay score)
 - Total Symptom Score (TSS)
 - Difficulty with sense of smell (DSS score)
- ☐ Proportion of patients requiring surgery or systemic corticosteroids over 24 weeks

*SoC issued is an inhaled corticosteroid;
Q12W, every 12 weeks; SC, subcutaneous; SoC, standard of care.

VIBRANT ITT population disposition

93% of subjects completed the study



* One participant randomized to verekitug arm in error despite being a screen failure; was not dosed

Baseline characteristics were balanced across treatment groups

Slightly higher blood eosinophils observed in placebo group

	Verekitug	Placebo	Total (n=81)
Age (years), mean (SD)	49.8 (13.26)	49.6 (13.42)	49.7 (13.25)
CRSwNP duration (years), mean (SD)	13.7 (9.92)	11.7 (6.78)	12.7 (8.52)
Patients with systemic corticosteroid use in the preceding 2 years, n (%)	17 (41.5)	15 (37.5)	32 (39.5)
Patients with ≥ 1 prior NP surgery, n (%)	26 (63.4)	26 (65.0)	52 (64.2)
Patients with comorbid asthma, n (%)*	24 (58.5)	23 (57.5)	47 (58.0)
Bilateral endoscopic NPS (mean)	5.9 (1.62)	6.1 (1.30)	6.0 (1.47)
Baseline NCS (mean)	2.6 (0.43)	2.6 (0.44)	2.6 (0.43)
Blood eosinophil count (mean, cells/ μ L)	404 (260)	496 (378)	449 (324)

*Includes participants with AERD.
AERD, aspirin-exacerbated respiratory disease; SD, standard deviation.

Verekitug was generally well tolerated

Adverse Event Category, n, subjects (%)

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)

- Overall, incidence of AEs was similar across treatment groups
- TEAEs related to study treatment occurred more frequently in placebo
- No serious adverse events reported

Most common TEAEs in the study population ($\geq 5\%$) were consistent with CRSwNP symptoms

These occurred more frequently in the placebo group

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)

Verekitug led to significant and clinically meaningful improvements in NPS and key secondary endpoints, including reduction in need for surgery or systemic corticosteroids

		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

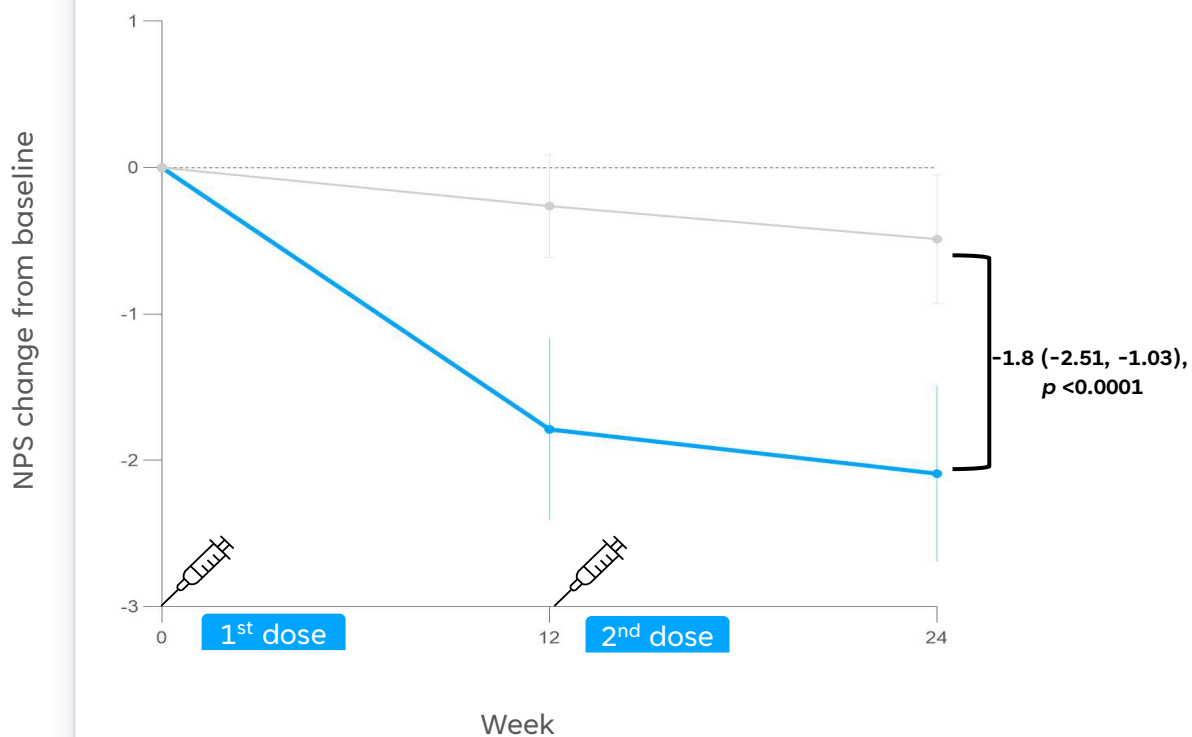
[†]p values for secondary endpoints are nominal and not adjusted for multiple comparisons.

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

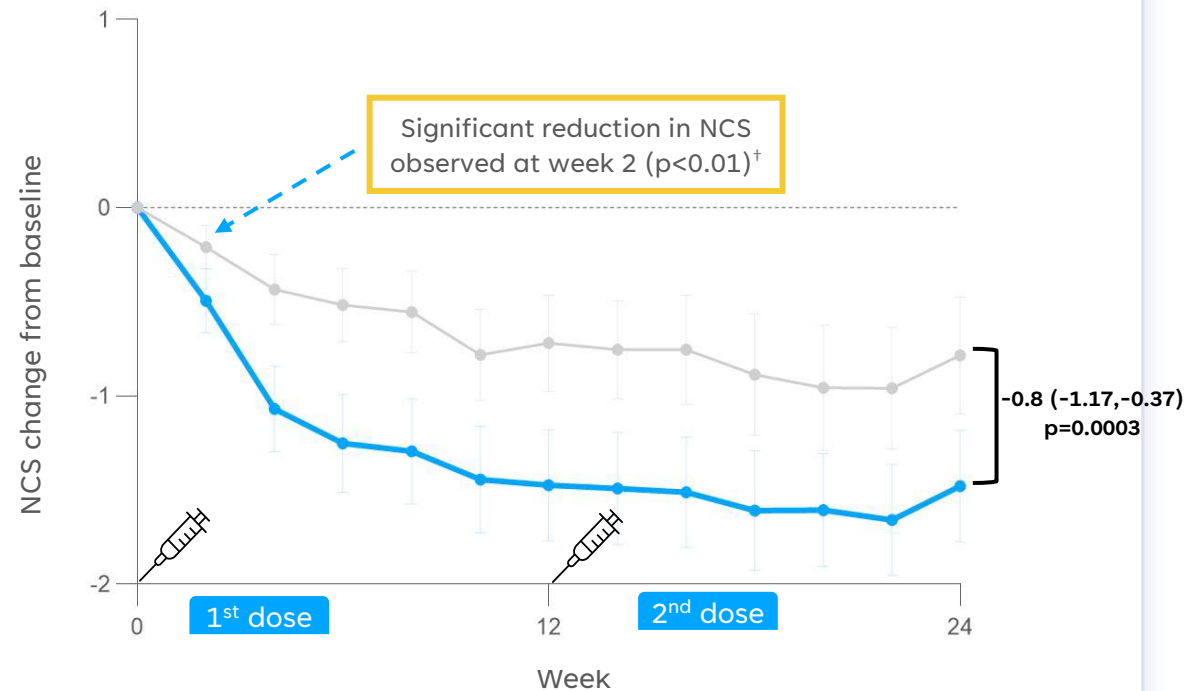
NPS range: 0–8; NCS range: 0–3 over 2 weeks; LMK CT score (0–24); TSS range: 0–24; 8 symptoms over 2 weeks; DSS range: 0–3 over 2 weeks.

Verekitug dosed every 12 weeks led to significant reductions in NPS and NCS over 24 weeks

Endoscopic NPS change



Total NCS change*

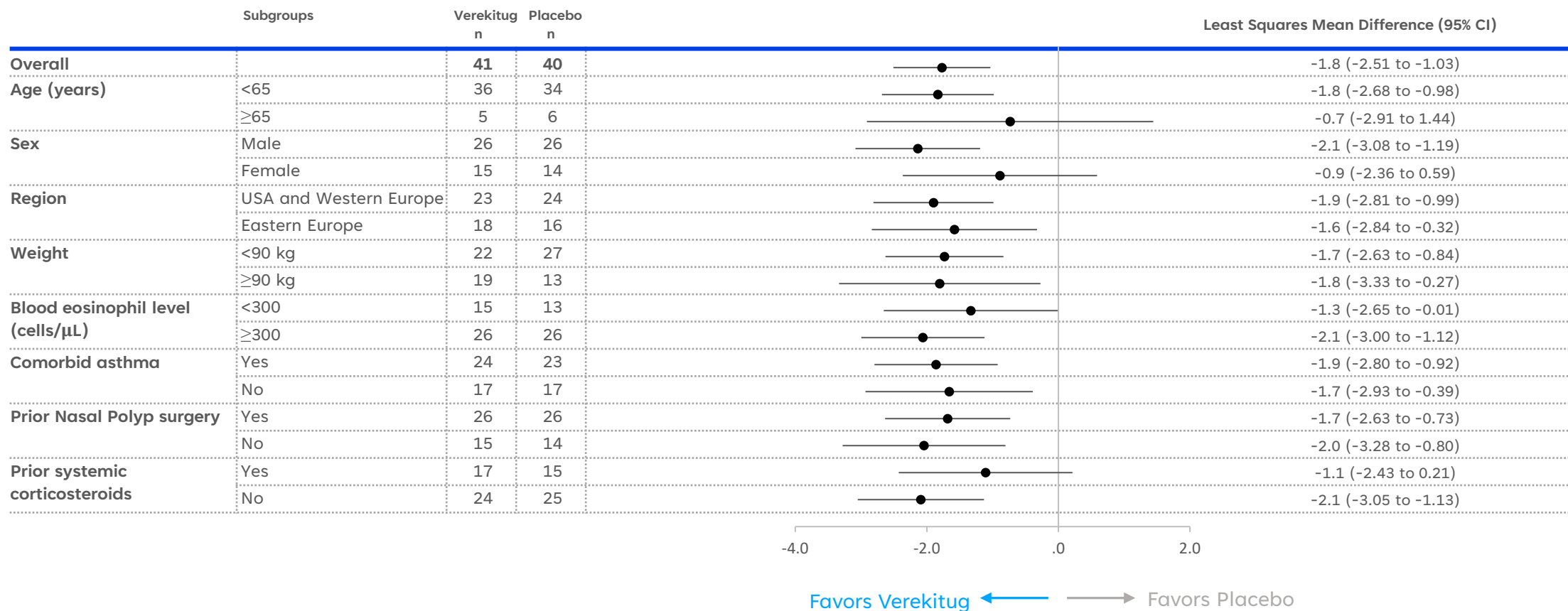


*NCS was calculated as the 14-day average of the daily scores.

[†]Nominal p-value

Changes are shown as least-squares means. I bars indicate 95% confidence intervals (CI).

Verekitug demonstrated clinical effect in NPS across all subgroups



VIBRANT population generally similar to CRSwNP studies of other biologics

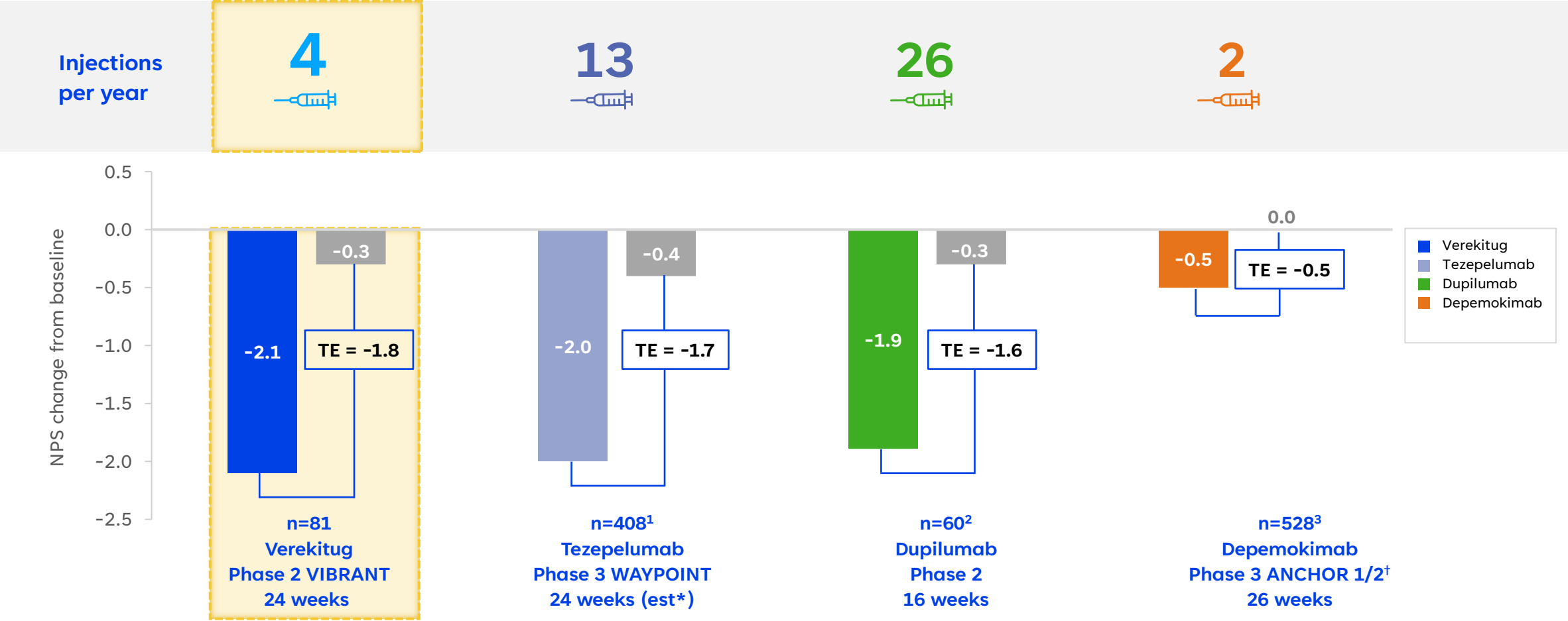
	Verekitug Ph 2 VIBRANT	Tezepelumab ¹ Ph 3 WAYPOINT	Dupilumab ² Ph 2	Depemokimab ³ Ph 3 ANCHOR 1/2 [†]
Patients (n)	81	408	60	528
Age years (mean)	49.7	49.7	48.4	52
CRSwNP duration years, (mean)	12.7	12.8	9.6	12
Patients with systemic corticosteroid use in the preceding 1 ^{1,2} or 2 ^{3,4} years (%)	39.5	65.4	N/A	61
Patients with ≥1 prior NP surgery (%)	64.2	71.4	58	64
Patients with comorbid asthma (%) [‡]	58.0	60.8	58	55
Bilateral endoscopic NPS (mean)	6.0	6.1	5.8	5.9
Baseline NCS (mean)	2.6	2.6	1.7	N/A
Baseline blood eosinophils cells/μL (mean)	449	258	430	344

[†]Integrated data from ANCHOR 1/2, estimated. Nasal polyp score (NPS); range: 0–8; [‡]Includes participants with asthma and AERD.

No head-to-head studies of Verekitug and these products have been conducted.

1. Lipworth et al *N Engl J Med*, (2025). 2. Gevaert et al *Lancet*, (2025). 3. Bachert et al *JAMA*, (2016). 4. Verekitug, VIBRANT.

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Only Dupilumab is FDA-approved for use in CRSwNP.

TE, Placebo-adjusted treatment effect.

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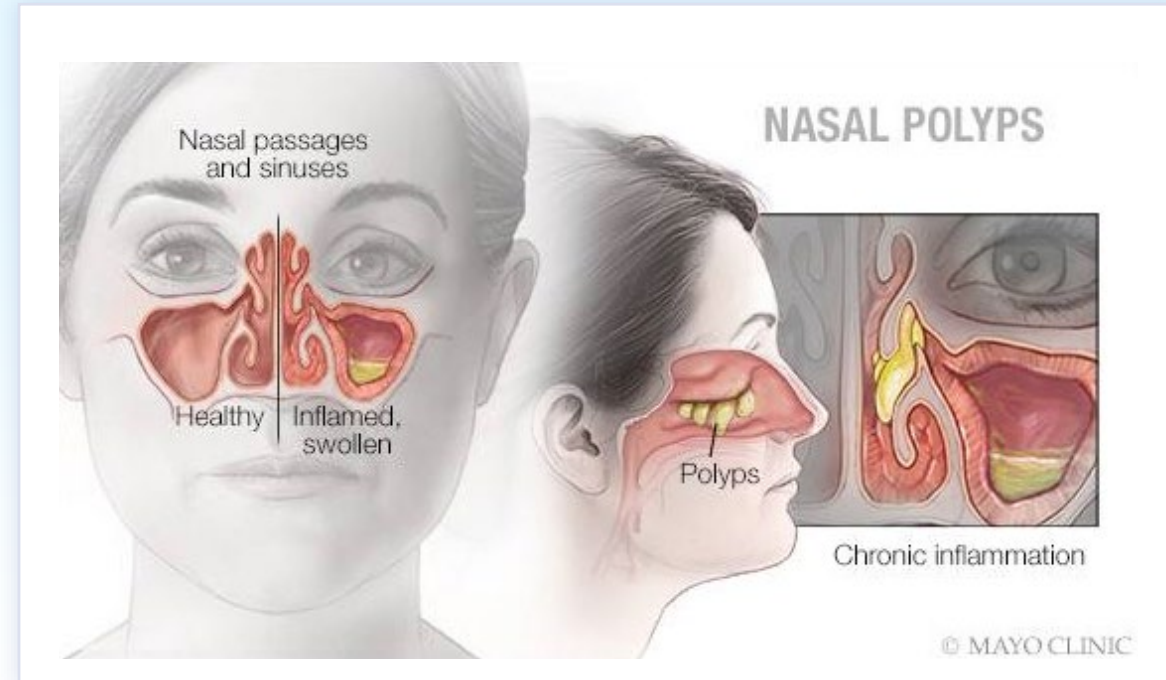
*Nominal p values

Looking Ahead

Rand Sutherland, MD
Chief Executive Officer

Verekitug has the potential to advance the standard of care in CRSwNP and other respiratory diseases

- Verekitug delivered significant effects on the primary and key secondary CRSwNP endpoints in the VIBRANT trial
- This broad clinical activity was delivered at a differentiated dosing interval of every 12 weeks
- Verekitug's safety profile continues to be favorable
- Verekitug is the first extended-dosing interval anti-TSLP agent to demonstrate this profile, which is uniquely driven by potency rather than antibody engineering
- Given the role of TSLP in other respiratory diseases, including severe asthma and COPD, these data support further development of verekitug in multiple indications with substantial unmet need and commercial opportunity



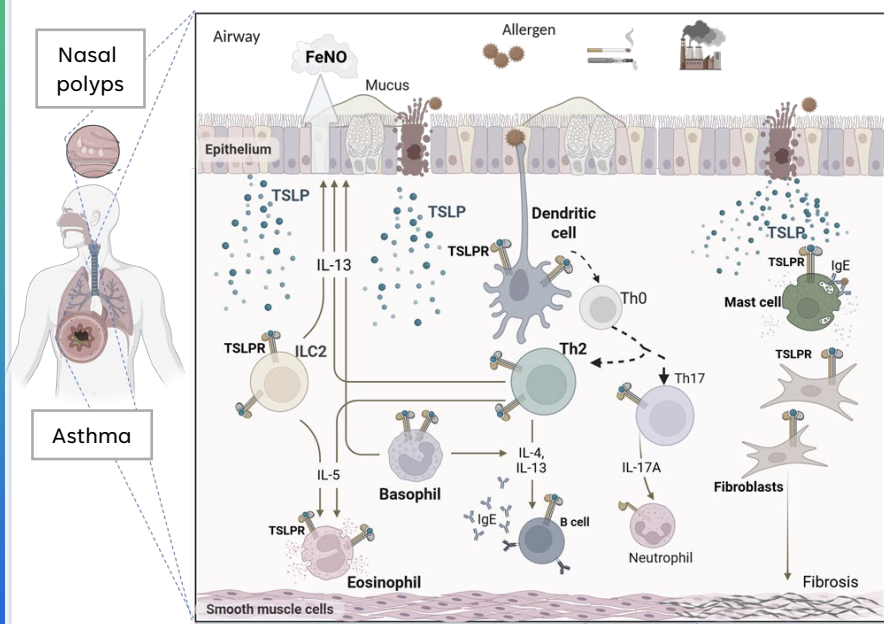
CRSwNP and Severe Asthma

Biological, Epidemiological and Clinical Overlap

Shared biology with central role of TSLP driving activation of common cytokine pathways¹⁻⁴

Shared Epidemiology¹

Common biologic therapies and magnitude of response⁵



In patients with CRSwNP

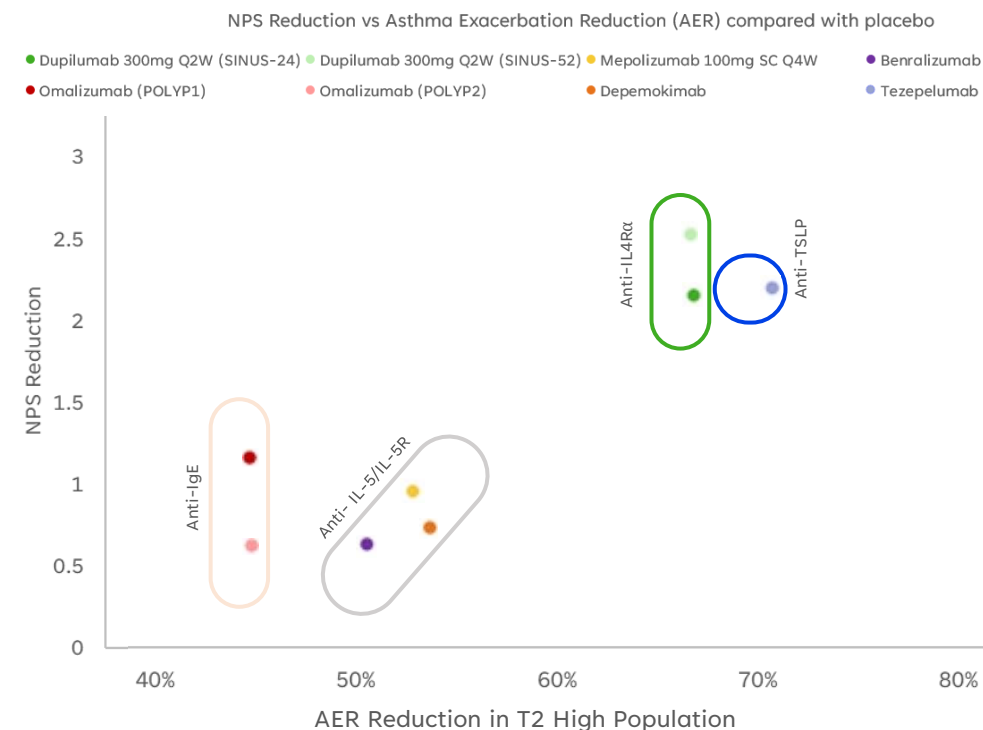


Up to 70% have **comorbid asthma**

In patients with asthma



Over 40% have **comorbid CRSwNP**



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AER, annualized exacerbation rate; BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyps; NPS, nasal polyp score; TSLP, thymic stromal lymphopoietin.

1. Bachert et al *J Allergy Clin Immunol Pract*, (2023); 2. Castagnoli et al *Exp Rev Respir Med*, (2020); 3. Giombi et al *Int J Mol Sci*, (2024); 4. Pelaia C, et al *J Clin Med*, (2023); 5. Data derived: Dupilumab AER reduction based on BEC ≥ 300 (QUEST only); NPS based on SINUS-24 (Week 24) & SINUS-52 at (Week 52), Mepolizumab AER reduction based on USPI, 100 mg SC in MENSA trial only; NPS based on SYNAPSE at Week 52, Benralizumab AER reduction based on SIROCCO trial only in USPI, CALIMA was 37% reduction; NPS based on OSTRO at Week 40, Omalizumab AER reduction based on Normansell R, et al *Cochrane Database Syst Rev*, (2014); NPS based on POLYP1/2 at Week 24, Depemokimab AER reduction based on Pooled SWIFT-1/2; NPS based on ANCHOR-1/2 at Week 52, Tezepelumab AER reduction based on Pooled Analysis of the PATHWAY and NAVIGATOR Clinical Trials, BEC ≥ 300 ; NPS based on WAYPOINT at Week 52.

Thank you to our trial participants and investigators

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Q&A