Targeting of TSLP and IL-13 by the novel NANOBODY® molecule SAR443765 reduces FeNO in asthma following single-dose exposure

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Disclosure to Learners

All authors are Sanofi employees and may hold stock and/or stock options in the company.

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Introduction

Despite the availability of a range of biologic monotherapies targeting IgE, IL-5, IL-5R, IL-4R, or TSLP, patients with asthma may continue to experience incomplete disease control, resulting in exacerbations, reduced lung function, and poor quality of life[1–3]

Anti-TSLP therapy is effective in reducing exacerbations in asthma with type 2 and non-type 2 inflammation[6–9]; anti-IL-13 therapy has mixed effects on exacerbations, but improves lung function[10–14]

Combining anti-TSLP and anti-IL-13 therapies could potentially result in an additive effect, particularly against type 2 inflammation, which may yield superior improvements in exacerbations and lung function than therapy with either agent alone

Elevated fraction exhaled nitric oxide (FeNO) is a marker of persistent uncontrolled asthma and is associated with a greater risk of exacerbation and loss of lung function[4,5]. Reductions in FeNO are associated with reduced exacerbation rates and improved lung function and may represent a predictive biomarker of treatment efficacy[15]

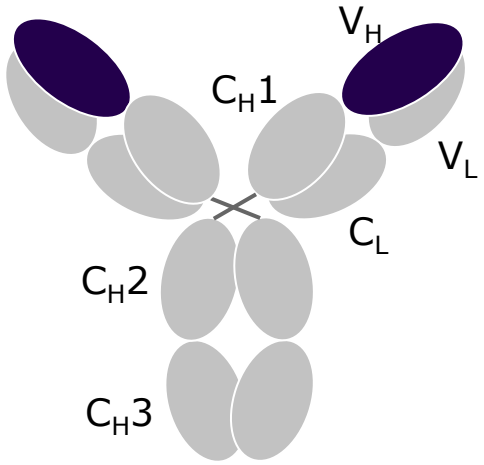
FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; TSLP, thymic stromal lymphopoietin.

1. Kaplan AP, et al. *Allergy*. 2017;72:519-533; 2. Ridhima W, et al. *Eur Respir Review.* 2019;28:153. 3. Schleich F, et al. *Eur Respir Rev.* 2023;32:220193; 4. Pavord ID, et al. *J Allergy Clin Immunol Pract*. 2023;11:1213-20; 5. Malinovschi A, et al. *J Allergy Clin Immunol*. 2016;138:1301-08; 6. Gavreau GM, et al *NEJM*. 2014;370:2102-10; 7. Corren JC, et al. *NEJM.* 2017;377:936; 8. Menzies-Gow A, et al. *NEJM*. 2021;384:1800-09; 9. Weschler M, et al. *Lancet Respir Med*. 2022;10:650-60; 10. Corren JC, et al. *NEJM*. 2011;365:1088-98; 11. Austin CD, et al. *Clin Exp Allergy*. 2020;50:1342-51; 12. Hanania NA, et al. *Thorax*. 2015;70:748-56; 13. Panettieri RA, et al. *Lancet Respir Med*. 2018;6:511-25; 14. Russell RJ, et al. *Lancet Respir Med*. 2018;6:499-510;; 15. Busse WW, et al. *Lancet Respir Med*. 2021;9:1165-73.

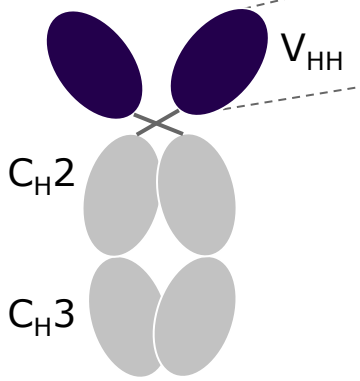
NANOBODY® Molecules: A Unique Technology

NANOBODY® molecules are a type of miniature, engineered antibody, derived from *Camelid* heavy-chain only monoclonal antibodies:

- Stable and fully functional
- Represent the next generation of antibody-derived biologics
- Multispecific/multivalent NANOBODY® molecules can address multiple targets in a single drug molecule



Conventional antibodies



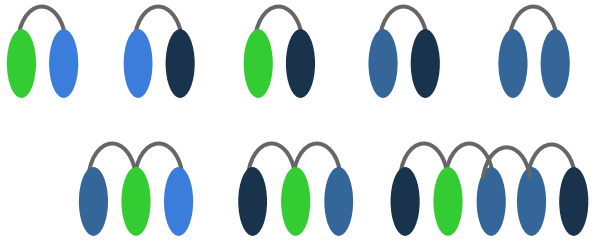
Heavy-chain only antibodies

NANOBODY® molecule

- Small and robust
- Easily linked together
- Nano- to pico-molar affinities
- Multiple administration routes
- Sequence homology compared to humanized/human antibodies

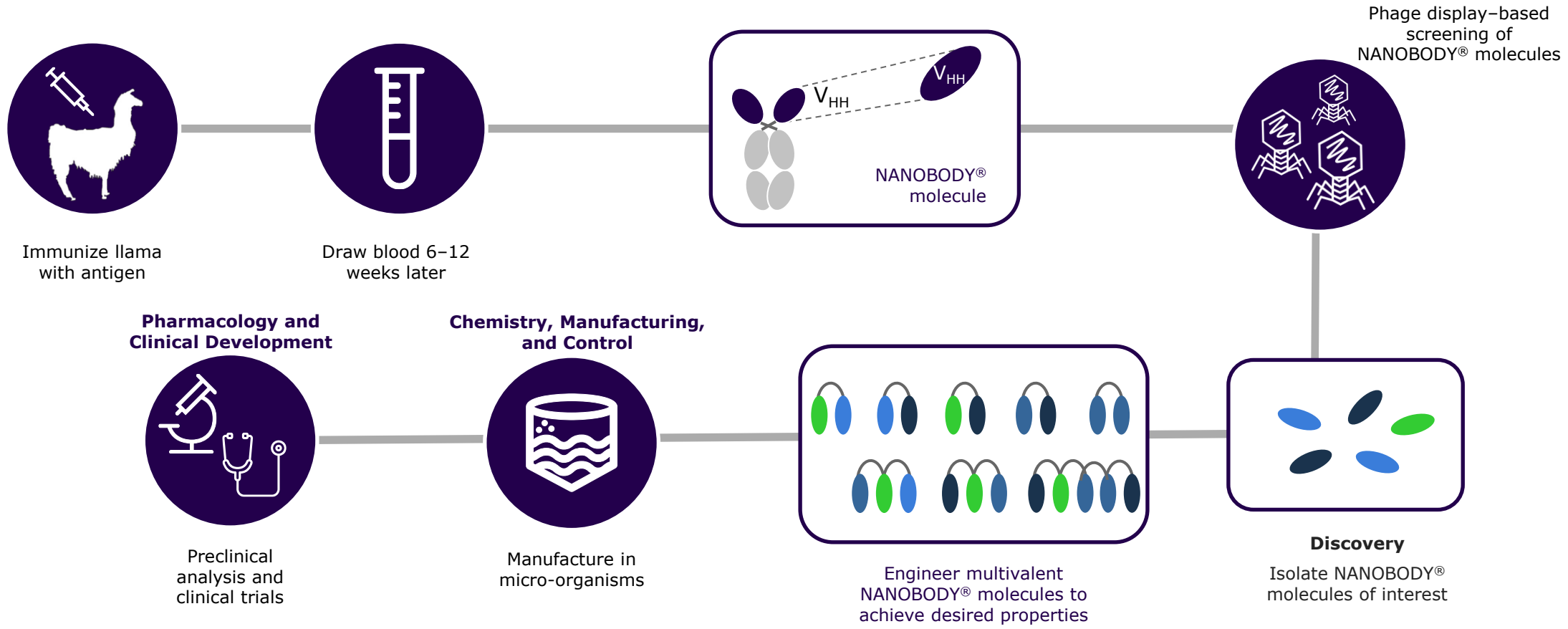
Mix and match

Multispecific/multivalent NANOBODY® molecules that bind multiple targets in a single drug molecule with flexible glycine-serine linker lengths



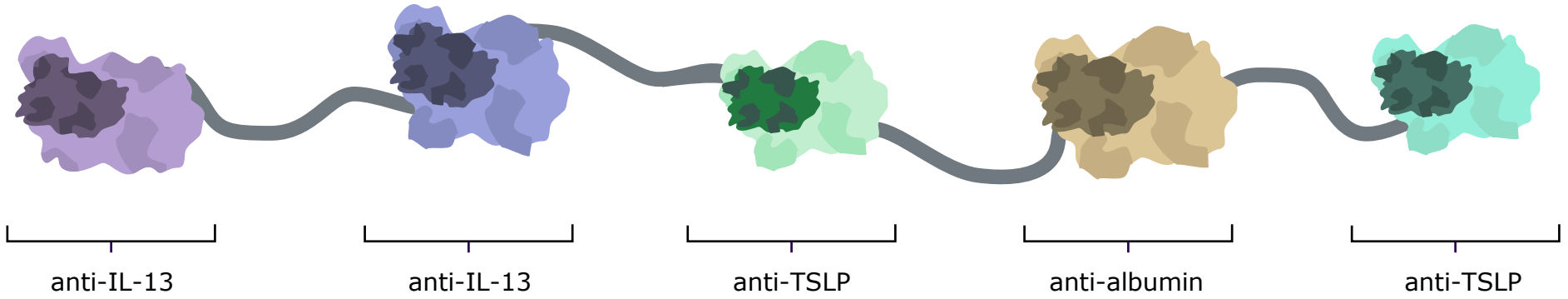
Hanlon A, et al. *Ther Adv Hematol*. 2020;11:2040620720902904.

NANOBODY® Molecules: From Llamas to Medicines



Van Roy M, et al. *Arthritis Res Ther*. 2015;17:135.

SAR443765: First NANOBODY® Molecule in Development for Asthma



- 2 sites binding TSLP (2 different epitopes)
- Potent blockade of TSLP effects

2 sites binding IL-13 (2 different epitopes)

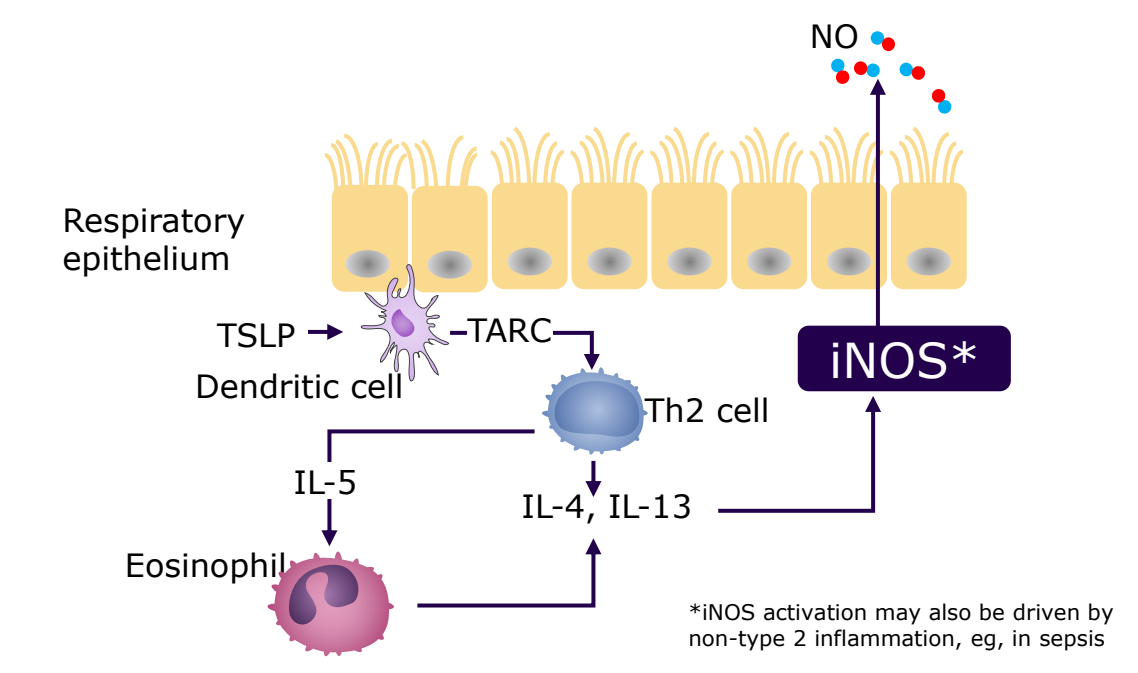
1 site binding human serum albumin to increase half-life

IL-13, interleukin 13; TSLP, thymic stromal lymphopoietin.

Hypothesis

Type 2 inflammation[1–3]

- Mainly driven by IL-4, IL-5, and IL-13
- Drives IgE synthesis, eosinophil recruitment, and NO production, indicating nitrosative/oxidative stress



FeNO[2,3]

- A recognized marker of type 2 airway inflammation associated with an increased risk of exacerbations, worse FEV_1, and accelerated loss of lung function
- Readily measured in the breath
- Rapid reduction in FeNO has been observed after the first dose of monospecific mAbs[4–6]
  - anti-TSLP
  - anti-IL-13
  - anti-IL-4R
- FeNO reductions sustained throughout treatment[4–6]

Hypothesis

FeNO will be significantly reduced in people with asthma following a single dose of NANOBODY® molecule SAR443765, which blocks TSLP and IL-13

FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; iNOS,, inducible nitric oxide synthase; NO, nitric oxide; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.

1. Ziegler, S, et al. *Nat Immunol.* 2006;7:709-14; 2. Ricciardolo FL, et al. *Allergol Immunopathol (Madr)*. 2015;43:609-16; 3. Munakata M. *Allergol Int*. 2012;61:365-72; 4. Corren J, et al. *N Engl J Med*. 2017;377:936-46; 5. Corren J, et al. *N Engl J Med*. 2011;365:1088–98; 6. Gauvreau GM, et al. *N Engl J Med*. 2014;370:2102-10.

SAR443765 Phase 1 Trial Design:

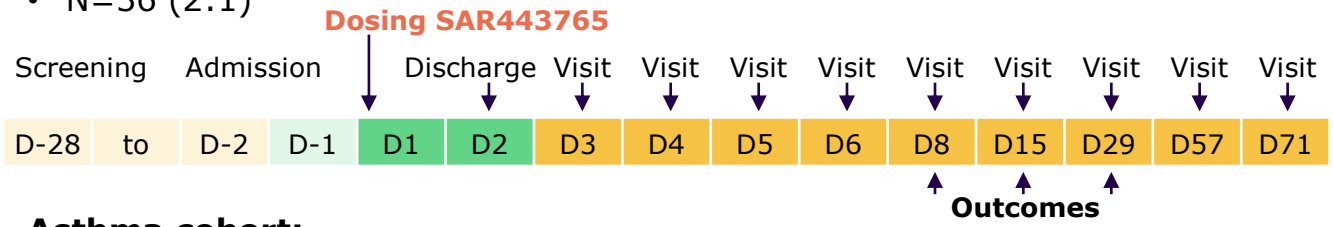
Double-blind, randomized, placebo-controlled, parallel-design, SAD/MAD in healthy participants and single-dose proof of mechanism in patients with mild-to-moderate asthma

1. Single ascending dose in healthy participants

- 5 IV cohorts (10–400 mg vs placebo)
- 1 SC cohort (400 mg vs placebo)
- N=48 (3:1)

2. Proof of mechanism (Phase 1b) in asthma

- Mild/moderate asthma with elevated FeNO
- Single dose (400 mg vs placebo) SC
- N=36 (2:1)



Asthma cohort:

- GINA 2020 Guidelines Steps 1–3 and moderate Step 4 (fluticasone propionate ≤500 µg/day or similar) with as-needed SABA use
- ICS-naïve or on stable treatment (≥3 months) with low/medium dose ICS
- Additional controllers allowed: LABA and/or LAMA as second controller, and/or with stable daily leukotriene receptor antagonist, leukotriene synthesis inhibitor, and/or chromones
- Controlled asthma: ≤1 canister rescue inhaler/month for ≥3 months
- Elevated FeNO (≥25 ppb) at baseline
- FEV_1 ≥60% of predicted normal at baseline with positive bronchodilator or bronchoconstrictor response within past 5 years

3. Multiple ascending dose in healthy participants

- 2 SC cohorts (100–200 mg vs placebo)
- 3 doses Q2W (Day 1, Day 15, & Day 29)
- N=40 (4:1)

The primary outcome was safety, and change in FeNO from baseline versus placebo at Day 29 post-dose was a secondary endpoint

FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MAD, multiple ascending dose; ppb, parts per billion; SABA, short-acting beta agonist; SAD, single ascending dose; SC, subcutaneous.

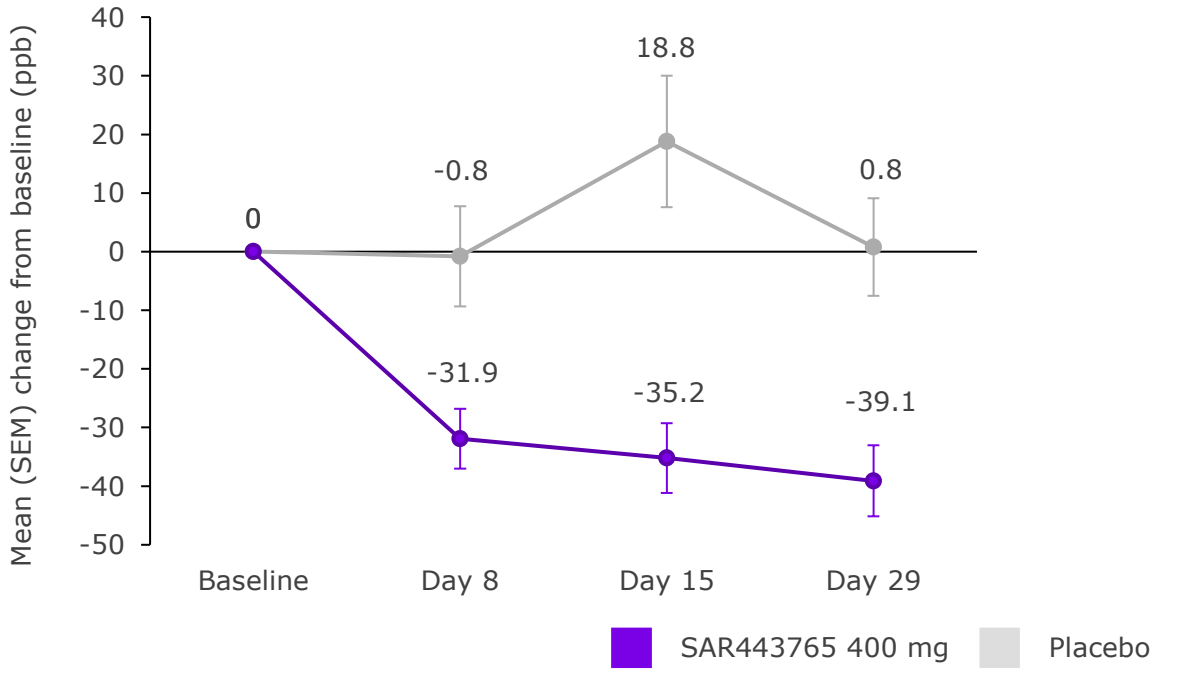
Baseline Characteristics of Patients with Mild-to-Moderate Asthma in Proof of Mechanism Study

	Placebo (N=12)	SAR443765 (N=24)	Overall (N=36)
Demography			
Male/female, n/n (%/%)	5/7 (42/58)	13/11 (54/46)	18/18 (50/50)
Age [y], mean (SD)	30.3 (8.8)	36.2 (11.4)	34.2 (10.9)
Race white, n (%)	12 (100)	21 (88)	33 (92)
Baseline BMI [kg/m^2], mean (SD)	24.2 (3.61)	24.2 (2.77)	24.2 (3.03)
Disease characteristics			
Disease duration [y], median (min–max)	19 (12–31)	25 (4–44)	21 (4–44)
Childhood asthma, n (%)	8 (67)	18 (75)	26 (72)
Pre-BD FEV_1 [L], median (min–max)	2.9 (2.0–4.5)	3.2 (1.6–6.1)	3.1 (1.6–6.1)
Pre-BD FEV_1 [%predicted], median (min–max)	82.8 (62.0–95.6)	77.2 (61.8–115.6)	78.6 (61.8–115.6)
Pre-BD FEV_1/FVC ratio, median (min–max)	64.2 (49.7–83.2)	67.1 (50.5–81.4)	66.7 (49.7–83.2)
Blood eosinophil levels [cells/µL], median (min–max)	275 (140–590)	250 (100–680)	250 (100–680)
Blood eosinophil levels [cells/µL], n (%)			
<150	1 (8.3)	2 (8.3)	3 (8.3)
150–300	7 (58.3)	14 (58.3)	21 (58.3)
≥300	4 (33.3)	8 (33.3)	12 (33.3)
FeNO [ppb], median (min–max)	54.5 (28–148)	60.5 (25–184)	59.0 (25–184)
Asthma treatment			
Selective short-acting beta agonists, n (%)	12 (100)	24 (100)	36 (100)
ICS low-to-medium daily dose, n (%)	5 (42)	11 (46)	16 (44)
Other, n (%)	5/12 (42)	8/24 (33)	13/36 (36)
Medical history			
History of allergies, n (%)	8 (67)	19 (79)	27 (75)
History of nasal polyps, n (%)	2 (17)	2 (8)	4 (11)

- Enrolled population was broadly representative of those with mild-to-moderate asthma
- Patients selected for baseline FeNO ≥25 ppb; enriched for ↑FeNO in mild-to-moderate asthma population
- Lung function was well-preserved (normal to near-normal)
- High eosinophil levels and history of allergies at baseline consistent with predominance of type 2 inflammation
- Main baseline characteristics were well balanced across the two groups

BD, bronchodilator; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids; ppb, parts per billion; SD, standard deviation.

Significant Reduction in FeNO with SAR443765, Compared with Placebo

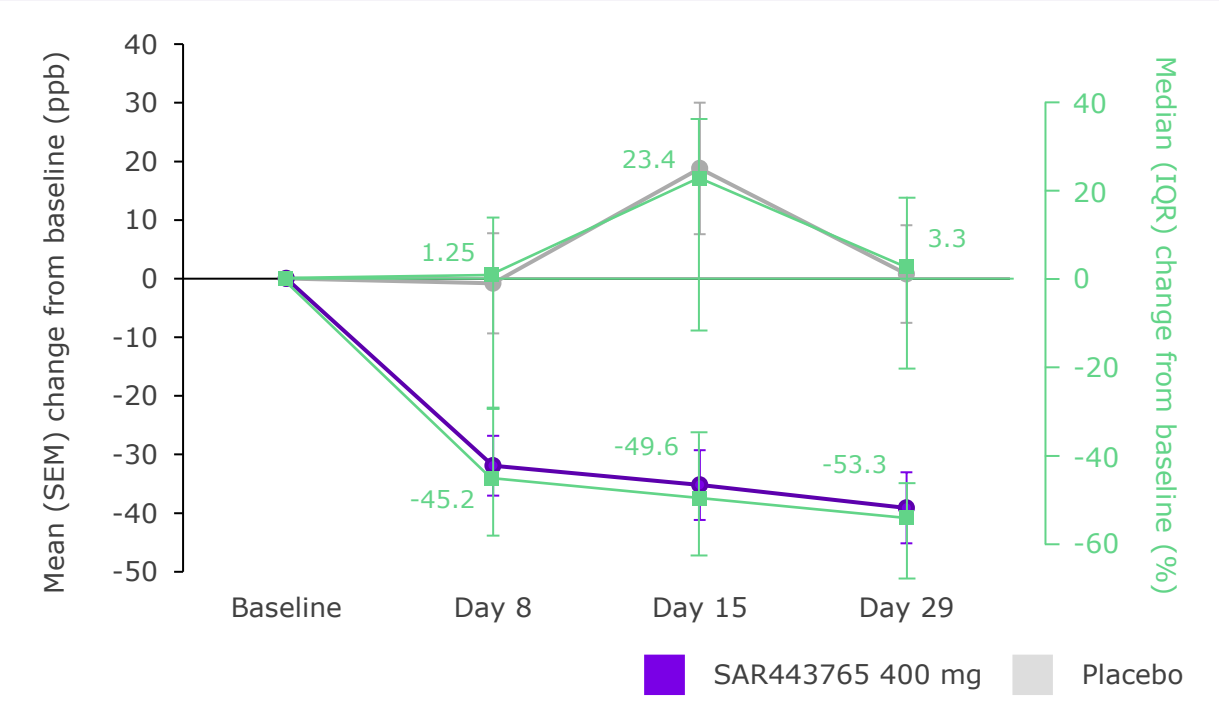


- Highly elevated FeNO at baseline, consistent with active, type 2 airway inflammation (59.0 ppb [25–184])
- Near-maximal reduction in FeNO at Day 8, maintained to Day 29
- Significant change from baseline at Day 29 of –40.9 ppb (90% CI: –55.4 to –26.4) change from baseline, versus placebo*
- Significant changes (mixed-effects model) also at:
  - Day 8 (–33.0 ppb [90% CI: –46.3 to –19.8])*
  - Day 15 (–54.9 ppb [90% CI: –74.0 to –35.8])*

Confirmed pharmacodynamic effect, with FeNO as clinically relevant biomarker for type 2 airway inflammation

CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; SEM, standard error of the mean.
*Point estimates and 90% CI from a mixed-effects model over time taking into account baseline FeNO and sex as co-variates.

Significant Reduction in FeNO with SAR443765, Compared with Placebo



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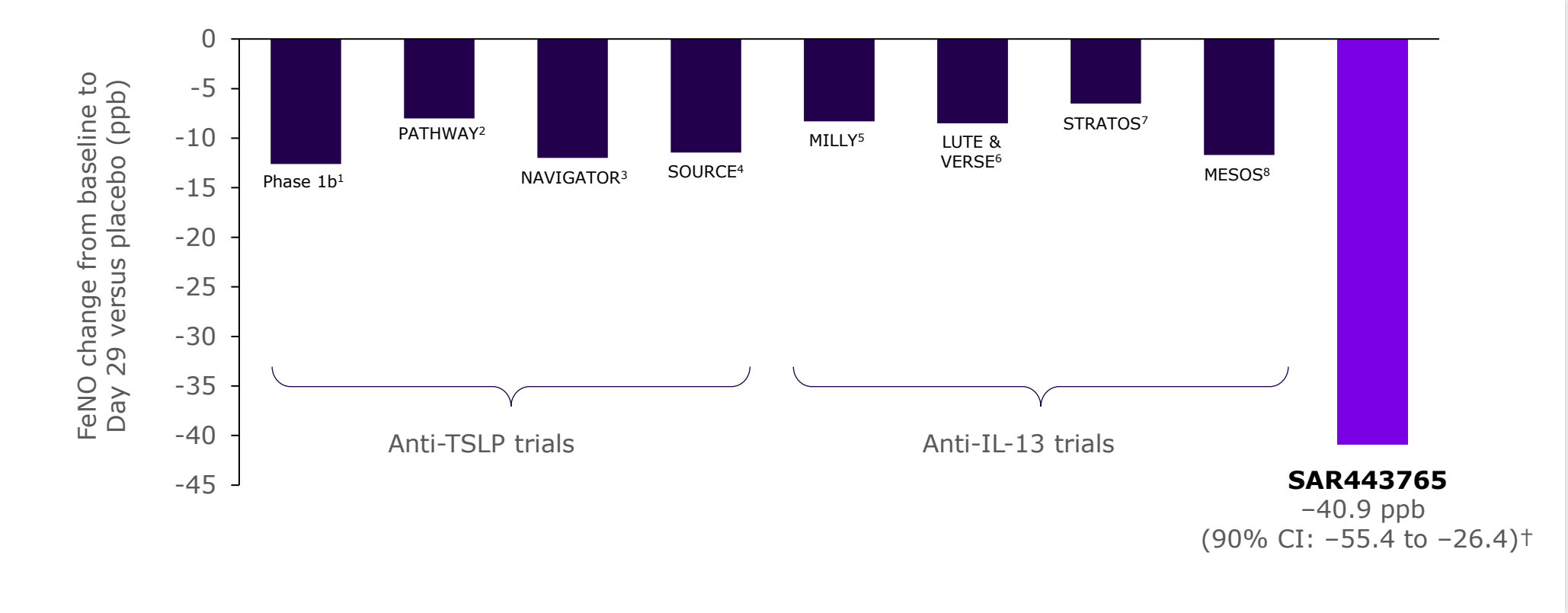
  - Day 8 (–33.0 ppb [90% CI: –46.3 to –19.8])*
  - Day 15 (–54.9 ppb [90% CI: –74.0 to –35.8])*
- The median % change from baseline for SAR443765 at Day 29 is –57.6% versus placebo

Confirmed pharmacodynamic effect, with FeNO as clinically relevant biomarker for type 2 airway inflammation

CI, confidence interval; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; SEM, standard error of the mean.
*Point estimates and 90% CI from a mixed-effects model over time taking into account baseline FeNO and sex as co-variates.

Effect of existing asthma biologics and SAR443765 on FeNO at Day 29 vs placebo*[1–8]



FeNO, fractional exhaled nitric oxide.
*Not head-to-head comparisons; patient populations and baseline characteristics may differ between studies. Estimates of FeNO change from baseline versus plaecbo derived from published data. †Difference vs placebo estimate from a mixed-effects model over time taking into account baseline FeNO and sex as co-variates.

1. Gavreau GM, et al *NEJM*. 2014;370:2102-10; 2. Corren JC, et al. *NEJM.* 2017;377:936; 3. Menzies-Gow A, et al. *NEJM*. 2021;384:1800-09;
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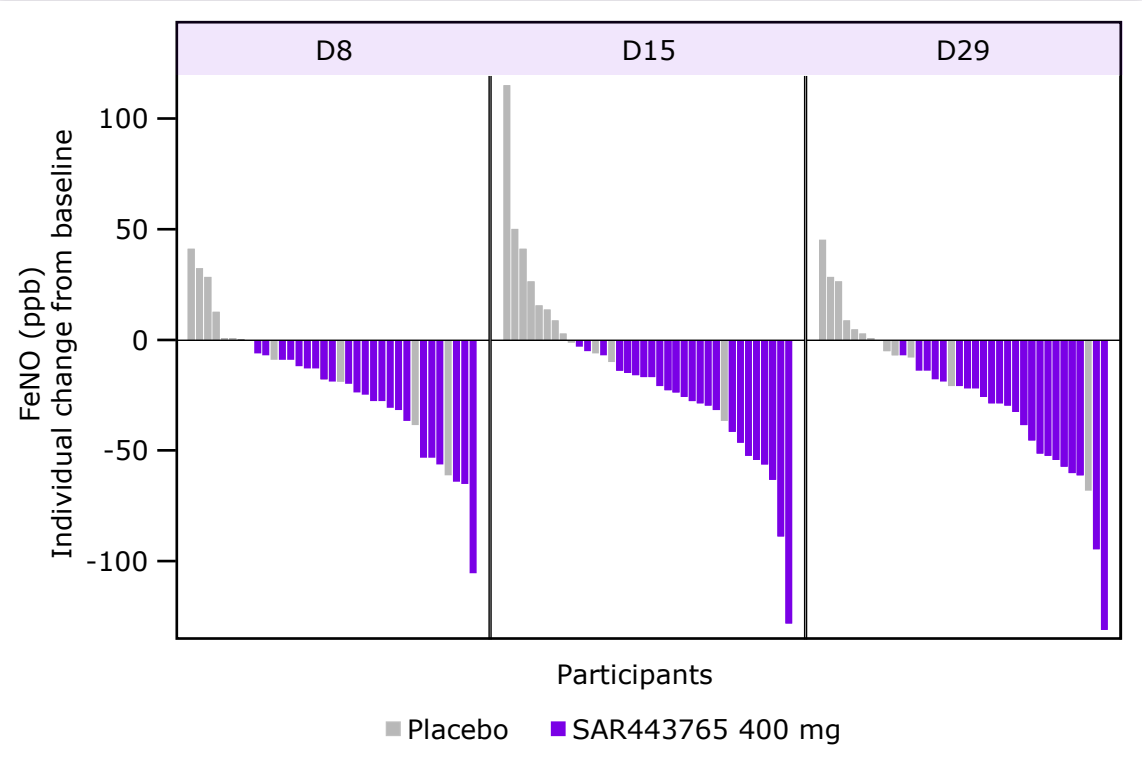
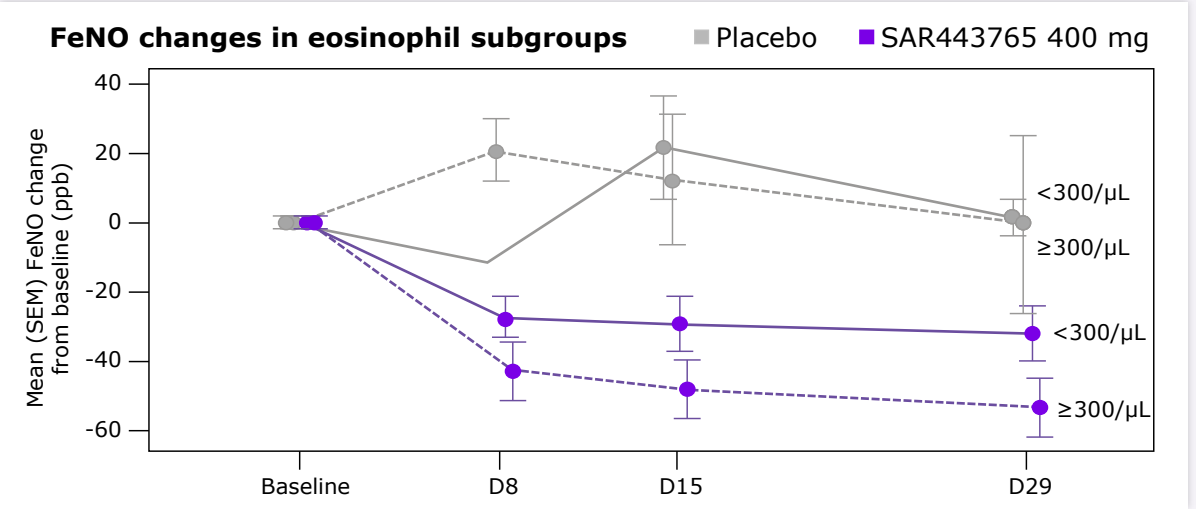
Effect Seen Across Subgroups, Including Low-Eosinophil Group

- Reduction in FeNO observed in every participant exposed to SAR443765 at every timepoint
- Robust effects for eosinophil-high and eosinophil-low subgroups (cut-off: 300 cells/µL)



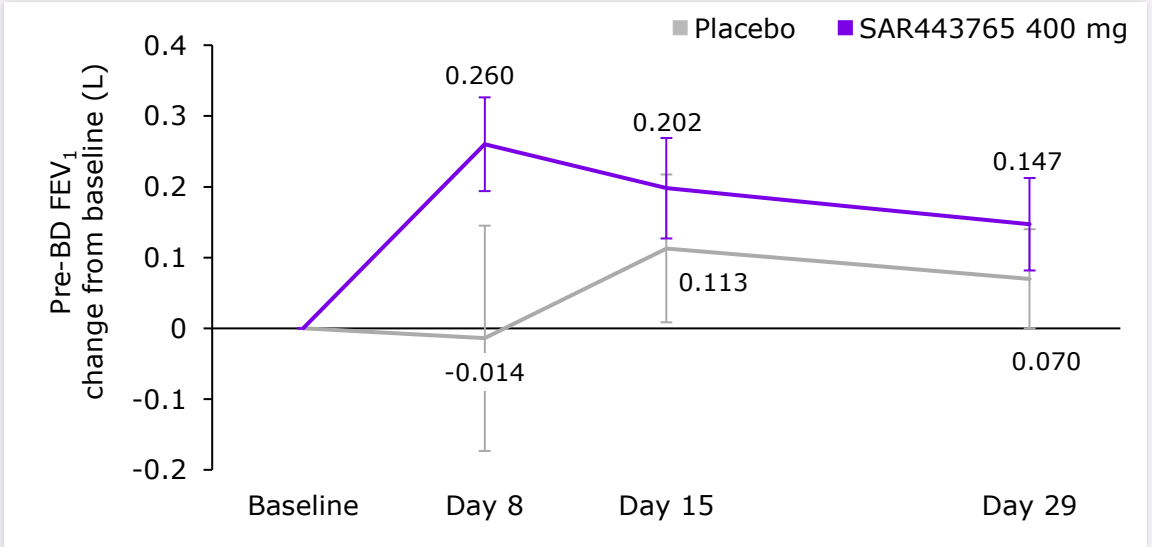


Group	Baseline FeNO Mean (SD)	Change from baseline to Day 29 (SD)	% change from baseline to Day 29 (SD)
Placebo with EOS <300 cells/µL (N=8)	56.1 (38.7)	1.4 (13.9)	−1.9% (23.5)
Placebo with EOS ≥300 cells/µL (N=4)	103.5 (43.3)	−0.3 (50.9)	3.9% (47.8)
SAR443765 with EOS <300 cells/µL (N=16)	59.3 (35.9)	−32.1 (30.1)	−49.5% (21.2)
SAR443765 with EOS ≥300 cells/µL (N=8)	85.1 (31.8)	−53.3 (24.3)	−60.4% (9.8)

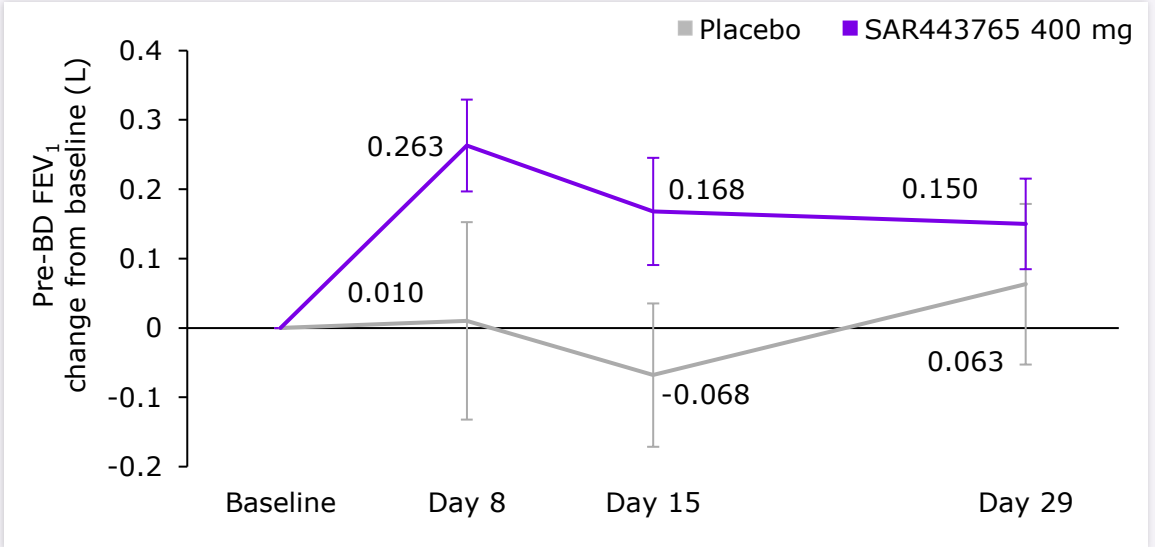
EOS, eosinophils; FeNO, fractional exhaled nitric oxide;
SEM, standard error of the mean.

Numerical Improvement Seen in Lung Function

- Confirmed PD effect: FEV_1 is a clinically relevant marker for lung function
- Maximal improvement in pre-BD FEV_1 at Day 8; numerical improvement largely maintained through Day 29
- Normal to mildly impaired airflow obstruction at baseline, making a 'ceiling effect' likely
- Imbalance in absolute pre-BD FEV_1 at baseline (SAR443765 mean higher by 218 mL than placebo [median 330 mL])
- Study was not designed to demonstrate significant effects on pre-BD FEV_1



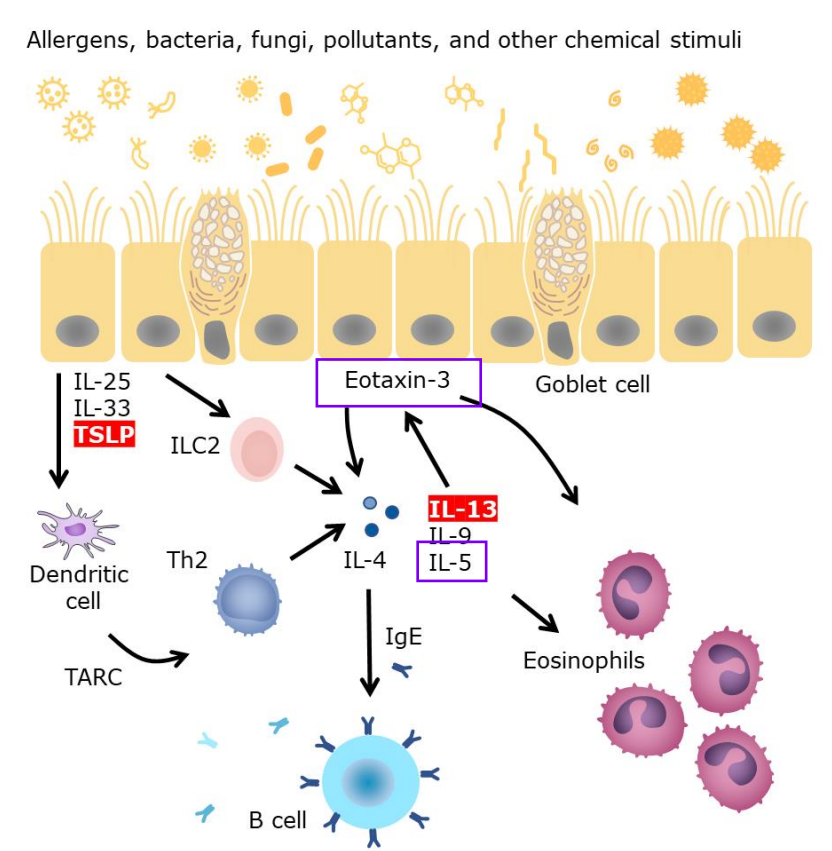
FEV_1 measured in triplicate. If the difference between the 2 largest FEV_1 values was ≥0.150 L, the triplicate set was excluded. Maximal FEV_1 value from the triplicate used for analysis

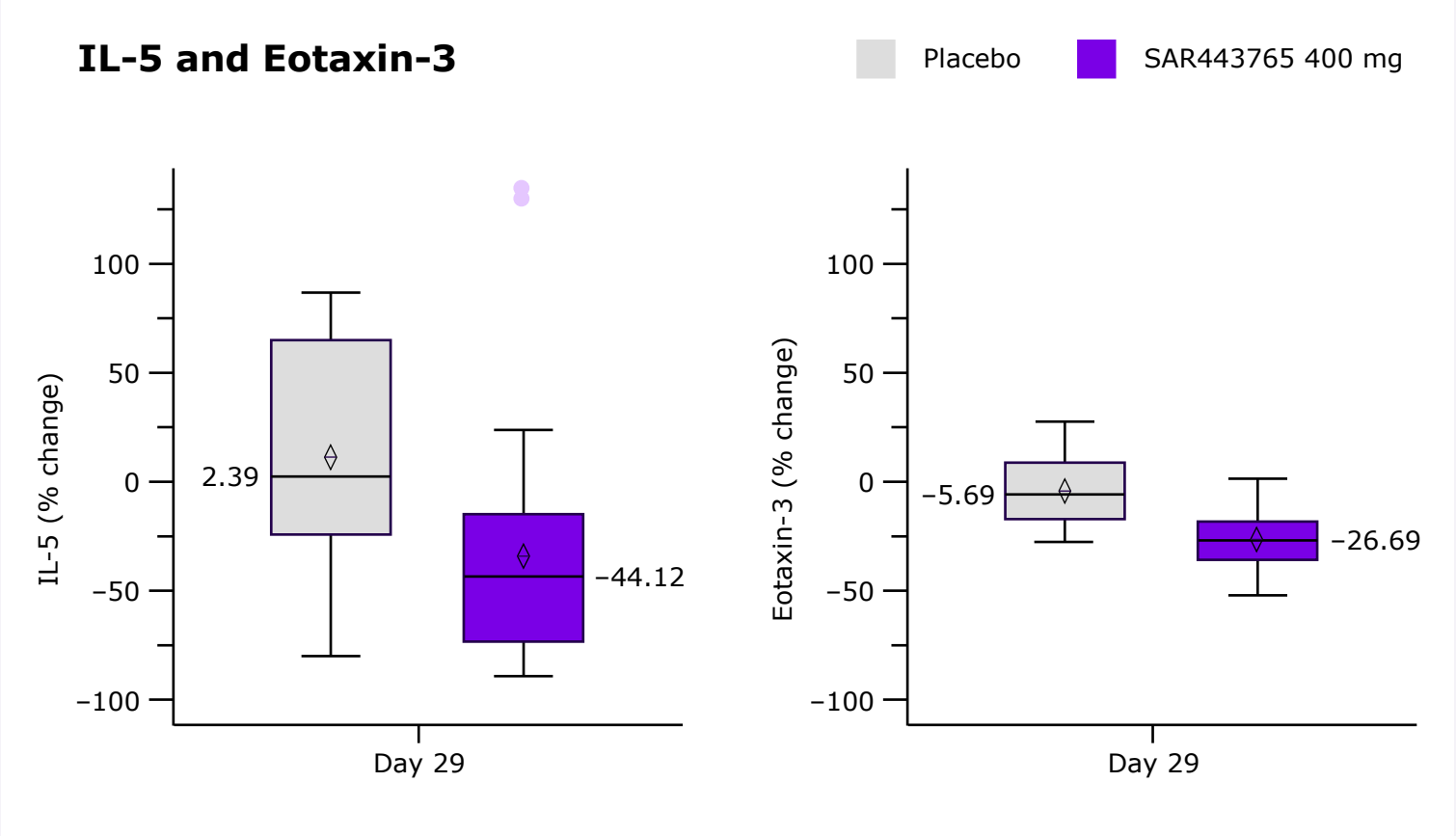


Sensitivity analysis: The maximum value of each FEV_1 triplicate was used, whatever the distance between the 2 largest FEV_1 values observed. Maximal FEV_1 value from the triplicate used for analysis

BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; PD, pharmacodynamic; SEM, standard error of the mean.

Downstream Type 2 Biomarkers Confirm PD Effect





- Key response biomarkers for TSLP and IL-13 target engagement were identified *a priori*
- The relative change from baseline on Day 29 is consistent with the anticipated downstream PD effects of SAR443765

IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cells; PD, pharmacodynamic; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.
Chart shows median (data label and line), mean (diamond), interquartile range, min and max, and outliers.

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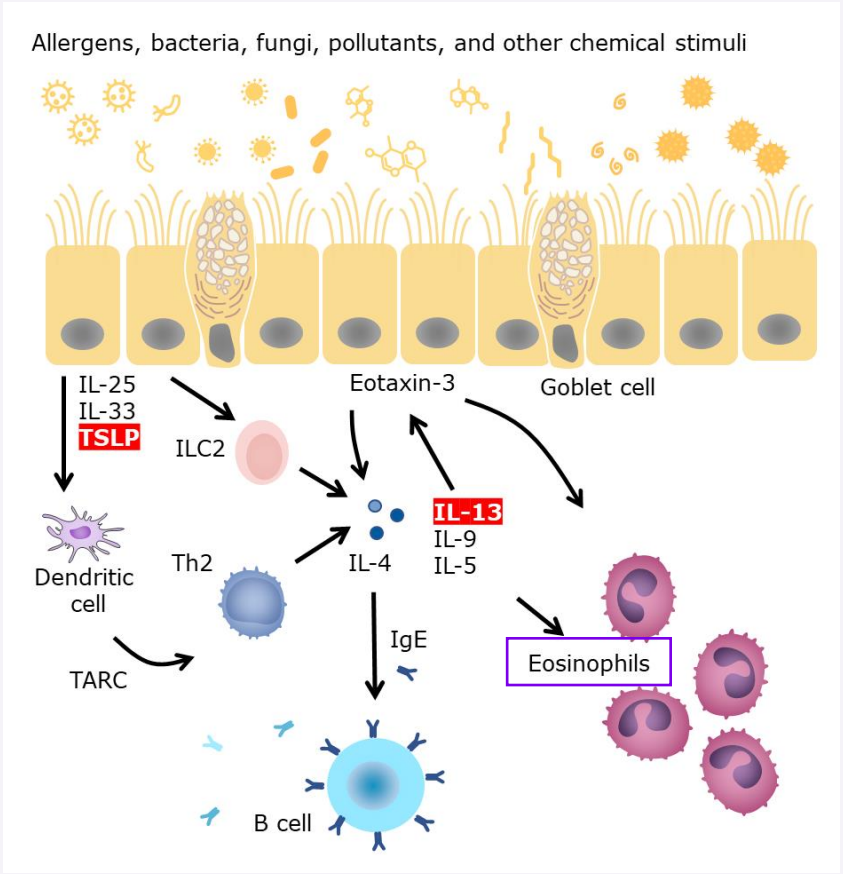

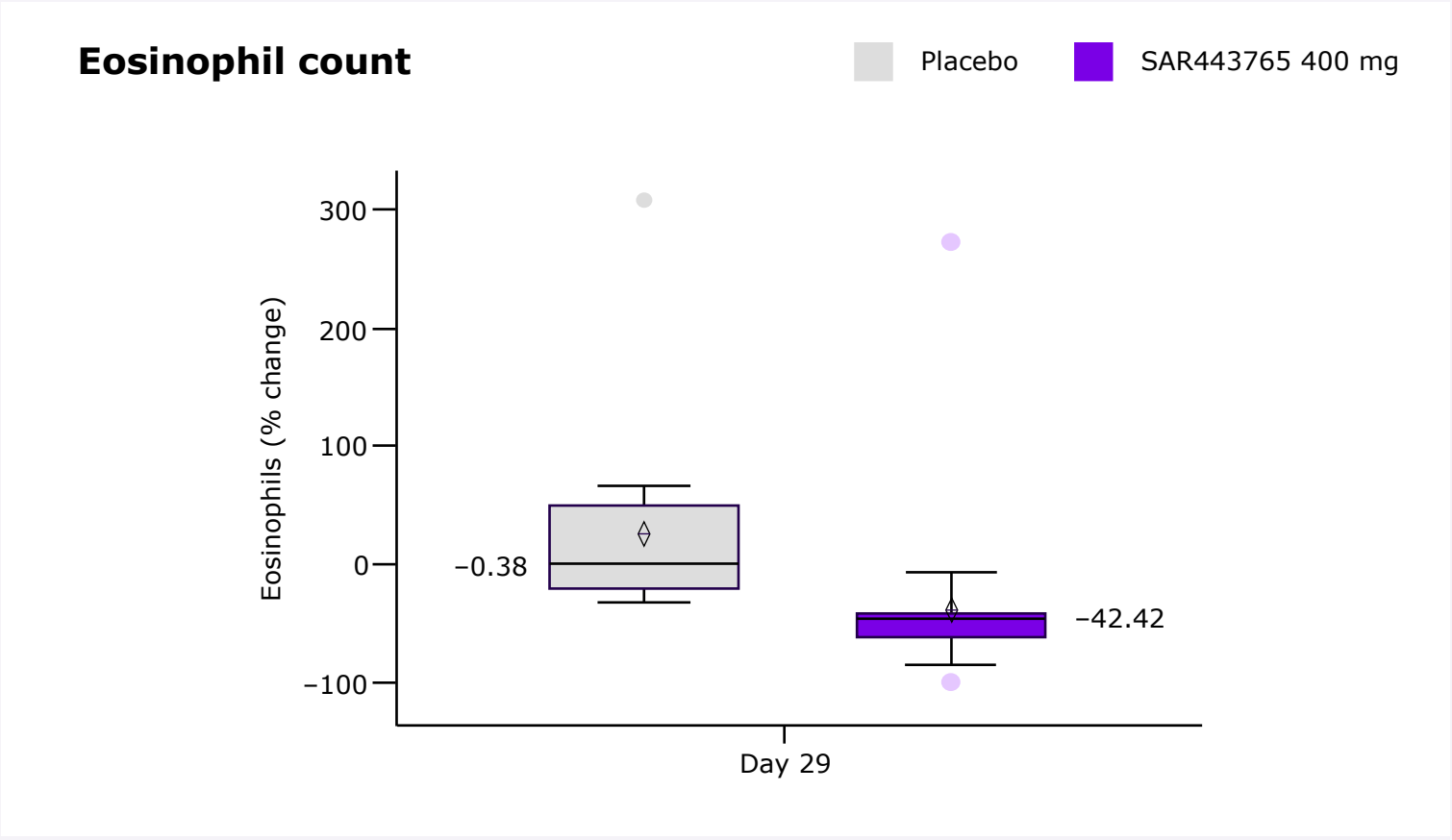

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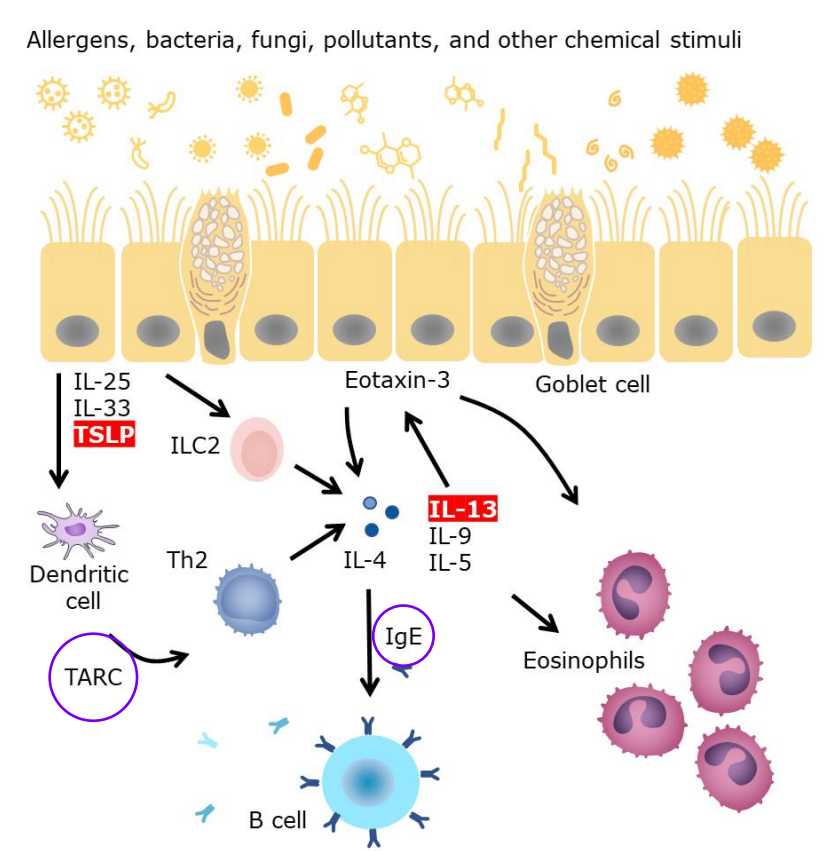

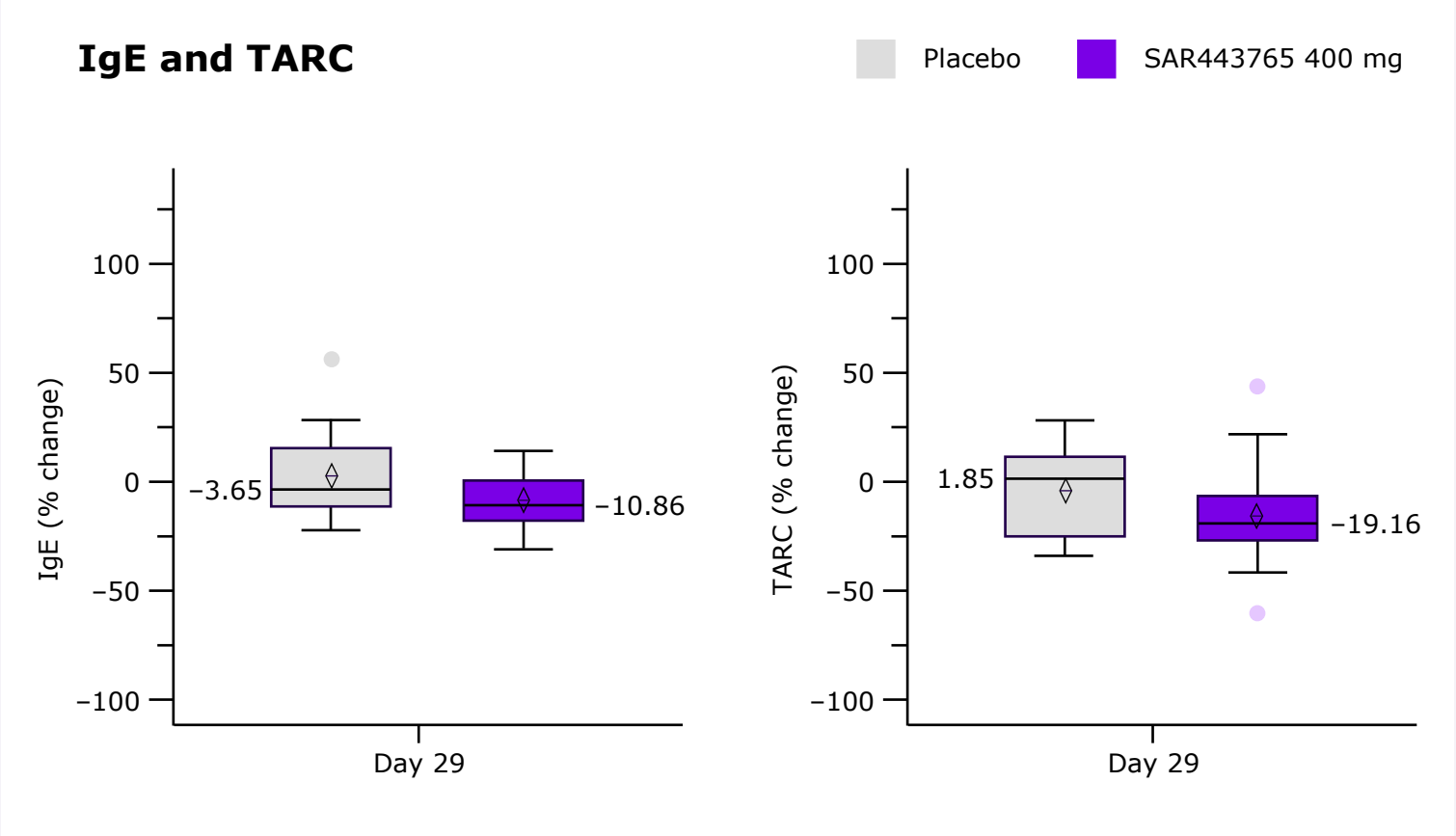

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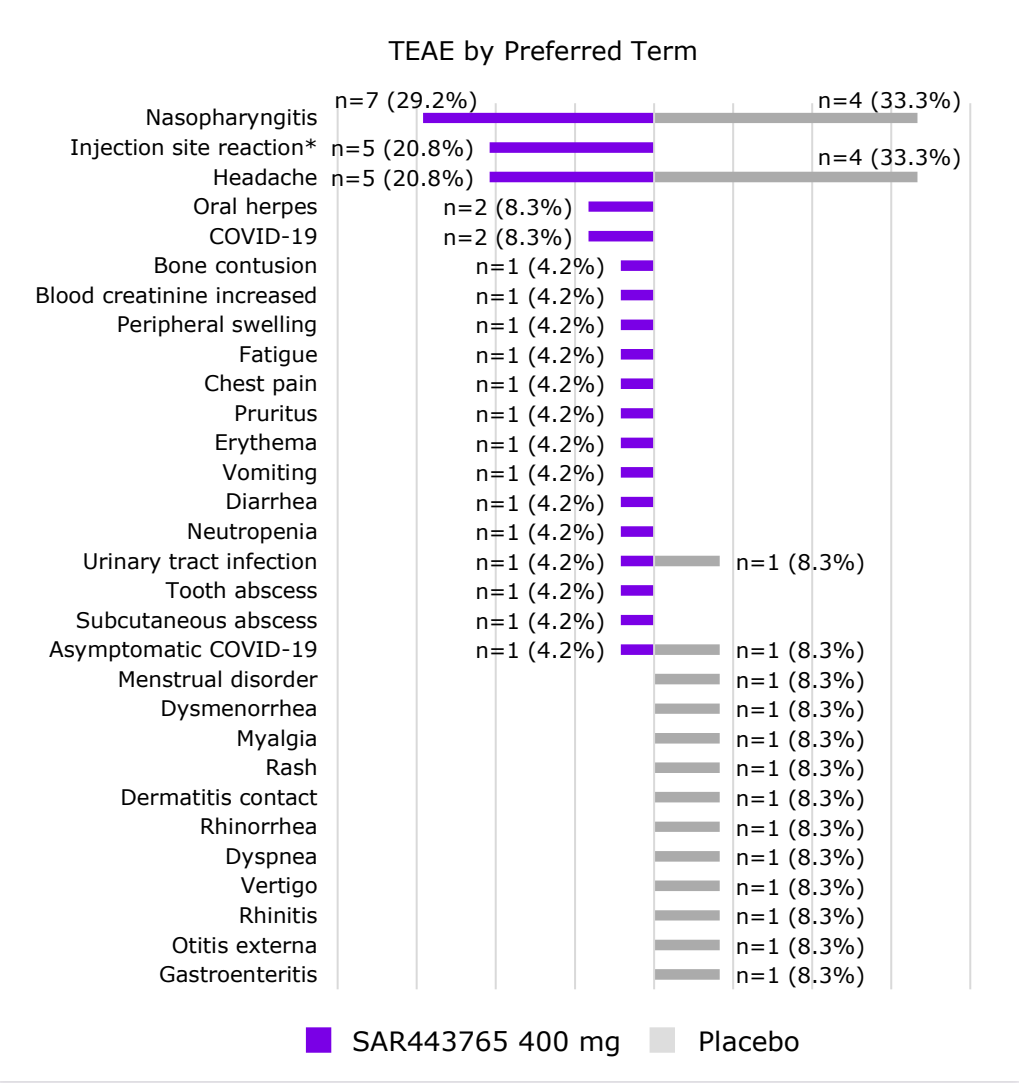
A Single Dose of SAR443765 Was Safe and Well-Tolerated in Mild-to-Moderate Asthma

- 43 TEAEs reported in 18 of 24 patients (75%) who received SAR443765
- 24 TEAEs reported in 9 of 12 patients (75%) who received placebo
- No serious AEs
- 4 AEs of special interest (all COVID-19, not treatment-related)
- No TEAEs ≥ Grade 3 severity
- Imbalances between groups due to small size
- Mild injection site reactions* for SAR443765 only (Grade 1–2)
- No TEAEs related to immunogenicity
- No safety signal based on vital signs, ECG, or laboratory parameters
- Safety profile consistent with results in healthy participants



AE, adverse event; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.
*'solicited' injection site reactions.

Summary

This is the first report of a novel biologic treatment targeting both TSLP and IL-13

The rapid and substantial reduction in FeNO after administration of SAR443765 NANOBODY® molecule (40.9 ppb, 90% CI: −55.4 to −26.4, vs placebo) appears to be greater than that seen in previous studies of monovalent agents that target one of these pathways

Corresponding reductions were seen in relevant blood biomarkers of TSLP and IL-13 activity and asthma pathogenesis

Rapid, numerical improvement was seen in FEV_1 and was largely maintained throughout the 4-week observation period

These findings suggest the potential for SAR443765 to suppress airway inflammation and preserve airway function in asthma

FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IL, interleukin; ppb, parts per billion; TSLP, thymic stromal lymphopoietin.