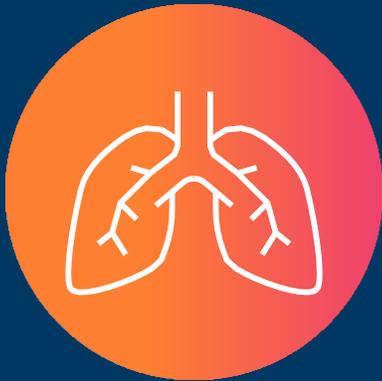


# Severe asthma and the role of thymic stromal lymphopoietin (TSLP)

# SEVERE ASTHMA IS ASSOCIATED WITH:



Recurrent exacerbations and hospitalisations<sup>1,2</sup>



Poor asthma-related quality of life<sup>3</sup>



Life-changing side effects due to OCS use<sup>4</sup>



Increased risk of mortality<sup>5</sup>



Higher healthcare costs compared with controlled disease<sup>6</sup>

OCS = Oral Corticosteroids

1. Global Initiative for Asthma (GINA);2022(cited 2023 Jan 11; <https://ginasthma.org/gina-reports/> 2. Wang E, Wechsler ME, Tran TN et al. *Chest*. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry 2020;157:790–804; 3. Chung KF, Wenzel SE, Brozek JL et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma *Eur Respir J*. 2014;43:343–373; 4. Price DB, Trudo F, Voorham J et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study *J Asthma Allergy*. 2018;11:193–204; 5. Fernandes AG, Souza-Machado C, Coelho RCP et al. Risk factors for death in patients with severe asthma *J Bras Pneumol*. 2014;40:364–372; 6. Chen S, Golam S, Myers J et al. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment *Curr Med Res Opin*. 2018;34:2075–2088

# SEVERE ASTHMA IS A COMPLEX AND HETEROGENEOUS DISEASE



Of asthma patients **have severe asthma**<sup>1</sup>



Have **multiple drivers of inflammation**<sup>2</sup>

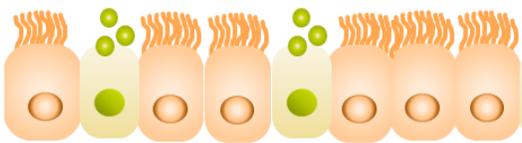


Have **Eos  $\leq 300$  cells/ $\mu$ L**<sup>3</sup>

# THE AIRWAY EPITHELIUM IS THE FIRST POINT OF CONTACT WITH ENVIRONMENTAL TRIGGERS<sup>1</sup>

## Epithelium<sup>1-3</sup>

- Key role in tissue homeostasis
- Mediator between environment and immune system
- Rapid production of epithelial cell-derived cytokines in response to triggers



## Environmental Triggers<sup>1,4</sup>

Allergens



Viruses



Pollutants/  
smoke



Bacteria



Physical  
injury

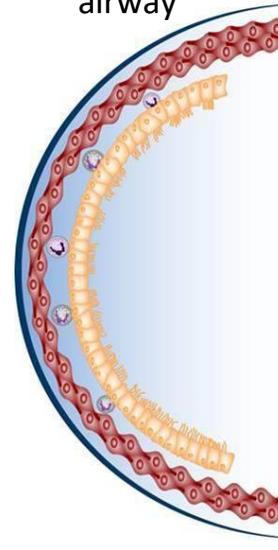


Other external  
stimuli

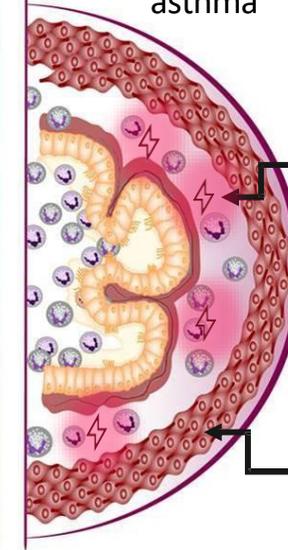


## Variable Bronchoconstriction<sup>3,4a</sup>

Healthy  
airway



Severe  
asthma



Two hallmarks of asthma

Airway  
inflammation<sup>5</sup>

Airway  
hyperresponsiveness<sup>5</sup>

Adapted from ref a

<sup>a</sup>Figure adapted from the Centre of Excellence in Severe Asthma as part of the Centre of Research Excellence in Severe Asthma (<https://toolkit.severeasthma.org.au>)

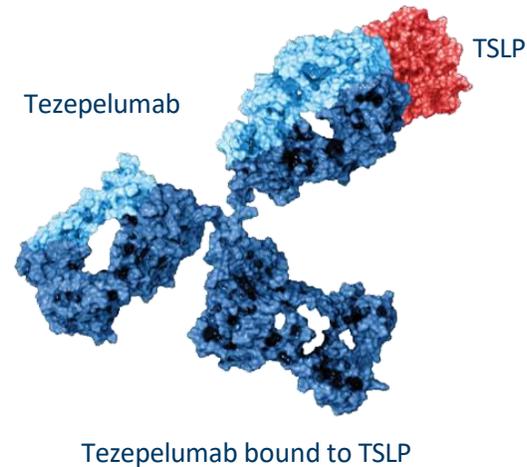
1. Bartemes KR, Kita H; Dynamic role of epithelium-derived cytokines in asthma; *Clin Immunol.* 2012; 143: 222–235; 2. Watson B, Gauvreau GM. *Expert Opin Ther Targets.* 2014;18:771–785; 3. Loxham M, Davies DE, Blume C; Epithelial function and dysfunction in asthma *Clin Exp Allergy.* 2014;44:1299–1313; 4. Pelaia G, Vatrella A, Maselli R; The potential of biologics for the treatment of asthma; *Nat Rev Drug Discov.* 2012;11:958–972; 5. Global Initiative for Asthma (GINA);2022(cited 2023 Jan 11); <https://ginasthma.org/gina-reports>

# TSLP IS A KEY EPITHELIAL CYTOKINE IN ASTHMA<sup>1,2</sup>

**TSLP** is expressed and released in response to a **broad range of stimuli** (e.g., allergens, viruses, pollutants)<sup>4</sup>

Epithelial cells are the primary source of TSLP.<sup>5</sup>

TSLP initiates multiple **downstream immune responses** involved in **asthma inflammation** and pathology<sup>4</sup>



Variants at **TSLP gene loci** have been associated with **increased risk of developing asthma**<sup>6</sup>

**Tezepelumab** is a human monoclonal antibody that binds to TSLP, specifically blocking it from interacting with its receptor<sup>7</sup>

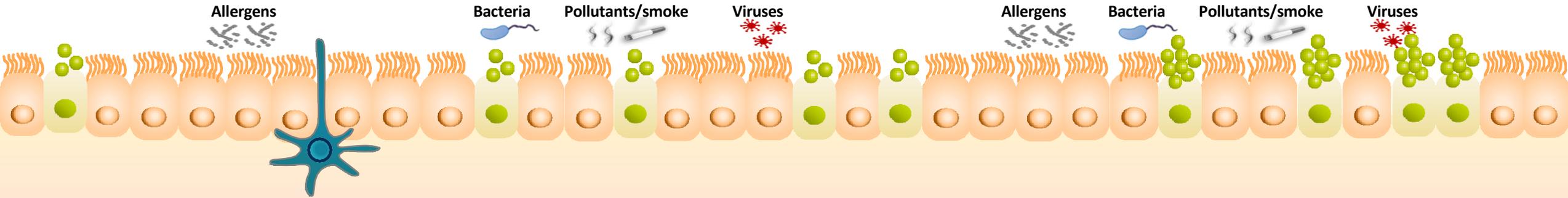
TEZSPIRE bound to TSLP figure adapted from Verstraete K et al. *Nat Commun* 2017;8:14937

TSLP = Thymic Stromal Lymphopoietin

1. Van Rompaey D, Verstraete K, Peelman F et al; Virtual screening for inhibitors of the human TSLP:TSLPR interaction *Sci Rep.* 2017;7:17211; 2. Corren J, Ziegler SF. TSLP: from allergy to cancer *Nat Immunol.* 2019;20:1603–1609; 4. Gauvreau GM, Sehmi R, Ambrose CS et al. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma; *Expert Opin Ther Targets.* 2020;24:777–792; 5. Bartemes

5 KR, Kita H; Dynamic role of epithelium-derived cytokines in asthma; *Clin Immunol.* 2012;143:222–235; 6. Torgerson DG, Ampleford EJ, Chiu GY et al. Meta-analysis of Genome-wide Association Studies of Asthma in Ethnically Diverse North American Populations; Article and supplementary information. *Nat Genet.* 2011;43:887–892; 7. Menzies-Gow A, Wechsler ME, Brightling CE; Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option?; *Respir Res.* 2020;21:268

# TSLP IS AN EPITHELIAL CYTOKINE THAT PLAYS AN IMPORTANT ROLE IN DRIVING ASTHMA<sup>1-3</sup>



TSLP is released after epithelial damage or immune cell activation<sup>1,2</sup>

Leading to airway inflammation<sup>1,2</sup>

Leading to airway hyperresponsiveness via smooth muscle dysfunction<sup>1-3</sup>

6 TSLP = Thymic Stromal Lymphopoietin

1. Bartemes KR, Kita H; Dynamic role of epithelium-derived cytokines in asthma; Clin Immunol. 2012;143:222-235; 2. Roan F, Obata-Ninomiya K, Ziegler SF; Epithelial cell-derived cytokines: more than just signaling the alarm; J Clin Invest. 2019;129:1441-1451; 3. Redhu NS, Gounni AS; Function and mechanisms of TSLP/TSLPR complex in asthma and COPD Clin Exp Allergy. 2012;42:994-1005

# TSLP DRIVES AIRWAY INFLAMMATION AND AIRWAY HYPERRESPONSIVENESS FROM THE TOP OF THE CASCADE<sup>1-3</sup>

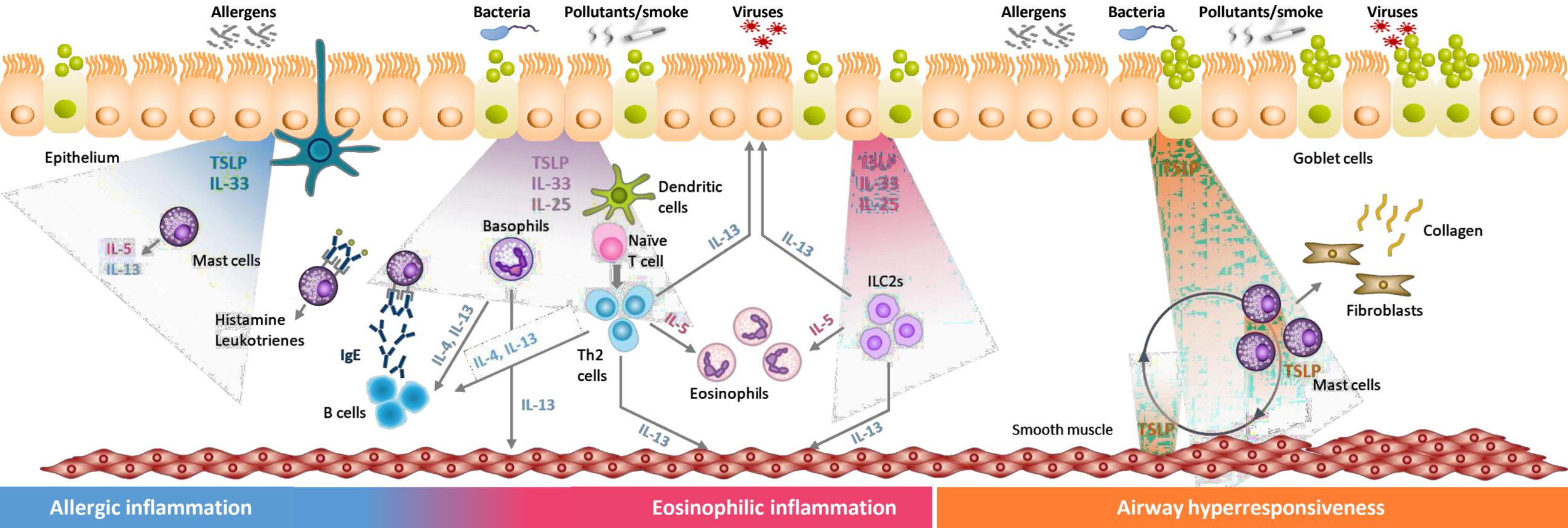
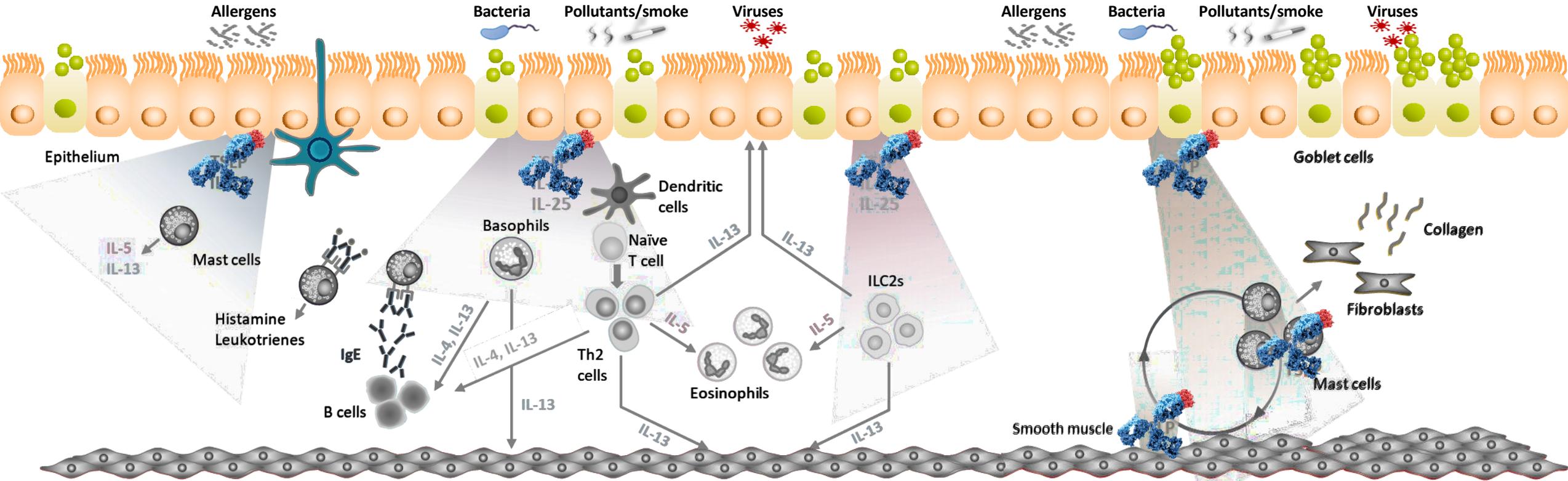


Figure adapted from ref. 1

IgE = Immunoglobulin E; IL = Interleukin; ILC2 = Type 2 Innate Lymphoid Cell; Th = T Helper; TSLP = Thymic Stromal Lymphopoeitin

1. Gauvreau GM, Sehmi R, Ambrose CS et al. Thymic stromal lymphopoeitin: its role and potential as a therapeutic target in asthma; Expert Opin Ther Targets. 2020;24:777–792; 2. Roan F, Obata-Ninomiya K, Ziegler SF; Epithelial cell–derived cytokines: more than just signaling the alarm; J Clin Invest. 2019;129:1441–1451; 3. Menzies-Gow A, Wechsler ME, Brightling CE; Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option?; Respir Res. 2020;21:268

# TEZEPELUMAB TARGET TSLP AT THE TOP OF THE INFLAMMATORY CASCADE<sup>1-7</sup>



**Allergic inflammation**                      **Eosinophilic inflammation**                      **Airway hyperresponsiveness**

IgE = Immunoglobulin E; IL = Interleukin; ILC2 = Type 2 Innate Lymphoid Cell; Th = T Helper; TSLP = Thymic Stromal Lymphopoietin

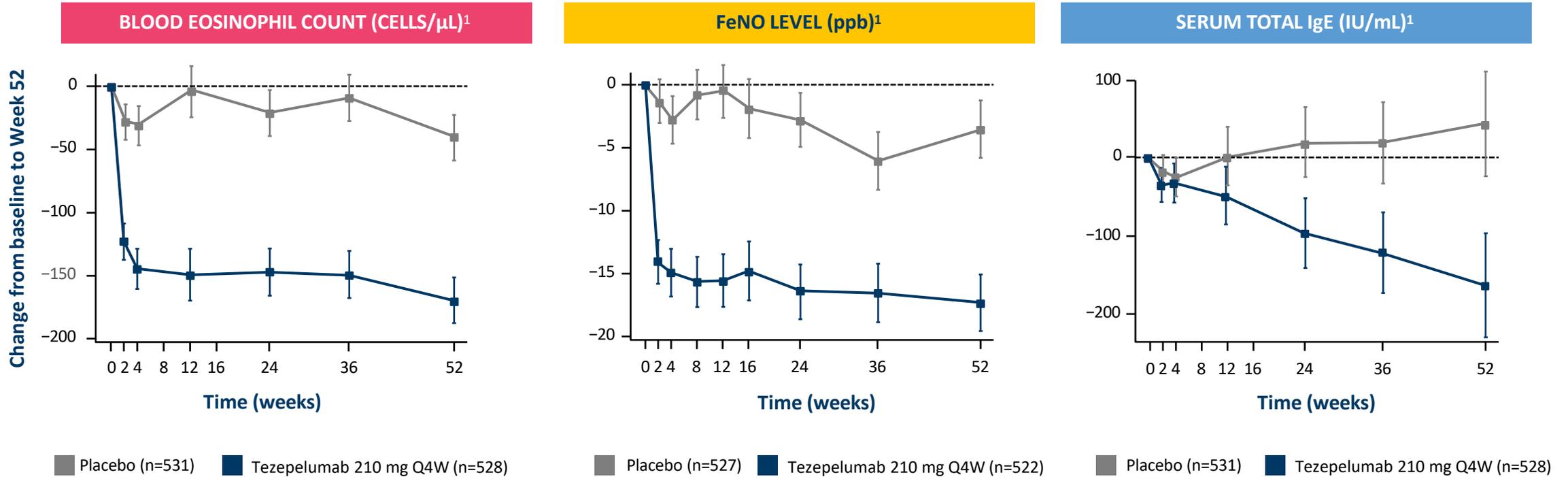
Figure based on ref. 2

1. Menzies-Gow A, Wechsler ME, Brightling CE; Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option?; *Respir Res.* 2020;21:268; 2. Gauvreau GM, O'Byrne PM, Boulet LP et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses *N Engl J Med.* 2014;370:2102–2110; 3. Diver S, Khalfaoui L, Emson C et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial *Lancet Respir Med.* 2021;9:1299–1312; 4. Menzies-Gow A, Corren J, Bourdin A et al.; Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma Supplementary information. *N Engl J Med.* 2021;384:1800–1809; 5. Corren J, Parnes JR, Wang L et al. Tezepelumab in Adults with Uncontrolled Asthma *N Engl J Med.* 2017;377:936–946; 6. Gauvreau GM, Sehmi RB, Brose GS et al. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma; *Expert Opin Ther Targets.* 2020;24:777–792; 7. Tezpire SmPC last update 2023.01.12



# TEZPELUMAB REDUCES AIRWAY INFLAMMATION ACROSS ALL KEY BIOMARKERS<sup>1</sup>

## NAVIGATOR<sup>1</sup>



Data are LS means and 95% CIs over time;

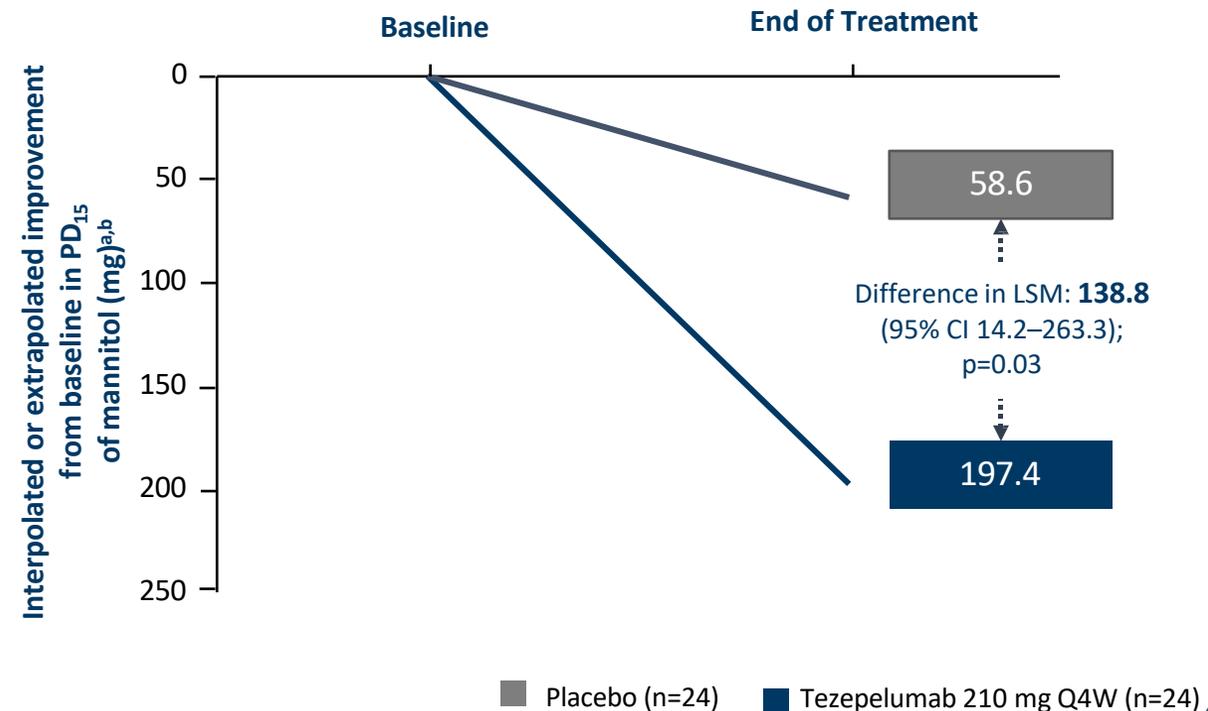
Figures adapted from ref.1 fig S6 a,b,c

# TEZPELUMAB REDUCE TISSUE EOSINOPHILS AND AIRWAY HYPERRESPONSIVENESS <sup>1</sup>

## Primary Endpoint

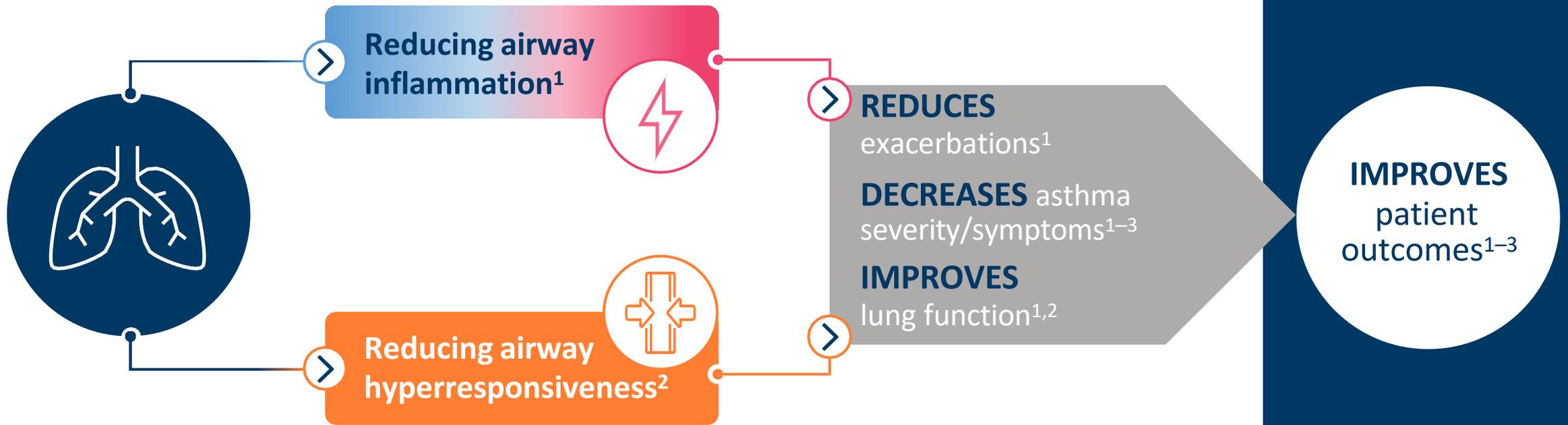
- **Airway submucosal eos** were **reduced** from baseline to EOT with tezepelumab versus placebo, by **6.7-fold** (nominal  $p < 0.001$ )<sup>1</sup>
  - Tezepelumab: **89% reduction**
  - Placebo: **25% reduction**
- **No significant differences between treatment groups** in change in other submucosal inflammatory cells were observed from baseline to EOT in neutrophils, CD3+ T cells, CD4+ T cells, tryptase+ mast cells, and chymase+ mast cells<sup>1</sup>

## Select exploratory endpoint: Reduction from baseline to EOT in AHR



<sup>a</sup>Interpolated/extrapolated absolute change in PD<sub>15</sub> to mannitol. PD<sub>15</sub> is defined as the cumulative provoking dose of mannitol required to induce  $\geq 15\%$  reduction in FEV<sub>1</sub> from baseline zero mannitol dose, or otherwise  $\geq 10\%$  reduction in FEV<sub>1</sub> between successive non-zero mannitol doses. PD<sub>15</sub> mannitol dose is considered the positive response dose at the first occurrence of the provoking dose; <sup>b</sup>Data are mean with differences from baseline to end of treatment and between treatment groups shown as difference in LS means (95% CI);<sup>1</sup> CI = Confidence Interval; Eos = Eosinophils; FeNO = Fractional Exhaled Nitric Oxide; FEV<sub>1</sub> = Forced Expiratory Volume in 1 Second; IgE = Immunoglobulin E; IL = Interleukin; LS = Least Squares; PD<sub>15</sub> = Provoking Dose Causing a 15% Decline in FEV<sub>1</sub>; Q4W = Every 4 Weeks; TSLP = Thymic Stromal Lymphopoietin

# ADDRESSING TWO HALLMARKS OF ASTHMA MAY HELP TO IMPROVE OUTCOMES<sup>1,2</sup>



# THE CLINICAL PROGRAM WITH TEZPELUMAB<sup>1-3</sup>



**PATHWAY<sup>1</sup>**

**Phase IIb**

Efficacy and safety of Tezepelumab  
in **adults with SUA**

**N=550<sup>a</sup>**  
Age range = 18–75 years

**No biomarker  
restrictions**



**NAVIGATOR<sup>2</sup>**

**Phase III**

Efficacy and safety of Tezepelumab  
in **adults and adolescents with  
SUA**

**N=1061<sup>a</sup>**  
Age range = 12–80 years

**No biomarker  
restrictions**



**CASCADE<sup>3</sup>**

**Phase II**

Effect of Tezepelumab on **airway  
inflammatory cells**, remodelling  
and **hyperresponsiveness** in  
patients with uncontrolled asthma

**N=116<sup>a</sup>**  
Age range = 18–75 years

**No biomarker  
restrictions**

<sup>a</sup>Intention-to-treat population; SUA = Severe Uncontrolled Asthma

1. Corren J, Parnes JR, Wang L et al. Tezepelumab in Adults with Uncontrolled Asthma article inkl. Supplement; N Engl J Med. 2017;377:936–946; 2. Menzies-Gow A, Corren J, Bourdin A et al.; Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma article and Supplement; N Engl J Med. 2021;384:1800–1809; 3. Diver S, Khalifaovi L, Emson C et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial Lancet Respir Med. 2021;9:1299–1312

# REDUCTION OF EXACERBATIONS<sup>1,2</sup>

## PATHWAY<sup>1</sup>

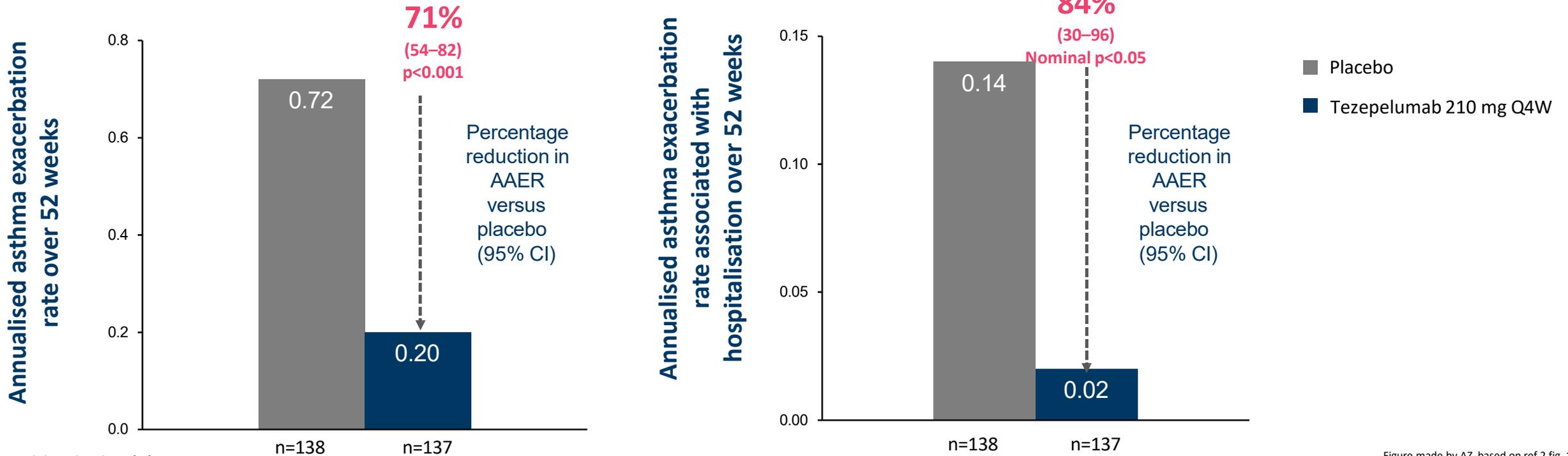


Figure made by AZ based on ref 1 fig S4 a

Figure made by AZ based on ref 2 fig. 1 a

# REDUCTION OF EXACERBATIONS<sup>1</sup>

## NAVIGATOR<sup>1</sup>

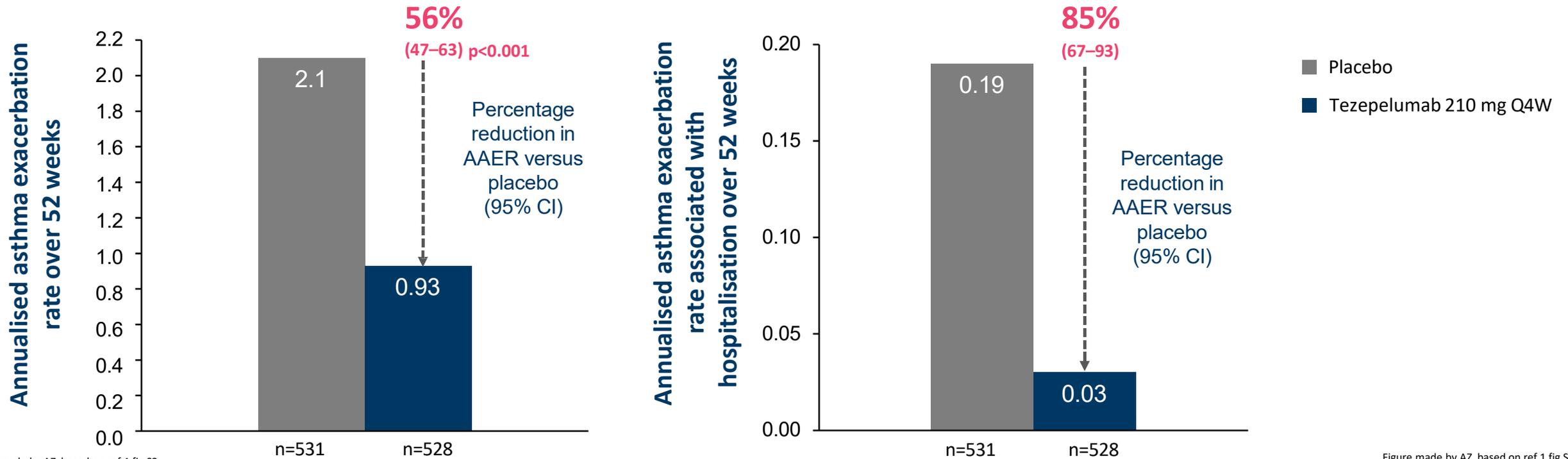


Figure made by AZ based on ref 1 fig S2

Figure made by AZ based on ref 1 fig S4 b

# REDUCTION OF EXACERBATIONS, ACROSS PHENOTYPES AND IRRESPECTIVE OF BIOMARKER LEVELS<sup>1,a</sup>

## NAVIGATOR

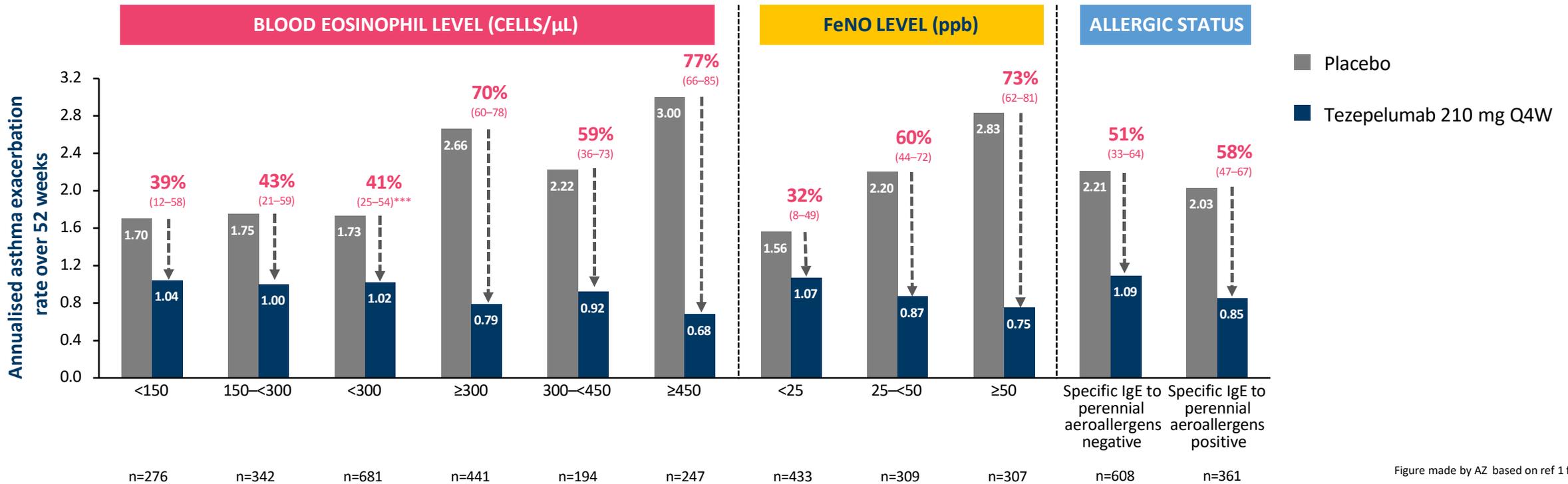


Figure made by AZ based on ref 1 fig 1

# IMPROVEMENTS IN LUNG FUNCTION<sup>1</sup>

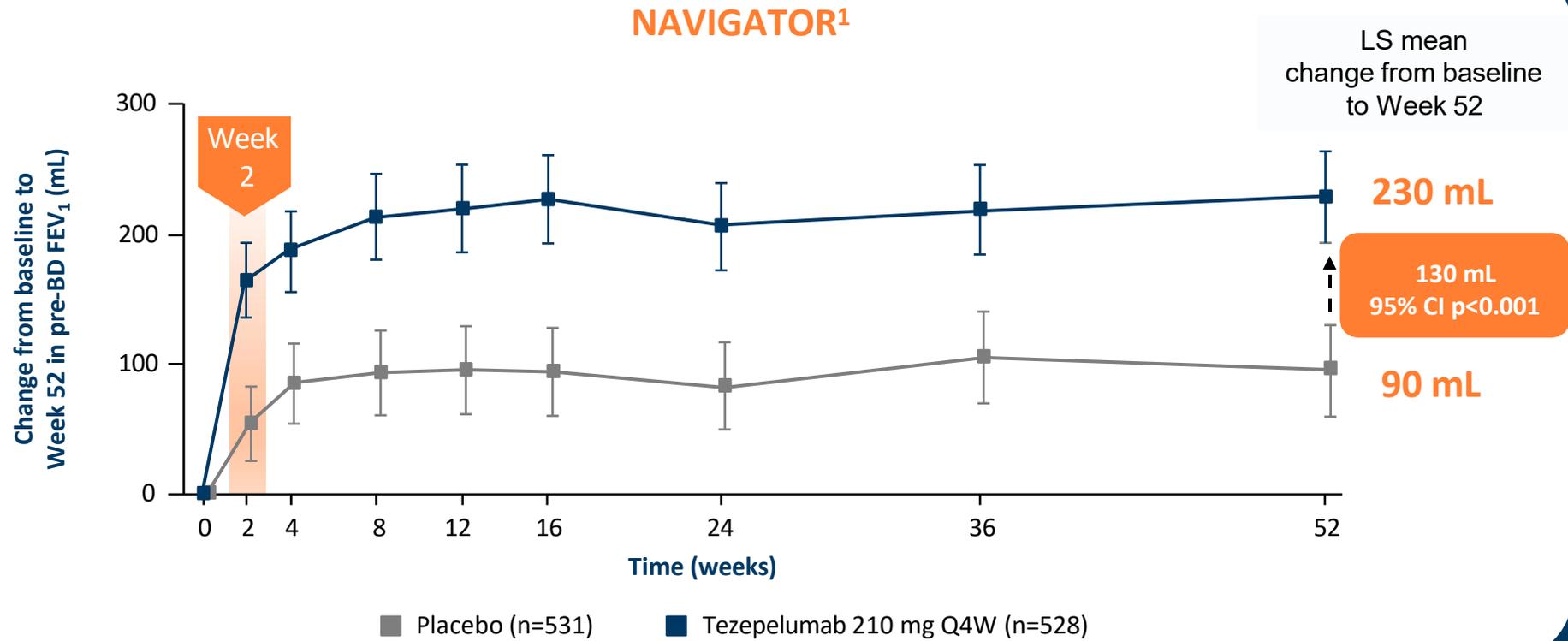
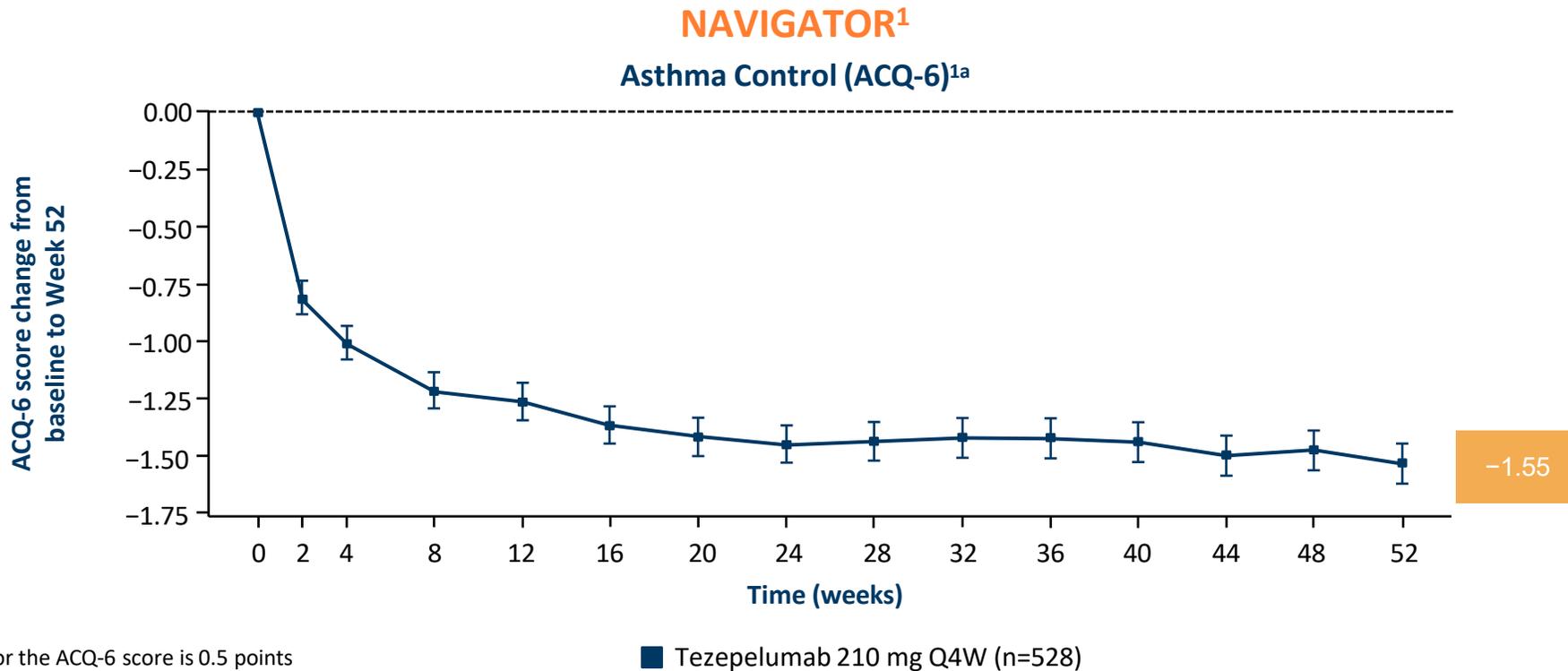


Figure made by AZ based on ref 1 fig 1

# CLINICALLY MEANINGFUL IMPROVEMENTS IN ASTHMA CONTROL FROM BASELINE<sup>1</sup>



MCID for the ACQ-6 score is 0.5 points

Figure made by AZ based on ref 1 fig S3 a

17 <sup>a</sup>LS mean change in the placebo group, -1.22 (n=531)

ACQ-6 = Asthma Control Questionnaire-6; LS = Least Squares; MCID = Minimal Clinically Important Difference; Q4W = Every 4 Weeks

<sup>1</sup>Menzies-Gow A, Corren J, Bourdin A et al.; Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma article and Supplement; N Engl J Med. 2021;384:1800-1809

# ADVERSE EVENTS<sup>1</sup>

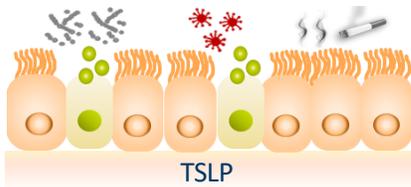
## NAVIGATOR<sup>1</sup>

Most Common AEs occurring in ≥3% of patients who received Tezepelumab, n (%)	Tezepelumab 210 mg Q4W n=528	Placebo n=531
Nasopharyngitis	113 (21.4)	114 (21.5)
Upper respiratory tract infection	59 (11.2)	87 (16.4)
Headache	43 (8.1)	45 (8.5)
Asthma	27 (5.1)	59 (11.1)
Bronchitis	25 (4.7)	33 (6.2)
Bronchitis bacterial	24 (4.5)	17 (3.2)
Hypertension	23 (4.4)	22 (4.1)
Urinary tract infection	22 (4.2)	22 (4.1)
Back pain	21 (4.0)	15 (2.8)
Arthralgia	20 (3.8)	13 (2.4)
Influenza-like illness	19 (3.6)	22 (4.1)
Sinusitis	19 (3.6)	40 (7.5)
Pharyngitis	17 (3.2)	15 (2.8)
Gastroenteritis	17 (3.2)	16 (3.0)
Viral upper respiratory tract infection	17 (3.2)	14 (2.6)
Rhinitis allergic	16 (3.0)	17 (3.2)
Rhinitis	14 (2.7)	17 (3.2)

# SUMMARY

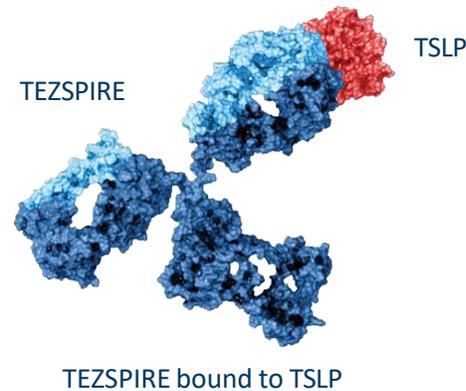
## Severe Asthma and the Role of TSLP

- Severe asthma is a complex and heterogeneous disease<sup>1</sup>
- TSLP is an epithelial cytokine, released in response to a variety of triggers, that drives airway inflammation and airway hyperresponsiveness<sup>2</sup>



## First-in-Class Mechanism of Action

- Tezepelumab target TSLP, at the top of the cascade, reducing multiple drivers of airway inflammation and airway hyperresponsiveness<sup>2-7</sup>



## Efficacy and Safety Profile

- Tezepelumab treats across phenotypes and irrespective of biomarker levels<sup>5,6</sup>
  - Significant reduction in exacerbations and exacerbation related hospitalisations<sup>5,6</sup>
  - Early improvement in lung function, asthma control and quality of life<sup>5,6</sup>
  - No clinically meaningful differences in adverse events versus placebo<sup>5,6</sup>

<sup>1</sup>Global Initiative for Asthma (GINA);2022(cited 2023 Jan 11; <https://ginasthma.org/gina-reports/>); <sup>2</sup>Menzies-Gow A, Wechsler ME, Brightling CE; Unmet need in severe, uncontrolled asthma: can anti-TSLP therapy with tezepelumab provide a valuable new treatment option?; Respir Res. 2020;21:268; <sup>3</sup>. Gauvreau GM, O'Byrne PM, Boulet LP et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses N Engl J Med. 2014;370:2102–2110; <sup>4</sup>. Diver S, Khalfaoui L, Emson C et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial Lancet Respir Med. 2021;9:1299–1312; <sup>5</sup>. Menzies-Gow A, Corren J, Bourdin A et al.; Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma article and Supplement; N Engl J Med. 2021;384:1800–1809; <sup>6</sup>. Corren J, Parnes JR, Wang L et al. Tezepelumab in Adults with Uncontrolled Asthma article inkl. Supplement;N Engl J Med. 2017;377:936–946 <sup>7</sup>. Gauvreau GM, Sehmi R, Ambrose CS et al. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma; Expert Opin Ther Targets. 2020;24:777–792

**▼ TEZSPIRE (tezepelumab) - viktig informasjon (utvalg)**

**Indikasjon: Astma:** Tezspire er indisert som tillegg til vedlikeholdsbehandling hos voksne og ungdom i alderen 12 år og eldre med alvorlig astma som er utilstrekkelig kontrollert til tross for høye doser inhalasjonskortikosteroider i tillegg til et annet legemiddel for vedlikeholdsbehandling. **Kronisk rhinosinussitt med nesepolypper (CRSwNP):** Tezspire er indisert som tillegg til behandling med intranasale kortikosteroider hos voksne pasienter med alvorlig CRSwNP der behandling med systemiske kortikosteroider og/eller kirurgi ikke gir tilstrekkelig sykdomskontroll. **Dosering: Astma:** Voksne og ungdom (fra 12 år og eldre) Den anbefalte dosen er 210 mg tezepelumab som subkutan injeksjon hver 4. uke. **CRSwNP:** Den anbefalte dosen for voksne pasienter er 210 mg tezepelumab som subkutan injeksjon hver 4. uke. **Forsiktighetsregler:** Skal ikke brukes til å behandle akutte astmaeksasjoner. Astmarelaterede symptomer eller eksasjoner kan oppstå. Pasienten bør instrueres om å oppsøke lege hvis astmaen forblir ukontrollert eller forverres. Alvorlige infeksjoner bør behandles før oppstart av behandling. Ved utvikling av alvorlig infeksjon under behandling, bør behandlingen seponeres inntil denne er over. Graviditet og amming: Bruk under graviditet bør unngås med mindre forventet nytte for den gravide oppveier mulig risiko for fosteret. **Vanlige bivirkninger:** Faryngitt, utslett, artralgi, reaksjon på injeksjonsstedet. **Pakninger og priser:** Injeksjonsvæske, oppløsning i ferdigfylt penn (210 mg): 1 stk. kr. : 15 053,40. Injeksjonsvæske, oppløsning i ferdigfylt sprøyte (210 mg): 1 stk. kr. : 15 053,40 **Reseptgruppe: C. Refusjon: H-resept. Refusjonsberettiget bruk:** Vilkår: 216 Refusjon ytes kun etter resept fra sykehuslege eller avtalespesialist. Der det er utarbeidet nasjonale handlingsprogrammer/nasjonal faglig retningslinje og/eller anbefalinger fra RHF/LIS spesialistgruppe skal rekvirering gjøres i tråd med disse Tezspire inngår i RHF anbefalinger for alvorlig ukontrollert T2-høy astma. **Beslutning i Beslutningsforum for nye metoder 18.03.2024.** Tezepelumab (Tezspire) innføres som tillegg til vedlikeholdsbehandling ved alvorlig astma med eosinofili hos voksne og ungdom i alderen 12 år og eldre som er utilstrekkelig kontrollert til tross for høye doser inhalasjonskortikosteroider i tillegg til et annet legemiddel for vedlikeholdsbehandling. **Beslutning i beslutningsforum for nye metoder 19.01.2026.** Tezspire (tezepelumab) innføres som tillegg til behandling med intranasale kortikosteroider hos voksne pasienter med alvorlig CRSwNP der behandling med systemiske kortikosteroider og/eller kirurgi ikke gir tilstrekkelig sykdomskontroll.

For fullstendig informasjon, les mer på [www.felleskatalogen.no](http://www.felleskatalogen.no)  
**AstraZeneca AS** - [www.astrazeneca.no](http://www.astrazeneca.no) – P. box 6050 Etterstad - 0601 Oslo

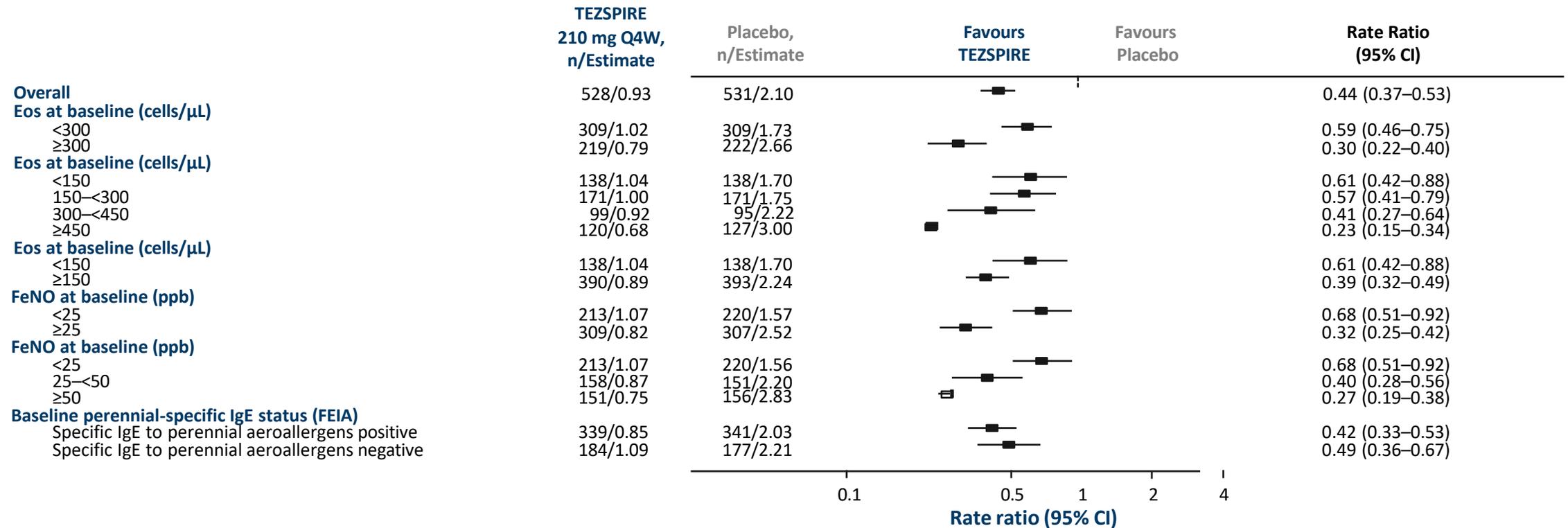
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# EKSTRA

# Tezepelumab Reduced Exacerbations across a broad range of inflammatory profiles<sup>1</sup>

## NAVIGATOR<sup>1</sup>

### Annualised Asthma Exacerbation Rate (over 52 Weeks) According to Baseline Biomarkers



CI = Confidence Interval; Eos = Eosinophils; FEIA = Fluorescence Enzyme Immunoassay; FeNO = Fractional Exhaled Nitric Oxide; IgE = Immunoglobulin E; Ppb = Parts per Billion; Q4W = Every 4 Weeks

NO-13980 Expiration Date: 08/04/2026

1. Menzies-Gow A, Corren J, Bourdin A et al.; Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma article and Supplement; N Engl J Med. 2021;384:1800–1809;