Received: 11 August 2023 | Revised: 5 December 2023 | Accepted: 10 December 2023

DOI: 10.1111/all.15986

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW ARTICLE

Tezepelumab in patients with allergic and eosinophilic asthma

Marco Caminati[1] | Roland Buhl[2] | Jonathan Corren[3] | Nicola A. Hanania[4] | Harold Kim[5,6] | Stephanie Korn[7,8] | Marek Lommatzsch[9] | Neil Martin[10,11] | Andrea Matucci[12] | Shuaib M. Nasser[13] | Ian D. Pavord[14] | Christian Domingo[15]

[1]Asthma Center and Allergy Unit, Verona Integrated University Hospital & Department of Medicine, University of Verona, Verona, Italy

[2]Pulmonary Department, Mainz University Hospital, Mainz, Germany

[3]David Geffen School of Medicine, University of California, Los Angeles, California, USA

[4]Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas, USA

[5]Department of Medicine, Western University, London, Ontario, Canada

[6]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[7]IKF Pneumologie Mainz, Mainz, Germany

[8]Thoraxklinik Heidelberg, Heidelberg, Germany

[9]Department of Pneumology and Critical Care Medicine, University of Rostock, Rostock, Germany

[10]Respiratory and Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK

[11]University of Leicester, Leicester, UK

[12]Immunoallergology Unit, Careggi University Hospital, Florence, Italy

[13]Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[14]Respiratory Medicine, NIHR Oxford Biomedical Research Centre, Nuffield Department of Medicine, University of Oxford, Oxford, UK

[15]Servei de Pneumologia, Corporació Sanitària Parc Taulí, Sabadell, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

Correspondence
Marco Caminati, Asthma Center and Allergy Unit, Verona Integrated University Hospital & Department of Medicine, University of Verona, Piazzale Ludovico Antonio Scuro 10, Verona 37134, Italy.
Email: marco.caminati@univr.it

Funding information
AstraZeneca; Amgen

Abstract

Asthma is a heterogeneous disease commonly driven by allergic and/or eosinophilic inflammation, both of which may be present in severe disease. Most approved biologics for severe asthma are indicated for specific phenotypes and target individual downstream type 2 components of the inflammatory cascade. Tezepelumab, a human monoclonal antibody (immunoglobulin G2λ), binds specifically to thymic stromal lymphopoietin (TSLP), an epithelial cytokine that initiates and sustains allergic and eosinophilic inflammation in asthma. By blocking TSLP, tezepelumab has demonstrated efficacy across known asthma phenotypes and acts upstream of all current clinically used biomarkers. In a pooled analysis of the phase 2b PATHWAY (NCT02054130) and phase 3 NAVIGATOR (NCT03347279) studies, compared with placebo, tezepelumab reduced the annualized asthma exacerbation rate over 52 weeks by 62% (95% confidence interval [CI]: 53, 70) in patients with perennial aeroallergen sensitization (allergic asthma); by 71% (95% CI: 62, 78) in patients with a baseline blood eosinophil

Abbreviations: AAER, annualized asthma exacerbation rate; AHR, airway hyperresponsiveness; BEC, blood eosinophil count; CI, confidence interval; EU, European Union; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; Ig, immunoglobulin; IL, interleukin; ILC2, type 2 innate lymphoid cell; kUA/L, kilounits of allergen-specific IgE per litre; Q4W, every 4 weeks; SCIT, subcutaneous allergen immunotherapy; T2, type 2; Th, t helper; TSLP, thymic stromal lymphopoietin; US, United States.

count ≥300 cells/μL; and by 71% (95% CI: 59, 79) in patients with allergic asthma and a baseline blood eosinophil count ≥300 cells/μL. This review examines the efficacy and mode of action of tezepelumab in patients with allergic asthma, eosinophilic asthma and coexisting allergic and eosinophilic phenotypes.

KEYWORDS
allergic asthma, eosinophilic asthma, tezepelumab, thymic stromal lymphopoietin

1 | INTRODUCTION

Asthma is a complex, heterogeneous disease having various phenotypes and endotypes that are based on underlying clinical and inflammatory mechanisms.[1] Patient asthma phenotypes are determined using a combination of clinical characteristics and biomarker profiles, which inform asthma diagnosis, risk assessment, treatment selection and monitoring response to treatment.[2]

Allergic asthma is the most common phenotype of asthma, accounting for approximately 60% of patients with severe asthma,[3–5] and its prevalence is increasing.[6] Allergic asthma is usually defined clinically, from the patient's symptoms, and by confirmed sensitization to a perennial aeroallergen characterized by elevated allergen-specific immunoglobulin E (IgE) levels[7] or a positive test for immediate hypersensitivity.[8] Another common phenotype of severe asthma, which can coexist with allergic asthma, is (intrinsic) eosinophilic asthma, typically characterized by a blood eosinophil count of at least 300 cells/μL.[9–11] According to the Global Initiative for Asthma, an eosinophilic phenotype is present in approximately 50% of patients with severe asthma.[12] However, results from a historical global registry study conducted to assess the prevalence of eosinophilic and noneosinophilic phenotypes in patients with severe asthma suggest that the eosinophilic severe asthma phenotype is more prevalent than previously estimated (>80% vs approximately 50%).[13]

Patients with allergic asthma often have elevated blood eosinophil counts.[14] For example, in the omalizumab EXTRA study in patients with uncontrolled allergic asthma, 48.7% of the study population (414/850) had blood eosinophil counts of at least 260 cells/μL.[15] Furthermore, cluster analyses from different asthma cohorts have identified substantial overlap in asthma phenotypes, with allergic and eosinophilic phenotypes commonly present in the same cluster.[16] Additionally, allergen challenges in patients with allergic asthma have consistently demonstrated transient and substantial increases in eosinophils present in bronchoalveolar lavage fluid.[17] Therefore, allergic and eosinophilic asthma phenotypes are not mutually exclusive, but identifying the predominant phenotype driving severe asthma can be challenging. Patients with allergic and eosinophilic asthma are likely to be eligible for more than one approved biologic therapy, and phenotype identification and treatment selection are further complicated because asthma phenotypes in an individual can evolve over time.[18,19]

Most biologics currently approved for severe asthma selectively target individual inflammatory mediators that underlie specific asthma phenotypes: omalizumab, a monoclonal antibody that targets IgE, is indicated for the treatment of allergic asthma[7]; mepolizumab, reslizumab and benralizumab (anti-interleukin [IL]-5/IL-5 receptor monoclonal antibodies) are indicated for the treatment of eosinophilic asthma; and dupilumab (anti-IL-4/IL-13 monoclonal antibody) is indicated for the treatment of moderate-to-severe asthma with type 2 inflammation (elevated blood eosinophils and/or fractional exhaled nitric oxide [FeNO]), or oral corticosteroid-dependent asthma (Figure 1).[7,10,11,20–22] Although not primarily indicated for allergic asthma, mepolizumab, reslizumab, benralizumab and dupilumab have demonstrated efficacy in subgroups of patients with evidence of allergic asthma.[22–24] Similarly, although not primarily indicated for eosinophilic asthma, omalizumab has demonstrated efficacy in subgroups of patients with eosinophilia in addition to allergic asthma.[15,25] Tezepelumab is a human monoclonal antibody (immunoglobulin G2λ [IgG2λ]) that blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine that can drive both allergic and eosinophilic inflammation in asthma.[26] Tezepelumab has demonstrated efficacy across the broad spectrum of severe asthma phenotypes (Box 1).[27–29]

TSLP is produced in response to environmental and pro-inflammatory stimuli. TSLP plays a key role in the initiation and persistence of airway inflammation in asthma, acting at the top of and throughout the asthma inflammatory cascade, on multiple pathways involving type 2 helper T (Th2) cells, mast cells, basophils, eosinophils, type 2 innate lymphoid cells (ILC2s) and other immune cells (Figure 2, Box 1).[30] It also has effects on airway structural cells and airway hyperresponsiveness (AHR) (Figure 2).[30,31] By blocking TSLP, tezepelumab has broad anti-inflammatory effects that affect a range of downstream pathways.[30] Tezepelumab has been shown to decrease the activity of IL-4, IL-5 and IL-13; this was evidenced by direct reductions in these cytokines and reductions in their associated biomarkers, namely serum total IgE, blood and airway eosinophils, and FeNO.[28,32,33] In addition to its effects on type 2-mediated inflammation, tezepelumab has been shown to reduce AHR; this reduction may be due to effects on airway mast cells and smooth muscle cells.[32,34,35]

The aim of this review is to examine the efficacy and mode of action of tezepelumab in patients with allergic asthma, eosinophilic asthma and coexisting allergic and eosinophilic phenotypes, using published data from randomized, placebo-controlled trials. The

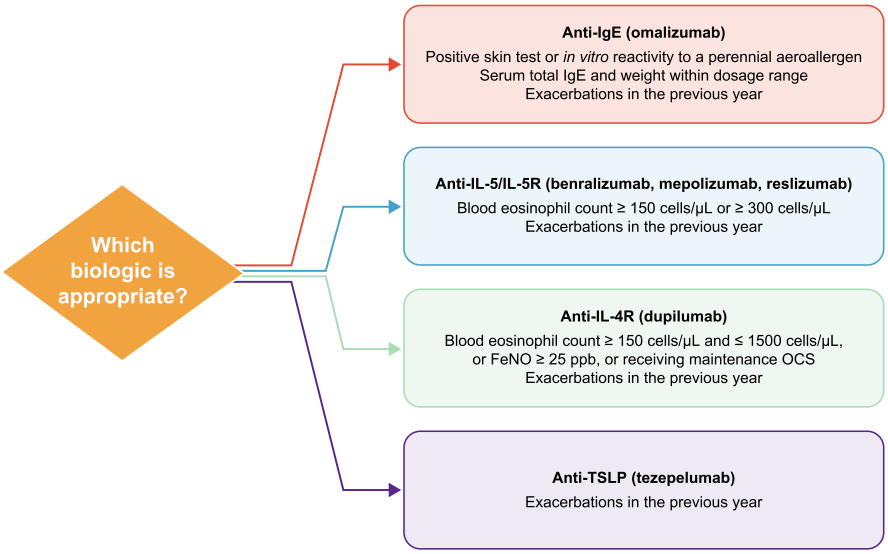

FIGURE 1 Eligibility criteria for approved severe asthma biologics as of July 2023.[9] FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; OCS, oral corticosteroids; TSLP, thymic stromal lymphopoietin.

BOX 1 Major milestone discoveries

- TSLP plays a key role in the initiation and persistence of airway inflammation in asthma, acting at the top of and throughout the asthma inflammatory cascade, on multiple inflammatory pathways.[30,31]
- By targeting TSLP, tezepelumab has an impact on multiple inflammatory pathways known to drive severe asthma.[26–29,32,33,46]
- Tezepelumab has demonstrated efficacy across the broad spectrum of severe asthma phenotypes.[27,28,46]
- Tezepelumab has the potential to treat patients with coexisting asthma phenotypes, namely patients whose disease is driven by both allergic and eosinophilic mechanisms.

effects of tezepelumab in nonallergic and noneosinophilic phenotypes are also discussed.

2 | IMPACT OF TEZEPELUMAB ON THE ALLERGIC IMMUNE RESPONSE

TSLP (in conjunction with the other alarmin cytokines, IL-25 and IL-33) has a central role in the allergic immune response in asthma (Figure 2). Following its release from the airway epithelium in response to airborne allergen exposure, TSLP facilitates antigen presentation by dendritic cells to naive T cells and accelerates differentiation of naive T cells to Th2 cells.[36,37] Th2 cells produce IL-4, IL-5 and IL-13, leading to IgE switching in B cells, degranulation of mast cells, airway eosinophilia, mucus hypersecretion from goblet cells and smooth muscle contraction resulting in AHR.[38] Additionally, mast cells and basophils release type 2 cytokines directly in response to TSLP.[39–41]

The effect of tezepelumab treatment on IgE levels demonstrates its mechanistic impact on the allergic immune response. Substantial reductions in serum total IgE over 52 weeks were reported in the phase 2b PATHWAY (ClinicalTrials.gov Identifier: NCT02054130) and phase 3 NAVIGATOR (ClinicalTrials.gov Identifier: NCT03347279) studies with tezepelumab 210 mg every 4 weeks (Q4W).[27,28] These reductions were maintained for an additional 52 weeks during the phase 3 DESTINATION long-term extension study (ClinicalTrials.gov Identifier: NCT03706079) into which patients were enrolled from NAVIGATOR and the phase 3 SOURCE study (ClinicalTrials.gov Identifier: NCT03406078),[26] and were sustained throughout the 36-week extended follow-up period of DESTINATION, after patients stopped treatment with tezepelumab.[42]

Tezepelumab 700 mg Q4W also demonstrated a prolonged and progressive reduction in IgE compared with placebo over 52 weeks of combined treatment with subcutaneous allergen immunotherapy (SCIT) in a double-blind, placebo-controlled study of patients with cat allergy (CATNIP; ClinicalTrials.gov Identifier: NCT02237196) (Figure 3A–D).[43] This effect continued throughout the 52 weeks of follow-up without treatment, suggesting that TSLP inhibition has a potential class-switching effect on IgE-producing B cells. Furthermore, transcription of the gene encoding for tryptase alpha/beta 1 (*TPSAB1*), an important mast cell mediator of the immediate allergic response, was significantly decreased in patients who received a combination of tezepelumab and SCIT compared with in those who received SCIT alone. Accordingly, tezepelumab may directly affect mast cell function, which plays a central role in the allergic response.[43] Total nasal symptom score (TNSS) data from CATNIP indicated that tezepelumab augments the efficacy and durability of SCIT. At Week 52, nasal allergen challenge-induced TNSS (calculated as area under the curve [$AUC_{0\text{-}1h}$] and as peak score [$Peak_{0\text{-}1h}$] during the first hour after allergen challenge) were significantly reduced in patients receiving combination tezepelumab/SCIT versus SCIT alone. At Week 104, 1 year after stopping treatment, TNSS $Peak_{0\text{-}1h}$ was significantly lower in those receiving tezepelumab/SCIT treatment versus SCIT alone, although TNSS $AUC_{0\text{-}1h}$ was not

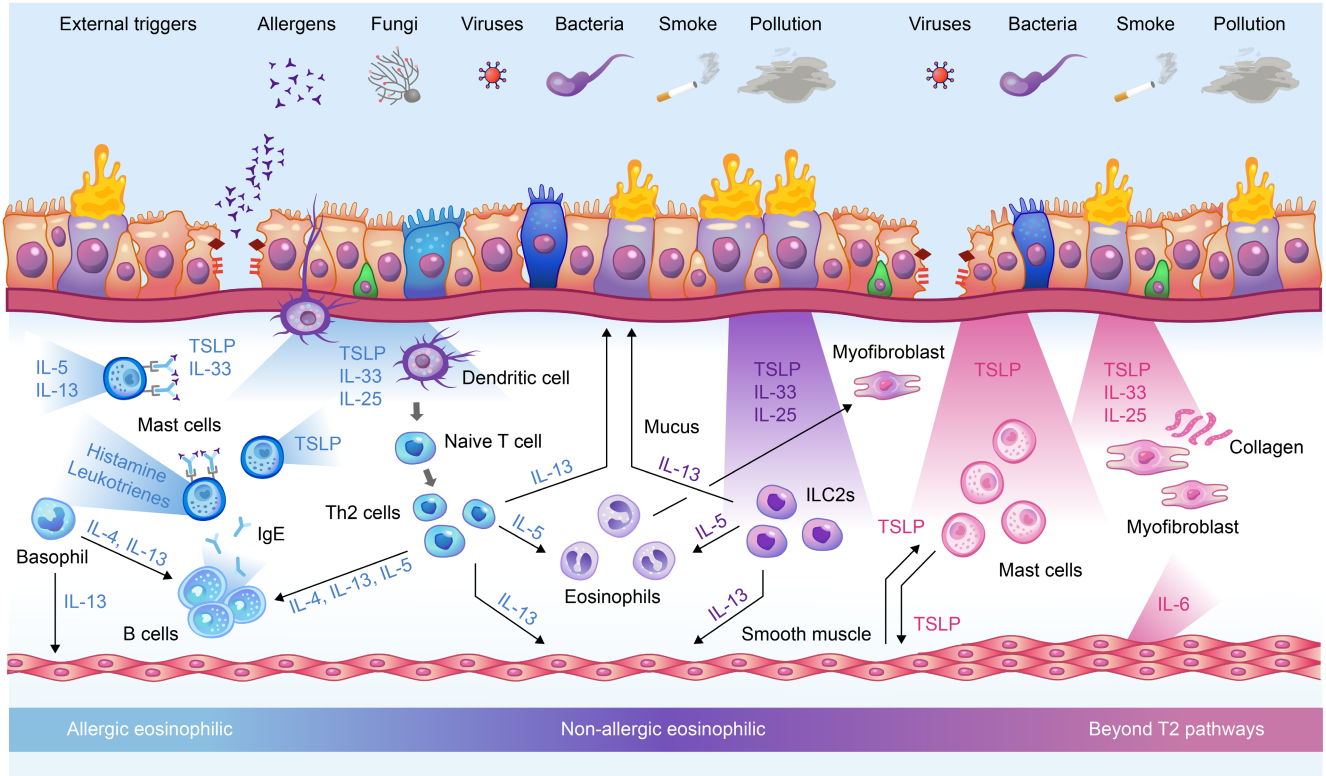

FIGURE 2 The role of TSLP in driving asthma disease mechanisms via different inflammatory pathways. In allergic eosinophilic inflammation, TSLP (in conjunction with the other epithelial alarmin cytokines, IL-33 and IL-25) initiates pathways involving Th2 lymphocytes, basophils and mast cells to drive airway eosinophilia. In nonallergic eosinophilic inflammation, TSLP contributes to the activation of innate lymphocytes such as ILC2s that contribute to airway eosinophilia. TSLP also has a role in mediating structural mechanisms that contribute to airway remodelling, involving airway smooth muscle cells and fibroblasts. IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; T2, type 2; Th, T helper; TSLP, thymic stromal lymphopoietin. Figure adapted from Gauvreau GM, et al. *Expert Opin Ther Targets* 2020; 24:777–792.

significantly different (Figure 3E,F). Although larger trials exploring the combined use of allergy immunotherapy with tezepelumab are needed, SCIT therapy may be valuable for patients established on tezepelumab who continue to experience poor symptom control following allergen exposure.

In a phase 1, allergen inhalation challenge, proof-of-concept study (ClinicalTrials.gov Identifier: NCT01405963), tezepelumab 700 mg administered Q4W for 3 months reduced early (0–2 h) and late (3–7 h) allergen-induced bronchoconstriction (maximum percentage decrease in forced expiratory volume in 1 second [FEV_1]) in patients with mild allergic asthma (confirmed by positive results on a skin prick test).[35] Tezepelumab demonstrated a 34% smaller maximum percentage decrease in FEV_1 during the late response than that with placebo on Day 42 ($p = .09$). This increased to 46% compared with placebo (12% vs. 22%) on Day 84 ($p = .02$).[35] Tezepelumab also significantly decreased blood and sputum eosinophil counts and FeNO levels for the duration of the study. In addition, tezepelumab treatment significantly increased the concentration of methacholine required to reduce the FEV_1 by 20% compared with placebo, indicative of a reduction in non-specific AHR.[35] This effect was also found in a recent study that assessed the efficacy of ecleralimab, an inhaled anti-TSLP antibody fragment, in patients with mild allergic asthma using an allergen inhalation challenge model.[44] These findings support the role of TSLP in allergen-induced airway responses and persistent airway inflammation in patients with allergic asthma, and support the potential therapeutic effect of tezepelumab in this patient population.[35]

3 | EFFICACY OF TEZEPELUMAB ON EXACERBATIONS IN ALLERGIC ASTHMA

Tezepelumab has also demonstrated efficacy in patients with severe allergic asthma in prespecified and post hoc analyses of phase 2 and phase 3 clinical studies. Patients included in these analyses had perennial aeroallergen sensitization, which was defined as at least one positive fluorescence enzyme immunoassay test result for specific IgE to a specific perennial aeroallergen (cat dander, dog dander, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* or mould mix).[45] In the phase 2b PATHWAY study, tezepelumab reduced the annualized asthma exacerbation rate (AAER) over 52 weeks compared with placebo in patients with perennial aeroallergen sensitization. The reductions in AAER ranged from 73% (95% confidence interval [CI]: 64, 80) in the low-dose (tezepelumab 70 mg Q4W) group to 80% (95% CI: 72, 86) in the medium-dose

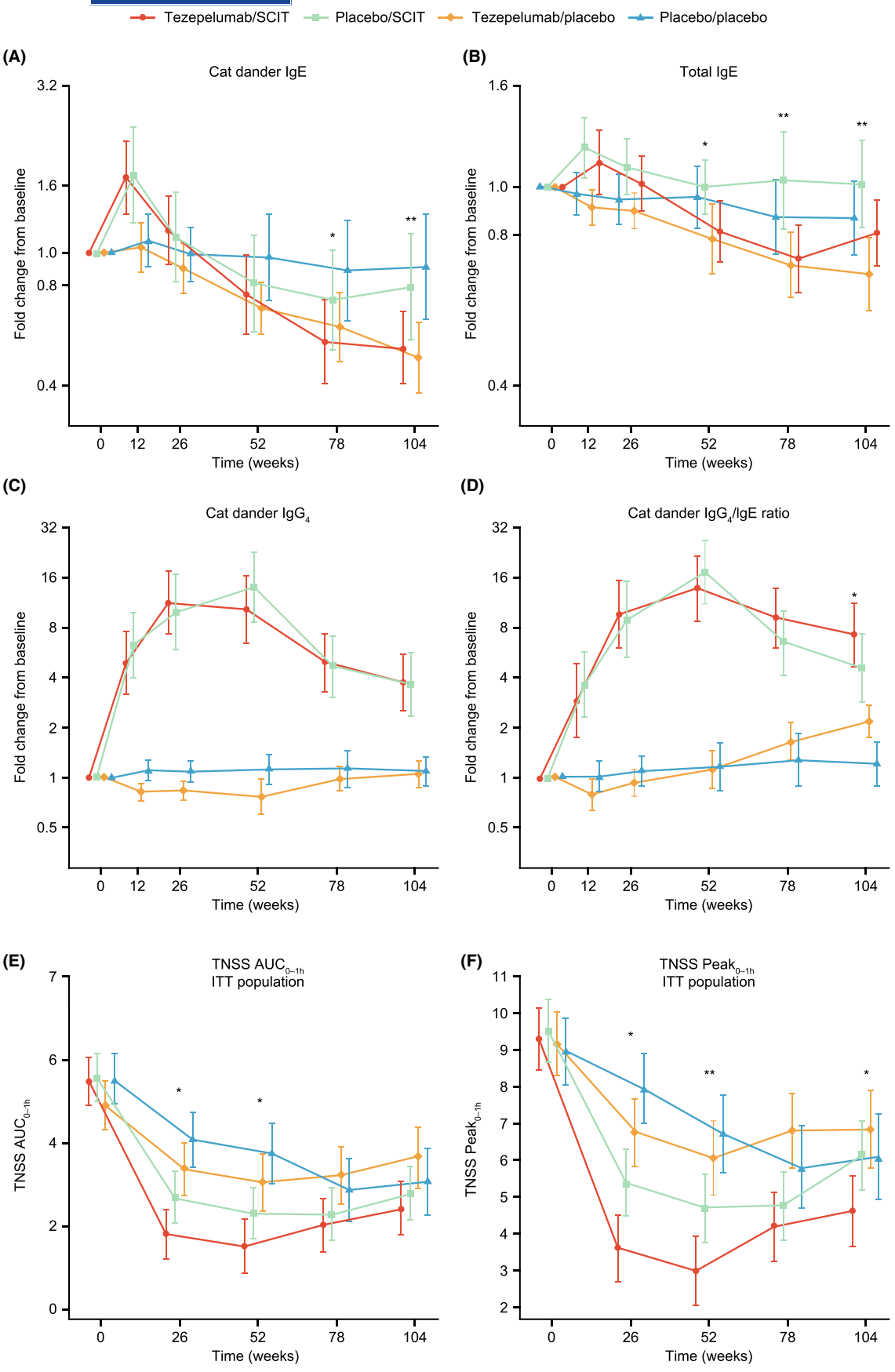

FIGURE 3 Reduction in serum total and specific IgE, and in TNSS, in patients with cat allergy treated with tezepelumab and subcutaneous cat immunotherapy. Fold change from baseline in serum cat dander-specific IgE (A), total IgE (B), cat dander-specific IgG_4 (C) and cat dander-specific IgG_4/IgE ratios (D). Longitudinal changes in TNSS AUC_{0-1h} (E) and TNSS $Peak_{0-1h}$ (F) following nasal allergen challenge with cat allergen extract at Weeks 0, 26, 52, 78 and 104. Data are shown as means with 95% confidence intervals. $^{*}p < .05$ and $^{**}p < .01$ for comparisons of tezepelumab/SCIT and placebo/SCIT. Reprinted from J Allergy Clin Immunol. volume 151. Corren J et al. Effects of combination treatment with tezepelumab and allergen immunotherapy on nasal responses to allergen: a randomized controlled trial. Pages 191–201. Copyright 2023, with permission from Elsevier. AUC, area under the curve; IgE, immunoglobulin E; IgG, immunoglobulin G; SCIT, subcutaneous allergen immunotherapy; TNSS, total nasal symptom score.

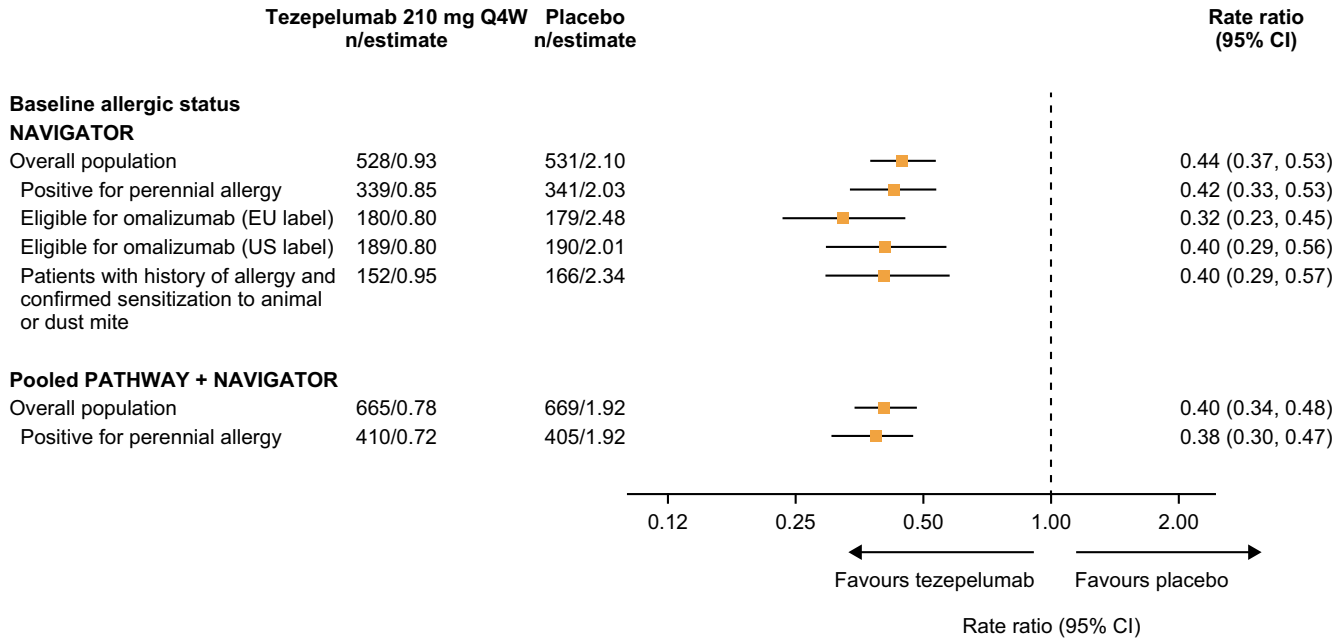

FIGURE 4 AAER over 52 weeks in patients with perennial aeroallergen sensitization from randomized controlled trials with tezepelumab. Omalizumab-eligible patients were not previously treated with omalizumab. Perennial aeroallergen sensitization was defined as at least one positive fluorescence enzyme immunoassay test result for specific IgE against a specific perennial aeroallergen: cat dander, dog dander, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* or mould mix. AAER, annualized asthma exacerbation rate; CI, confidence interval; EU, European Union; IgE, immunoglobulin E; Q4W, every 4 weeks; US, United States.

(tezepelumab 210 mg Q4W) group.[27] In the phase 3 NAVIGATOR study, tezepelumab 210 mg Q4W reduced the AAER over 52 weeks by 56% (95% CI: 47, 63) compared with placebo in patients with perennial aeroallergen sensitization.[28]

These findings are further supported by a pooled analysis of data from PATHWAY and NAVIGATOR, in which an AAER reduction over 52 weeks of 62% (95% CI: 53, 70) with tezepelumab 210 mg Q4W compared with placebo was reported in patients with perennial aeroallergen sensitization (Figure 4).[46] Furthermore, in this pooled analysis, tezepelumab reduced the rate of exacerbations that required hospitalization or an emergency department visit over 52 weeks by 80% (95% CI: 61, 90) in this patient subgroup.

Additional post hoc analyses of NAVIGATOR data (Figure 4) have demonstrated that tezepelumab reduced the AAER over 52 weeks compared with placebo in patients who would have been eligible for omalizumab (reductions of 60% [95% CI: 44, 71] and 68% [95% CI: 55, 77] with treatment according to the United States [US] label and European Union [EU] label, respectively)[29]; patients with reported comorbid allergic rhinitis (reduction of 58% [95% CI: 47, 67])[47]; and patients with a history of allergy and confirmed sensitization to dust mite or animal allergen (reduction of 60% [95% CI: 43, 71]).[48] Tezepelumab also reduced the AAER over 52 weeks compared with placebo irrespective of the threshold of serum specific IgE positivity to any perennial aeroallergen (Figure S1)[49]; the season (reductions in winter, spring, summer and autumn of 63% [95% CI: 52, 72], 46% [95% CI: 26, 61], 62% [95% CI: 48, 73] and 54% [95% CI: 41, 64], respectively)[50]; and age at asthma onset (reductions for childhood-onset, adult-onset and late-onset of 48% [95% CI: 29, 62], 63% [95% CI: 49, 73] and 56% [95% CI: 37, 69], respectively).[51] The AAER reductions in omalizumab-eligible patients from NAVIGATOR compare favourably with those reported for omalizumab in randomized, placebo-controlled studies in patients with severe asthma (25%).[52,53]

4 | EFFICACY OF TEZEPELUMAB ON LUNG FUNCTION AND PATIENT-REPORTED OUTCOMES IN ALLERGIC ASTHMA

In patients with perennial aeroallergen sensitization, pooled secondary outcome data from the PATHWAY and NAVIGATOR studies

demonstrated improvements from baseline to Week 52 with tezepelumab 210 mg Q4W compared with placebo in lung function (FEV_1: 0.22 L vs. 0.13 L; difference, 0.09 L [95% CI: 0.03, 0.14]; minimum clinically important difference [MCID], 0.1 L[54]).[46] Improvements were also reported with tezepelumab compared with placebo in patient-reported outcome measures: Asthma Control Questionnaire-6 score (−1.48 vs. −1.23; difference, −0.25 [95% CI: −0.39, −0.10]; MCID, 0.5[55]) and Asthma Quality of Life Questionnaire (standardized) for patients 12 years or older overall score (1.49 vs. 1.21; difference, 0.28 [95% CI: 0.12, 0.44]; MCID, 0.5[56]).[46]

5 | IMPACT OF TEZEPELUMAB ON THE EOSINOPHILIC IMMUNE RESPONSE

TSLP is also a key player in the (nonallergic) eosinophilic immune response in asthma (Figure 2). Exposure to viruses, bacteria, air pollutants, cigarette smoke and other insults induces the release of TSLP (together with IL-25 and IL-33) from the airway epithelium, which activates ILC2s.[57,58] Activated ILC2s produce IL-5 and IL-13,[57] leading to eosinophilia, FeNO production, mucus hypersecretion and AHR.[59] TSLP may also have direct effects on eosinophils, promoting their viability and recruitment to airway tissue.[60,61]

The mechanistic impact of tezepelumab treatment on the eosinophilic immune response is demonstrated by the notable reductions in blood eosinophil counts and FeNO levels reported in the PATHWAY and NAVIGATOR studies.[28,33] These reductions were noted as early as Week 2 and were maintained over the 52-week treatment period in both studies.[27,28] Furthermore, in a post hoc analysis of the PATHWAY study, tezepelumab treatment reduced levels of IL-5 and IL-13 (downstream biomarkers of blood eosinophils and FeNO, respectively) over 52 weeks.[33] Reductions in the levels of these biomarkers were accompanied by reductions in the AAER (irrespective of baseline blood eosinophil count or FeNO level in PATHWAY and NAVIGATOR, and irrespective of baseline serum IL-5 or IL-13 level in PATHWAY).[28,33]

In the phase 2 CASCADE bronchoscopy study in patients with moderate-to-severe asthma (ClinicalTrials.gov Identifier: NCT03688074), reductions in blood eosinophil counts were recorded after treatment with tezepelumab 210 mg Q4W, with reductions also seen in airway submucosal eosinophil counts (89% reduction compared with a 25% reduction in the placebo group among patients who completed ≥20 weeks of treatment). Reductions in the levels of FeNO, IL-5, IL-13 and plasma eosinophil-derived neurotoxin were all numerically greater with tezepelumab than with placebo at Week 12 in CASCADE.[32] In an exploratory analysis of CASCADE that compared computed tomography scans obtained before and after treatment, tezepelumab reduced mucus plug scores (calculated as the number of lung segments with at least one mucus plug) compared with placebo.[62] Taken together, these findings demonstrate that TSLP inhibition by tezepelumab affects multiple key downstream mediators of eosinophilic inflammation.

6 | EFFICACY OF TEZEPELUMAB ON EXACERBATIONS IN EOSINOPHILIC ASTHMA

In clinical studies, tezepelumab has been shown to reduce exacerbations in patients with elevated blood eosinophil counts, with pooled data from the PATHWAY and NAVIGATOR studies indicating a 71% (95% CI: 62, 78) reduction in the AAER over 52 weeks with tezepelumab 210 mg Q4W compared with placebo in patients with a baseline blood eosinophil count of at least 300 cells/μL (Figure 5).[46] A reduction compared with placebo was also observed in patients with a baseline blood eosinophil count of at least 150 cells/μL (63% [95% CI: 54, 70]).[46] In a post hoc analysis of NAVIGATOR data, tezepelumab reduced the AAER compared with placebo by 77% (95% CI: 65, 85), 77% (95% CI: 54, 89) and 74% (95% CI: 29, 90) in patients with a blood eosinophil count of at least 500, at least 750 and at least 1000 cells/μL, respectively.[63] Additionally, in a pooled analysis of data from the PATHWAY and NAVIGATOR studies, tezepelumab reduced the rate of exacerbations that required hospitalization or an emergency department visit by 90% (95% CI: 76, 96) in patients with a baseline blood eosinophil count of at least 300 cells/μL.[46]

7 | EFFICACY OF TEZEPELUMAB ON LUNG FUNCTION AND PATIENT-REPORTED OUTCOMES IN EOSINOPHILIC ASTHMA

In line with the reductions in exacerbations, in patients from NAVIGATOR with a blood eosinophil count of at least 300 cells/μL, improvements were also noted in lung function and patient-reported outcomes. At Week 52, improvements from baseline were greater with tezepelumab 210 mg Q4W than with placebo in prebronchodilator FEV_1 (0.37 L vs. 0.14 L; least-squares [LS] mean difference, 0.23 L [95% CI: 0.15, 0.31]), Asthma Control Questionnaire-6 score (−1.78 vs. −1.28; LS mean difference, −0.50 [95% CI: −0.69, −0.31]) and Asthma Quality of Life Questionnaire (standardized) for patients 12 years or older overall score (1.71 vs. 1.21; LS mean difference, 0.51 [95% CI: 0.30, 0.71]).[28]

8 | EFFICACY OF TEZEPELUMAB IN ALLERGIC AND EOSINOPHILIC ASTHMA

Tezepelumab has demonstrated efficacy in patients with evidence of both allergic and eosinophilic asthma phenotypes. In a post hoc analysis of NAVIGATOR data, tezepelumab 210 mg Q4W reduced the AAER over 52 weeks by 69% (95% CI: 56, 79) compared with placebo in patients with a baseline blood eosinophil count of at least 300 cells/μL and perennial aeroallergen sensitization (Figure 6).[64] In an additional post hoc analysis of patients from NAVIGATOR, who were grouped by their eligibility for omalizumab and their baseline blood eosinophil count, tezepelumab reduced the AAER by 65% (95% CI: 44, 79) compared with placebo in patients who would have

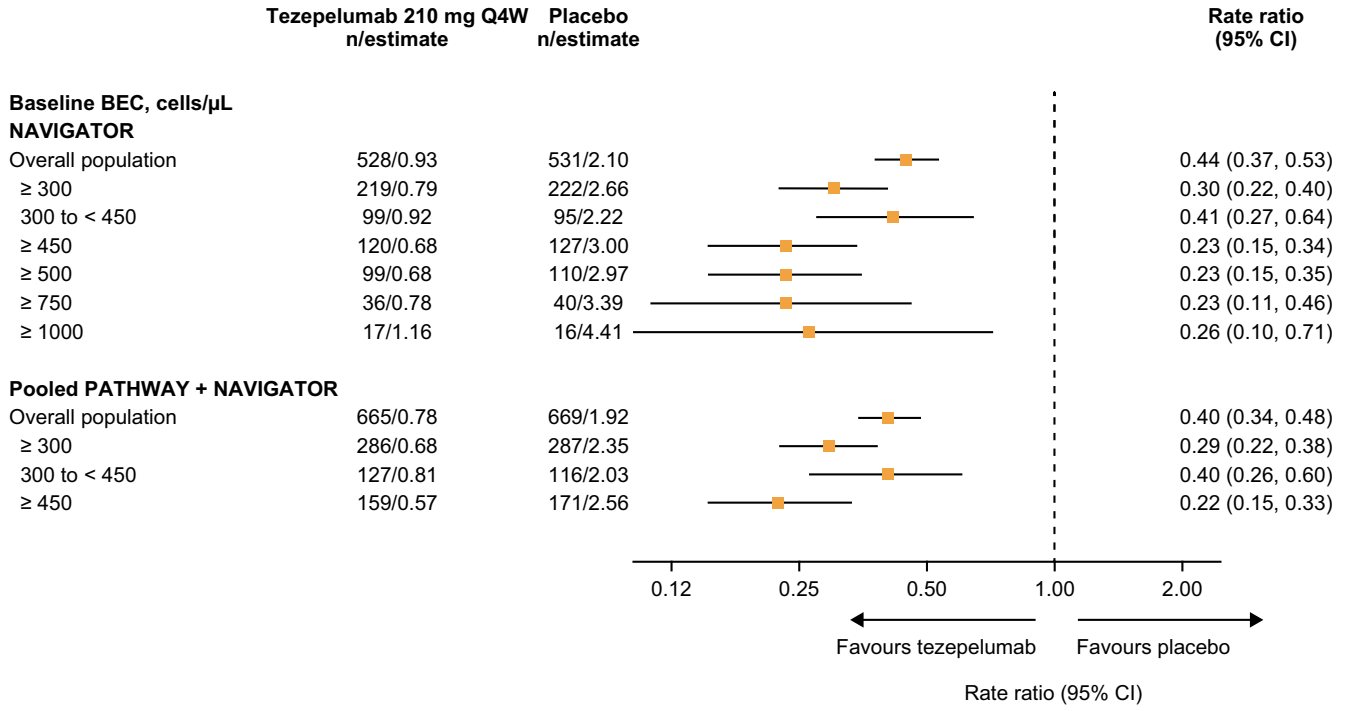

FIGURE 5 AAER over 52 weeks in patients with eosinophilic asthma from randomized controlled trials with tezepelumab. AAER, annualized asthma exacerbation rate; BEC, blood eosinophil count; CI, confidence interval; Q4W, every 4 weeks.

been eligible for omalizumab according to the US label and had a blood eosinophil count of at least 300 cells/μL.[29] A similar reduction in the AAER was observed in patients with a baseline blood eosinophil count of at least 300 cells/μL who would have been eligible for omalizumab according to the EU label (72% [95% CI: 55, 83]) (Figure 6).[29] In a pooled analysis of PATHWAY and NAVIGATOR data, a reduction in the AAER over 52 weeks of 71% (95% CI: 59, 79) with tezepelumab compared with placebo was observed in patients with a baseline blood eosinophil count of at least 300 cells/μL with perennial aeroallergen sensitization[46]; the AAER reduction in patients with sensitization to mould (and a baseline blood eosinophil count of ≥300 cells/μL) was also 71% (95% CI: 46, 84; unpublished data) (Figure 6). Furthermore, in the DESTINATION extension study, an AAER reduction over 104 weeks of 68% (95% CI: 55, 78) was observed with tezepelumab compared with placebo in patients with a baseline blood eosinophil count of at least 300 cells/μL and perennial aeroallergen sensitization (unpublished data) (Figure 6). In patients pooled from the PATHWAY and NAVIGATOR studies who had perennial aeroallergen sensitization, tezepelumab reduced exacerbations that required hospitalization or an emergency department visit by 81% (95% CI: 21, 96) in those with a baseline blood eosinophil count of 150 to less than 300 cells/μL, by 78% (95% CI: −10, 96) in those with a baseline blood eosinophil count of 300 to less than 450 cells/μL and by 93% (95% CI: 69, 98) in those with a baseline blood eosinophil count of at least 450 cells/μL (unpublished data).

9 | EFFICACY AND MECHANISM OF TEZEPELUMAB IN NONALLERGIC AND NONEOSINOPHILIC ASTHMA

Positive results have been observed with tezepelumab treatment in patients with nonallergic and noneosinophilic (type 2-low) severe asthma phenotypes.[28,46] Of note, in the pooled analysis of data from PATHWAY and NAVIGATOR, tezepelumab 210 mg Q4W reduced the AAER over 52 weeks by 54% (95% CI: 38, 66) in patients without perennial aeroallergen sensitivity, and by 48% (95% CI: 34, 59) and 48% (95% CI: 26, 64) in patients with baseline blood eosinophil counts of less than 300 cells/μL and less than 150 cells/μL, respectively, compared with placebo (Figure S2).[46] Similar results were observed in patients without perennial aeroallergen sensitivity who also had low baseline blood eosinophil counts (Figure S2).[46] Exacerbations that required hospitalization or an emergency department visit were reduced by 74% (95% CI: 41, 88) in patients without perennial aeroallergen sensitivity and by 67% (95% CI: 38, 83) and 60% (95% CI: 7, 82) in patients with baseline blood eosinophil counts of less than 300 cells/μL and less than 150 cells/μL, respectively, compared with placebo.[46]

Mechanistically, the efficacy of tezepelumab in nonallergic and noneosinophilic patients is likely a result of effects on TSLP-responsive cells that act beyond classical Th2 cell, IgE and eosinophilic pathways (Figure 2). TSLP has been shown to promote inflammation by mediating activation of and crosstalk between mast cells and airway smooth muscle cells,[65,66] and AHR is related to increased airway

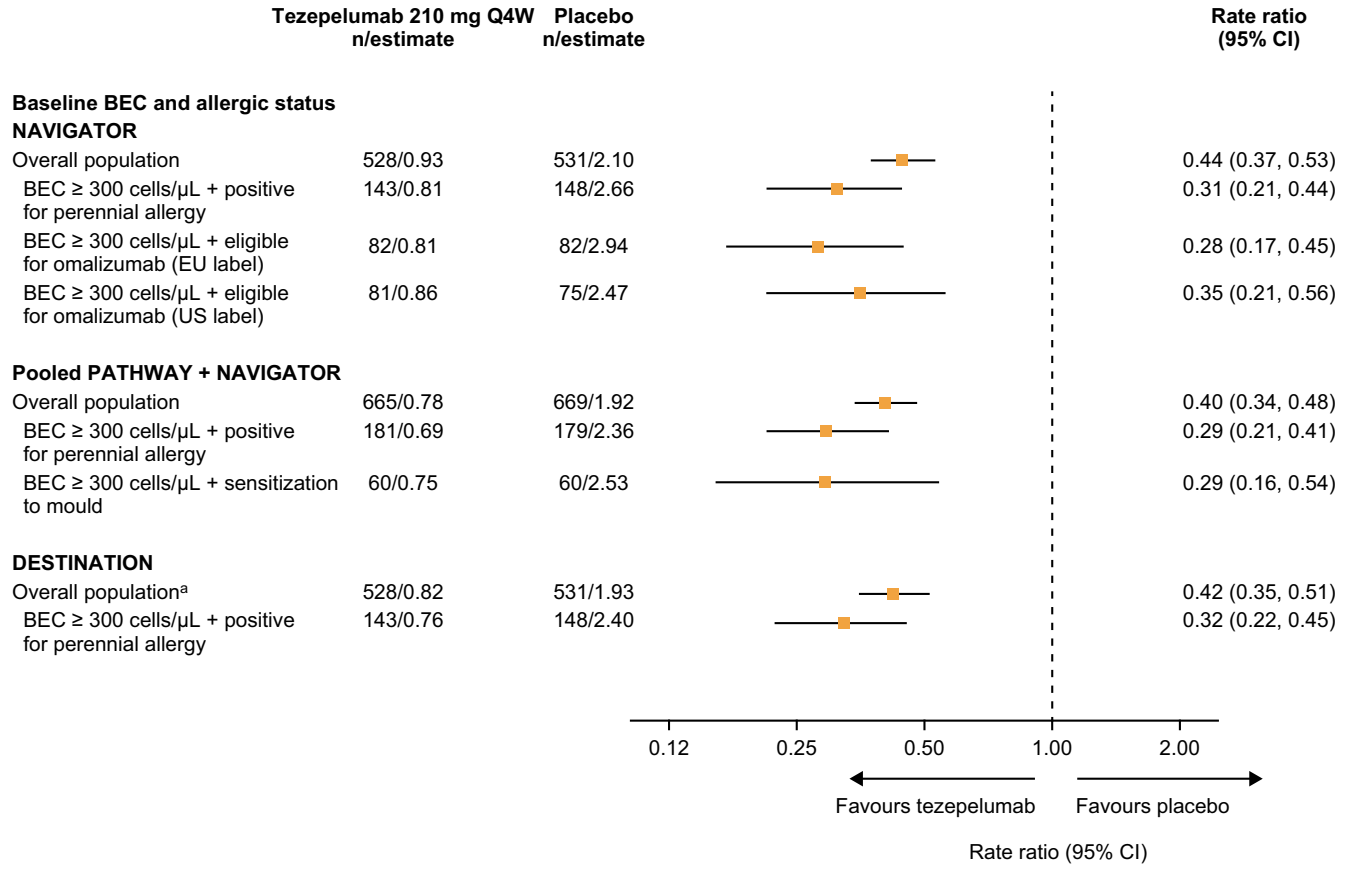

FIGURE 6 AAER over 52 weeks (PATHWAY, NAVIGATOR) or 104 weeks (DESTINATION) in patients with perennial aeroallergen sensitization and eosinophilic asthma from randomized controlled trials with tezepelumab. Omalizumab-eligible patients were not previously treated with omalizumab. Perennial aeroallergen sensitization was defined as at least one positive fluorescence enzyme immunoassay test result for specific IgE against a specific perennial aeroallergen: cat dander, dog dander, cockroach, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus* or mould mix. AAER, annualized asthma exacerbation rate; BEC, blood eosinophil count; CI, confidence interval; EU, European Union; Q4W, every 4 weeks; US, United States.

smooth muscle contractility caused by mast cell infiltration and airway inflammation.[67,68] Accordingly, tezepelumab's ability to reduce AHR to mannitol and methacholine is consistent with tezepelumab reducing mast cell and airway smooth muscle cell activation.[32,34] AHR reduction with tezepelumab was shown to be independent of patients' baseline blood eosinophil count and FeNO level,[69] indicating an effect beyond suppression of type 2 pathways. Other potential non-type 2 effects of TSLP inhibition by tezepelumab include the reduction of airway remodelling through reduced airway smooth muscle cell migration, fibroblast activation and epithelial-mesenchymal transition.[70–73]

10 | DISCUSSION

Coexisting, biomarker-identified asthma phenotypes in the same patient are prevalent in severe asthma.[74] Patients with allergic asthma may have elevated blood eosinophil counts, while patients with (intrinsic) eosinophilic asthma may have clinical or biomarker-based evidence of allergy. Therefore, effective treatment is required to address both allergic and eosinophilic inflammation.

For biologics that target individual components of the inflammatory cascade, the assessment of the clinical, inflammatory and biomarker-based phenotypes for each patient is required to inform which biologic therapy they are most likely to respond to. However, even with this information, it is difficult to know which component of the disease is most significant. Targeting a broader range of inflammatory pathways increases the likelihood of the patient having a beneficial clinical response and enables a broader population of patients to benefit from treatment. As summarized in this review, randomized controlled trials have demonstrated the efficacy of tezepelumab in patients with an allergic severe asthma phenotype and/or an eosinophilic severe asthma phenotype, as well as in patients with nonallergic and noneosinophilic (type 2-low) severe asthma phenotypes.[28,46] This evidence indicates that tezepelumab has efficacy across the currently known severe asthma phenotypes, making it a suitable therapeutic option for a broader range of patients than other approved biologics. It should be noted, however, that in the phase 3 SOURCE study in patients with oral corticosteroid-dependent asthma, there was no significant reduction in oral corticosteroid dose with tezepelumab versus placebo in the overall population, although an oral corticosteoid-sparing effect was observed in participants with baseline blood eosinophil counts of at least 150 cells/μL.[75]

TSLP has been shown to play a key role in the pathology and pathogenesis of asthma, particularly affecting both allergic and eosinophilic

BOX 2 Future research perspectives

- Tezepelumab may help to address the challenges that arise during the management of patients with severe asthma who may be eligible for multiple biologic treatments and whose asthma phenotype may evolve over time.
- Real-world evidence of the efficacy of tezepelumab in a broad range of patients with severe, uncontrolled asthma is required to support findings from clinical trials.

inflammatory mechanisms within the lung.[30,44] Therefore, TSLP represents an important therapeutic target in severe asthma treatment. The efficacy findings across various asthma phenotypes and biomarker subgroups may be due to TSLP, the target of tezepelumab, acting at the top of and throughout the inflammatory cascade, on multiple inflammatory pathways, which may lead to broader effects on inflammation.[23]

In conclusion, by targeting TSLP at the top of and throughout the inflammatory cascade, tezepelumab has an impact on multiple inflammatory pathways. Therefore, tezepelumab can affect disease pathobiology more broadly than biologics that only target specific downstream type 2 pathways. Tezepelumab has the potential to treat more than one asthma phenotype, including patients whose disease is driven by both allergic and eosinophilic mechanisms (Box 1). The mechanism of action of tezepelumab and clinical evidence of the efficacy of this treatment enable it to address the challenges that arise during the management of patients who may be eligible for multiple biologics and whose asthma phenotype may evolve over time (Box 2). Currently, these challenges substantially contribute to the complexity of managing severe asthma. Based on this perspective, tezepelumab is a highly efficacious treatment option for patients with coexisting allergic and eosinophilic phenotypes in severe, uncontrolled asthma.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the review and the analysis and interpretation of the data, were involved in the drafting of the manuscript and revising it critically for important intellectual content, provided final approval of the version to be published and agree to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

Medical writing support was provided by Laura Knapp, PhD, of PharmaGenesis London, London, UK, with funding from AstraZeneca and Amgen Inc.

FUNDING INFORMATION

Funding for this article was provided by AstraZeneca and Amgen Inc.

CONFLICT OF INTEREST STATEMENT

Marco Caminati has received fees from AstraZeneca for serving on advisory boards and speaker fees from GSK and Sanofi. Roland Buhl has received grants to Mainz University from Boehringer Ingelheim, GSK, Novartis and Roche; fees for lectures from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, Cipla, GSK, Novartis, Roche, Sanofi and Teva; and consulting fees for serving on advisory boards from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, GSK, Novartis, Roche and Sanofi. Jonathan Corren has received grants and personal fees from AstraZeneca, Genentech and Vectura; and grants from Optinose, Sanofi and Teva. Nicola A. Hanania has served as an advisor or consultant for Amgen, AstraZeneca, Genentech, GSK, Sanofi, Teva and Verona Pharma; and his institution has received research grant support from AstraZeneca, Genentech, GSK, Sanofi and Teva. Harold Kim is a member of the speakers' bureau and/or advisory boards of ALK, AstraZeneca, Bausch Health, CSL Behring, GSK, Miravo, Novartis, Pediapharm, Pfizer, Sanofi, Shire and Takeda. Stephanie Korn has received fees for lectures and/or advisory board meetings from AstraZeneca, GSK, Novartis, Roche, Sanofi Aventis and Teva. Marek Lommatzsch has received honoraria for lectures and/or consultant fees from ALK, Allergopharma, AstraZeneca, Bencard Allergie, Berlin-Chemie, Boehringer Ingelheim, Bosch, Chiesi, Circassia, GSK, HAL Allergy, Janssen-Cilag, MSD, Mundipharma, Novartis, Nycomed/Takeda, Sanofi, Teva and UCB; and research support from AstraZeneca, DFG and GSK. Neil Martin is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. Andrea Matucci has received a fee for serving on an advisory board and is a speaker for AstraZeneca, Boerhinger Ingelheim, Chiesi, CSL, GSK, Novartis, Sanofi and Takeda. Shuaib M. Nasser has received consultancy fees from ALK and AstraZeneca. Ian D. Pavord has received speaker fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia AB, GSK, Novartis, Regeneron, Sanofi and Teva; payments for the organization of educational events from AstraZeneca, GSK, Regeneron, Sanofi and Teva; consultant fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia AB, Genentech, GSK, Knopp Biosciences, Merck, MSD, Mylan Specialty, Napp, Novartis, Regeneron, RespiVert, Sanofi and Teva; international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp, Regeneron, Sanofi and Teva; and a research grant from Chiesi. Christian Domingo reports travel and speaker fees from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, MSD, GSK, HAL Allergy, ImmunoTek, Menarini, Novartis, Pfizer, Sanofi, Stallergenes Greer and Teva.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Marco Caminati https://orcid.org/0009-0009-1134-059X
Marek Lommatzsch https://orcid.org/0000-0002-9305-9348
Andrea Matucci https://orcid.org/0000-0002-3499-992X
Ian D. Pavord https://orcid.org/0000-0002-4288-5973

REFERENCES

1. Chen M, Shepard K 2nd, Yang M, et al. Overlap of allergic, eosinophilic and type 2 inflammatory subtypes in moderate-to-severe asthma. *Clin Exp Allergy*. 2021;51(4):546-555.
2. Wenzel SE. Severe adult asthmas: integrating clinical features, biology, and therapeutics to improve outcomes. *Am J Respir Crit Care Med*. 2021;203(7):809-821.
3. Csoma Z, Gál Z, Gézsi A, Herjavecz I, Szalai C. Prevalence and characterization of severe asthma in Hungary. *Sci Rep*. 2020;10(1):9274.
4. Tran TN, Zeiger RS, Peters SP, et al. Overlap of atopic, eosinophilic, and T_H2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol*. 2016;116(1):37-42.
5. Domingo C, Sicras-Mainar A, Sicras-Navarro A, Sogo A, Mirapeix RM, Engroba C. Prevalence, T2-biomarkers and cost of severe asthma in the era of biologics: the BRAVO-1 study. *J Investig Allergol Clin Immunol*. 2022;34. doi:10.18176/jiaci.0871
6. Backman H, Räisänen P, Hedman L, et al. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016-results from three population surveys. *Clin Exp Allergy*. 2017;47(11):1426-1435.
7. US Food and Drug Administration. XOLAIR® (omalizumab) Prescribing Information. 2021 Accessed May 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf
8. Vaillant AA, Vashisht R, Zito PM. Immediate hypersensitivity reactions. 2023 Accessed July 6, 2023. https://www.ncbi.nlm.nih.gov/books/NBK513315/
9. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2022 Accessed November 8, 2022. https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf
10. US Food and Drug Administration. FASENRA™ (benralizumab) Prescribing Information. 2017 Accessed May 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf
11. US Food and Drug Administration. NUCALA® (mepolizumab) Prescribing Information. 2015 Accessed May 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125526Orig1s000Lbl.pdf
12. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2020 Accessed July 26, 2021. https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf
13. Heaney LG, Perez de Llano L, Al-Ahmad M, et al. Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest*. 2021;160(3):814-830.
14. Oppenheimer J, Hoyte FCL, Phipatanakul W, Silver J, Howarth P, Lugogo NL. Allergic and eosinophilic asthma in the era of biomarkers and biologics: similarities, differences and misconceptions. *Ann Allergy Asthma Immunol*. 2022;129(2):169-180.
15. Hanania NA, Wenzel S, Rosén K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804-811.
16. Albers FC, Mullerova H, Gunsoy NB, et al. Biologic treatment eligibility for real-world patients with severe asthma: the IDEAL study. *J Asthma*. 2018;55(2):152-160.
17. Lommatzsch M, Julius P, Kuepper M, et al. The course of allergen-induced leukocyte infiltration in human and experimental asthma. *J Allergy Clin Immunol*. 2006;118(1):91-97.
18. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Respir Crit Care Med*. 2018;197(1):22-37.
19. Ricciardolo FLM, Guida G, Bertolini F, Di Stefano A, Carriero V. Phenotype overlap in the natural history of asthma. *Eur Respir Rev*. 2023;32(168):220201.
20. US Food and Drug Administration. CINQAIR® (reslizumab) Prescribing Information. 2016 Accessed May 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf
21. US Food and Drug Administration. Dupixent® (dupilumab) Prescribing Information. 2017 Accessed May 15, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf
22. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526.
23. Menzies-Gow A, Steenkamp J, Singh S, et al. Tezepelumab compared with other biologics for the treatment of severe asthma: a systematic review and indirect treatment comparison. *J Med Econ*. 2022;25(1):679-690.
24. Prazma CM, Idzko M, Douglass JA, et al. Response to mepolizumab treatment in patients with severe eosinophilic asthma and atopic phenotypes. *J Asthma Allergy*. 2021;14:675-683.
25. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. *Allergy*. 2018;73(2):490-497.
26. Menzies-Gow A, Wechsler ME, Brightling CE, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. *Lancet Respir Med*. 2023;11:425-438.
27. Corren J, Parnes J, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.
28. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800-1809.
29. Corren J, Ambrose CS, Griffiths JM, et al. Efficacy of tezepelumab in patients with evidence of severe allergic asthma: results from the phase 3 NAVIGATOR study. *Clin Exp Allergy*. 2022;53:417-428.
30. Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets*. 2020;24(8):777-792.
31. Domingo C, Mirapeix RM. From the allergic cascade to the epithelium-driven disease: the long road of bronchial asthma. *Int J Mol Sci*. 2023;24(3):2716.
32. 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(11):1299-1312.
33. Corren J, Pham TH, Garcia Gil E, et al. Baseline type 2 biomarker levels and response to tezepelumab in severe asthma. *Allergy*. 2022;77(6):1786-1796.
34. Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J*. 2022;59(1):2101296.
35. 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(22):2102-2110.
36. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002;3(7):673-680.
37. Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med*. 2005;202(9):1213-1223.
38. Lambrecht BN, Hammad H, Fahy JV. The cytokines of asthma. *Immunity*. 2019;50(4):975-991.
39. Allakhverdi Z, Comeau MR, Jessup HK, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. *J Exp Med*. 2007;204(2):253-258.
40. Nagarkar DR, Poposki JA, Comeau MR, et al. Airway epithelial cells activate Th2 cytokine production in mast cells through IL-1 and thymic stromal lymphopoietin. *J Allergy Clin Immunol*. 2012;130(1):225-232 e4.

41. Salter BM, Oliveria JP, Nusca G, et al. Thymic stromal lymphopoietin activation of basophils in patients with allergic asthma is IL-3 dependent. *J Allergy Clin Immunol*. 2015;136(6):1636-1644.
42. Caminati M, Llanos JP, Spahn JD, et al. Changes in serum total IgE after cessation of tezepelumab after 2 years of treatment (DESTINATION). *Eur Respiratory J*. 2023;62:OA1419.
43. Corren J, Larson D, Altman MC, et al. Effects of combination treatment with tezepelumab and allergen immunotherapy on nasal responses to allergen: a randomized controlled trial. *J Allergy Clin Immunol*. 2023;151(1):192-201.
44. Gauvreau GM, Hohlfeld JM, FitzGerald JM, et al. Inhaled anti-TSLP antibody fragment, ecleralimab, blocks responses to allergen in mild asthma. *Eur Respir J*. 2023;61(3):2201193.
45. Corren J, Ambrose CS, Salapa K, et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma and perennial allergy. *J Allergy Clin Immunol Pract*. 2021;9:4334-4342.e6.
46. Corren J, Menzies-Gow A, Chupp G, et al. Efficacy of tezepelumab in severe, uncontrolled asthma: pooled analysis of PATHWAY and NAVIGATOR studies. *Am J Respir Crit Care Med*. 2023;208(1):13-24.
47. Carr TBJ, Cook B, Hunter G, et al. Efficacy of Tezepelumab in patients with severe, uncontrolled asthma with respiratory comorbidities: results from the phase 3 NAVIGATOR study. *J Allergy Clin Immunol*. 2022;149(2 Suppl):AB152.
48. Bourdin A, Corren J, Ambrose C, et al. *Efficacy of tezepelumab in patients with perennial allergic asthma: results from the NAVIGATOR Phase 3 Study*. 2021 76 (S110):586–587.
49. Lindsley A, Colice G, Martin N, et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma by specific perennial allergen immunoglobulin E thresholds. *J Allergy Clin Immunol*. 2023;151:AB18.
50. Hoyte F, Martin N, Kmita K, et al. Tezepelumab reduces exacerbations across all seasons in patients with severe, uncontrolled asthma: results from the phase 3 NAVIGATOR study. *J Allergy Clin Immunol*. 2022;149:AB63.
51. Brusselle G, Spahn JD, Hunter G, Martin N, Llanos-Ackert J-P, Ponnasrambil S. Efficacy of tezepelumab according to age at asthma onset in NAVIGATOR. *Eur Respir J*. 2022;60:1835.
52. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573-582.
53. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;(1):Cd003559.
54. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol*. 2012;129(3 Suppl):S65-S87.
55. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902-907.
56. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the asthma quality of life questionnaire. *Chest*. 1999;115(5):1265-1270.
57. Bartemes KR, Kephart GM, Fox SJ, Kita H. Enhanced innate type 2 immune response in peripheral blood from patients with asthma. *J Allergy Clin Immunol*. 2014;134(3):671-678 e4.
58. Machida K, Aw M, Salter BMA, et al. The role of the TL1A/DR3 Axis in the activation of group 2 innate lymphoid cells in subjects with eosinophilic asthma. *Am J Respir Crit Care Med*. 2020;202(8):1105-1114.
59. Matsuyama T, Machida K, Mizuno K, et al. The functional role of group 2 innate lymphoid cells in asthma. *Biomolecules*. 2023;13(6):893.
60. Wong CK, Hu S, Cheung PF, Lam CW. Thymic stromal lymphopoietin induces chemotactic and prosurvival effects in eosinophils: implications in allergic inflammation. *Am J Respir Cell Mol Biol*. 2010;43(3):305-315.
61. Cook EB, Stahl JL, Schwantes EA, Fox KE, Mathur SK. IL-3 and TNFalpha increase thymic stromal lymphopoietin receptor (TSLPR) expression on eosinophils and enhance TSLP-stimulated degranulation. *Clin Mol Allergy*. 2012;10(1):8.
62. Nordenmark L, Hellqvist A, Emson C, et al. Tezepelumab and mucus plugs in patients with moderate-to-severe asthma. *NEJM Evid*. 2023;2.
63. Jain N, Llanos-Ackert J, Ambrose C, et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma and high baseline blood eosinophil counts. *Ann Allergy Asthma Immunol*. 2022;129(5):S36-S37.
64. Menzies-Gow AC, Cook J, Kmita B, et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma, according to baseline blood eosinophil count and allergic status: results from the phase 3 NAVIGATOR study. *Allergy*. 2021;76:1026.
65. Allakhverdi Z, Comeau MR, Jessup HK, Delespesse G. Thymic stromal lymphopoietin as a mediator of crosstalk between bronchial smooth muscles and mast cells. *J Allergy Clin Immunol*. 2009;123(4):958-960 e2.
66. Kaur D, Doe C, Woodman L, et al. Mast cell-airway smooth muscle crosstalk: the role of thymic stromal lymphopoietin. *Chest*. 2012;142(1):76-85.
67. Brightling CE, Bradding P, Symon FA, Holgate ST, Wardlaw AJ, Pavord ID. Mast-cell infiltration of airway smooth muscle in asthma. *N Engl J Med*. 2002;346(22):1699-1705.
68. Sverrild A, Bergqvist A, Baines KJ, et al. Airway responsiveness to mannitol in asthma is associated with chymase-positive mast cells and eosinophilic airway inflammation. *Clin Exp Allergy*. 2016;46(2):288-297.
69. Brightling CE, O'Byrne PM, Porsbjerg C, et al. Effect of tezepelumab on airway hyperresponsiveness by baseline blood eosinophil count in patients with severe, uncontrolled asthma in the phase 2 CASCADE study. *Am J Respir Crit Care Med*. 2023;207:A4750.
70. Wu J, Liu F, Zhao J, et al. Thymic stromal lymphopoietin promotes asthmatic airway remodelling in human lung fibroblast cells through STAT3 signalling pathway. *Cell Biochem Funct*. 2013;31(6):496-503.
71. Cao L, Liu F, Liu Y, et al. TSLP promotes asthmatic airway remodeling via p38-STAT3 signaling pathway in human lung fibroblast. *Exp Lung Res*. 2018;44(6):288-301.
72. Redhu NS, Shan L, Movassagh H, Gounni AS. Thymic stromal lymphopoietin induces migration in human airway smooth muscle cells. *Sci Rep*. 2013;3:2301.
73. Cai LM, Zhou YQ, Yang LF, et al. Thymic stromal lymphopoietin induced early stage of epithelial-mesenchymal transition in human bronchial epithelial cells through upregulation of transforming growth factor beta 1. *Exp Lung Res*. 2019;45(8):221-235.
74. Denton E, Price DB, Tran TN, et al. Cluster analysis of inflammatory biomarker expression in the international severe asthma registry. *J Allergy Clin Immunol Pract*. 2021;9(7):2680-2688.e7.
75. Wechsler ME, Menzies-Gow A, Brightling CE, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. *Lancet Respir Med*. 2022;10(7):650-660.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Caminati M, Buhl R, Corren J, et al. Tezepelumab in patients with allergic and eosinophilic asthma. *Allergy*. 2024;79:1134-1145. doi:10.1111/all.15986