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REVIEW ARTICLE

Role of the *TSLP* and its Receptor in the Treatment of Asthma

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ABSTRACT

Thymic stromal lymphopoietin (*TSLP*) is a crucial cytokine in initiating and regulating immune responses. Various cell types, including epithelial cells, fibroblasts, and dendritic cells, synthesize *TSLP*. *TSLP* activates dendritic cells, which subsequently promote the differentiation of T cells into T-helper 2 (T_H2) cells, a subset of T cells that produce cytokines involved in allergic responses. Genetic studies have linked *TSLP* to the development of asthma and other inflammatory disorders, indicating its importance in the pathogenesis of these diseases. Inhibiting the *TSLP-TSLR* axis has been suggested as a precision medicine strategy for treating several phenotypes and endotypes of asthma. Tezepelumab is a human monoclonal antibody that selectively binds to *TSLP*, thereby blocking its interaction with its heterodimeric receptor, reducing inflammation in the airways, and improving asthma symptoms.

Keywords: Anti-*TSLP*. Severe asthma. Tezepelumab. Thymic stromal lymphopoietin. *TSLP-TSLP*R.

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INTRODUCTION

Asthma is characterized by inflammation in the airways and variable obstruction to airflow that gives rise to recurrent attacks of dyspnea and wheezing. These symptoms currently affect more than 350 million people worldwide[1].

According to the recent Prevalence, characterization and costs of severe asthma in Spain (Bravo-1) study[2], the prevalence of asthma in Spain is 5.5%. Of them, 7.7% had severe asthma (81.2% had T2 asthma, 31.2% received oral corticosteroids, and 3.8% had biological treatment)[2]. T2-asthma is characterized by T_H2 inflammation mediated by the cytokines interleukin (IL)-4, IL-5, IL-13, specific IgE, and elevated eosinophil counts.

Although there are treatments that allow the disease to be controlled to a large extent, as shown in the Bravo-1 study, asthma remains uncontrolled in a high proportion of patients, particularly those with severe asthma[2].

Diagnosing and treating asthma in developed countries generate an estimated healthcare cost of around 19 billion € annually, representing a significant burden on the healthcare system[3]. Also, the costs of severe uncontrolled asthma are reported to double those of controlled severe asthma[2]. Approximately 70-80% of asthma patients may have substantial variability in clinical response to commonly used treatments, partly caused by poor patient adherence, ineffective drug administration methods, and inappropriate selection of active ingredients. However, in a significant proportion of cases, inter-individual differences cannot be explained solely by these factors, suggesting that there may be a genetic component that could play an essential role in this variability. Asthma is a markedly heterogeneous disease resulting from the interaction of multiple biological pathways, which are poorly understood, despite notable advances in the immunological mechanisms of asthma in recent years[4].

Severe asthma is defined as a type of asthma that is difficult to control despite treatment with high doses of inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or remaining uncontrolled despite this therapy[5]. These patients have difficulties with sleep, exercise, and other activities of daily living, and frequent exacerbations may occur, further compromising the patient's quality of life[6].

PATHOGENESIS OF ASTHMA

The underlying mechanism of asthma is the inflammation of the airways, which is driven by a complex interplay of immune cell types, cytokines, chemokines, and other mediators of inflammation[4]. When the airway epithelium is exposed to allergenic proteins, epithelial cells can release cytokines such as thymic stromal lymphopoietin (*TSLP*), IL-25, and IL-33, which contribute to establishing T_H2 responses[4]. These epithelial-derived cytokines activate several immune cells, such as eosinophils, T_H2 cells, mast cells, and basophils[4]. *TSLP* and IL-33, in turn, activate dendritic cells that present antigens to naïve CD4+ Tcells[7] that migrate from the lung tissue to the lymph nodes[8,9]. In the context of IL-4 and other signals, this process leads to the development of allergen-specific T_H2 cells that produce cytokines IL-4, IL-5, and IL-13[10]. IL-4 promotes B cells to class-switch from IgM to IgE[10]. IgE antibodies bind to the

high-affinity receptor I of mast cells and basophils, triggering the release of mediators and cytokines[4]. IgE also binds to dendritic cells, which play a role in facilitated antigen presentation, indicating their potential involvement in the maintenance of allergic sensitization[11]. IL-5 is essential for eosinophil production, differentiation, survival, and activation in peripheral tissues[4]. Prostaglandin D2 and eosinophil cationic protein (ECP) are potent inducers of eosinophil chemotaxis, which, in turn, can cause severe damage to the epithelial lining of the airways and lead to bronchospasm and bronchial hyperresponsiveness[12].

T2 cytokines also induce stimulation of B-cell growth, upregulation of vascular cell adhesion molecule 1 (VCAM-1) expression, the release of the chemokine eotaxin, stimulation of goblet cell development and secretion of mucus, impairment of smooth airway responsiveness[10,13] (Fig. 1).

Viruses and pollutants may also elicit the release of epithelial alarmins that activate type 2 innate lymphoid cells (ILC2) and mast cells, leading to similar inflammatory changes as noted above but without inducing IgE synthesis. Non-allergic T2-type asthma is characterized by clinical asthma with airway eosinophilic inflammation in the absence of allergen-specific T_H2 cells and IgE[14].

Asthma patients who exhibit no signs of T2-type inflammation or low-T2-type asthma are diverse. These patients may develop airway disease later in life, usually lack typical T2-type asthma comorbidities, have limited specific IgE, and may not respond well to inhaled corticosteroids (ICSs)[11,15]. In induced sputum, patients with the non-T2-type disease may display sputum neutrophilia (> 60% of cells) or minimal pathologic signs of active inflammation (paucigranulocytic)[16].

In addition, some patients present mixed granulocytic asthma, also known as neutrophilic asthma with eosinophilia. These patients have been shown to have worse asthma control, more frequent exacerbations, and poorer response to standard asthma therapies than patients with either predominantly eosinophilic or predominantly neutrophilic asthma. This phenotype's underlying mechanisms and optimal treatment strategies are still being investigated[14].

THERAPIES APPROVED FOR SEVERE ASTHMA

Targeted biological therapies have been available for patients with severe asthma for over 15 years. Omalizumab, a monoclonal antibody (mAb) that binds free IgE, was the first drug of this type approved for patients with severe asthma and an allergic phenotype[17]. Other mAbs such as mepolizumab and reslizumab, targeted against IL-5; benralizumab, targeted against the α chain of the IL5 receptor; and dupilumab, targeted against the α chain of the IL-4/IL-13 receptor, have also been approved for patients with T2 severe asthma, usually with an eosinophilic phenotype[18-21]

These antibody therapies have shown significant improvement in asthma exacerbation rates, pulmonary function, and patient-reported outcomes (PROs) and have proven to be safe. However, many patients with non-allergic, non-T2 asthma still do not respond well to current standard-of-care treatments, including all previously mentioned biological therapies[14].

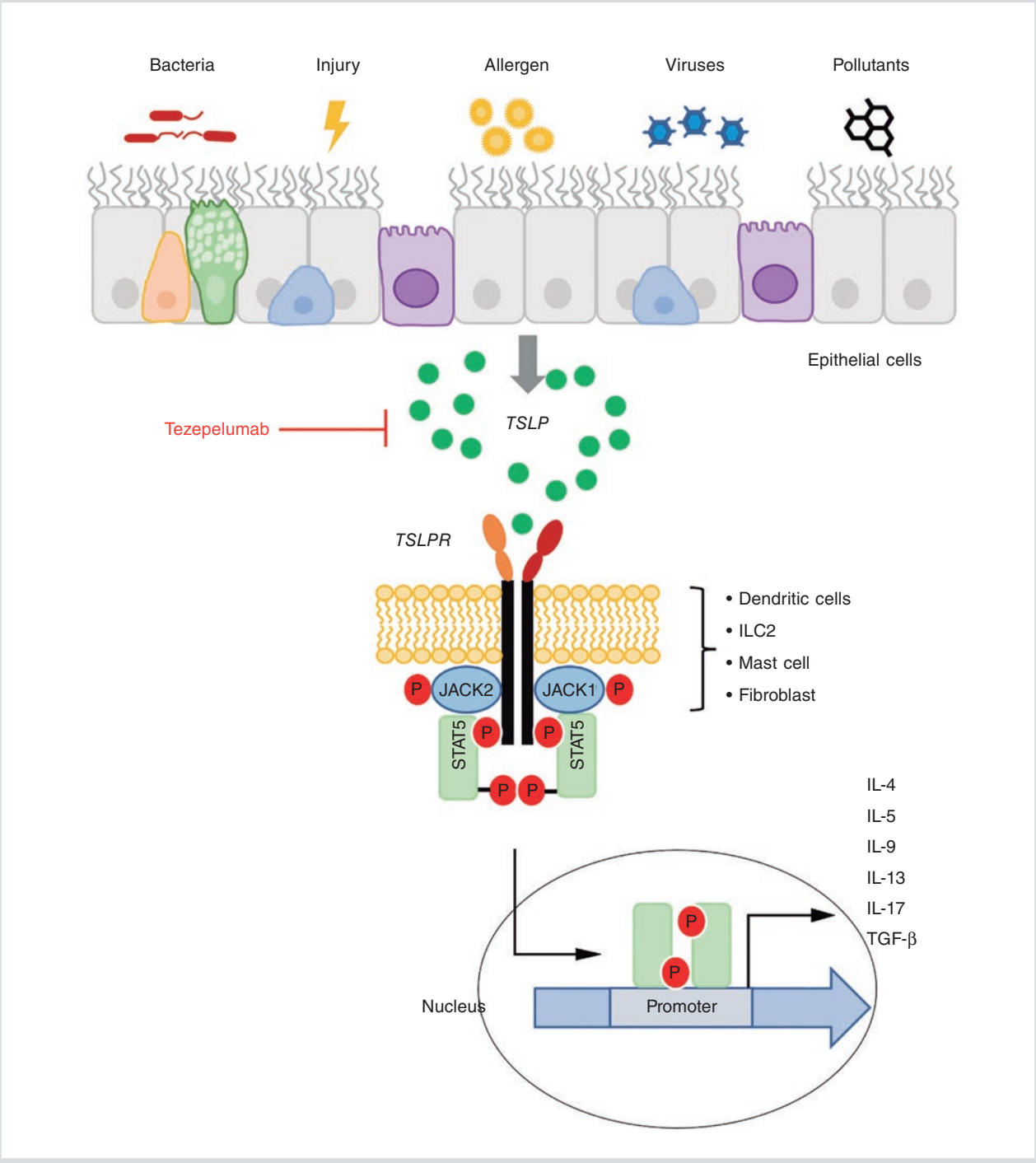

Figure 1. Schematic representation of thymic stromal lymphopoietin signaling. Environmental triggers, including allergens, viral or bacterial products, pollutants, and mechanical injuries, can activate the epithelial cells to release *TSLP*. *TSLP* binds to a heterodimeric receptor comprising *TSLPR* and IL-7Rα. This heterodimer is expressed on *TSLP* target cells such as dendritic cells, mast cells, macrophages, ILC2 cells, T cells, and fibroblasts. Upon *TSLP* binding to its receptor, Janus kinases JAK1 and JAK2 phosphorylate, and, in turn, they phosphorylate STAT5, which promotes the transcription of target genes, like type 2 cytokines, and initiate proinflammatory signaling. Tezepelumab specifically blocks *TSLP* from binding to its heterodimeric receptor, inhibiting the production of inflammatory cytokines and cell types.
IL: interleukin; ILC2: innate lymphoid cells; TGF-β: transforming growth factor beta; *TSLP*: thymic stromal lymphopoietin; *TSLPR*: *TSLP* receptor.

TSLP AND *TSLPR*

Thymic stromal lymphopoietin (*TSLP*) is a pleiotropic innate cytokine that, together with IL-25 and IL-33, forms part of the group of alarmins. These molecules are released due to degranulation, cellular damage, death, or as part of an immune response[22]. *TSLP* is released by the epithelium of the airways when stimulated by allergens, viruses, bacteria, pollutants, or physical damage, initiating a subsequent inflammatory process[23]. *TSLP* activates dendritic cells by binding to its specific receptor, a dimer composed of *TSLPR* (encoded by cytokine receptor like factor 2 [*CRLF2*] and IL-7Rα. The downside of signaling by *TSLP* is that it induces the differentiation of naive T lymphocytes into T_H2 cells[24]. In addition, *TSLP* also acts on innate type 2 lymphocytes (ILC2) by increasing their survival and inducing T_H2 cytokine production[25]. It is also capable of activating eosinophils and basophils[26] (Fig. 1).

The *TSLP* gene is located in humans on chromosome 5q22.1, near the group of atopic cytokine genes of the 5q31 region, where the genes encoding *IL-4*, *IL-5*, *IL-9*, and *IL-13* are located[27]. Messenger RNA expression of *TSLP* and *TSLPR* is higher in neutrophils and epithelial macrophages of asthmatics compared to healthy controls, and a negative correlation has been observed between lung function and *TSLP* expression[27]. Recent studies have demonstrated the crucial role of *TSLP* in developing and maintaining allergic diseases. It is currently considered that *TSLP* is involved in most allergic pathologies, such as allergic asthma or atopic dermatitis, as well as other diseases, such as eosinophilic esophagitis[28]. In asthmatic patients, it has been described that *TSLP* expression levels in the airway epithelium correlate with disease severity, regardless of corticosteroid therapy[29].

Genetic studies have shown that specific alleles located at the human *TSLP* gene locus are associated with the onset of asthma and bronchial hyperresponsiveness, indicating that *TSLP* and *TSLPR* may play a role in developing these conditions. Several polymorphisms have been described in European ancestry asthmatic adults[30,31], and some polymorphisms appear to contribute to a predominance of T_H2 response, rather than T_H1, against viral infections by increasing the production of *TSLP* in the lung epithelium[32].

There are two isoforms of *TSLP*, whose expression is regulated by different gene promoters: the short form (sf*TSLP*), consisting of 63 amino acids, is constitutively expressed and participates in tissue homeostasis, while the long form (lf*TSLP*), consisting of 150 amino acids, only appears during inflammatory processes[33].

An increase in *TSLP* and *TSLPR* mRNA expression has also been observed in the nasal epithelium and bronchi of asthmatic patients[34-36].

TARGETING *TSLP* (THYMIC STROMAL LYMPHOPOIETIN) AND *TSLPR* FOR THE TREATMENT OF ASTHMA

Due to their importance in the development and progression of asthma disease and other T2-type inflammatory diseases, *TSLP* and *TSLPR* have been considered appropriate targets for biological therapy in treating severe asthma.

In recent years, numerous efforts have been made to develop biological therapies that target

TSLP-TSLPR signaling. Among these approaches, two antibodies have been generated against *TSLPR*. One of these, Rg7258, is a humanized antibody designed to bind to the human *TSLPR*[37]. In vitro studies have demonstrated that Rg7258 can potently block *TSLP*-mediated responses, and in an Ascaris-sensitive cynomolgus monkey model, this antibody was shown to reduce inflammation and bronchoconstriction[37]. However, it is important to note that the study line regarding Rg7258 has since been discontinued.

Another antibody, ASP7266 (also known as UPB-101), is a fully human IgG1 monoclonal antibody that targets *TSLPR*[38]. In vitro studies have shown that ASP7266 can effectively inhibit *TSLP*-induced cell proliferation and CCL17 production, and *TSLP*-stimulated mDC-mediated naive CD4+ T-cell differentiation and IL-5 production by lineage-negative peripheral blood mononuclear cells. In an animal study, ASP7266 could completely suppress Ascaris extract-induced allergic skin reactions in sensitized monkeys[38].

Currently, two phase 1 clinical trials are investigating the safety and efficacy of the ASP7266 antibody (ClinicalTrials.gov identifiers: NCT05653479 and NCT05448651). As these trials progress, monitoring their results and evaluating the potential of these antibodies as therapeutic agents for *TSLP-TSLPR* signaling-related conditions will be essential.

Two anti-*TSLP* antibodies, ecleralimab, and tezepelumab, have advanced to clinical trials. Ecleralimab (CSJ117) is an antibody fragment of the immunoglobulin G1/λ isotype subclass that binds to soluble *TSLP* and prevents *TSLP* receptor activation[39]. It is delivered via inhalation. One phase 1 (ClinicalTrials.gov identifier: NCT03138811) and three phase 2 (ClinicalTrials.gov identifiers: NCT04882124, NCT04410523, and NCT04946318) clinical trials have been completed. In a double-blind, placebo-controlled study, ecleralimab was safe and effective in reducing allergen-induced bronchoconstriction, sputum eosinophilia, and pre-challenge fractional exhaled nitric oxide (FeNO) levels in atopic asthmatics[40].

THE USE OF TEZEPELUMAB FOR TREATING ASTHMA

Tezepelumab (AMG-157 and MEDI9929) is a fully human monoclonal immunoglobulin G2λ that specifically targets and binds to human *TSLP*, thereby preventing interaction with its receptor complex. It is administered via subcutaneous injections[41]. Numerous clinical trials have been conducted to evaluate the safety and efficacy of tezepelumab in the treatment of asthma. As of February 2023, 14 clinical trials have been completed (Tables 1 and 2), and eight more are ongoing. Tezepelumab is the first biological therapy against *TSLP* authorized for treating adult and pediatric patients aged 12 years and older with severe asthma. Its use was approved by the United States Food and Drug Administration (FDA) in December 2021[42] and by the European Medicines Agency (EMA) in September 2022[43].

It is currently too early for real-world studies to evaluate the efficacy of tezepelumab in treating severe asthma. Therefore, the only available conclusions on the efficacy of tezepelumab are from the clinical trials conducted thus far. These trials have demonstrated that tezepelumab has the potential to improve

Table 1. Completed clinical trials studying Tezepelumab in asthma (ClinicalTrials.Gov)

ID - Name	Condition	Phase	Participants	Masking	Primary End-Point	Start Date
NCT01405963	Adults with mild atopic asthma	1	31	Quadruple	Early and late asthmatic responses (FEV_1)	October 31, 2011
NCT01913028	Healthy subjects	1	64	Single	Safety and tolerability	August 2013
NCT02054130 - PATHWAY	Adult uncontrolled severe asthma	2	584	Double	Annualized asthma exacerbation rate	December 13, 2013
NCT02512900	Adolescents with mild to moderate asthma	1	21	Open Label	Pharmacokinetics in adolescents	September 10, 2015
NCT02698501 - UPSTREAM	Adults with asthma	2	40	Quadruple	Decrease in airway hyperresponsiveness to mannitol in response (FEV_1)	August 2016
NCT03347279 - NAVIGATOR	Adults and adolescents with severe uncontrolled asthma	3	1061	Triple	Annualized asthma exacerbation rate	November 23, 2017
NCT03406078 - SOURCE	Adults with OCS-dependent asthma	3	150	Triple	Reduction from baseline in the daily OCS dose	March 5, 2018
NCT03688074 - CASCADE	Adults with inadequately controlled asthma on ICS and at least one additional asthma controller	2	116	Double	Airway submucosal inflammatory cells	November 2, 2018
NCT03706079 - DESTINATION	Adults and adolescents with severe uncontrolled asthma	3	951	Triple	Long-term asthma exacerbation incidence	January 7, 2019
NCT03968978 - PATH-HOME	Adults and adolescents with severe asthma	3	216	Open Label	Successfully administered tezepelumab in the clinic or at home by device type	May 21, 2019
NCT03989544 - PATH-BRIDGE	Healthy subjects	1	315	Open Label	Pharmacokinetics and safety of tezepelumab administration	June 19, 2019
NCT04048343 - NOZOMI	Japanese adults and adolescents with inadequately controlled severe asthma	3	65	Open Label	Adverse events	June 10, 2019
NCT04673630 - TRAILHEAD	Children (5 to 11 years) with mild, moderate, or severe asthma	1	18	Open Label	Pharmacokinetics	February 23, 2021
NCT05062759 - VECTOR	Adolescents and young adults with moderate to severe asthma	3	70	Triple	Humoral immune response to seasonal quadrivalent influenza vaccination	August 23, 2021

FEV_1: forced expiratory volume in one second; OCS: oral corticosteroids.

lung function, reduce asthma exacerbations, and improve the quality of life in patients with asthma, including those with severe asthma who are unresponsive to standard therapies. However, further studies are needed to confirm this biological therapy's long-term effectiveness and safety.

Clinical trials in asthma typically evaluate several outcomes, including improvement in lung

Table 2. Name of the completed clinical trials studying tezepelumab in asthma (ClinicalTrails.Gov)

ID	Name
NCT01405963	Randomized, double-blind, placebo-controlled, parallel design, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 157 in subjects with mild atopic asthma
NCT01913028	A Phase 1, single-center, single-blind, randomized, placebo-controlled parallel-group study to evaluate the safety, tolerability, pharmacokinetics, and immunogenicity of MEDI9929 after administration of single ascending doses in healthy male Japanese subjects
NCT02054130	A Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MEDI9929 in adult subjects with inadequately controlled, severe asthma - PATHWAY
NCT02512900	A Phase 1, open-label study to evaluate the pharmacokinetics of MEDI9929 (AMG 157) in adolescents with mild to moderate asthma
NCT02698501	Effects of anti-*TSLP* on airway hyperresponsiveness and mast cell phenotype in asthma - a randomized, double-blind, placebo-controlled trial of MEDI9929 - UPSTREAM
NCT03347279	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe uncontrolled asthma (NAVIGATOR)
NCT03406078	A multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid-dependent asthma (SOURCE)
NCT03688074	A Phase 2, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the effect of tezepelumab on airway inflammation in adults with inadequately controlled asthma on inhaled corticosteroids and at least one additional asthma controller (CASCADE)
NCT03706079	A multicenter, double-blind, randomized, placebo-controlled, parallel-group, Phase 3, safety extension study to evaluate the safety and tolerability of tezepelumab in adults and adolescents with severe uncontrolled Asthma (DESTINATION)
NCT03968978	A multicenter, randomized, open-label, parallel-group, functionality, and performance study of an accessorized pre-filled syringe and autoinjector with home-administered subcutaneous tezepelumab in adolescent and adult subjects with severe asthma (PATH-HOME)
NCT03989544	An open-label, randomized, parallel-group study to evaluate the pharmacokinetics of tezepelumab administered subcutaneously via accessorized pre-filled syringe (APFS) or autoinjector (AI) compared with vial and syringe in healthy adult subjects (PATH-BRIDGE)
NCT04048343	A 52-week, open-label, multicenter study to evaluate the safety of tezepelumab in Japanese adults and adolescents with inadequately controlled severe asthma (NOZOMI)
NCT04673630	A Phase I, open-label study to evaluate the pharmacokinetics of tezepelumab in children ≥ 5 to 11 years of age with mild, moderate, or severe asthma (TRAILHEAD)
NCT05062759	A multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase 3b study to evaluate the potential effect of tezepelumab on the humoral immune response to seasonal quadrivalent influenza vaccination in adolescent and young adult participants with moderate to severe asthma (VECTOR)

function, reduction in FeNO levels, exacerbation rates, and inflammatory markers such as blood and respiratory airway eosinophil counts, IgE, IL5, IL-13, and others. PROs, such as subjective quality of life improvements, are also assessed. The following summary outlines the observed effects of tezepelumab on these clinical outcomes.

Effect of tezepelumab on exacerbations

Asthma exacerbations are acute events characterized by worsening asthma symptoms, such as coughing, wheezing, chest tightness, and difficulty breathing, which can be life-threatening. In clinical trials of tezepelumab, the

frequency and severity of asthma exacerbations have been assessed as primary outcomes.

In the Efficacy and potential positioning of tezepelumab in the treatment of severe asthma (PATHWAY) phase 2 clinical trial (ClinicalTrials.gov identifier: NCT02054130), treatment with tezepelumab significantly reduced the annualized asthma exacerbation rate (AAER) of 62-72% at week 52[44]. This reduction in AAER was observed regardless of baseline T2 inflammatory status, as determined by blood eosinophil count, FeNO, serum total IgE, IL-5, IL-13, periostin, Thymus and activation regulated chemokine (TARC), and *TSLP* levels[45]. However, the reduction was more pronounced compared to placebo in atopic-treated patients[46]. A *post hoc* analysis of the PATHWAY trial indicated that tezepelumab reduced exacerbations across all seasons[47]. Moreover, tezepelumab-treated patients reduced the rate of asthma exacerbations requiring hospitalizations or emergency department visits over 52 weeks and spent fewer days in the hospital and ICU during the 52-week treatment period than those who received placebo[48].

In the phase 3 clinical trial Study to evaluate tezepelumab in adults and adolescents with severe uncontrolled asthma (NAVIGATOR, ClinicalTrials.gov identifier: NCT03347279), treatment with tezepelumab resulted in a 56% reduction in AAER. This reduction was more significant in patients with high (≥ 300) eosinophils/µL than in patients with low (< 300) eosinophils/µL, with AAER reduced by 70% and 41%, respectively, compared to placebo. Tezepelumab also reduced hospitalizations and emergency department visits and prolonged the time to first exacerbation[49,50]. In severe allergic asthma, tezepelumab also reduced AAER over 52 weeks from 58% to 68% compared to placebo[51].

Long-term treatment evaluation was assessed in the Extension study to evaluate the safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma (DESTINATION clinical trial, ClinicalTrials.gov identifier: NCT03706079), which confirmed that the reduction in asthma exacerbations with tezepelumab was sustained over time[52,53].

Overall, the data suggest that treatment with tezepelumab significantly reduces the frequency and severity of asthma exacerbations, regardless of baseline T2 inflammatory status, and with sustained efficacy over time.

Effect of tezepelumab on oral corticosteroids sparing

Oral corticosteroids (OCSs) have been used for a long time to treat asthma patients for short-term relief after an emergency department visit or for severe acute exacerbations[54]. The Global INitiative for Asthma (GINA) guidelines recommend maintenance OCSs for more severe asthma patients poorly controlled with other treatments[55].

A *post hoc* analysis of pooled patient populations of the NAVIGATOR and PATHWAY clinical trials compared tezepelumab effect on patients with maintenance OCS at baseline with those with moderate asthma treatments, finding a greater improvement in the first group, including a higher reduction on AAER and AAER that required hospitalization or emergency room visits[56].

Nevertheless, the phase 3 clinical trial SOURCE (ClinicalTrials.gov identifier: NCT03406078) evaluated the oral corticosteroid-sparing effect of

tezepelumab in adults with oral corticosteroid-dependent asthma and did not observe statistically significant improvement in the primary objective, i.e., OCS dose reduction. However, it has been stated that methodological issues could have influenced the results. Still, improvements were observed in participants with baseline blood eosinophil counts above 150 cells per µL[57,58]. A new study (NTC05274815) evaluating OCS sparing with tezepelumab is in the course and is expected to be finished in July 2024.

Effect of tezepelumab on lung function

In individuals with asthma, the airways can become inflamed and narrowed, leading to impaired lung function and reduced forced expiratory volume in one second (FEV_1), making breathing difficult. In a phase 1 clinical trial (ClinicalTrials.gov identifier: NCT01405963), administration of tezepelumab was shown to partially attenuate both the early and late asthmatic responses, resulting in a lower decrease in FEV_1 upon allergen challenge compared to placebo. Moreover, tezepelumab treatment significantly inhibited airway hyperresponsiveness in methacholine PC20 compared to the placebo in the pre-allergen challenge on day 84[41].

The PATHWAY clinical trial demonstrated improved lung function with tezepelumab treatment. Notably, irrespective of patients' atopic or perennial allergic status, a significant increase in FEV_1 of 0.12-0.15 L was observed at week 52 in patients treated with tezepelumab compared to placebo-treated patients[44,46].

In the NAVIGATOR clinical trial, patients with severe uncontrolled asthma treated with tezepelumab showed a pre-bronchodilator FEV_1 increase as early as two weeks after initiating treatment. The lung function improvement was sustained throughout the study, with a 0.13 L higher than the placebo increase in FEV_1[49,50]. In this clinical trial, similar findings were observed in patients with severe allergic asthma[51]. Further studies in this clinical trial reported similar findings in patients recruited in Japan[50].

Additionally, the phase 3 safety of tezepelumab in Japanese adults and adolescents with inadequately controlled severe asthma (NOZOMI) clinical trial (ClinicalTrials.gov identifier: NCT04048343) showed a mean increase in FEV_1 of 0.075L after one year of treatment[60].

Effect of tezepelumab on FeNO

Nitric oxide is a gaseous molecule produced by the airway epithelium, and its levels increase in response to airway inflammation, making it a helpful marker for asthma diagnosis and management. FeNO has been evaluated in clinical trials to assess the effects of tezepelumab in patients with asthma. In the phase I clinical trial, treatment with tezepelumab led to a significant reduction in FeNO levels throughout the study and attenuated allergen-induced changes 24 hours after the challenge compared to placebo[41].

In the PATHWAY clinical trial, significant and sustained decreases in FeNO levels were observed in all tezepelumab-treated groups, starting from week four after treatment initiation[44]. Baseline cut-offs for blood eosinophil count and FeNO determined high and low T2 (Type 2) inflammatory status. Subgroup analysis based

on eosinophil counts and FeNO showed that patients with at least 150 eosinophils/µL and a baseline FeNO level above 25ppb demonstrated the most significant reduction in FeNO levels from baseline condition[45].

In the NAVIGATOR clinical trial, treatment with tezepelumab reduced FeNO counts as early as two weeks after the initiation of treatment[49]. The most significant improvements in FeNO reduction were observed in patients with a baseline blood eosinophil count of at least 300 cells per microliter[49,50]. Further studies demonstrated that the FeNO reduction was sustained up to week 104[53] and that this reduction in FeNO was also observed in patients with severe allergic asthma[51].

Overall, the data indicate that treatment with tezepelumab leads to significant and sustained reductions in FeNO levels, particularly in patients with high baseline blood eosinophil counts. The reduction in FeNO is associated with improved lung function, as evidenced by the increased pre-bronchodilator FEV_1 observed.

Effect of tezepelumab on blood eosinophils

Eosinophilic inflammation is a crucial contributor to asthma symptoms and exacerbations. Elevated levels of eosinophils in the blood or airway of individuals with asthma are associated with increased inflammation and airway hyperresponsiveness. Tezepelumab's effect on blood and respiratory airways eosinophil counts has been evaluated in various clinical trials. Results have demonstrated that treatment with tezepelumab leads to a significant reduction in mean baseline blood eosinophil counts, from 296.5 ± 40.2 to 121.9 ± 14.7 per cubic millimeter. Furthermore, the treatment has been shown to reduce sputum eosinophil levels both before and after the allergen challenge, compared to placebo[41].

In the PATHWAY clinical trial, treatment with tezepelumab resulted in substantial and persistent decreases in blood eosinophil counts, beginning from week four after treatment initiation[44]. These findings were independent of the patients' atopic or perennial allergic status[46], and the most significant reduction in eosinophil counts from baseline was observed in patients with at least 150 eosinophils/µL[45].

In the NAVIGATOR clinical trial, a reduction in blood eosinophil counts was already observed two weeks after the first dose, and by week 52, the reduction in blood eosinophil counts compared to placebo was 28%[49]. Moreover, the reduction in eosinophil counts was demonstrated to be sustained up to week 104[53]. Further studies in this clinical trial reported similar findings in patients with severe allergic asthma and patients recruited in Japan[50,51].

Additionally, in NOZOMI clinical trial, a 53% reduction in blood eosinophil counts was observed after 52 weeks of treatment, reaching a mean value of 162 cells/µL[60].

Regarding airway submucosal eosinophils, in phase 2 clinical trial Study to evaluate tezepelumab on airway inflammation in adults with uncontrolled asthma (CASCADE, ClinicalTrials.gov identifier: NCT03688074)[61], treatment with tezepelumab significantly reduced airway submucosal eosinophil counts[62].

Effect of tezepelumab on total IgE and serum markers

In individuals with asthma, elevated levels of IgE may be present, particularly in those with allergic asthma triggered by exposure to allergens like pollen, dust mites, or animal dander. Other inflammatory markers, such as IL-5 and IL-13, are present in type 2 (T2) inflammatory asthma. The initial phase 1 clinical trial of tezepelumab did not demonstrate a significant effect on total IgE levels or other serum markers evaluated[41]. However, subsequent phase 2 clinical trials, namely PATHWAY, showed a progressive reduction in total serum IgE and serum markers such as IL-5, IL-13, periostin, and TARC compared to placebo[44,45]. These reductions were observed regardless of the patient's atopic status and were most significant in those with at least 150 eosinophils/μL[45,46]. Furthermore, *post hoc* analysis demonstrated that tezepelumab reduced IL-5 and IL-13 levels in patients with severe, uncontrolled asthma to levels resembling those observed in age-matched healthy individuals[63].

The phase 3 NAVIGATOR clinical trial further supported the effectiveness of tezepelumab in decreasing serum total IgE levels, with a gradual decrease over 52 weeks[49,50]. Additionally, reductions in serum IL-5, IL-13, and plasma eosinophil-derived neurotoxin were observed with tezepelumab compared to the placebo in the phase 2 CASCADE trial[61,62]. However, this trial showed no significant changes in IgE serum levels.

These findings suggest that tezepelumab may act to normalize levels of proinflammatory mediators in individuals with severe, uncontrolled asthma, including serum markers like IL-5 and IL-13. However, the effect of tezepelumab on IgE serum levels remains controversial.

Effect of tezepelumab on quality of life and asthma control

Asthma symptoms can be challenging to be measured objectively and they vary widely between individuals. PROs can provide important information about a person's asthma experience, including the frequency and severity of symptoms, the impact of asthma on daily activities, quality of life, and the effectiveness of asthma treatments.

In clinical trials evaluating the efficacy of tezepelumab, improvements in PROs related to quality of life (QoL) and asthma control were observed. In a *post hoc* analysis of the PATHWAY study, patients treated with tezepelumab were more likely to be responders in the Asthma Control Questionnaire 6 (ACQ-6), as per a reduction of $\geq$ 0.5 in their score (minimal clinically important difference) than those treated with placebo.

Furthermore, the proportion of responders in the Asthma Quality of Life Questionnaire (standardized) for patients aged 12 years or older (AQLQ(S)+12), as per an increase of $\geq$ 0.5 in their score, was higher in the treatment groups than in the placebo group[64]. Similarly, the NAVIGATOR trial showed that patients with severe uncontrolled asthma treated with tezepelumab reported improved PROs (although without achieving the minimal clinically important difference compared to placebo), as assessed by ACQ-6 and AQLQ(S)+12, with the most significant improvements observed in those with baseline blood eosinophil counts

of at least 300 cells per microliter[49-51]. The CASCADE trial also demonstrated improvements in asthma control for tezepelumab-treated patients, with a higher ACQ-6 mean reduction from baseline to end of treatment of –1.1 (± 0.91) than placebo (–0.66 ± 0.88) and a higher proportion of responder patients[62].

Additionally, in the Japanese phase 3 NOZOMI clinical trial, 71.4% of the patients were classified as responders at the end of the study as they showed ≥ 0.5 decreases in ACQ-6[60].

Overall, the findings suggest that treatment with tezepelumab may improve patient-reported asthma control and quality of life outcomes in individuals with severe, uncontrolled asthma.

Adverse events

In recent years, six meta-analyses have been conducted to evaluate the efficacy and safety of tezepelumab across different clinical trials and to compare its efficacy and safety with other biologics for the treatment of asthma. The results of these meta-analyses suggest that tezepelumab is effective and well-tolerated, with a safety profile similar to placebo[65-70].

CONCLUDING REMARKS

The cytokine *TSLP* triggers various innate and adaptive immune responses, contributing to the inflammation observed in asthma. Therefore, targeting the *TSLP-TSLPR* axis has become a subject of great interest in developing potential therapies for treating severe uncontrolled asthma. Several approaches have been investigated in this direction, anti-*TSLP* tezepelumab being the first biological therapy to block *TSLP* signaling.

The current evidence strongly supports the potential use of tezepelumab as a promising therapeutic option for the treatment of asthma. Various clinical trials have demonstrated its ability to improve several clinical outcomes linked to asthma severity and quality of life in patients with severe, uncontrolled asthma. Ongoing studies are investigating its usage in different patient populations and in combination with existing asthma therapies, which could contribute to a better understanding of tezepelumab's role in treating T2-high inflammatory disorders such as asthma. Notwithstanding, biological therapies targeting *TSLP*, such as tezepelumab, have also shown effectiveness in treating non-T2 asthma, a condition without specific treatments[71,7].

Despite the promising results, more research is needed to fully confirm the safety and effectiveness of tezepelumab, particularly over an extended time and in diverse patient populations. Nevertheless, with its potential to offer a new treatment option for patients with severe, uncontrolled asthma, tezepelumab represents a promising future in asthma management.

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DISCLOSURES

In the last three years, Ignacio Dávila has received payment for lectures, including service on speaker's bureaus from Allergy Therapeutics, Astra-Zeneca, Chiesi, Diater, GSK, Leti, Novartis, and Sanofi; for a consultancy from Allergy Therapeutics, ALK-Abello, Astra-Zeneca, GSK, Merck, MSD, Novartis, Sanofi; and grants for Thermofisher Diagnostics. Miguel Estravís has received payment for lectures, including service on speaker's bureaus from Sanofi. Asunción García-Sánchez has received payment for lectures, including service on speaker's bureaus from Leti.

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