Positioning of Tezepelumab in Severe Asthma

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Abstract

Asthma is one of the most common chronic diseases and is estimated to be severe in 3%-10% of affected patients. There is a need for additional biologic treatments that are highly efficacious across the spectrum of severe uncontrolled asthma. Currently available drugs inhibit 1 or 2 specific cytokines or IgE antibodies and thus only partially suppress the complex type 2 (T2) inflammatory cascade. Biologics targeting more upstream molecules in the pathophysiological pathway of asthma could treat asthma more effectively.

Tezepelumab is a human monoclonal immunoglobulin G2λ antibody that targets the cytokine thymic stromal lymphopoietin (TSLP). It is the first marketed biologic against an epithelial cell–derived cytokine, preventing binding of TSLP to its receptor and reducing the immune stimuli that TSLP can trigger in different asthma endotypes. Tezepelumab reduces downstream biomarkers of inflammation, such as blood and airway eosinophils, FeNO, IgE, IL-5, and IL-13.

Tezepelumab provides a clinical benefit in severe asthma, reducing the annualized asthma exacerbation rate in patients with either high or low levels of biomarkers of T2 inflammation, although the effect is greater among those with high levels. The drug has been shown to improve asthma control, quality of life, and lung function and reduce airway hyperresponsiveness. Therefore, tezepelumab can be used across the spectrum of patients with severe uncontrolled asthma, especially in T2-high patients.

This review includes a positioning statement by the authors, all of whom are members of the SEAIC Asthma Committee.

Key words: Tezepelumab. Severe asthma. Efficacy. Positioning.

Resumen

El asma es una de las enfermedades crónicas más frecuentes, y la prevalencia estimada del asma grave es del 3-10% de la población asmática total. Se necesitan tratamientos biológicos adicionales que tengan una alta eficacia en todo el espectro del asma grave no controlada. Los fármacos disponibles en la actualidad inhiben una o dos citocinas específicas o anticuerpos IgE y, por tanto, sólo suprimen parcialmente la compleja cascada de la inflamación de tipo 2. Los fármacos biológicos dirigidos a moléculas más proximales de la vía fisiopatológica del asma podrían tratar el asma con mayor eficacia.

El tezepelumab es un anticuerpo monoclonal humano, inmunoglobulina G2λ (IgG2λ), dirigido contra la citoquina linfopoyetina estromal tímica (TSLP). Es el primer biológico comercializado contra una citocina derivada del epitelio, que impide la unión de la TSLP a su receptor y reduce los estímulos inmunitarios que la TSLP puede realizar en diferentes endotipos de asma. Tezepelumab reduce los biomarcadores de inflamación, como los eosinófilos sanguíneos y de las vías respiratorias, el FeNO, la IgE, la IL-5 y la IL-13.

Tezepelumab proporciona un beneficio clínico en el asma grave, reduciendo la tasa anualizada de exacerbaciones de asma en pacientes con niveles altos o bajos de biomarcadores de inflamación T2, aunque el efecto fue mayor entre los que tenían niveles altos; también se ha demostrado que mejora el control del asma, la calidad de vida y la función pulmonar, y reduce la hiperreactividad de las vías respiratorias. Por lo tanto, tezepelumab puede utilizarse en todo el espectro de pacientes con asma grave no controlada, especialmente en pacientes con T2 alto. Esta revisión incluye una declaración de posicionamiento de los autores, miembros del Comité de Asma de la SEAIC.

Palabras clave: Tezepelumab. Asma grave. Eficacia. Posicionamiento.

1. Introduction

Asthma is one of the most frequent chronic diseases and is estimated to affect more than 300 million people worldwide [1]. It is a heterogeneous condition, with significant variability in severity, patterns of airway inflammation, and disease control using current medication. Lack of control is more commonly reported in patients with severe asthma.

The term severe asthma is used to describe asthma that (*a*) requires treatment with high-dose inhaled corticosteroids combined with a long-acting β_2-agonist and/or another controller drug taken during the previous year or treatment with systemic corticosteroids for at least half the previous year to prevent it from becoming uncontrolled or (*b*) remains uncontrolled despite this therapy [2]. Severe asthma is estimated to affect 3%-10% of the total population of asthma patients [2,3]. The prevalence in Spain is 3.9% [4].

To reach a diagnosis of severe asthma, it is necessary to rule out common problems such as incorrect inhaler technique, comorbidities, ongoing environmental exposure, and poor adherence [5], and in this sense, the Severe Asthma Working Group of the Spanish Society of Allergology and Clinical Immunology (SEAIC) proposed a diagnostic algorithm for uncontrolled severe persistent asthma [6].

Patients with severe asthma must be properly evaluated to determine the possibility of clinically relevant allergic sensitization. This should include a consistent clinical record, evidence of specific IgE by skin testing and/or measurement of serum levels or specific challenge tests when necessary. When biologic therapy is considered for a patient with severe asthma, it is critical to define the phenotype in order to select the correct drug and identify the most suitable candidate [5]. The phenotypes that can be distinguished based on the inflammatory mechanism involved are allergic T2 asthma, eosinophilic T2 asthma, and non-T2 asthma.

The first biologic agent used in severe asthma was omalizumab, followed by mepolizumab, reslizumab, benralizumab, and, more recently, dupilumab. These biological products have distinct mechanisms of action: omalizumab targets immunoglobulin E (IgE); mepolizumab and reslizumab target interleukin 5 (IL-5); benralizumab binds to the α-chain of the IL-5 receptor (IL5RA) and induces natural killer cells to provoke apoptosis of the receptor-bearing cells; and dupilumab binds to IL-4RA, which is shared by both IL-4 and IL-13, thus inhibiting the signals of both cytokines [7].

These biological drugs have been shown to reduce the number of asthma exacerbations in patients with severe asthma. However, their treatment effects are restricted mainly to eosinophilic and allergic asthma, with limited efficacy in patients with blood eosinophil counts less than 150/μL and variable efficacy in patients with eosinophil counts of 150 to 300/μL. Besides, their use in clinical practice and real-life studies shows that there are a significant number of patients with severe asthma who, despite having the eosinophilic and allergic phenotypes, generate only a partial or even inadequate response.

Consequently, there is a need for additional biological treatments with high efficacy across the spectrum of severe uncontrolled asthma [8]. All these previously mentioned drugs inhibit 1 or 2 specific cytokines or IgE antibodies and thus only partially suppress the complex type 2 inflammatory cascade; therefore, biologics targeting more upstream molecules in the pathophysiological pathway of asthma could prove to be more effective.

The response to monoclonal antibodies should be assessed comprehensively, considering all clinically significant therapeutic goals and not only exacerbations or reduction in oral corticosteroid dose, with symptoms, asthma control, and lung function also playing a relevant role [9,10].

2. Role of Thymic Stromal Lymphopoietin in Severe Asthma and Airway Diseases

Asthma is a heterogeneous and chronic inflammatory disease with numerous processes involving innate and acquired immunity and promoting a feedback loop that increases bronchial mucosa thickness, hypersecretion, and bronchial smooth muscle hyperreactivity. Depending on the immune mediators driving these processes, asthma is characterized by predominantly T2 inflammation (T2-high asthma), where IL-4, IL-5, and IL-13 are the key cytokines involved in the pathological processes, and little or no T2 inflammation (T2-low), which is driven by cytokines such as tumor necrosis factor α, IL-17A, and interferon γ [11-13]. However, in both inflammatory subtypes of asthma, the inflammatory response begins with the interaction between microbes, aeroallergens, diesel exhaust particles, tobacco smoke, and endogenous triggers such as proinflammatory cytokines and the bronchial epithelium [14]. This interaction in some individuals can produce a deterioration of intercellular junctions, such as tight and adherens junctions and hemidesmosomes, which result in epithelial cells producing specific cytokines called alarmins [15]. These include thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, all of which interact with various immune system cells to produce inflammation in the airways.

TSLP is a pleiotropic cytokine first described in 1994 as an IL-7–like cytokine, whose receptor is a heterodimer (TSLP receptor, a common γ-receptor chain, plus IL-7 receptor) [14]. It has 2 isoforms: a short isoform involved in several immunoregulatory mechanisms and a long isoform involved in proinflammatory pathological processes [16]. TSLP is secreted mainly by epithelial cells prior to pathogenic stimuli. Numerous other cells are TSLP producers, including type 2 helper cells (T_H2), eosinophils, mast cells, fibroblasts, macrophages, and group 2 innate lymphoid cells (ILC-2). In addition, many cell types have receptors for TSLP, including hematopoietic progenitor cells, eosinophils, basophils, mast cells, airway smooth muscle cells, ILC-2, lymphocytes, dendritic cells, and monocytes/macrophages. The broad spectrum of interactions between TSLP and the innate and acquired immune systems highlights the ability of TSLP to initiate and maintain the inflammatory response in airway diseases [17].

In the case of allergic asthma, TSLP is released upon the interaction of the allergen with the epithelium. It can subsequently induce OX40-ligand (OX40L) expression in the absence of IL-12 in dendritic cells. OX40L expressed in dendritic cells induced by TSLP results in the differentiation

of T helper naïve cells (T_H0) into T_H2 [18]. T_H2 cells can produce IL-4, IL-5, and IL13, all of which stimulate plasma cell differentiation into IgE-specific antibody-producing B cells that activate mast cells and basophils and activate, attract, and increase the survival of eosinophils. Besides, mast cells have TSLP receptors, which imply a greater amplification of the allergic response and airway remodeling processes. In nonallergic eosinophilic asthma, on the other hand, TSLP binds to its receptor in ILC-2, inducing the production of IL-5, IL-13, and, according to some authors, IL-4, resulting in eosinophilia in lung tissue in addition to significant mucus secretion and bronchial hyperreactivity. Furthermore, TSLP may also have a direct effect on eosinophils, promoting eosinophil viability and decreasing eosinophil apoptosis. Given the production of IL-13 in patients with epithelial disruption, the biomarkers that are elevated in T2-high asthma are fractional exhaled nitric oxide (FeNO) and peripheral and sputum eosinophilia. Thus, the biomarkers that decrease with TSLP blockade are FeNO and eosinophils in sputum and blood [17,19].

Although the mechanisms by which TSLP acts in low T2 asthma are poorly understood, TSLP could direct dendritic cell–mediated differentiation of T_H0 cells to IL-17A–producing T_H17 cells. IL-17A can stimulate the bronchial epithelium, leading to neutrophilia in bronchial tissue through C-X-C motif chemokine ligand 8 and granulocyte-macrophage colony-stimulating factor. In addition, 1L-17A acts directly on the bronchial smooth muscle, thus increasing bronchial hyperreactivity. Furthermore, TSLP can induce the production of collagen by fibroblasts and activate mast cells, promoting airway remodeling [17].

Given its significant role in the pathogenesis of asthma, TSLP has been identified as a potential therapeutic target in severe asthma. Several studies have investigated the use of TSLP-targeted therapies, such as monoclonal antibodies, to block the effects of TSLP. Tezepelumab is a human monoclonal immunoglobulin G2λ antibody that targets TSLP. It is the first marketed biologic against an epithelial cell–derived cytokine, preventing the binding of TSLP to its receptor and reducing the immune stimuli that TSLP can trigger in different endotypes of asthma.

3. Clinical Development of Tezepelumab

The clinical development of tezepelumab involves a growing number of clinical trials investigating several clinical variables.

3.1. Proof of Concept (ClinicalTrials.gov Number NCT01405963)

In this proof-of-concept double-blind, placebo-controlled study, 31 patients with mild allergic asthma were randomly assigned to receive 3 monthly doses of AMG 157 (anti-TSLP) (700 mg) or placebo intravenously over a 12-week treatment period (see Supplementary Table) [20]. The researchers conducted allergen and methacholine challenges on days 42 and 84 to evaluate the effect of anti-TSLP in reducing the maximum percentage decrease in FEV_1. The other variables measured were FeNO, blood and sputum eosinophils, and airway hyperresponsiveness. The primary endpoint was the late asthma response (3-7 hours after the allergen challenge).

The maximum percentage reduction in FEV_1 during the late response with AMG 157 was 34.0% lower in the AMG 157 group than in the placebo group on day 42 (*P*=.09) and 45.9% lower on day 84 (*P*=.02). The authors' main conclusion was that treatment with AMG 157 decreased allergen-induced bronchoconstriction and airway inflammation indices before and after allergen provocation.

3.2. Phase 2 studies

3.2.1. PATHWAY (ClinicalTrials.gov Number NCT02054130)

PATHWAY was a phase 2, randomized, double-blind, placebo-controlled that assessed assessed subcutaneous tezepelumab at 3 dose levels (70 mg/4 wk, 210 mg/4 wk, and 280 mg/2 wk) over a 52-week treatment period [21] (see Supplementary Table). It was the first clinical trial to demonstrate the efficacy of tezepelumab in adults with severe uncontrolled asthma. The primary endpoint was the annualized asthma exacerbation rate (AAER) at week 52.

The study showed that tezepelumab caused a statistically significant reduction in the AAER at week 52 of 0.27 (low dose), 0.20 (medium dose), and 0.23 (high dose), resulting in a relative decrease in exacerbation rates compared with placebo of 62%, 71%, and 66%, respectively. The results were similar regardless of blood eosinophil counts at inclusion. Interestingly, the time to the first asthma exacerbation was longer in the tezepelumab groups than in the placebo group. The risk of an exacerbation was lower in the low-dose group (HR, 0.62), medium-dose group (HR, 0.45), and high-dose group (HR, 0.54) than in the placebo group.

Regarding asthma control, the Asthma Control Questionnaire (ACQ) 6 scores were significantly reduced in the medium-dose regimen (–0.29) and in the high-dose regimen (–0.31). In terms of quality of life, the Standardized Asthma Quality of Life Questionnaire (AQLQ[S]+12) score improved significantly in the high-dose regimen (0.34) compared with placebo. In this clinical trial, the use of systemic corticosteroids was not specifically evaluated.

FEV_1 improved significantly over placebo at all 3 doses used, the increase being 0.12 L with the low dose, 0.11 L with the medium dose, and 0.15 L with the high dose. When stratified by eosinophil count, significant differences in FEV_1 were only achieved in patients with >250/μL (0.16, 0.17, and 0.21 L, respectively).

The PATHWAY study concluded that tezepelumab reduced clinically significant asthma exacerbations by 62%-71% compared with placebo, independent of baseline eosinophil counts.

Moreover, a post hoc analysis of the Phase 2b PATHWAY study showed that tezepelumab reduced the AAER to a higher extent in patients with nasal polyps than in those without nasal polyps (75% vs 73%, respectively) [22].

In another post hoc analysis of the phase 2b PATHWAY study, treatment with tezepelumab reduced exacerbations, improved lung function, and reduced type 2 biomarkers compared with placebo in patients with severe uncontrolled asthma sensitized or not sensitized to perennial aeroallergens [23].

3.2.2. UPSTREAM (ClinicalTrials.gov Number NCT02698501)

The UPSTREAM trial was a phase 2, double-blind, placebo-controlled randomized trial that assessed adult patients with asthma and airway hyperresponsiveness (AHR) to mannitol who received intravenous tezepelumab 700 mg or placebo every 4 weeks for 12 weeks [24] (see Supplementary Table).

The primary endpoint was the change in AHR from baseline to week 12 (change in PD15 to inhaled mannitol from baseline to week 12, supported by the number of patients who reached a negative mannitol test at week 12). Secondary outcomes were changes in airway inflammation. AHR to mannitol and bronchoscopy were assessed at baseline and after 12 weeks.

AHR to mannitol improved, although not significantly, from baseline to week 12 in patients treated with tezepelumab in comparison to the placebo group, with a mean change in PD15 of 1.9 (95%CI, 1.2-2.5) versus 1.0 (95%CI 0.3-1.6) doubling doses. Interestingly, patients with eosinophilic asthma benefited even more, although AHR to mannitol improved both in patients with ≥250/μL and/or sputum eosinophils ≥3% and in those with ≤250 and/or sputum eosinophils ≤3%. A negative mannitol test result was observed to a significantly greater extent in patients treated with tezepelumab than in those who received placebo. However, the sample was small.

The ACQ-6 score decreased nonsignificantly by 1.0 (95%CI −0.6 to −1.4) point in the tezepelumab group compared with 0.5 (95%CI −0.1 to −0.9) points in those who received placebo. Moreover, AQLQ improved in the tezepelumab group and in the placebo group (1.0 and 0.7, respectively).

The UPSTREAM study concluded that 12 weeks of treatment with tezepelumab to block TSLP signaling reduced the number of patients with AHR compared with placebo, although the difference was not statistically significant.

3.2.3. CASCADE (ClinicalTrials.gov Number NCT03688074)

The CASCADE trial was a phase 2, exploratory, double-blind, placebo-controlled, parallel-group randomized trial that evaluated adult patients with moderate-to-severe asthma who received subcutaneous tezepelumab 210 mg or placebo every 4 weeks for 28 weeks (extended to 52 weeks in the case of COVID-19-related disruption) and who underwent bronchoscopy with transbronchial biopsy [25,26] (see Supplementary Table).

The primary endpoint was the change in the number of inflammatory airway submucosal cells in bronchoscopic biopsy samples from baseline to week 28. The study was conducted in 5 countries (27 sites) and included 116 adult patients (aged 18-75 years).

There was a significant reduction in airway submucosal eosinophils from baseline to the end of treatment versus placebo in the active group. Moreover, as an exploratory outcome, the reduction in AHR to mannitol was significantly greater in the tezepelumab group than with placebo.

The ACQ-6 score decreased nonsignificantly by 1.10 points in the tezepelumab group compared with 0.66 points in the placebo group. The AQLQ was not applied in this study.

CASCADE concluded that the improvements brought about by tezepelumab in clinical asthma outcomes in previous studies may be partially explained by reductions in eosinophilic airway inflammation, regardless of baseline blood eosinophil counts. The study showed that tezepelumab significantly reduced eosinophils in the submucosa compared with placebo across blood eosinophil count subclasses despite low mean submucosal eosinophil counts at baseline. The reduction in AHR to mannitol indicates that blocking TSLP could have further benefits beyond decreasing type 2 airway inflammation.

3.3. Phase 3 Studies

3.3.1. Phase 3 Studies: Designs

3.3.1.1. NAVIGATOR (ClinicalTrials.gov Number, NCT03347279)

The NAVIGATOR study was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial that assessed subcutaneous tezepelumab at 210 mg/4 wk or placebo/4 wk over a 52-week treatment period [27]. The primary endpoint was the AAER at week 52 (see Supplementary Table).

A recent exploratory analysis evaluated the efficacy of tezepelumab in patients from the NAVIGATOR study with severe allergic asthma defined in several ways [28]. The definitions included sensitization to common perennial aeroallergens, concomitant sensitization to both perennial and seasonal aeroallergens, and confirmed allergy with reported symptoms, as well as eligibility for omalizumab treatment in the EU and the US.

The primary patient population of interest in this study comprised individuals sensitized to perennial aeroallergens, including house dust mites, cockroaches, cat dander, dog dander, and molds. Patients not sensitized to perennial aeroallergens were considered the reference group. The authors also investigated patients sensitized to seasonal aeroallergens, which included grass pollen, mixed ragweed pollens, and tree pollens.

To assess the efficacy of tezepelumab in patients with severe allergic asthma, the primary endpoint (AAER over 52 weeks) was first evaluated in patients sensitized and not sensitized to perennial aeroallergens [28]. Other endpoints assessed included changes in prebronchodilator FEV_1 and patient-reported outcomes (ACQ-6, AQLQ, Asthma Symptom Diary, and St George's Respiratory Questionnaire) from baseline to week 52. Further analyses were performed in other subgroups according to allergic status: patients sensitized to both perennial and seasonal aeroallergens; patients with confirmed symptomatic sensitization to perennial aeroallergens; and patients who were candidates for omalizumab therapy according to EU or US prescribing information [28]. Confirmed symptomatic sensitization to perennial aeroallergens was defined as a researcher-reported history of allergy to house dust mites or animal allergens (cats and/or dogs) and a positive ImmunoCAP result to the corresponding allergen at baseline.

3.3.1.2. SOURCE (ClinicalTrials.gov Number NCT03406078)

The SOURCE trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled study that evaluated subcutaneous tezepelumab 210 mg or placebo every 4 weeks

over a 48-week treatment period [29]. The primary endpoint was the categorized percentage reduction from baseline in daily oral corticosteroid dose at week 48 without losing control of asthma (see Supplementary Table).

3.3.1.3. DESTINATION (ClinicalTrials.gov Number NCT03706079)

The DESTINATION study was the first long-term extension study of a biological treatment for severe asthma. The study included a placebo arm [30,31]. Patients who completed either the NAVIGATOR or SOURCE studies were eligible, and the aim was to assess the long-term (1 year) tolerability and safety of tezepelumab compared with placebo. Therefore, out of 1061 previously randomized patients in the NAVIGATOR study, 570 entered extended follow-up (DESTINATION study), and out of 150 randomized from the SOURCE study, 109 completed the extended follow-up (DESTINATION study). If required, physicians were allowed to up- or down-titrate participants' medication during this study. Those patients who were randomized to receive tezepelumab 210 mg every 4 weeks (Q4W) in either predecessor study continued to receive this regimen for 1 year; those who were previously randomized to receive placebo were re-randomized (1:1) to receive either tezepelumab 210 mg Q4W or placebo for 1 year. The primary endpoints were exposure-adjusted incidence of adverse events (AEs) and serious adverse events (SAEs). The secondary endpoint was the AAER over 104 weeks. Both primary and secondary endpoints were evaluated from week 0 (predecessor studies) to week 104 (DESTINATION study) (see Supplementary Table).

3.3.2. Phase 3 Studies: Results

3.3.2.1 Exacerbations

The NAVIGATOR study showed a lower AAER in patients taking subcutaneous tezepelumab 210 mg/4 wk (0.93) compared with placebo (2.10) (RR, 0.44; 95%CI, 0.37-0.53; *P*<.001), regardless of blood eosinophil counts at inclusion. Nevertheless, the effect was more marked in patients with ≥300/μL and FeNO ≥25 ppb who were positively sensitized to perennial allergens. Moreover, the time to first exacerbation was longer in the tezepelumab group [32]. The NAVIGATOR study concluded that tezepelumab reduced asthma exacerbations compared with placebo, independent of baseline eosinophil counts, finding greater effects in patients with ≥300/μL, but also in those with <150/μL [32].

In the exploratory study of NAVIGATOR in patients with evidence of severe allergic asthma [28], tezepelumab decreased the AAER compared with placebo by 58% (95%CI, 47%-67%) in patients sensitized to perennial aeroallergens, by 58% (95%CI, 42%-70%) in patients with both perennial and seasonal allergy, by 59% (95%CI, 41%-71%) in patients with perennial allergy only, and by 60% (95%CI, 43%-71%) in patients with confirmed symptomatic perennial allergy. In patients who were candidates for omalizumab in accordance with EU and US labels, tezepelumab reduced the AAER compared with placebo by 68% (95%CI, 55%-77%) and by 60% (95%CI, 44%-71%), respectively. Similar results were observed in nonallergic individuals and in patients who were not eligible for omalizumab.

AAER was the key secondary endpoint in the SOURCE study, and the tezepelumab group had an AAER of 1.38 (95%CI, 0.98-1.95) over 48 weeks compared with 2.00 (1.46-2.74) in the placebo group. The RR was 0.69 (95%CI, 0.44-1.09), ie, a reduction of 31%. According to baseline blood eosinophil count, the RR was 0.43 (0.24-0.76) in patients with ≥150/μL, 0.29 (0.14-0.63) in those with ≥300/μL (corresponding to a reduction of 57% and 71%, respectively), and 1.35 (0.64-2.87) in participants with counts <150/μL [33].

In DESTINATION [31], tezepelumab reduced the AAER over 104 weeks compared with placebo, both in patients initially participating in the NAVIGATOR study (0.42; 95%CI, 0.35-0.51) and in the SOURCE study (0.61; 95%CI, 0.38-0.96). In participants from NAVIGATOR, the AAER was systematically lower in the tezepelumab group than in the placebo group, regardless of baseline inflammatory biomarkers and clinical features over 104 weeks; time-to-first exacerbation of asthma in these patients was longer in the tezepelumab group than in the placebo group (HR, 0.64; 95%CI, 0.54-0.75). Exacerbations generally decreased independently of baseline clinical characteristics and biomarkers. However, there were greater reductions in patients with elevated levels of type 2 inflammatory biomarkers or nasal polyposis.

The DESTINATION study concludes that tezepelumab achieves clinically meaningful reductions in asthma exacerbations in adolescents and adults with severe uncontrolled asthma.

3.3.2.2. Reduction in Oral Corticosteroid Dose

The SOURCE study yielded no significant differences between groups in the percentage reduction in daily oral corticosteroid (OCS) dose. After grouping by baseline eosinophil count, OCS used decreased in patients with >150/μL [33]. The reduction in daily dosage noted in the placebo group in SOURCE was higher than in previous studies of biological drugs in asthma regarding the OCS-sparing effect. Moreover, SOURCE had a considerably longer tapering phase than other studies of the OCS-sparing effect with asthma biologics, thus providing all participants with more time to lower their OCS dosage. In the post hoc analyses of the SOURCE study, the percentage of patients assigned to placebo who had a daily OCS dose of 0 mg was lower when the treatment time was reduced from 48 to 20 weeks. Researchers were not allowed to further decrease the OCS dose in patients who had experienced 1 or 2 exacerbations or did not fulfill the criteria for asthma control. The SUNRISE study [34] is currently underway to try to demonstrate the role of tezepelumab when reducing the use of oral corticosteroids.

3.3.2.3. Lung Function

In NAVIGATOR [32], FEV_1 improved significantly compared with placebo: 0.23 vs 0.09 L; difference, 0.13 L (95%CI, 0.08-0.18; *P*<.001). However, when stratified by eosinophil level, significant differences in FEV_1 were only achieved in patients with >150/μL (0.17 L [0.11-0.23]).

In the study of patients with severe allergic asthma [28], FEV_1 improved by 0.15 L in patients receiving tezepelumab compared with placebo, regardless of allergic status.

In SOURCE [33], the change in FEV_1 was 0.21 L in the tezepelumab group and −0.04 L in the placebo group (least

squares mean difference, 0.26 L [95%CI, 0.13-0.39]). These differences were also significant in patients with more than 150/μL (0.32 L [95%CI, 0.17-0.48]), although they did not achieve statistical significance in patients with less than 150/μL (0.16 [95%CI, −0.06 to 0.38).

FEV_1 also improved with tezepelumab vs placebo in the DESTINATION study [31]: 0.08 L (95%CI, 0.02-0.15) in patients from NAVIGATOR [32] and 0.19 L (95%CI, 0.03-0.35) in those from SOURCE [33].

3.3.2.4. Patient-Reported Outcomes

In NAVIGATOR [32], regarding asthma control, ACQ-6 scores were significantly reduced in the tezepelumab group: –0.33 (95%CI, –0.46 to –0.20). In terms of quality of life, the AQLQ(S)+12 score improved significantly by 0.34 (95%CI, 0.20-0.47) compared with placebo. The Asthma Symptom Diary score improved significantly in the active group (–0.12 [95%CI, –0.19 to –0.04]). These improvements in patient-reported outcomes were observed regardless of the patients' allergic status [28].

In the SOURCE study [33], an improvement was also observed with respect to placebo in the tezepelumab group (ACQ-6, −0.37 [95%CI, −0.71 to −0.02] and AQLQ(S)+12, 0.36 [95%CI, 0.01 to –0.70]). In the DESTINATION study [31], no improvement in ACQ-6 was observed in patients with <150/μL or in the ACQ-6 and St George's Respiratory Questionnaire throughout the treatment period.

3.3.2.5. Effect on Biomarkers

Tezepelumab reduces but does not entirely abolish downstream biomarkers of inflammation, such as blood and airway eosinophils, FeNO, and IgE [21,32,35,36]. It also lowers serum interleukin (IL) 5 and IL-13 in patients with severe, uncontrolled asthma to levels approaching those observed in healthy individuals [37]. In addition, compared with placebo, tezepelumab reduces airway inflammation, as measured by decreases in bronchial submucosal eosinophil counts [26].

Across studies, tezepelumab reduced blood eosinophil counts from baseline compared with placebo, with an effect seen at 2 to 4 weeks and maintained for up to 52 weeks. Results were generally comparable across studies and, in global data, the average reduction in blood eosinophils was 40%-45% in the first 4 weeks and 50%-55% at the end of the studies (48 or 52 weeks) [36].

Tezepelumab reduced FeNO levels from baseline compared with placebo, with an effect seen at 2 to 4 weeks and maintained for up to 52 weeks. Results were comparable across studies, and the average reduction was similar at 4 weeks and at the end of the studies (30%-35%) [36].

Tezepelumab has been shown to reduce total serum IgE levels gradually from baseline to the end of treatment compared with placebo. The average reduction in IgE levels was around 10% in the first 4 weeks and 25%-30% at the end of the studies [36].

Across studies, tezepelumab reduced serum IL-5 levels from baseline compared with placebo, with an effect seen at 2 to 4 weeks and maintained for up to 52 weeks. In global data, the average reduction in IL-5 levels was 45%-50% in the first 4 weeks and 55%-60% at 52 weeks [36].

Tezepelumab reduced serum IL-13 levels from baseline compared with placebo, exerting an effect at 2 to 4 weeks that was maintained for up to 52 weeks. Results were generally comparable across studies, and the average reduction was similar at 4 weeks and at the end of the studies (50%-55%) [36].

3.3.3. PATH-HOME (ClinicalTrials.gov Number NCT03968978)

The PATH-HOME study was a phase 3, open-label, parallel-group, randomized trial that assessed 216 currently nonsmoking patients aged 12 to 80 years with severe uncontrolled asthma who received 6 subcutaneous doses of tezepelumab 210 mg via an accessorized prefilled syringe (APFS) or an autoinjector, with the first dose being administered by a health care professional (HCP). The first, second, and third doses (weeks 0, 4, and 8) and the final dose (week 20) were administered in the clinic [38]. The fourth and fifth doses (weeks 12 and 16) were administered at home (see Supplementary Table).

The primary endpoint was to evaluate the success of administering subcutaneous tezepelumab 210 mg with an APFS or autoinjector in the clinic and at home by HCPs and patients or caregivers.

Clinically meaningful improvements in the ACQ-6 score were observed after 24 weeks in 81.1% and 76.2% of patients in the APFS and autoinjector groups, respectively.

Tezepelumab was successfully administered via an APFS by 91.7% of HCPs, patients, or caregivers. Similarly, tezepelumab was successfully administered by 92.4% via autoinjector. At weeks 12 and 16, at-home administration of tezepelumab was successful in 95.4% of the patients/caregivers in the APFS group. Regarding the autoinjector device, 97.1% of the patients or caregivers used it successfully at home.

The former data indicate that treatment with tezepelumab after at-home self-administration using an APFS or autoinjector is sufficient to achieve the clinical effect found in the PATHWAY study.

3.4. Currently Recruiting/Open Clinical Studies

Studies that are currently recruiting include SUNRISE (ClinicalTrials.gov Identifier: NCT05398263) [34], PASSAGE (ClinicalTrials.gov Identifier: NCT05329194) [39], DIRECTION (ClinicalTrials.gov Identifier: NCT03927157), and WAYFINDER (ClinicalTrials.gov Identifier: NCT05274815) (see supplementary Table).

4. Safety

The primary safety pool included 615 patients receiving tezepelumab 210 mg Q4W for up to 1 year. The incidence of AEs was generally similar between the tezepelumab group and the placebo group. The most common AEs during treatment were pharyngitis (4.1%), injection site reaction (4%), and arthralgia (3.8%). The most common SAEs were respiratory, thoracic, and mediastinal disorders (15 patients [2.3%]) and infections and infestations (13 patients [2.0%]). The most frequent SAEs in both groups were asthma symptoms, reported by 15 patients (2.3%) in the tezepelumab group and 46 patients (6.9%) in the placebo group. Besides the SAEs of asthma, no SAEs were reported in >2 patients in the tezepelumab group [36].

Tezepelumab may inhibit immune responses mediated by T_H2 cells. However, for the AE of severe infections, the number of SAEs was low and similar in both treatment groups (2% for tezepelumab vs 2.2% for placebo) in the primary safety pool. No opportunistic or helminth infections occurred in the main safety group or the SOURCE study. However, a warning is included in the datasheet for parasitic (helminth) infection, as TSLP may be involved in the immune response to some helminth infections [35]. Neither anaphylactic nor severe allergic reactions to tezepelumab appeared in the primary safety pool or the SOURCE study. In the primary safety pool, a slightly higher number of patients reported malignancy in the on-study period in the tezepelumab group than in the placebo group [36].

In the extension study DESTINATION [31], the incidence per exposure of any AE, SAE, or AE leading to discontinuation of treatment during the treatment period was lower in the tezepelumab group than in the placebo group in both main studies. In the primary safety analysis set, the most frequent AEs (occurring in ≥10% of patients) were nasopharyngitis, upper respiratory tract infection, headache, asthma, and bronchitis in the treatment arms of both main studies.

A numerical imbalance in serious cardiac events was demonstrated, with more events in the tezepelumab group than in the placebo group [31]. However, a causal relationship between tezepelumab and these events has not been established, and no patient population at risk of these events has been identified. Of note, the DESTINATION safety study has a placebo arm, unlike other long-term studies of other biologics for severe asthma, which are open-label. The rate of cardiac SAEs in the placebo group was lower than in the real-world population with severe asthma and pooled studies with a placebo dataset comprising severe asthma patients. The incidence rates of cardiac SAEs with tezepelumab were consistent with those estimated based on published data with other biologics evaluated in severe asthma populations [36]. If the patients present a severe cardiac event while receiving tezepelumab, treatment should be discontinued until the acute event has stabilized [35].

5. Tezepelumab in Concomitant T2 Diseases

5.1. Chronic Rhinosinusitis With Nasal Polyps

The prevalence of chronic rhinosinusitis with nasal polyps (CRSwNP) can reach 40% in severe asthma patients. Moreover, affected patients usually experience more severe disease burden, and many of the histological and inflammatory features present in T2 asthma are also present in CRSwNP [40]. With the disruption of the epithelial barrier, TSLP expression is increased in response to allergens and other environmental factors damaging the airway epithelium, thus promoting T2 asthma and, quite possibly, initiating non-T2 inflammation and tissue remodeling in the nose [41]. The number of eosinophils in nasal polyp tissue has been related to TSLP levels [42].

Since tezepelumab prevents the interaction between TSLP and its receptor, it might induce a synergic effect in patients with asthma and CRSwNP, although evidence is still lacking. The year 2021 saw the publication of the results of a post hoc analysis of the phase 2b pivotal PATHWAY study [22], which evaluated the effect of 3 different regimens of tezepelumab (70 mg Q4W, 210 mg Q4W, and 280 mg Q2W) in 550 patients with severe uncontrolled asthma despite medium or high doses of inhaled corticosteroids and with self-reported CRSwNP (n=82) or without self-reported CRSwNP. At baseline, CRSwNP patients had higher blood eosinophil counts and FeNO levels than those without (CRSwoNP). Tezepelumab 210 mg reduced the AAER compared with placebo in both groups to a similar extent (CRSwNP, 75% [95%CI, 15-93], n=23 vs CRSwoNP, 73% [95%CI, 47-86], n=112). However, interestingly, greater reductions in blood eosinophil count and levels of FeNO than in placebo-treated patients were observed, irrespective of NP status. Nevertheless, a major limitation of this post hoc study was the size of the sample of CRSwNP patients, which was smaller than in other, similar studies, probably because NP status was self-reported, whereas diagnosis was confirmed endoscopically in other studies [43]. Furthermore, similar findings were observed in the post hoc analysis of the phase III NAVIGATOR study, supporting the benefits of tezepelumab in a broad population irrespective of NP status. An ongoing multicenter, randomized, double-blind, placebo-controlled, parallel-group study is evaluating the efficacy and safety of tezepelumab in adults with severe CRSwNP. It is intended to recruit approximately 400 participants, and the primary outcome measure is the change from baseline in the total Nasal Polyp Score over a 52-week treatment period [44].

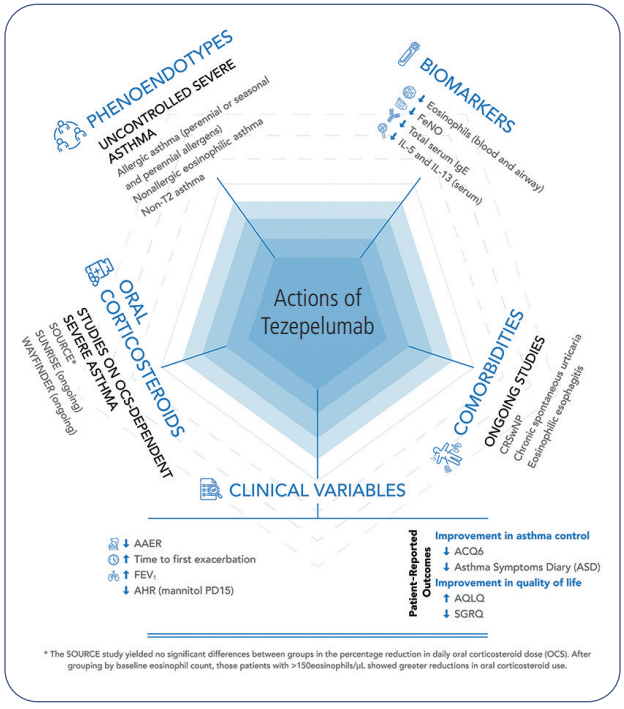

Figure 1. Actions of tezepelumab. AAER indicates annualized asthma exacerbation rate; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; AHR, airway hyperresponsiveness; CRSwNP, chronic rhinosinusitis with nasal polyps; OCS, oral corticosteroids; SGRQ, Saint George's Respiratory Questionnaire.

5.2. Allergic Rhinitis

A recent study reported that the addition of tezepelumab to subcutaneous immunotherapy with cat extract for 1 year improved efficacy and reduced the early allergic nasal response to specific nasal allergen challenge compared with allergen immunotherapy alone in patients with allergic rhinitis [45].

5.3. Allergic Bronchopulmonary Aspergillosis

Theoretically, tezepelumab could be a suitable treatment in patients with allergic bronchopulmonary aspergillosis, since TSLP is implicated in multiple downstream processes, including those related to IL-13, which plays an important role in mucus hypersecretion, and IL-5, which drives airway

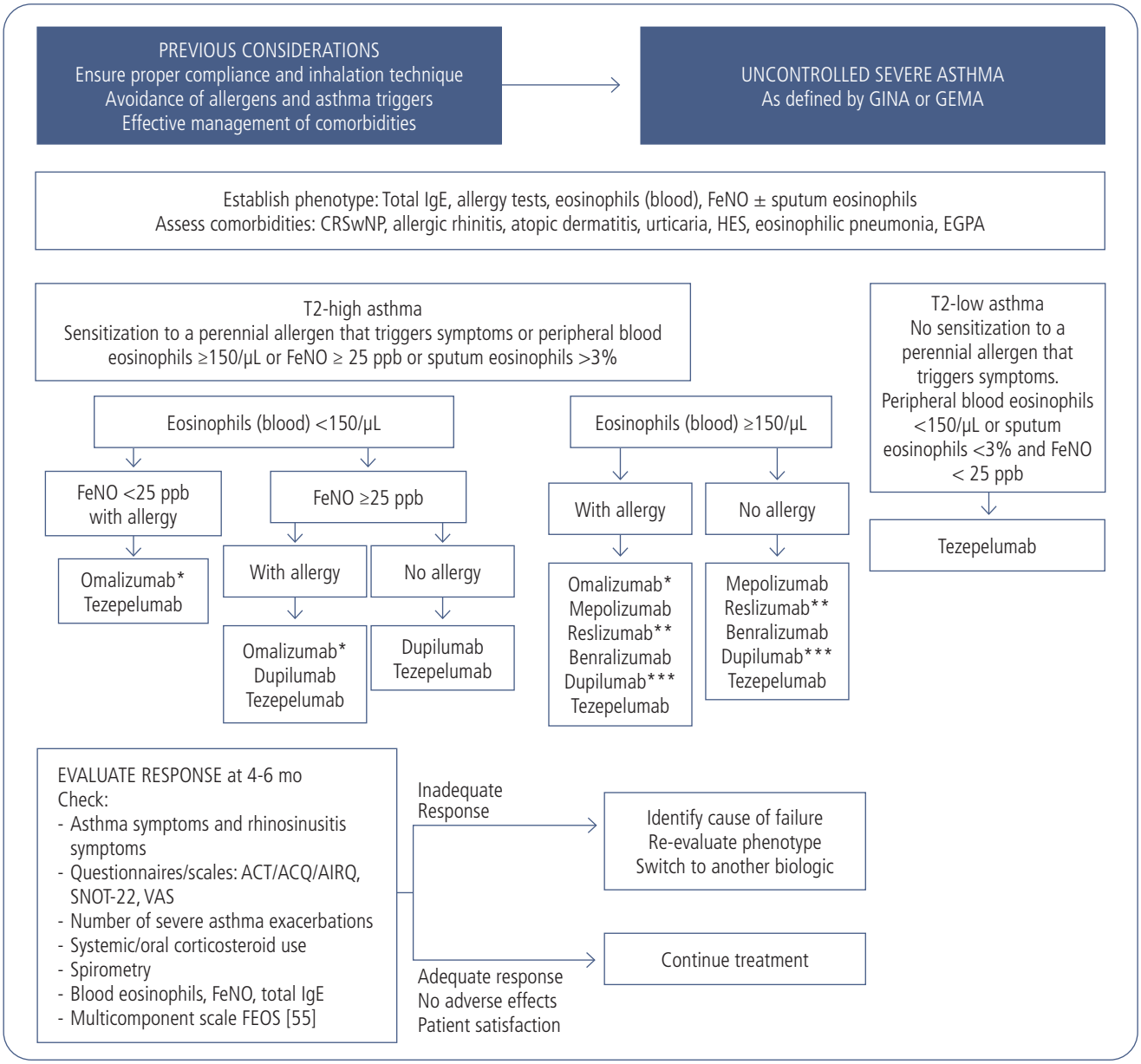

Figure 2. Positioning of tezepelumab in uncontrolled severe asthma. Modified from GEMA 5.3 [53].
EGPA indicates eosinophilic granulomatosis with polyangiitis; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; GEMA, Spanish Asthma Management Guidelines (Guía Española de Manejo del Asma); HES, hypereosinophilic syndrome; IgE, immunoglobulin E, CRSwNP, chronic rhinosinusitis with nasal polyposis; ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AIRQ, Asthma Impairment and Risk Questionnaire; SNOT-22, Sino-nasal Outcome Test; VAS, visual analog scale; FEOS, FEV_1, Exacerbations, Oral corticosteroids, Symptoms.
*Omalizumab: with IgE from 30 to 1500 IU/mL.
**Reslizumab: with blood eosinophils ≥400/µL
***Dupilumab: do not use if eosinophils ≥1500/µL
Comorbidities: Omalizumab is indicated in chronic urticaria and CRSwNP. Mepolizumab is indicated in CRSwNP, EGPA, and HES. Dupilumab is indicated in atopic dermatitis, CRSwNP, and eosinophilic esophagitis.
Mepolizumab, reslizumab, benralizumab, and dupilumab have been shown to reduce the use of oral corticosteroids.

eosinophilia [46,47]. The presence of fungi activates production of TSLP by epithelial cells and, probably, under certain inflammatory conditions, by other cells, including fibroblasts, smooth muscle cells, dendritic cells, and mast cells, ultimately leading to the production of T2 proinflammatory cytokines and initiating a T_H17 response [48]. To our knowledge, only 1 isolated clinical case has been published. Tezepelumab was associated with a corticosteroid-sparing effect in an 82-year-old man who had previously received mepolizumab (diminishing mucus plugs and improved asthma control) [46].

5.4 Other Possible Indications

A phase 2 study has been completed to evaluate tezepelumab in adults with chronic spontaneous urticaria (INCEPTION, NCT04833855), although, at the time of writing, no results have been published [49].

Finally, regarding food allergy, the expression of alarmins, including TSLP, was higher in eosinophilic esophagitis than in normal esophageal tissues [50]. An ongoing randomized, double-blind, placebo-controlled multicenter, phase 3 study is evaluating the efficacy and safety of tezepelumab in adult and adolescent patients with eosinophilic esophagitis (NCT05583227) [51].

6. Positioning of Tezepelumab

Tezepelumab acts by blocking TSLP, an epithelial cytokine, and exerts its effect early in the asthma inflammatory cascade. Therefore, an effect on different phenotypes of asthma patients, in which different biomarker profiles are expressed, is to be expected (Figure 1). Clinical trials have consistently demonstrated efficacy in both T2 and non-T2 asthma patients [52]. This broad range of action of tezepelumab is already reflected in GEMA guideline 5.3 [53].

Tezepelumab has been shown to improve asthma control, quality of life, and lung function and reduce AHR. However, the best results have been obtained in patients with elevated eosinophilia [28], and although tezepelumab has been shown to reduce exacerbations in patients with <150 eosinophils/μL in peripheral blood, no significant improvement in lung function has been observed [32].

In the SOURCE study [33], no significant differences in the reduction in oral corticosteroid dose could be demonstrated, probably owing to methodological problems (in the placebo group, 46% were able to discontinue oral corticosteroids), although the OR was significantly higher in patients with more than 150 eosinophils/μL than in the placebo group. The SUNRISE study is currently underway to clarify this finding [34].

Another possible indication for tezepelumab would be in patients with uncontrolled severe asthma who have elevated biomarkers, such as IgE, eosinophils, and FeNO, and in those whose disease is not adequately controlled with anti-IgE, anti–IL-5, or anti–IL-4/13 drugs and in whom some of these parameters are elevated, in which case tezepelumab could preclude the use of a second biologic.

Given that expression of TSLP is increased in nasal polyps [54], tezepelumab is being evaluated for nasal polyposis in the WAYPOINT study [44].

Figure 2 shows an algorithm for the use of tezepelumab in patients with uncontrolled severe asthma.

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The authors declare that no funding was received for the present study.

Conflicts of Interest

Juan Carlos Miralles López has received consultancy fees from Chiesi and Astra Zeneca and speaker fees from Novartis, GSK, Astra Zeneca, Sanofi, Chiesi, Bial, and Organon.

Darío Antolín-Amérigo has received consulting fees from ALK-Abelló, Astra Zeneca, Chiesi, and Gebro and speaker's fees from Astra Zeneca, Chiesi, Gebro, GSK, Leti Pharma, Mundipharma, Novartis, Roxall, and Sanofi.

Ismael Garcia-Moguel has participated on advisory boards for Novartis, AstraZeneca, GSK, Sanofi Genzyme, and Stallergenes and has received speaker's honoraria from Novartis, AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy Therapeutics, Leti, Stallergenes, ALK-Abelló, Mundipharma, Pfizer, and Orion Pharma.

Javier Dominguez-Ortega has participated on advisory boards and received speaker's honoraria from AstraZeneca, Teva, Novartis, GSK, Sanofi Genzyme, Chiesi, Allergy Therapeutics, Leti Pharma, and ALK-Abelló.

Julio Delgado-Romero has participated on advisory boards for Bial and Sanofi. He has also received speaker's honoraria from AstraZeneca, Bial, Chiesi, GSK, Novartis, Sanofi, and TEVA and grant/research support from AstraZeneca and Orion.

Santiago Quirce has participated on advisory boards for and has received speaker's honoraria from ALK, Allergy Therapeutics, AstraZeneca, Chiesi, GSK, Leti, Mundipharma, Novartis, Sanofi-Regeneron, and Teva.

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