Summary Report of Benefit-Risk Assessment

TEZSPIRE SOLUTION FOR INJECTION 210MG IN PRE-FILLED SYRINGE
TEZSPIRE SOLUTION FOR INJECTION 210 MG IN PRE-FILLED PEN

NEW DRUG APPLICATION

Active Ingredient(s)	Tezepelumab
Product Registrant	AstraZeneca Singapore Pte Ltd
Product Registration Number	SIN16815P, SIN16817P
Application Route	Full evaluation
Date of Approval	4 July 2023

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A INTRODUCTION

Tezspire is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite medium or high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

Tezspire contains tezepelumab. Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP) human monoclonal antibody (IgG2λ) that binds to human TSLP to prevent its interaction with the heterodimeric TSLP receptor. TSLP, an epithelial cell-derived cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, and inducing downstream inflammatory processes and bronchial hyper-responsiveness. In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with inflammation.

Tezspire is presented as solution for injection in pre-filled syringe and pre-filled pen. Other ingredients in the solution are glacial acetic acid, L-proline, Polysorbate 80, sodium hydroxide and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, tezepelumab, is manufactured at Amgen Inc. (Amgen Thousand Oaks), California, USA. The drug product, Tezspire, is manufactured at Amgen Manufacturing Limited, Puerto Rico, USA.

Drug substance:
Adequate controls have been presented for the raw materials, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Process-related and product related impurities are adequately controlled in the manufacturing process.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at -30°C ± 10°C with a shelf life of 48 months. The packaging is a 12 L, single-use, triple layer-film bag with associated lines (tubing and fittings).

Drug product:
The manufacturing process involves drug product formulation, followed by bioburden reduction filtration, sterile filtration and aseptic filling. This is a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B, and impurity limits were adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the approved shelf-life of 36 months when stored at 2 - 8°C. The prefilled syringe consists of a 2.25 mL Type I glass syringe with a staked stainless steel needle covered with an elastomeric needle shield and an elastomeric plunger-stopper laminated with a fluoropolymer film on the product contact surface. The pre-filled pen consists of the prefilled syringe subassembly and a handheld, mechanical (spring-based) injection device.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of tezepelumab in the treatment of asthma was primarily based on data from 1 pivotal study, NAVIGATOR, and 2 supportive studies, PATHWAY and SOURCE.

NAVIGATOR

The pivotal study, NAVIGATOR, was a Phase 3, randomised, double-blind, placebo-controlled study of tezepelumab 210 mg every 4 weeks (Q4W) administered subcutaneously (SC) in adult and adolescent patients with inadequately controlled asthma. Patients were randomised 1:1 to tezepelumab or placebo for 52 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or resulting in hospitalisation in the past 12 months, despite have been on regular treatment with medium or high dose inhaled corticosteroids (ICS) and at least 1 additional asthma controller with or without oral corticosteroids (OCS). Throughout the duration of the study, patients continued on their background asthma therapy.

The primary efficacy endpoint was annualised asthma exacerbation rate measured over 52 weeks. Asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or systemic corticosteroids for at least 3 days or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or systemic corticosteroids and/or hospitalisation. Change from baseline in FEV1 was assessed as a main secondary endpoint. Other secondary endpoints included changes from baseline in Standardised Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12][1],

[1]AQLQ(S)+12 assesses disease-specific health-related quality of life. The questionnaire comprised 4 separate domains: symptoms, activity limitations, emotional function, and environmental stimuli. At each visit, subjects were asked to recall their experiences during the previous 2 weeks and to score each question on a 7-point scale ranging

Asthma Control Questionnaire 6 (ACQ-6)[2], and weekly mean Asthma Symptom Diary (ASD)[3]. A hierarchical testing strategy was implemented to test for superiority of tezepelumab over placebo in each of the primary and key secondary endpoints. The efficacy endpoints investigated and the statistical methods employed were deemed appropriate.

A total of 1,059 patients including 82 adolescents aged 12 to 17 years were randomised to receive either tezepelumab or placebo (528 and 531 patients respectively). The mean age of the population was 49.5 years. Majority of the patients were female (63.5%) and White (62.2%). At baseline, approximately 75% of patients were on high dose inhaled corticosteroids (ICS), 99% were on ICS/long-acting beta agonist (LABA) at baseline, and approximately 9% were on maintenance OCS. Baseline characteristics were generally balanced between the treatment groups, and between adults (18 to <65 years) and adolescents. There were some differences between the adolescent and adult (18 to <65 years) populations, with more adolescents receiving medium dose ICS (57.3% vs 22.2%) and had positive allergic status (90.2% vs 65.8%).

Summary of key efficacy results

	Tezepelumab	**Placebo**
Primary endpoint		
Annualised Asthma Exacerbation Rate		
N	528	531
Rate	0.93	2.10
Rate ratio (95% CI)	0.44 (0.37, 0.53)	
p value	<0.001	
Secondary endpoint		
Mean Change from Baseline in Pre-Bronchodilator FEV1		
N	471	453
LS Mean Change from Baseline (L)	0.23	0.10
LS Mean Difference from Placebo (L) (95% CI)	0.13 (0.08, 0.18)	
p value	<0.001	
AQLQ(S)+12 total score		
N	480	467
LS Mean Change from Baseline	1.48	1.14
Difference from Placebo (95% CI)	0.33 (0.20, 0.47)	
p value	<0.001	
ACQ-6 score		
N	485	472

from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions.

[2]ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and short-acting beta-agonist use via subject-report. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses.

[3]ASD is a twice-daily assessment that captures the severity of asthma symptoms. The ASD comprises a total of 10 questions divided equally between morning and evening assessments, each assessed on a 5-point scale. Each morning and evening, subjects were asked to report the severity of 4 experiences: wheezing, shortness of breath, cough, and chest tightness. The fifth item in the morning diary concerns frequency of night-time awakening, whereas the fifth item in the evening diary concerns activity limitation since waking. Items are scored from "0" (no symptom, no nighttime awakening, or no activity limitation) to "4" (very severe symptom, unable to sleep, or extreme activity limitation). A daily ASD score is the mean of the 10 items.

LS Mean Change from Baseline	-1.53	-1.20
Difference from Placebo (95% CI)	-0.33 (-0.46, -0.20)	
p value	<0.001	
ASD		
n	374	355
LS Mean Change from Baseline	-0.70	-0.59
Difference from Placebo (95% CI)	-0.11 (-0.19, -0.04)	
p value	0.004	

Tezepelumab treatment resulted in a statistically significant reduction in the primary endpoint with respect to the rate of asthma exacerbations over 52 weeks by 56% compared with placebo (rate ratio 0.44 [95% CI 0.37, 0.53]; p<0.001). The reduction in rate of asthma exacerbations were demonstrated regardless of the baseline levels of blood eosinophils (rate ratio 0.59 [95% CI 0.46, 0.75] for blood eosinophils<300 cells/µL; 0.30 [95% CI 0.22, 0.40] for blood eosinophils≥300 cells/µL), fractional exhaled nitric oxide (FeNO) (rate ratio 0.68 [95% CI 0.51, 0.92] for FeNO<25 ppb; 0.32 [95% CI 0.25. 0.42] for FeNO≥25 ppb), as well as allergic status (rate ratio 0.42 [95% CI 0.33, 0.53] for perennial aeroallergen-specific IgE positive; 0.49 [95% CI 0.36, 0.67] for perennial aeroallergen-specific IgE negative). Similarly, reduction in rate of asthma exacerbations were observed in patients receiving either medium or high dose ICS (rate ratio 0.64 [95% CI 0.43, 0.95]; 0.40 [95% CI 0.32, 0.49] respectively).

Patients receiving tezepelumab also demonstrated a statistically significant improvement from baseline in FEV1 compared with placebo at 52 weeks (0.23 L vs 0.10 L, difference 0.13 L [95% CI 0.08, 0.18]; p<0.001). Similarly, significant improvements in patient reported outcomes, AQLQ(S)+12; ACQ-6; ASD, were observed for tezepelumab although the absolute differences were numerically marginal (mean difference of 0.33 [95% CI 0.20, 0.47]; p<0.001; -0.33 [95% CI -0.46, -0.20]; p<0.001; and -0.11 [95% CI -0.19, -0.04]; p=0.004 respectively).

In terms of patient reported outcomes, a greater proportion of patients in the tezepelumab group achieved improvements in AQLQ(S)+12, ACQ-6 and ASD as compared to placebo based on responder analyses (77.5% vs 71.7%; 86.2% vs 76.5%; 58.0% vs 50.1% respectively), further supporting the efficacy of tezepelumab.

Although the small subgroup of adolescent patients was not specifically powered to demonstrate statistical significance, numerical improvements in asthma exacerbation rate (rate ratio 0.70; 95% CI 0.34, 1.46) and FEV1 (LS mean change from placebo 0.17 L; 95% CI -0.01, 0.35) were also observed in patients treated with tezepelumab compared to placebo. While there were more adolescent patients receiving medium dose ICS and had positive allergic status compared to adult patients, reduction in rate of asthma exacerbations were demonstrated in the overall population regardless of background ICS dose and allergic status. Given that the pathophysiology for asthma in adults and adolescents is essentially similar, the results from adults can be extrapolated to supplement the limited efficacy data in adolescents.

PATHWAY

Study PATHWAY was a Phase 2, randomised, double-blind, placebo-controlled dose-ranging study of tezepelumab 70 mg SC Q4W, tezepelumab 210 mg SC Q4W or tezepelumab 280 mg SC Q2W in adult with inadequately controlled asthma. Patients were randomized in a 1:1:1:1 ratio to receive one of 3 dose levels of tezepelumab or placebo for 52 weeks. The inclusion

criteria was similar to study NAVIGATOR. A total of 550 patients received either tezepelumab or placebo.

The primary efficacy endpoint was annualised asthma exacerbation rate measured over 52 weeks. Lung function, assessed as change from baseline in FEV1, was the key secondary endpoint.

The study met its primary efficacy endpoint with statistically significant reduction in asthma exacerbation rate of 62%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups respectively, compared with placebo ($p<0.001$) at Week 52. Improvements in FEV1 was also observed for all 3 tezepelumab dose groups (difference vs placebo of 0.121L, 0.132L and 0.153L respectively; $p<0.05$). Based on the efficacy results, the 210 mg tezepelumab Q4W dose was chosen for the pivotal Phase 3 confirmatory study, NAVIGATOR. This was due to the 210 mg Q4W dose enhanced the reduction in asthma exacerbation rate and improvement in lung function compared to the 70 mg Q4W dose, whereas increasing the dose to 280 mg Q2W did not lead to further reduction in asthma exacerbation rate despite additional improvement in lung function.

SOURCE

Study SOURCE was a Phase 3, randomised, double-blind, placebo-controlled study designed to evaluate the effect of tezepelumab 210 mg Q4W on OCS dose reduction in adult patients with severe, OCS dependent asthma. The study randomised 150 patients who were receiving a stable daily dose of between ≥7.5 mg and ≤30 mg prednisone or prednisolone daily, or daily equivalent. Eligible patients were randomly randomised 1:1 to receive either tezepelumab or placebo for 48 weeks.

The primary efficacy endpoint was the categorised percent reduction from baseline in final daily OCS dose at Week 48 (≥90% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50% reduction, and no change or no decrease in OCS), while maintaining asthma control. The key secondary endpoint was annualised asthma exacerbation rate.

The results of this study did not achieve statistical significance. For the primary endpoint, the odds of reaching a category of greater percent OCS reduction were numerically higher with tezepelumab treatment versus placebo, with a cumulative OR of 1.28 (95% CI 0.69, 2.35; p= 0.434), but was not statistically significant. Despite patients reducing their maintenance dose, numerical improvement in annualised asthma exacerbation rate of 31% was shown with tezepelumab treatment (rate ratio, 0.69, 95% CI, 0.44, 1.09).

Overall, the results of studies NAVIGATOR and PATHWAY supported the efficacy of tezepelumab for treatment in adults and adolescents 12 years and older with severe asthma. Although study SOURCE failed to achieve statistical significance, the results were numerically in favour of tezepelumab.

D ASSESSMENT OF CLINICAL SAFETY

The evaluation of safety data to support the safety profile of tezepelumab was based on the Primary Safety Pool consisting of the pooled data from the studies NAVIGATOR and

PATHWAY for the 210 mg Q4W SC dose group and placebo group. In addition, a long-term extension study, DESTINATION, was also reviewed.

The Primary Safety Pool included 1,336 randomised patients, of whom 1,334 received treatment, 665 in the tezepelumab 210 mg Q4W treatment group and 669 in the placebo group. The mean duration of exposure was similar in both treatment groups: 350 days in the tezepelumab group and 348 days in the placebo group. In study SOURCE, the mean duration of exposure for patients in the tezepelumab group was 319 days.

Study DESTINATION was a multicentre, double-blind, randomised, placebo-controlled Phase 3 extension study that evaluated the long-term safety and tolerability of tezepelumab in adult and adolescent patients with severe asthma over 104 weeks. Patients who completed either predecessor studies NAVIGATOR or SOURCE were eligible to enrol in study DESTINATION. The total treatment period for study DESTINATION was 104 weeks followed by a 12-week safety follow-up period. Re-randomisation into the study resulted in an overall patient distribution of 3:1 (tezepelumab:placebo) (i.e., a subset of patients switched from placebo to tezepelumab). Across studies NAVIGATOR, SOURCE, and DESTINATION studies, 839 patients (1282.9 patient-years) were exposed to tezepelumab and 607 patients (799.0 patient-years) were exposed to placebo.

Overview of safety profile (Primary Safety Pool)

Number (%) of patients with	Tezepelumab (N=665)	Placebo (N=669)
Any AE	496 (74.6)	512 (76.5)
SAE	57 (8.6)	87 (13.0)
Discontinuations due to AE	13 (2.0)	20 (3.0)
Deaths due to AE	0 (0)	0 (0)

AE: Adverse Event; SAE: Serious Adverse Event

The majority (1,008 out of 1,334) of patients in the Primary Safety Pool experienced one or more AEs during the on-treatment period. The overall incidence of AEs was similar between the tezepelumab and placebo groups (74.6% versus 76.5% of patients, respectively). Most AEs for patients treated with tezepelumab were mild or moderate in intensity and were not considered related to the Investigational Product by the Investigators. The 4 most common AEs reported in the tezepelumab group were nasopharyngitis, upper respiratory tract infection, headache and asthma, reported by 19.5%, 9.3%, 7.8%, and 7.4% of patients respectively, compared with 19.1%, 13.3%, 7.5%, and 15.7% patients in the placebo group.

The overall incidence of patients experiencing SAEs during the on-treatment period was 8.6% in the tezepelumab group and 13.0% in the placebo group. The most common SAE in both treatment groups was asthma (2.3% vs 6.9%). Apart from asthma, the incidences of other SAEs were generally low (<0.3%) and balanced between treatment groups. The incidence of serious infections was similar between tezepelumab and placebo (2.0% vs 2.2%) and there were no events of opportunistic infections or helminth infection reported with tezepelumab treatment. The incidence of serious hypersensitivity reaction was also comparable between tezepelumab and placebo (0.2% vs 0.3%). There were 2.0% of patients in the tezepelumab group and 3.0% of patients in the placebo group who had AEs leading to discontinuation. In the small subgroup of adolescent patients (82 patients in study NAVIGATOR), the safety profile of tezepelumab was similar to that observed in adults.

In study SOURCE, the incidences of patients with AEs were 71.6% in the tezepelumab group and 85.5% in the placebo group, while 14.9% in the tezepelumab group and 21.1% in the placebo group reported an SAE. Overall, the safety profile observed in the study was similar to that seen in the Primary Safety Pool.

In the long-term extension study, DESTINATION, the safety profile of tezepelumab appeared similar to that observed in the Primary Safety Pool. However, there were numerically more cardiac-related SAEs in the tezepelumab versus placebo patients (exposure-adjusted incidence rates [95% CI] on-study 1.30 [0.77, 2.06] per 100 patient-years versus 0.23 [0.03, 0.83] per 100 patient-years, respectively). The SAEs included acute myocardial infarction, congestive cardiac failure, coronary artery disease, atrial flutter, cardiac arrest, coronary artery occlusion, myocardial infarction, prinzmetal angina, supraventricular tachycardia, ventricular extrasystoles, atrial tachycardia and myocarditis (incidence rate 0.07 – 0.22 per 100 patient-years) with no pattern in specific events. Additionally, there was no pattern in the time to onset for the events with respect to duration of tezepelumab treatment, hence no causal relationship to tezepelumab treatment as deemed by both Investigators and a blinded Independent Adjudication Committee (IAC) and a plausible mechanism by which blocking TSLP would lead to cardiac pathophysiology has not been identified. It was also noted that all patients reporting cardiac-related SAEs had existing cardiovascular disorders and/or other cardiovascular risk factors There was also a small numerical imbalance in deaths (incidence rate on study 0.80 [95% CI 0.40, 1.43] per 100 patient-years with tezepelumab and 0.58 [95% CI 0.19, 1.34] per 100 patient-years with placebo). Similarly, the review of deaths showed no apparent pattern in cause and all events were assessed by the blinded IAC as unlikely to be causally related to tezepelumab treatment.

While the causal relationship between the use of tezepelumab and the numerical imbalances in cardiac-related SAEs and deaths observed study DESTINATION has not been established, the package insert contains precautionary information to highlight that patients should be advised of the signs and symptoms suggestive of a cardiac event to seek medical attention. The company will be required to conduct a post-authorisation safety study to further characterise the safety concern in the post-marketing setting and submit the study results as a condition attached to the registration of this product.

Overall, the safety profile of tezepelumab is acceptable for the target patient population with severe asthma, and appropriate warnings and precautions on cardiac safety, infections and hypersensitivity reactions are described in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Current treatment strategies for controlling asthma are primarily aimed at reducing airway inflammation, with inhaled corticosteroids being the mainstay of treatment for patients with persistent asthma. Many asthmatic patients remain symptomatic despite treatment with inhaled corticosteroids and long-acting beta agonist combinations. Treatment options include the addition of other controller therapies such as long-acting muscarinic antagonist, leukotriene receptor antagonist, theophylline, oral corticosteroids and biologics. Some patients may not respond adequately to currently available therapies. Therefore, there remains an unmet need in severe asthma for therapies that are effective in a broad patient population, including those with phenotypes that are difficult to treat or do not respond to available treatments.

In study NAVIGATOR, tezepelumab treatment resulted in a statistically significant 56% reduction in annualized asthma exacerbations rate over 52 weeks compared with placebo (rate ratio 0.44 [95% CI 0.37, 0.53]; p<0.001). Tezepelumab treatment also demonstrated improvements from baseline in key secondary outcomes of lung function (FEV1), health-related quality of life (AQLQ(S)+12), asthma control ACQ-6), and asthma symptoms (ASD) that were each statistically significant versus placebo. Similar efficacy results were also observed for tezepelumab treatment in the Phase 2, dose-ranging study, PATHWAY. While study SOURCE failed to achieve statistical significance, more patients receiving tezepelumab attained a reduction from baseline in maintenance OCS dose without losing asthma control and consistent with studies NAVIGATOR and PATHWAY, numerical improvement in annualised asthma exacerbation rate were demonstrated for tezepelumab. In Study NAVIGATOR, only a small subgroup of 82 adolescent patients aged 12 to 17 years were included. Numerical reduction in the rate of asthma exacerbation (rate ratio 0.70; 95% CI 0.34, 1.46) along with improvement in lung function compared to placebo were demonstrated in this subgroup. While the data in adolescent was limited, the efficacy in this population can be further supported by extrapolation of results from adults as the pathophysiology for asthma in adults and adolescents are essentially similar.

Tezepelumab was well tolerated in patients with severe asthma. The overall incidence of AEs was similar between the tezepelumab and placebo groups in the Primary Safety Pool. Most AEs were mild or moderate in intensity and not considered to be related to investigational product by the Investigator. The overall incidence of SAEs was lower in the tezepelumab group compared with the placebo group, while the incidence of AEs resulting in treatment discontinuation was low and similar between the tezepelumab and the placebo groups. The most common SAE was asthma, which was reported at a higher frequency in placebo patients than tezepelumab patients, which was not unexpected given the efficacy observed with tezepelumab. Adolescents treated with tezepelumab in NAVIGATOR showed a similar safety profile to what is seen in the adult population.

In the long-term extension study DESTINATION, numerical imbalances in cardiac-related SAEs with more events occurring in the tezepelumab group compared with placebo were observed. While the occurrence of the events was not deemed causally related to tezepelumab by the investigators and a blinded Independent Adjudication Committee, the long-term safety of tezepelumab remained uncertain. Accordingly, the company will conduct a post-authorisation safety study to further characterise the safety concern in the post-marketing setting.

Overall, the benefit-risk profile of tezepelumab was considered favourable as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite medium or high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

F CONCLUSION

Based on the review of the quality, safety and efficacy data, the benefits of tezepelumab outweighed the risks in the treatment of adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite medium or high dose inhaled corticosteroids plus another medicinal product for maintenance treatment. Approval of the product registration was granted on 4 July 2023. The approval of this application is subject to the submission of the final study report of the post-authorisation safety study.

APPROVED PACKAGE INSERT AT REGISTRATION

TEZSPIRE ™
(Tezepelumab)

1. NAME OF THE MEDICINAL PRODUCT

TEZSPIRE 210 mg solution for injection in pre-filled syringe.
TEZSPIRE 210 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled syringe

Each single-use pre-filled syringe contains 210 mg tezepelumab in 1.91 mL (110 mg/mL).
Each single-use pre-filled pen contains 210 mg tezepelumab in 1.91 mL (110 mg/mL).

Tezepelumab is a human immunoglobulin G2λ (IgG2λ) monoclonal antibody directed against thymic stromal lymphopoietin (TSLP), produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Tezepelumab has a molecular weight of approximately 147 kDa.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection).
Solution for injection in pre-filled pen (injection).

The solution is a clear to opalescent, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TEZSPIRE is indicated as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite medium or high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

4.2 Posology and method of administration

Posology

Adults and adolescents (aged 12 years and older)

The recommended dose is 210 mg of TEZSPIRE by subcutaneous injection every 4 weeks. Available data for TEZSPIRE in adolescents aged 12 to 17 years are described in section 5.1.

Missed dose

If a dose is missed, administer the dose as soon as possible. Thereafter, the patient can resume dosing on the usual day of administration. If the next dose is already due, then administer as planned.

Special populations

Paediatric population

The safety and efficacy of TEZSPIRE in children under 12 years of age have not been established.

Elderly population (≥65 years old)

No dose adjustment is required for elderly patients age 65 or older (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required for patients with renal or hepatic impairment (see section 5.2).

Method of administration

TEZSPIRE is administered as a subcutaneous (SC) injection.

A patient may self-inject TEZSPIRE or the patient's caregiver may administer TEZSPIRE after training in SC injection technique. Provide proper training to patients and/or caregivers on the preparation and administration of TEZSPIRE prior to use according to the "Instructions for Use".

TEZSPIRE should be injected into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. If a healthcare professional or caregiver administers the injection, the upper arm can also be used. A patient should not self-inject in the arm. TEZSPIRE should not be injected into areas where the skin is tender, bruised, erythematous, or hardened. It is recommended to rotate the injection site with each injection. See section 6.6.

4.3 Contraindications

TEZSPIRE is contraindicated in patients who have known hypersensitivity to tezepelumab or any of its excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

General

TEZSPIRE should not be used to treat acute asthma exacerbations.

Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

Abrupt discontinuation of corticosteroids after initiation of TEZSPIRE therapy is not recommended. Reduction in corticosteroid doses, if appropriate, should be gradual and performed under the supervision of a physician.

Hypersensitivity reactions

Hypersensitivity reactions (e.g. anaphylaxis, rash) may occur following administration of TEZSPIRE (see section 4.8). These reactions may occur within hours of administration, but in some instances have a delayed onset (i.e. days).

In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated should be initiated.

Parasitic (Helminth) Infection

TSLP may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if TEZSPIRE may influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with TEZSPIRE. If patients become infected while receiving treatment with TEZSPIRE and do not respond to anti-helminth treatment, discontinue treatment with TEZSPIRE until infection resolves.

Serious cardiac events

In a long-term clinical study, a numerical imbalance in serious cardiac adverse events was observed in patients treated with tezepelumab compared to placebo. No causal relationship between tezepelumab and these events has been established, nor has a patient population at risk of these events been identified.

Patients should be advised of signs or symptoms suggestive of a cardiac event (for example, chest pain, dyspnoea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur. If patients develop a serious cardiac event while receiving tezepelumab treatment, therapy with tezepelumab should be discontinued until the acute event stabilises.

There is currently no data on re-treatment of patients who develop a serious cardiac event or serious infection.

Serious infections

Blocking thymic stromal lymphopoietin (TSLP) may theoretically increase the risk of serious infections. In placebo-controlled studies, no increase in serious infections was observed with tezepelumab.

Patients with pre-existing serious infections should be treated before initiating therapy with tezepelumab. If patients develop a serious infection while receiving tezepelumab treatment, therapy with tezepelumab should be discontinued until the serious infection resolves.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed. See section 5.2.

The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.

4.6 Pregnancy and lactation

Pregnancy

The data on pregnancy exposure from the clinical studies are insufficient to inform on drug-associated risk.

In a prenatal and postnatal development study conducted in cynomolgus monkeys, following intravenous (IV) administration of tezepelumab up to 300 mg/kg/week from early gestation through delivery, no adverse effects on maternal health, pregnancy outcome, embryo-foetal development, or neonatal development were observed (see section 5.3).

Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier; therefore, TEZSPIRE may be transmitted from the mother to the developing foetus.

It is recommended not to use TEZSPIRE during pregnancy unless the expected benefit to the pregnant mother is greater than any possible risk to the foetus.

Breast-feeding

It is unknown whether tezepelumab is excreted in human milk. However, IgG antibodies are known to be present in human milk. Risk to the breast-fed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from using TEZSPIRE, taking into account the benefit and risk of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of tezepelumab treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

TEZSPIRE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Overall summary of the safety profile

In clinical studies in patients with severe asthma, the most commonly reported adverse reaction during treatment were arthralgia and pharyngitis.

Adverse Drug Reactions

A total of 739 patients with uncontrolled, severe asthma received at least one dose of TEZSPIRE in 3 randomised, placebo-controlled, multicentre trials of 48 to 52 weeks duration (Trial 1 [PATHWAY], Trial 2 [NAVIGATOR], and Trial 3 [SOURCE]). The pooled safety population (Trial 1 and Trial 2) consists of 665 adults and adolescents who received at least one dose of TEZSPIRE during the two placebo-controlled clinical studies of 52 weeks duration (Table 1). The adverse reactions with tezepelumab seen in Trial 3 were similar to the pooled safety population of Trial 1 and Trial 2.

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data).

Table 1 Adverse drug reactions

MedDRA SOC	MedDRA Term	Tezepelumab Frequency
Infections & infestations	Pharyngitis*	Common
Skin and subcutaneous tissue disorders	Rash†	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Common
General disorders and administration site conditions	Injection site reaction	Common

* Pharyngitis was defined by the following grouped preferred terms: pharyngitis, pharyngitis bacterial, pharyngitis streptococcal and viral pharyngitis

† Rash was defined by the following grouped preferred terms: rash, rash pruritic, rash erythematous, rash maculo-papular, rash macular

Description of selected adverse reaction

Injection site reactions

In the pooled safety population, injection site reactions (e.g. injection site erythema, injection site swelling, injection site pain) occurred at a rate of 3.8% in patients treated with tezepelumab 210 mg SC every 4 weeks (Q4W) compared with 3.1% in patients treated with placebo.

4.9 Overdose

In clinical trials, doses of up to 280 mg SC every 2 weeks (Q2W) and doses of up to 700 mg IV Q4W were administered to patients with asthma without evidence of dose-related toxicities.

There is no specific treatment for an overdose with tezepelumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Tezepelumab is an anti-TSLP, human monoclonal antibody (IgG2λ) that binds to human TSLP with high affinity and prevents its interaction with the heterodimeric TSLP receptor. TSLP, an epithelial cell-derived cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. TSLP regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, and inducing downstream inflammatory processes and bronchial hyper-responsiveness. TSLP has also been shown to have indirect effects on airway structural cells (e.g. fibroblasts and airway smooth muscle). In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with inflammation (e.g. blood eosinophils, IgE, FeNO, IL-5, and IL-13).

Pharmacodynamics

In a Phase 1 allergen inhalation challenge study of patients with mild allergic asthma, administration of tezepelumab 700 mg IV Q4W for a total of 3 doses (n=16) suppressed the inhaled allergen-induced increase in blood and sputum eosinophils and FeNO relative to placebo (n=15) and reduced both the late and early asthmatic response following allergen challenge.

In Trial 2 (NAVIGATOR), administration of tezepelumab 210 mg SC Q4W (n=528) reduced inflammatory biomarkers and cytokines from baseline compared with placebo (n=531) with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5 concentration, and serum IL-13 concentration. Tezepelumab caused a progressive reduction in serum total IgE concentration, with levels continuing to decrease throughout 52 weeks of treatment. Similar effects were seen in Trial 1 (PATHWAY).

A 28-week Phase 2 randomised, double-blind, placebo-controlled, parallel-group mechanistic study evaluated the effect of tezepelumab 210 mg SC Q4W on airway inflammation in adults (n=116) with inadequately controlled moderate to severe asthma. Tezepelumab reduced submucosal eosinophil counts by 89% (end of treatment to baseline ratio 0.11 [90% CI 0.06, 0.21]) compared with a 25% reduction with placebo (0.75 [90% CI 0.41, 1.38]). Reduction was consistent regardless of baseline subgroup levels of blood eosinophils, FeNO, serum IL-5, serum IL-13 and allergic status (determined by a perennial aeroallergen specific IgE).

Immunogenicity

In Trial 2, anti-drug antibodies (ADA) were detected at any time in 26 (4.9%) out of 527 patients who received tezepelumab at the recommended dosing regimen during the 52-week study period. Of these 26 patients, 10 patients (1.9% of patients treated with tezepelumab) developed treatment-emergent antibodies and 1 patient (0.2% of patients treated with tezepelumab) developed neutralising antibodies. ADA titres were generally low and often transient. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.

Clinical efficacy in asthma

The efficacy of TEZSPIRE was evaluated in three randomised, double-blind, parallel group, placebo-controlled clinical trials (Trial 1 [PATHWAY] , Trial 2 [NAVIGATOR] and Trial 3 [SOURCE]) of 48 to 52 weeks in duration in patients aged 12 years and older. In all three trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or other inflammatory biomarkers (e.g. FeNO or IgE).

Trial 1 was an exacerbation trial 52-weeks in duration that randomised a total of 550 patients (18 years of age and older) with severe, uncontrolled asthma to receive treatment with tezepelumab 70 mg SC Q4W, tezepelumab 210 mg SC Q4W, tezepelumab 280 mg SC Q2W or placebo. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or 1 asthma exacerbation resulting in hospitalisation in the past 12 months.

Trial 2 was an exacerbation trial 52-weeks in duration that randomised a total of 1061 patients (adults and adolescents 12 years of age and older) with severe, uncontrolled asthma to receive treatment with tezepelumab 210 mg SC Q4W or placebo. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or systemic corticosteroid treatment or resulting in hospitalisation in the past 12 months.

In both Trial 1 and Trial 2, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening, and reduced lung function at baseline (pre-bronchodilator FEV_1 below 80% predicted in adults, and below 90% predicted in adolescents). Patients were required to have been on regular treatment with medium- or high-dose inhaled corticosteroids (ICS) and at least one additional asthma controller with or without oral corticosteroids (OCS). Patients continued background asthma therapy throughout the duration of the trials.

Trial 3 was an OCS reduction trial 48-weeks in duration that randomised a total of 150 asthma patients (18 years of age and older) who required treatment with daily OCS (7.5 mg to 30 mg per day) in addition to regular use of high-dose ICS and long-acting beta-agonist (LABA) with or without additional controller(s). Patients were required to have a history of at least 1 exacerbation in the past 12 months. After an up to 8-week OCS optimisation phase, patients

received either tezepelumab 210 mg SC Q4W or placebo for a total of 48 weeks. Patients continued to receive their baseline background asthma medications during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4 to 40), as long as asthma control was maintained. This was followed by an 8-week maintenance phase during which patients were to remain on the OCS dose achieved by Week 40. Median OCS dose at the end of the optimisation phase (baseline) was 10 mg for the two treatment groups.

Table 2 Demographics and Baseline Characteristics of Asthma Trials

	Trial 1 N=550	**Trial 2 N=1059**	**Trial 3 N=150**
Mean age (year) (SD)	52 (12)	50 (16)	53 (12)
Female (%)	66	64	63
White (%)	92	62	84
Black or African American (%)	3	6	1
Asian (%)	3	28	15
Hispanic or Latino (%)	1	15	16
Never smoked (%)	81	80	74
High-dose ICS use (%)	49	75	99
OCS use (%)	9	9	100
Mean number of exacerbations in previous year (SD)	2.4 (1.2)	2.8 (1.4)	2.0 (1.5)
Mean duration of asthma (years) (SD)	17 (12)	22 (16)	23 (15)
Mean baseline % predicted FEV_1 (SD)	60 (13)	63 (18)	54 (18)
Mean post-bronchodilator FEV_1 reversibility (%) (SD)	23 (20)	15 (15)	15 (15)
Mean baseline blood EOS count (cells/µL) (SD)	371 (353)	340 (403)	242 (180)
Positive allergic status (%)*	46	64	39
Mean FeNO (ppb) (SD)	35 (39)	44 (41)	41 (39)
Mean ACQ-6 (SD)	2.7 (0.8)	2.8 (0.8)	2.5 (1.1)

* Positive allergic status as defined by a positive serum IgE result specific to any perennial aeroallergen in the FEIA panel.

ACQ-6, Asthma Control Questionnaire 6; EOS, Eosinophils; FEIA, Fluorescent enzyme immunoassay; FeNO, Fractional exhaled nitric oxide; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; OCS, Oral corticosteroid; ppb, Parts per billion; SD, Standard deviation.

The results summarised below are for the recommended tezepelumab 210 mg SC Q4W dosing regimen.

Exacerbations

The primary endpoint for Trial 1 and Trial 2 was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or systemic corticosteroids for at least 3 days or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or systemic corticosteroids and/or hospitalisation.

In both Trial 1 and Trial 2, patients receiving TEZSPIRE had significant reductions in the annualised rate of asthma exacerbations compared with placebo (Table 3). There were also fewer exacerbations requiring emergency room visits and/or hospitalisation in patients treated with TEZSPIRE compared with placebo. Additionally, a greater proportion of patients receiving TEZSPIRE did not experience an asthma exacerbation during the 52-week treatment compared with placebo.

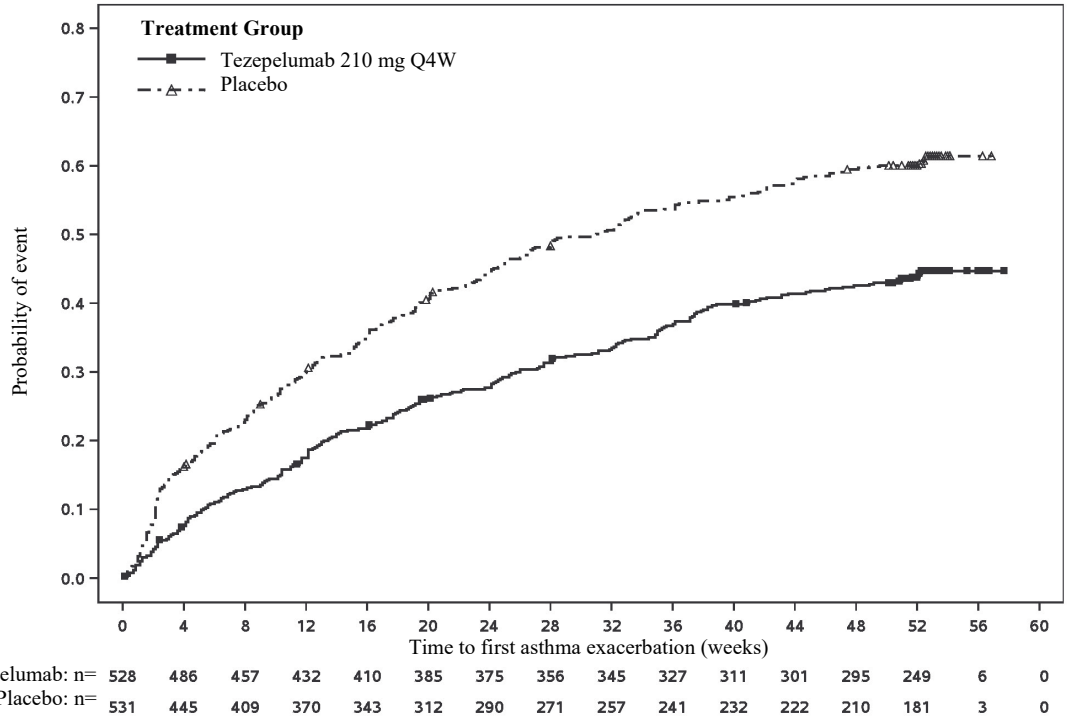
Table 3 Rate of Clinically Significant Exacerbations Over 52 Weeks, Trial 1 and Trial 2

	Trial 1		**Trial 2**	
	TEZSPIRE N=137	**Placebo N=138**	**TEZSPIRE N=528**	**Placebo N=531**
Annualised Asthma Exacerbation Rate				
Rate	0.20	0.72	0.93	2.10
Rate ratio (95% CI)	0.29 (0.16, 0.51)		0.44 (0.37, 0.53)	
p-value	<0.001		<0.001	
Exacerbations requiring hospitalisation/emergency room visit				
Rate	0.03	0.18	0.06	0.28
Rate ratio (95% CI)	0.15 (0.04, 0.58)		0.21 (0.12, 0.37)	
p-value	0.005*		<0.001*	
Exacerbations requiring hospitalisation				
Rate	0.02	0.14	0.03	0.19
Rate ratio (95% CI)	0.14 (0.03, 0.71)		0.15 (0.07, 0.33)	
p-value	0.017*		<0.001*	

* Nominal p-value

The time to first exacerbation was longer for the patients receiving TEZSPIRE compared with placebo Trial 2 (Figure 1). Similar results were seen in Trial 1.

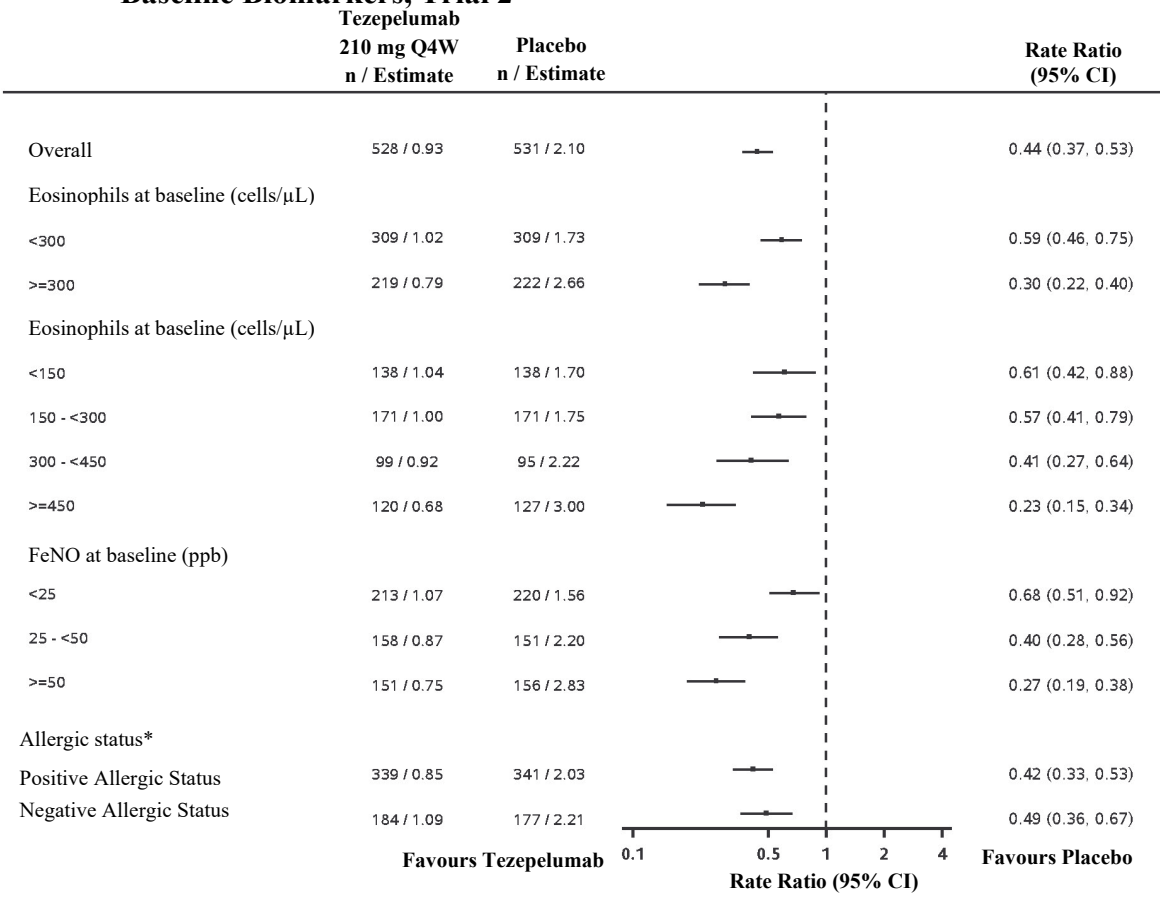
Figure 1 Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation Through Week 52, Trial 2



Subgroup Analysis

In Trial 2, TEZSPIRE demonstrated a reduction in the rate of asthma exacerbations regardless of the baseline levels of blood eosinophils, FeNO, as well as allergic status (determined by a perennial aeroallergen specific IgE) (Figure 2). Similar results were seen in Trial 1.

Figure 2 Annualised Asthma Exacerbation Rate Ratio Over 52 Weeks Across Different Baseline Biomarkers, Trial 2



*Allergic status as defined by a serum IgE result specific to any perennial aeroallergen in the FEIA panel

Lung Function

Change from baseline in FEV_1 was assessed as a secondary endpoint in Trial 1 and Trial 2. Compared with placebo, TEZSPIRE provided clinically meaningful improvements in the mean change from baseline in FEV_1 in both Trial 1 and Trial 2 (Table 4).

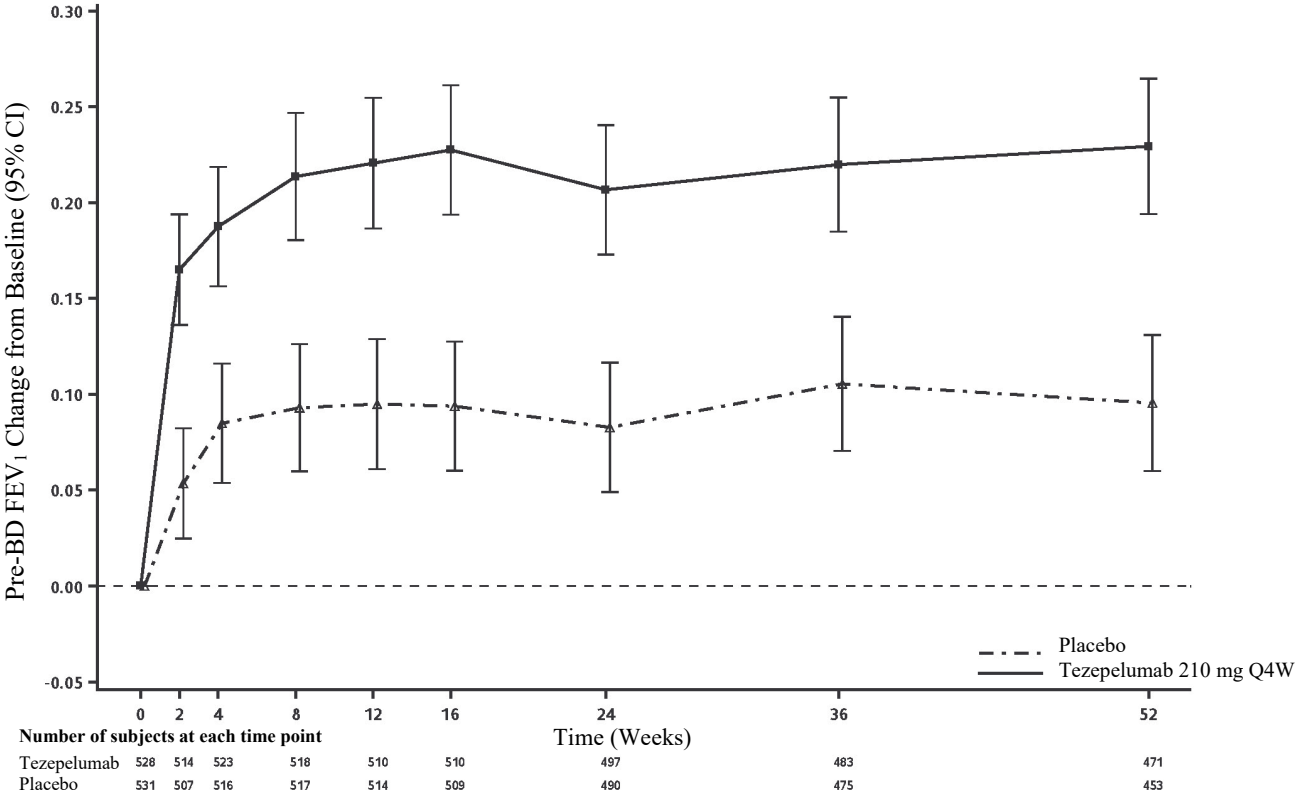
Table 4 Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 52, Trial 1 and Trial 2

	Trial 1		Trial 2	
	TEZSPIRE N=121	**Placebo N=131**	**TEZSPIRE N=471**	**Placebo N=453**
LS Mean Change from Baseline (L)	0.08	-0.06	0.23	0.10
LS Mean Difference from Placebo (L) (95% CI)	0.13 (0.03, 0.23)		0.13 (0.08, 0.18)	
p-value	0.009*		<0.001	

* Nominal p-value

In Trial 2, improvement in FEV_1 was seen as early as 2 weeks after initiation of treatment and was sustained through week 52 (Figure 3).

Figure 3 Mean Change (95% CI) from Baseline in Pre-Bronchodilator FEV1 (L) Over Time, Trial 2



Patient Reported Outcomes

Changes from baseline in Asthma Control Questionnaire 6 (ACQ-6) and Standardised Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] were assessed as secondary endpoints in Trial 1 and Trial 2. Results for Trial 2 are shown in Table 5. Improvements in ACQ-6 and AQLQ(S)+12 were seen as early as 2 weeks and 4 weeks after administration of TEZSPIRE, respectively, and sustained through Week 52 in both trials.

In both trials, more patients treated with TEZSPIRE compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for ACQ-6 and AQLQ(S)+12 was defined as improvement in score of 0.5 at end of trial. In Trial 2, the ACQ-6 responder rate for TEZSPIRE was 86% compared with 77% for placebo (odds ratio=1.99; 95% CI 1.43, 2.76) and the AQLQ(S)+12 responder rate for TEZSPIRE was 78% compared with 72% for placebo (odds ratio=1.36; 95% CI 1.02, 1.82). Similar findings were seen in Trial 1.

Weekly mean Asthma Symptom Diary (ASD) scores were also assessed as a secondary endpoint in Trial 2. Severity of wheezing, shortness of breath, cough, and chest tightness were assessed twice daily (morning and evening). Night-time awakening and activity were assessed on a daily basis. The total ASD score was calculated as the mean of 10 items. More patients treated with TEZSPIRE compared to placebo had a clinically meaningful improvement in the ASD score. Clinically meaningful improvement (responder rate) was defined as improvement

in score of 0.5 or more at end of trial. The ASD responder rate for TEZSPIRE was 58% compared with 51 % for placebo (odds ratio=1.68; 95% CI 1.12, 2.53).

Table 5 Results of AQLQ(s)+12, ACQ-6 and ASD at Week 52, Trial 2

	N	LS Mean Change from Baseline	Difference from Placebo (95% CI)	p-value
AQLQ(S)+12 total score				
TEZSPIRE	480	1.48	0.33 (0.20, 0.47)	<0.001
Placebo	467	1.11		
ACQ-6 score				
TEZSPIRE	485	-1.53	-0.33 (-0.46, -0.20)	<0.001
Placebo	472	-1.20		
ASD				
TEZSPIRE	374	-0.70	-0.11 (-0.19, -0.04)	<0.004
Placebo	355	-0.59		

Oral Corticosteroid Reduction

Trial 3 evaluated the effect of TEZSPIRE on reducing the use of maintenance OCS. The primary endpoint was categorised percent reduction from baseline of the final OCS dose at Week 48 (≥90% reduction, ≥75% to <90% reduction, ≥50% to <75% reduction, >0% to <50% reduction, and no change or no decrease in OCS), while maintaining asthma control. Compared with placebo, more patients receiving TEZSPIRE achieved a reduction from baseline in maintenance OCS dose without losing asthma control (cumulative odds ratio=1.28; 95% CI 0.69, 2.35), but the difference was not statistically significant. A total of 40 (54%) patients receiving tezepelumab compared with 35 (46%) patients receiving placebo achieved a ≥90% to 100% reduction in their OCS. Reductions of 50% or higher in the OCS dose were observed in 55 (74%) patients receiving TEZSPIRE compared to the 53 (70%) patients receiving placebo.

Paediatric Population

A total of 82 adolescents aged 12 to 17 with severe, uncontrolled asthma were enrolled in Trial 2 and received treatment with TEZSPIRE (n=41) or placebo (n=41). Compared with placebo, clinically meaningful improvements in annualised asthma exacerbation (rate ratio 0.70; 95% CI 0.34, 1.46) and FEV_1 (LS mean change from placebo 0.17 L; 95% CI -0.01, 0.35) were observed in adolescents treated with TEZSPIRE. The safety profile and pharmacodynamic responses in adolescents were generally similar to the overall study population.

5.2 Pharmacokinetic properties

The pharmacokinetics of tezepelumab were dose-proportional following SC administration over a dose range of 2.1 mg to 420 mg.

Absorption

Following a single SC administration, the maximum serum concentration was reached in approximately 3 to 10 days. Based on population pharmacokinetic analysis, the estimated

absolute bioavailability was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).

Distribution

Based on population pharmacokinetic analysis, central and peripheral volume of distribution of tezepelumab were 3.9 L and 2.2 L, respectively, for a 70 kg individual.

Metabolism

Tezepelumab is a human monoclonal antibody (IgG2λ) that is degraded by proteolytic enzymes widely distributed in the body and not metabolised by hepatic enzymes.

Elimination

As a human monoclonal antibody, tezepelumab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance. From population pharmacokinetic analysis, the estimated clearance for tezepelumab was 0.17 L/d for a 70 kg individual. The elimination half-life was approximately 26 days.

Special populations

Age, Gender, Race

Based on population pharmacokinetic analysis, age, gender, and race had no clinically meaningful effects on the pharmacokinetics of tezepelumab.

Body Weight

Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure. However, the effect of body weight on exposure had no meaningful impact on efficacy or safety and does not require dose adjustment.

Paediatric patients

Based on the population pharmacokinetic analysis, there was no clinically meaningful age-related difference in the pharmacokinetics of tezepelumab between adults and adolescents aged 12 to 17 years. Tezepelumab has not been studied in children under 12 years of age (see section 4.2).

Elderly patients (≥65 years old)

Based on population pharmacokinetic analysis, there was no clinically meaningful difference in the pharmacokinetics of tezepelumab between patients 65 years of age or older and younger patients.

Of the 665 patients with asthma exposed to TEZSPIRE in the two placebo-controlled clinical studies of 52 weeks duration, a total of 119 patients were 65 years or older. Safety in this age group were similar to the overall study population.

Efficacy in this age group was similar to the overall study population in Trial 2. Trial 1 did not include sufficient numbers of patients aged 65 and over to determine efficacy in this age group.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab. Based on population pharmacokinetic analysis, tezepelumab clearance was similar in patients with mild renal impairment (creatinine clearance 60 to < 90 mL/min), moderate renal impairment (creatinine clearance 30 to < 60 mL/min) and those with normal renal function (creatinine clearance ≥ 90 mL/min). Tezepelumab has not been studied in

patients with severe renal impairment (creatinine clearance < 30 mL/min); however, tezepelumab is not cleared renally.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. IgG monoclonal antibodies are not primarily cleared via hepatic pathway; change in hepatic function is not expected to influence tezepelumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.

Drug-Drug Interaction

No formal drug interaction studies have been conducted. A clinically relevant effect of tezepelumab on the pharmacokinetics of co-administered asthma medications is not expected. Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (including leukotriene receptor antagonists, theophylline/aminophylline, and OCS) had no effect on tezepelumab clearance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology and repeated dose toxicity studies in cynomolgus monkeys.

Mutagenicity and carcinogenicity

Tezepelumab is a monoclonal antibody, as such genotoxicity and carcinogenicity studies have not been conducted.

Reproductive toxicity

Developmental toxicity

In a prenatal and postnatal development study conducted in cynomolgus monkeys, following IV administration of tezepelumab up to 300 mg/kg/week from early gestation through delivery, no adverse effects on maternal health, pregnancy outcome, embryo-foetal development, or neonatal growth and development up to 6.5 months of age were observed. Tezepelumab concentrations in milk were <1% of the serum concentrations. Comparison of maternal and infant serum ratios suggested that the majority of tezepelumab transfer to the infant occurred in utero but transfer via milk cannot be excluded. No adverse effects on maternal health or neonatal health and development were observed.

Fertility

Effects on male and female fertility have not been directly evaluated in animal studies. Examination of surrogate fertility parameters (menstrual cycle, semen analysis, organ weights, and microscopic pathology) was performed in sexually mature male and female cynomolgus monkeys as part of a 6-month repeated dose toxicology study. There were no tezepelumab-related effects on these parameters at doses up to 300 mg/kg/week by SC administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
L-proline
Polysorbate 80
Sodium hydroxide

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

Refer to the outer carton and/or inner product label for expiration date.

TEZSPIRE may be kept at room temperature up to 30°C for a maximum of 30 days. When TEZSPIRE has reached room temperature, do not put it back in the refrigerator. After removal from the refrigerator, TEZSPIRE must be used within 30 days or discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). For storage after removal from refrigeration, see section 6.3.

Store the pre-filled syringe/pre-filled pen in the original package in order to protect from light.

Do not freeze. Do not shake. Do not expose to heat.

6.5 Nature and contents of container

Pre-filled syringe

1.91 mL solution in a siliconized Type I glass pre-filled syringe subassembly consisting of a 27-gauge 12.7 mm (½-inch) stainless steel special thin wall needle covered with a needle cover and plunger-stopper. The pre-filled syringe subassembly is assembled with a needle guard and an extended finger flange.

TEZSPIRE is available in a pack containing 1 single-use pre-filled syringe.

Pre-filled pen

1.91 mL solution in a siliconized Type I glass pre-filled syringe subassembly consisting of a 27-gauge 12.7 mm (½-inch) stainless steel special thin wall needle covered with a needle cover and plunger-stopper. The pre-filled pen consists of the pre-filled syringe subassembly and handheld, mechanical (spring-based) injection device.

TEZSPIRE is available in a pack containing 1 single-use pre-filled pen.

6.6 Instructions for use, handling and disposal

This medicinal product is for single-use only.

TEZSPIRE solution for injection is supplied in a sterile pre-filled syringe/pre-filled pen for individual use. Do not shake. Do not freeze. Protect from light.

Prior to administration, remove carton from refrigerator and allow TEZSPIRE to reach room temperature. This generally takes 60 minutes.

Visually inspect TEZSPIRE for particulate matter and discolouration prior to administration. TEZSPIRE is clear to opalescent, colourless to light yellow. Do not use TEZSPIRE if liquid is cloudy, discoloured, or if it contains large particles or foreign particulate matter.

Additional information and instructions for the preparation and administration of TEZSPIRE using the pre-filled syringe/pre-filled pen are given in the package leaflet and 'Instructions for Use'.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Product Owner

AstraZeneca AB
SE-151 85, Södertälje, Sweden

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