NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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 pre-filled syringe contains 210 mg tezepelumab in 1.91 mL solution (110 mg/mL).

Pre-filled pen

Each 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.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

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

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 high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should be initiated by physicians experienced in the diagnosis and treatment of severe asthma.

Posology

Adults and adolescents (aged 12 years and older)

The recommended dose is 210 mg of TEZSPIRE by subcutaneous injection every 4 weeks. TEZSPIRE is intended for long-term treatment. A decision to continue the therapy should be made at least annually based on the patient's level of asthma control.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, the patient can resume dosing on the scheduled day of administration. If the next dose is already due, then administer as planned. A double dose must not be administered.

Special patient populations

Renal and hepatic impairment

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

Use in the elderly

No dose adjustment is required for elderly patients (see section 5.2).

Use in paediatric patients

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

Method of administration

TEZSPIRE is administered as a subcutaneous 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 to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND 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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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

In a randomised, double-blind, parallel-group study of 70 patients aged between 12 and 21 years with moderate to severe asthma, tezepelumab treatment did not appear to affect the humoral antibody responses induced by seasonal quadrivalent influenza vaccination.

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

4.6 FERTILITY, 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

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.

Tabulated list of adverse events

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

Summary of post-marketing data

The following adverse reactions have been identified during post approval use of TEZSPIRE. It is generally not possible to reliably determine the frequency because such reactions have been reported spontaneously from a population of uncertain size. The frequency of these adverse reactions is therefore 'not known' (cannot be estimated from available data).

Immune system disorders: Anaphylaxis

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.

Long-term safety

In a long-term extension trial (Trial 4 [DESTINATION]) in patients with severe asthma, 839 patients from Trials 2 and 3 were treated with tezepelumab 210 mg SC Q4W for up to 104 weeks. The safety profile during the long-term extension trial was generally similar to the known safety profile of tezepelumab.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XK01

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). In the long-term extension trial (Trial 4 [DESTINATION]), reductions from baseline were maintained to Week 104 for blood eosinophils and FeNO and there was a progressive decrease in total IgE to Week 64 followed by a sustained reduction to Week 104 in patients treated with tezepelumab compared to placebo (see section 5.1).

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. The immunogenicity profile of tezepelumab was maintained over 76 weeks of treatment in Trial 4 for severe asthma patients originally enrolled in Trial 2 (n=415).

Clinical Efficacy and Safety

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.

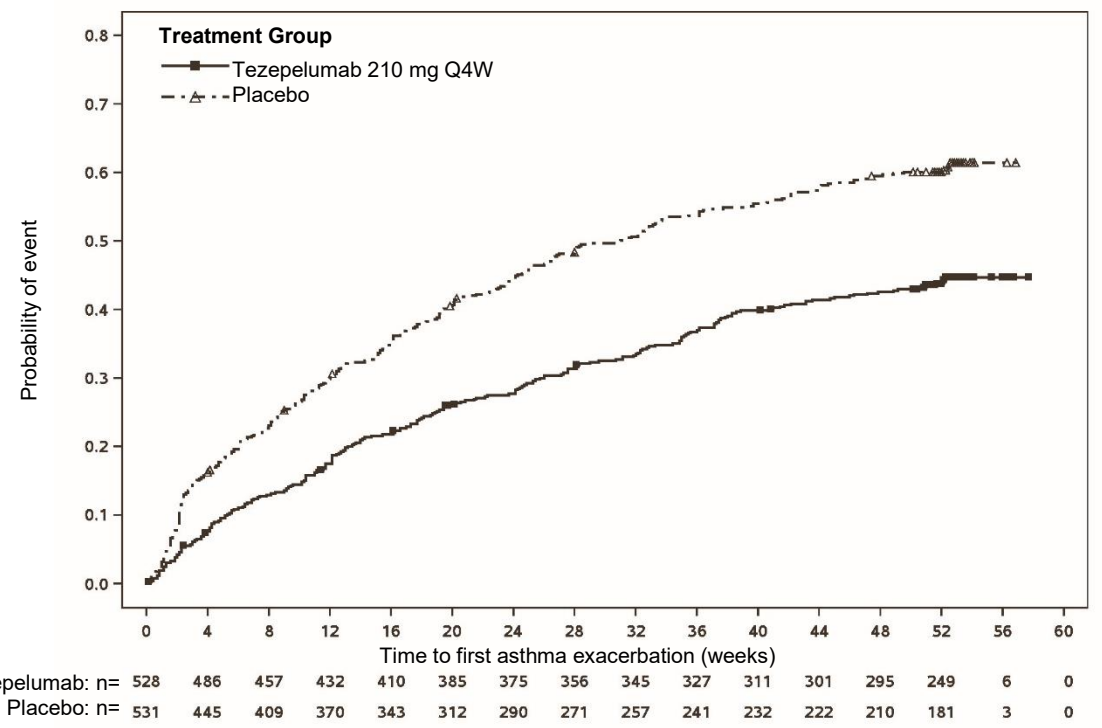
Table 3 Rate of Clinically Significant Exacerbations Over 52 Weeks, Trial 1 and Trial 2

	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.

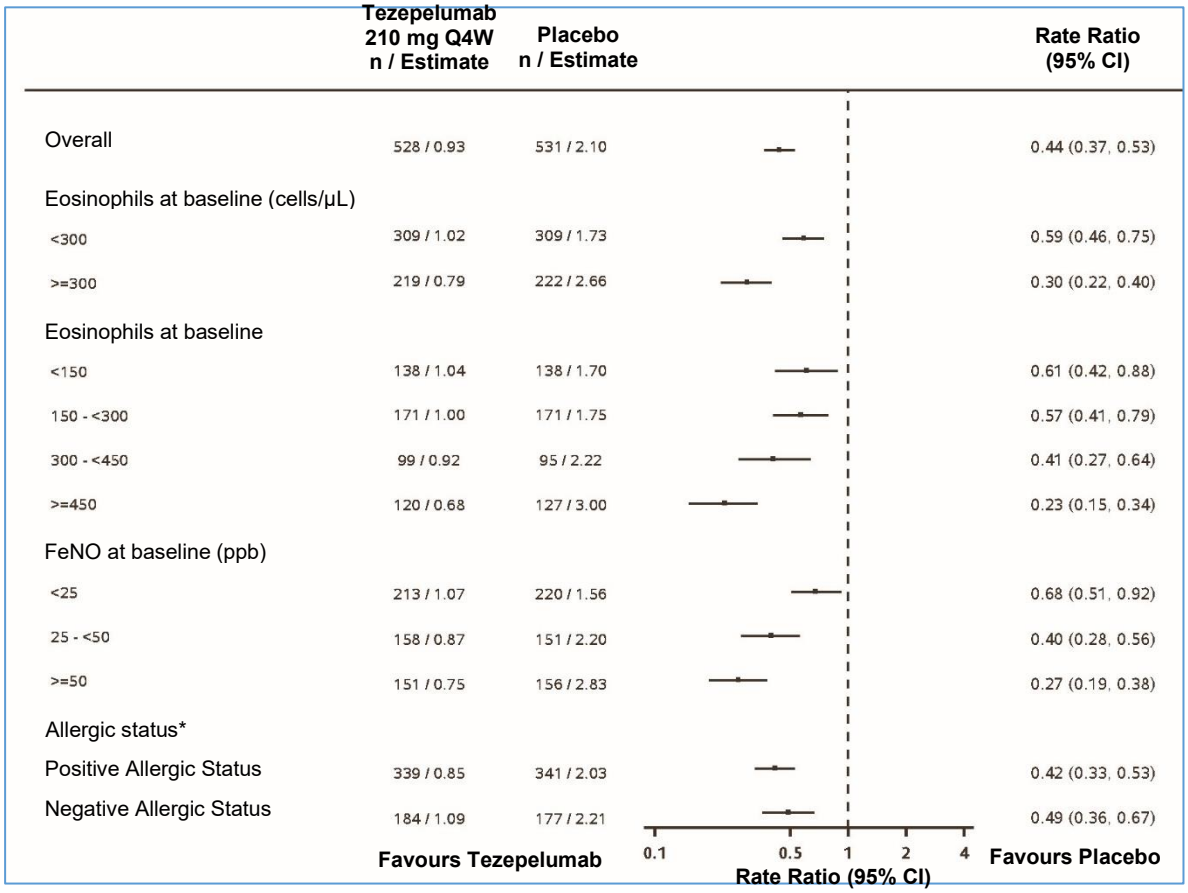
Figure 1 Kaplan-Meier Cumulative Incidence Curves for Time to First Exacerbation Through Week 52, Trial 2



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).

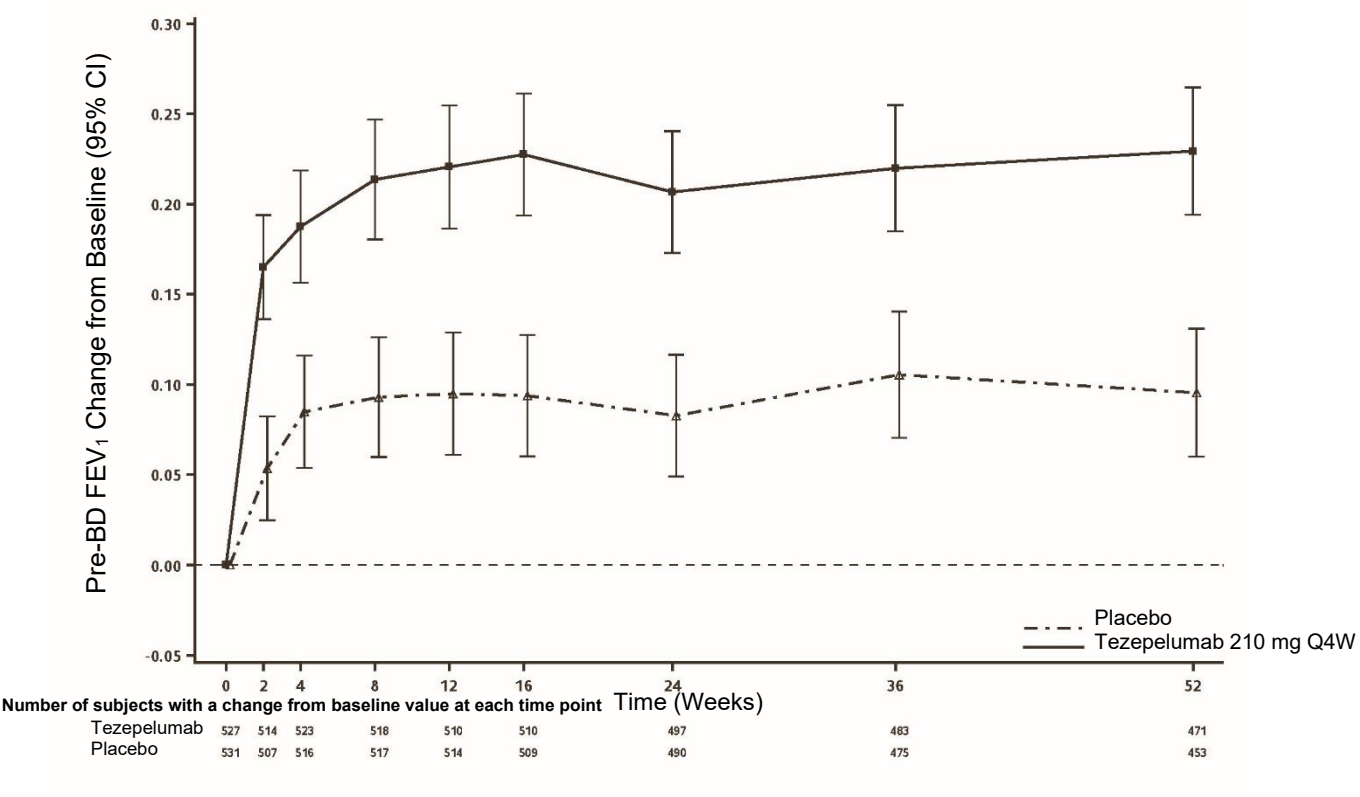
Table 4 Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 52, Trial 1 and Trial 2

	Trial 1		Trial 2	
	TEZSPIRE N=133*	**Placebo N=138***	**TEZSPIRE N=527***	**Placebo N=531***
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	

* Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value
† 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 FEV_1 (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	525	1.48	0.33 (0.20, 0.47)	<0.001
Placebo	526	1.14		
ACQ-6 score				
TEZSPIRE	527	-1.53	-0.33 (-0.46, -0.20)	<0.001
Placebo	531	-1.20		
ASD				
TEZSPIRE	525	-0.70	-0.11 (-0.19, -0.04)	0.004
Placebo	531	-0.59		

* Number of patients contributing to the full analysis (FA) with at least 1 change from baseline value

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 any increase 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.

Secondary outcomes in Trial 3, including the annualised rate of asthma exacerbations, change from baseline in pre-bronchodilator FEV_1, ACQ-6, and AQLQ(S)+12 improved with TEZSPIRE compared with placebo.

Long-term extension trial

The long-term efficacy and safety of tezepelumab was evaluated in a phase 3, randomised, double-blind, placebo-controlled, extension trial (Trial 4). The trial enrolled a total of 951 patients (879 adults and 72 adolescent patients aged 12 years and older) from Trial 2 and Trial 3. The results summarised below are based on the Trial 2 treatment groups.

Patients receiving tezepelumab had reductions in annualised rate of asthma exacerbations compared with placebo over 104 weeks (rate ratio 0.42 [95% CI 0.35, 0.51]) regardless of baseline levels of blood eosinophils, FeNO, as well as allergic status (determined by a perennial aeroallergen specific IgE). Tezepelumab treatment reduced the rate of asthma exacerbations associated with hospitalisation or emergency room visits compared with placebo over 104 weeks by 79% (rate ratio 0.21 [95% CI 0.13, 0.36]). Sustained improvement in FEV_1 (LS mean difference 0.08 L [95% CI 0.02, 0.15]) and ACQ-6 (LS mean difference -0.30 [95% CI -0.45, -0.15]) was observed in patients treated with tezepelumab compared with placebo at Week 104.

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.

A total of 72 adolescents aged 12 to 17 years with severe asthma were enrolled in the long-term study (Trial 4). The efficacy profile of tezepelumab in adolescent patients was sustained up to 104 weeks. Safety was generally similar with the known safety profile of tezepelumab.

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

3 years

TEZSPIRE may be kept at room temperature (20°C - 25°C) for a maximum of 30 days. 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

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 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

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.

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

16 May 2024

10. DATE OF REVISION OF THE TEXT

1 August 2024

TEZSPIRE is a trademark of Amgen Inc. and the AstraZeneca group of companies.

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Anaphyaxis is added.