EU RMP	
Drug substance	Tezepelumab
EMA Version number	2
AZ Version number	2
Succession number	2
Data lock point	31 August 2022
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR TEZSPIRE™ (TEZEPELUMAB)

QPPV oversight declaration: The content of this EU RMP has been reviewed and approved by the applicant's QPPV.

Administrative Information

Rationale for submitting an updated RMP

To support a Type II variation for the tezepelumab autoinjector presentation.

Summary of significant changes in this RMP

Section I (Part I): Addition of autoinjector presentation to the pharmaceutical form(s) and strengths listed in Table I-1.

Details of currently approved RMP	**Version number:** 1 **Approved with procedure:** EMEA/H/C/005588/0000 **Date of approval:** 19 September 2022

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PART VII: ANNEXES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
AI	Autoinjector
APFS	Accessorised pre-filled syringe
EEA	European Economic Area
ENFUMOSA	European Network for Understanding Mechanisms of Severe Asthma
EPAR	European Public Assessment Report
ER	Emergency room
EU	European Union
FEV_1	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IL-5α/5Rα	Interleukin-5 alpha/Interleukin-5 receptor alpha
IP	Investigational product
ISAR	International Severe Asthma Registry
IV	Intravenous
KLH	Keyhole limpet hemocyanin
LABA	Long-acting β2 agonist
LTE	Long-Term Extension
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
NOAEL	No adverse effect level
OCS	Oral corticosteroids
PASS	Post-Authorisation Safety Study
PK	Pharmacokinetic
PY	Person-years
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation

Abbreviation/ Special term	Definition/Explanation
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA Query
SOC	System Organ Class
Th2	T helper cell type 2
TSLP	Thymic stromal lymphopoietin
UK	United Kingdom
US	United States of America

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Tezepelumab
Pharmacotherapeutic group(s) (ATC Code)	R03DX11
Marketing Authorisation Applicant	AstraZeneca AB 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	2 (Tezspire-accessorised pre-filled syringe and Tezspire-autoinjector)
Invented name(s) in the EEA	TEZSPIRE™
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Tezepelumab is a human mAb IgG2λ directed against TSLP.
	Summary of mode of action: Tezepelumab is an anti-TSLP, human mAb 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 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 hyperresponsiveness. TSLP has also been shown to have indirect effects on airway structural cells (eg, fibroblasts and airway smooth muscle). In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces levels of a broad spectrum of biomarkers and cytokines associated with inflammation (eg, blood eosinophils, FeNO, IgE, IL-5, and IL-13).
	Important information about its composition: Tezepelumab is a human mAb IgG2λ directed against TSLP, expressed in a Chinese hamster ovary CS-9 cell line. The molecule is a heterotetramer consisting of 2 heavy chains of the IgG2 subclass and 2 light chains of the lambda subclass, which are covalently linked through disulphide bonds.
Hyperlink to the Product Information	Tezepelumab, Summary of Product Characteristics
Indication(s) in the EEA	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.

Table I-1 Product Overview

Dosage in the EEA	The recommended dose is 210 mg of tezepelumab by SC injection every 4 weeks.
Pharmaceutical form(s) and strengths	Tezepelumab Drug Product is presented as a sterile, single-use, preservative-free, clear, colourless to slightly yellow liquid in APFS or AI presentations for SC injection. Each APFS or AI contains 110 mg/mL of tezepelumab with a dose of 210 mg and is formulated in 10 mM acetate, 3% (weight per volume [w/v]) L-proline, 0.01% (w/v) polysorbate 80, pH 5.2.
Is/will the product be subject to additional monitoring in the EU?	Yes

AI, autoinjector; APFS, accessorised pre-filled syringe; ATC, anatomical therapeutic chemical; EEA, European Economic Area; EU, European Union; FeNO, fraction of exhaled nitric oxide; IgE, immunoglobulin E; IgG2λ, immunoglobulin G2λ; IL, interleukin; INN, international non-proprietary name; mAb, monoclonal antibody; RMP, risk management plan; SC, subcutaneous; TSLP, thymic stromal lymphopoietin; w/v, weight per volume.

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Incidence:

There are limited reports on asthma incidence data in the literature and none on the incidence of severe uncontrolled asthma. Data from the European Respiratory Health Survey conducted from 1999 to 2001 in 6 countries reported the incidence rate of asthma among adults to be 2.2 cases per 1000 person-years [PY] (Torén et al 2004). The incidence rate of asthma was higher among adult females (2.9 cases per 1000 PY) than adult males (1.5 cases per 1000 PY). In the United States (US)-based Asthma Call-back Survey conducted from 2006-2008 (Winer et al 2012), the incidence of asthma diagnosis in the previous 12 months was estimated to be 3.8 cases per 1000 in adults, compared with 12.7 cases per 1000 in children. The incidence of asthma was also higher among adult females (4.9/1000) than adult males (2.8/1000).

Prevalence:

Globally, the prevalence of asthma is approximately 358 million individuals (Global Initiative for Asthma [GINA], GINA 2020, GBD Collaborators 2017). The prevalence of asthma appears to range from 1% to 22% in different countries, with rates increasing over time in some, while stable in others (GINA 2020). Data from the European National Health and Wellness Survey of 37476 adults in France, Germany, Italy, Spain, and the United Kingdom (UK) reported the prevalence of diagnosed asthma to be 5.8% (Demoly et al 2009). Data from the World Health Survey conducted in 2002 to 2003 among adults (18 to 45 years) reported the prevalence of asthma to be 5.1% based on doctor diagnosis definition and 5.3% based on clinical asthma definition in Europe, varying from 1% to 20% by country (To et al 2012).

Severe asthma is characterised by either requiring use of high-dose inhaled corticosteroids (ICS) plus long-acting β2 agonists (LABAs) or asthma controllers to achieve asthma control, or remaining uncontrolled despite use of these medications (GINA 2020, Chung et al 2014). The prevalence of severe asthma as a percentage of all asthma varies from country to country, largely due to variation between clinical and epidemiological definitions (Wenzel 2003) and is estimated to be 5% to 10% of the total asthmatic population (Barnes and Woolock 1998, Busse et al 2000, O'Byrne et al 2012, Chung et al 2014), whilst based on GINA criteria, approximately 20% of asthma patients have severe asthma, of which 20% are inadequately controlled (Peters et al 2006). A multi-country database study using the severe asthma definition of high-dose ICS plus a second controller therapy for ≥ 120 days, reported severe asthma prevalence of 8.9%, 10%, 8.7%, 6%, and 1.7% of the overall asthma population, respectively for Netherlands, Denmark, UK, Italy, and Spain (Engelkes et al 2015). A systematic literature review (Chen et al 2018) reported the prevalence of severe uncontrolled asthma as between 8% to 87.4% of severe asthma patients. The wide variation was due to differences in definition of severe uncontrolled asthma across available studies, as well as variability in reporting methods across geographic regions (Chen et al 2018). A study in the Netherlands estimated 3.7% of the overall asthma patients had severe asthma, which was based on patients requiring GINA step 4 or 5 treatment, having poor symptom control but good adherence and inhaler technique (Hekking et al 2015). Furthermore, in 3 database analyses, the prevalence of severe uncontrolled disease among the overall asthma patient population was 1.6% in France, 2.7% in Italy, and 1.8% in Spain (Godard et al 2010, Allegra et al 2012, Quirce et al 2011). A more recent study using the primary care database in the UK showed that of the total asthma population, 31% of patients are classified as GINA step 4 or 5 and 2.9% as GINA step 5 (Kerkhof et al 2018).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) reported a higher proportion of females and higher body mass index in patients with severe uncontrolled asthma than those with mild to moderate asthma; there was a similar age distribution in severe uncontrolled asthma patients and controlled asthma patients (mean age 42.4 years [standard deviation (SD) 12.1] and 40.9 years [SD 14.3], respectively) and the mean percent predicted forced expiratory volume in one second (FEV_1) among the severe uncontrolled asthma patients was 71.8% (ENFUMOSA 2003). The International Severe Asthma Registry (ISAR), which characterised severe asthma worldwide, including the UK and Italy, reported that patients were predominantly female (59.3%), white (72.6%), had never smoked (60.5%), were overweight or obese (70.4%), were aged 55 to 79 years (52.1%) with a mean age at asthma onset of 30.7 (SD 17.7) years, 57.2% had poorly controlled disease and 34.9% were GINA Step 5 (Wang et al 2020). These demographics are similar to the European National Health and Wellness Survey, among severe uncontrolled asthma patients from UK,

Germany, France, Italy, and Spain (Demoly et al 2009), which reported that patients were predominately female (62.6%), had a mean age of 44.5 years, never smoked (66.1%), and were overweight or obese (62.8%).

Factors that influence the risk of asthma, including severe presentations, are divided by GINA into factors that cause development of the disease (mainly host factors, such as genetic predisposition) and factors that trigger symptoms (environmental factors, such as allergens). Risk factors for flare-ups (exacerbations), as outlined in the GINA 2020 report, include uncontrolled asthma symptoms, inadequate ICS treatment (either not prescribed, poor adherence, or incorrect inhaler technique), low FEV_1, exposures to smoking and allergens, sputum or blood eosinophilia, pregnancy, intubation or in an intensive care unit for asthma, and history of exacerbation (GINA 2020).

The main existing treatment options:

Current treatment strategies for controlling asthma are primarily aimed at reducing airway inflammation, with ICS being the mainstay of treatment for patients with persistent asthma due to their powerful anti-inflammatory effects (GINA 2020, NAEPP 2007). GINA guidelines for patients with severe asthma recommend the following:

- Medium-dose ICS-LABA maintenance therapy (or high-dose ICS plus add-on tiotropium or leukotriene receptor antagonist [LTRA]) plus as-needed low-dose ICS-formoterol for adults and adolescents (Step 4 treatment).
- High-dose ICS-LABA maintenance therapy plus as-needed low-dose ICS-formoterol and refer for phenotypic assessment and possible treatment with tiotropium, anti-immunoglobulin E (IgE), anti-interleukin (IL)-5/IL-5 receptor (IL-5R), anti-IL-4 receptor (IL-4R), and/or low-dose oral corticosteroids (OCS) as add-on therapy (Step 5 treatment).

Many asthmatic patients remain symptomatic despite treatment with ICS and LABA combinations (Rabe et al 2004). Treatment options then include the addition of other controller therapies including an LTRA, long-acting muscarinic antagonist, theophylline, and OCS.

Biologic therapies can provide additional asthma control for patients with severe, uncontrolled asthma, and those targeting IgE, IL-4, and IL-5 are now included in international treatment guidelines (GINA 2020) as an add-on treatment to patients uncontrolled with ICS/LABA treatment. Omalizumab may be suitable for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum IgE levels who remain inadequately controlled with ICS plus LABA (XOLAIR SmPC). Four additional biologics, mepolizumab, reslizumab, benralizumab, and dupilumab, have been approved for severe asthma with an eosinophilic phenotype and/or those requiring OCS therapy (NUCALA SmPC, CINQAERO SmPC, FASENRA SmPC, DUPIXENT SmPC). In addition, dupilumab has been approved in the European Union (EU) for severe asthma with T2 inflammation as characterised by raised blood eosinophils and/or

raised FeNO (DUPIXENT SmPC). However, based on the real-world observational study CHRONICLE (Ambrose et al 2020), it is estimated that 37% of patients with severe asthma have an inadequate response to, or are ineligible for currently approved biologics, and continue to experience exacerbations (Soong et al 2020).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Asthma is characterised by bronchial hyperresponsiveness, variable symptoms of wheezing, breathlessness, chest tightness and cough, and by variable expiratory airflow limitation. Asthma may also be characterised by exacerbations, which are episodes of worsening symptoms and lung function.

Patients with severe refractory asthma constitute approximately 5 to 10% of all asthma patients. As part of the severe refractory definition, these patients need at least 3 steroid bursts per year (Wenzel 2005). Approximately 30% of severe refractory asthma patients are OCS-dependent (Sullivan et al 2018).

Severe, uncontrolled disease is associated with a consistently greater clinical and patient burden than in patients with non-severe asthma, consuming the majority of asthma-related healthcare resources (Price et al 2014, Israel and Reddel 2017). Severe, uncontrolled asthma can lead to a dependence on OCS with systemic corticosteroid exposure potentially leading to serious short- and long-term adverse effects (Manson et al 2009, Price et al 2014). In one US observational study, patients with severe uncontrolled asthma had a substantially higher likelihood of having an emergency room (ER) visit (relative risk = 2.75) or asthma hospitalisation (relative risk = 4.54) compared with patients with asthma that was not severe and uncontrolled (Zeiger et al 2016). Although overall prevalence data regarding exacerbations resulting in hospitalisation or ER visits are variable across Europe, data from the UK, Italy, France, and Spain also show a 2- to 5-fold increase in rates of hospitalisation or ER visits among patients with moderate or severe asthma compared with those with milder asthma (Kerkhof et al 2018, Van Ganse et al 2006, Doz et al 2013).

It is estimated that asthma causes 495000 deaths worldwide every year (GINA 2020). Reported case fatality rates vary significantly, possibly due to differences in management. Engelkes et al conducted a multinational, database cohort study to assess all-cause mortality rate in the Netherlands, Denmark, UK, Italy, and Spain (Engelkes et al 2020). The study showed that age and sex standardised all-cause mortality rates ranged from 11.3 to 14.8 per 1000 PY in severe asthma patients (Engelkes et al 2020). The risk of respiratory-related mortality is approximately 8-times greater in patients with severe uncontrolled asthma compared with severe controlled asthma patients (Fernandes et al 2014).

Important comorbidities:

Concomitant allergies are commonly reported underlying conditions associated with the development of asthma; thus, the clinical presentation of asthma often includes seasonal exacerbations or exacerbations related to exposures to recognised allergens, including perennial aeroallergens, and environmental airborne irritants. Allergic rhinitis or other allergic disease, and eczema have also been identified as risk factors for the subsequent development of asthma, particularly in younger patients (Buelo et al 2018). Smoking does not cause asthma, but chronic obstructive pulmonary disease (COPD) and asthma may coexist in smoking asthmatics; the 2 diseases may sometimes be difficult to distinguish.

The following are often quoted as comorbid diseases in asthma: chronic sinusitis/rhinitis, gastroesophageal reflux disease, sleep apnoea, chronic or recurrent respiratory infections, and obesity. Psychological disturbances, such as depression and anxiety, are also more frequently reported in patients with asthma as compared with the general population (GINA 2020).

The International Severe Asthma Registry provides a more complete assessment of comorbid conditions most often seen in severe asthma. In that registry, which assessed 4990 patients with severe asthma in 7 countries, allergic rhinitis (49.4%) was the predominant comorbidity among severe asthma patients, followed by chronic rhinosinusitis (21.4%), eczema (9.6%), and nasal polyps (7.3%) (Wang et al 2020). Similar comorbidities including eczema and/or allergic rhinitis (range 11.5% to 37.8%), chronic rhinosinusitis (0.9% to 14.1%), and nasal polyps (1.0% to 6.8%) were reported among approximately 43000 severe asthma patents in Netherlands, Denmark, UK, Italy, and Spain during the study period 2008 to 2013 (Engelkes et al 2020). An Italian registry of 493 severe uncontrolled asthma patients assessed during 2011 to 2014, reported the most common comorbidities as allergic rhinitis (62.4%), gastroesophageal reflux (42.1%), sinusitis (37.9%), nasal polyps (30.2%), and allergic conjunctivitis (30.2%) (Maio et al 2018). Another source of information on comorbidities amongst patients with severe uncontrolled asthma is from a study in the UK of 2940 patients with severe uncontrolled eosinophilic asthma based on medical record data from 1989 to 2015 (Kerkhof et al 2018). This study found the following comorbidities: eczema (34.0%), allergic rhinitis (20.7%), chronic sinusitis (15.5%), nasal polyps (12.8%), gastro-oesophageal reflux disease (17.5%), and cardiovascular disease (37.7%).

As asthma patients age, the comorbid diseases commonly seen in an aging population may impact asthma treatment, such as cardiovascular disease including hypertension or ophthalmologic conditions. These diseases may require treatment with β-blockers which are contraindicated in asthma (Bateman et al 2008, Salpeter 2003).

II.2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings from Nonclinical Data

Toxicity

Cynomolgus monkeys were selected as the nonclinical toxicology species because tezepelumab binds to human and cynomolgus monkey thymic stromal lymphopoietin (TSLP) with picomolar affinity, and neutralised human and cynomolgus monkey TSLP with sub nanomolar potency in a cell-based functional bioassay. Tezepelumab did not cross-react with mouse, rat, or rabbit TSLP. The species specificity of tezepelumab precluded direct evaluation of carcinogenicity.

Key issues identified from acute or repeat-dose toxicity studies

Acute toxicity studies: No tezepelumab acute toxicology studies were conducted. In a single-dose safety pharmacology study in cynomolgus monkeys (Study 109453), no adverse effects were observed after a 300 mg/kg intravenous (IV) administration (a toxicologically relevant dose level).

Repeat-dose toxicity studies: In all nonclinical studies, the no observed adverse effect level (NOAEL) was the highest dose tested (up to 300 mg/kg) for each route of administration (IV and subcutaneous [SC]) in each repeat-dose study. Findings were limited to minimally-to-mildly decreased serum cholesterol at the 300 mg/kg dose level in most repeat-dose studies. The reversibility of the effect on serum cholesterol was confirmed during the recovery phases.

In a 3-month repeat-dose study (Study 108448), the T-cell dependent antibody response was evaluated by measuring the antibody response to keyhole limpet hemocyanin (KLH). Mean anti-KLH immunoglobulin G (IgG) titers were mildly-to-moderately decreased at 300 mg/kg. At 50 and 100 mg/kg, IgG titers were sporadically reduced but the changes were not statistically significant. Reduced anti-KLH IgG antibody titers may be related to the pharmacology of tezepelumab, even though not considered adverse since no changes related to infection were observed in the study. Similar changes in KLH titers were not evident in offspring in a subsequent cynomolgus enhanced pre- and postnatal development (ePPND) study.

Reproductive/developmental toxicity

Reproductive toxicity in cynomolgus monkeys:

Fertility parameters were evaluated in sexually mature cynomolgus monkeys in the 6-month IV and SC toxicity study (Study 108824). No adverse tezepelumab-related effects on menses

or semen analyses (sperm morphology, motility, or count) were observed. Reproductive organ weights (epididymides, ovaries, prostate, testes, and uterus), and macroscopic and microscopic pathology of reproductive tissues (testes, prostate, epididymides, seminal vesicles, ovaries, uterus, cervix, and vagina) were not impacted by tezepelumab administration. These findings suggest that that the reproductive risks associated with tezepelumab administration are low.

In a maternal, embryo-foetal, and neonatal toxicity study, tezepelumab was administered IV to pregnant female cynomolgus monkeys at 0, 50, or 300 mg/kg from approximately gestation Day 20 until parturition. The infants were studied until 6.5 months post-birth. There were no tezepelumab-related effects (maternal, foetal, or infant) up to 300 mg/kg. For all infants evaluated during the 6.5-month postnatal period, there were no tezepelumab-related changes in clinical signs, body weight, infant measurements, neurobehavioral assessment, haematologic parameters, peripheral blood lymphocyte immunophenotypes, anti-KLH humoral immune responses, or external, visceral, or skeletal evaluations. The NOAEL for this study was 300 mg/kg.

Genotoxicity

Tezepelumab is a monoclonal antibody (mAb) composed entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Thus, it is highly unlikely that tezepelumab would react directly with deoxyribonucleic acid (DNA) or other chromosomal material, and since tezepelumab is a large protein molecule, it is not expected to cross the nuclear or mitochondrial membranes. According to the current guidelines on the nonclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6 R1 2011), the range and type of standard studies evaluating genotoxicity routinely conducted for pharmaceuticals are not applicable for biotechnology-derived pharmaceuticals such as tezepelumab. Based on consideration of the product attributes and pharmaceutical class to which tezepelumab belongs, genotoxic risks associated with tezepelumab administration are low.

Carcinogenicity

An assessment of the carcinogenic risk associated with long-term inhibition of TSLP was completed using a weight-of-evidence approach, as outlined in ICH S6 (R1). This strategy involved a thorough review of nonclinical and clinical data generated with tezepelumab, as well as literature data related to TSLP mechanism of action and biology. TSLP literature data (ie, information on class effects, knockout mouse models, and human genetic mutations) did not indicate a potential carcinogenic concern associated with long-term tezepelumab treatment. Due to the evidence linking TSLP overexpression to the promotion of tumour growth and metastasis (Barooei et al 2015, Watanabe et al 2015, Xie et al 2015, Lo Kuan and Ziegler 2014) in both animal models and in human translational studies, inhibition of TSLP such as with tezepelumab may provide anti-tumour activity rather than increased cancer risk.

No evidence of proliferative or pre-neoplastic changes was observed in toxicology studies following repeated weekly administration of tezepelumab at doses up to 50 mg/kg IV or 300 mg/kg SC for 26 weeks.

In summary, following a thorough review of available data from literature, nonclinical and clinical studies, it is considered that chronic inhibition of TSLP would not increase the lifetime risk of cancer. A 2-year rodent bioassay with the clinical candidate is not possible due to lack of cross-reactivity to the target in rodents. It is considered that the available weight-of-evidence information regarding TSLP biology, gene deficient mice, and human genetic diseases, as well as the completed tezepelumab nonclinical safety studies, provide an adequate assessment of the nonclinical carcinogenic potential of chronic TSLP blockade.

Safety pharmacology

Effects of tezepelumab on cardiovascular, respiratory, and neurobehavioral endpoints were evaluated in a single-dose safety pharmacology study in telemetered cynomolgus monkeys (Study 109453). There were no treatment-related effects on cardiovascular function, respiratory rate, neurological behavior, and body temperature after a single 300 mg/kg IV tezepelumab administration.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The clinical trial exposure to tezepelumab is summarised for the Primary Safety Pool and the Exposure Pool.

The Primary Safety Pool consists of pooled data from the confirmatory asthma exacerbation studies D5180C00007 (Phase 3) and CD-RI-MEDI9929-1146 (Phase 2b). These studies had a similar design, similar inclusion/exclusion criteria, the same safety endpoints, and compatible frequency and timing of safety assessments. This pool provides the primary data to support the evaluation of the safety profile of tezepelumab 210 mg every 4 weeks (Q4W) SC dose in subjects with severe uncontrolled asthma and to support the evaluation of risks presented in this Risk Management Plan (RMP) in Section II.7.

The Exposure Pool consists of pooled data from all 5 of the tezepelumab Phase 2 and 3 asthma studies. This pool comprises 4 studies in subjects with severe asthma (D5180C00007, CD-RI-MEDI9929-1146, D5180C00009 [a Phase 3, OCS-reduction study], and D5180C00011 [a Phase 3, device functionality study]), and 1 study in subjects with moderate to severe asthma (D5180C00013 [a Phase 2 mechanistic study]). This pool provides a broader view of the extent of subject exposure to tezepelumab in the Phase 2/3 clinical programme including exposure data for 4 tezepelumab treatment groups: 70 mg Q4W SC, 210 mg Q4W SC, 280 mg every 2 weeks (Q2W) SC, and tezepelumab ‘all doses’ combined group.

Although 2 Phase 1 studies (Study 20101183 and D5180C00002) included subjects with asthma, these studies were not included in the Exposure Pool. Study 20101183 was a multiple dose study of tezepelumab 700 mg administered intravenously in adults with mild atopic asthma. Study D5180C00002 was a single-dose pharmacokinetic (PK) study of tezepelumab 140 mg administered SC in adolescents with mild to moderate asthma. Both studies were excluded from the pooling as they were conducted in study subjects with milder disease than those in the pooled studies, and the dosing regimen and/or method of administration was not in-line with the proposed 210 mg administered SC Q4W.

The duration of exposure, exposure by age group and sex, exposure by dose, and exposure by ethnic/racial origin for tezepelumab based on the Primary Safety Pool and the Exposure Pool are presented in Table II-1, Table II-2, Table II-3, and Table II-4, respectively.

Table II-1 Duration of Exposure

Duration of exposure	Patients (n [%])	Person Time (subject-years)
Primary Safety Pool[a]		
≥ 4 weeks	662 (99.5)	636.41
≥ 8 weeks	653 (98.2)	635.58
≥ 12 weeks	649 (97.6)	634.89
≥ 16 weeks	647 (97.3)	634.40
≥ 20 weeks	635 (95.5)	630.43
≥ 24 weeks	630 (94.7)	628.42
≥ 28 weeks	629 (94.6)	627.95
≥ 36 weeks	625 (94.0)	625.51
≥ 44 weeks	620 (93.2)	621.83
≥ 48 weeks	615 (92.5)	617.49
≥ 52 weeks	541 (81.4)	544.70
≥ 60 weeks	0 (0.0)	0
Total	665 (100.0)	636.56
Exposure Pool[b]		
≥ 4 weeks	1010 (99.6)	837.65
≥ 8 weeks	1001 (98.7)	836.82
≥ 12 weeks	995 (98.1)	835.75
≥ 16 weeks	992 (97.8)	835.02
≥ 20 weeks	976 (96.3)	829.71
≥ 24 weeks	971 (95.8)	827.71
≥ 28 weeks	752 (74.2)	723.13
≥ 36 weeks	703 (69.3)	695.58

Table II-1 Duration of Exposure

Duration of exposure	Patients (n [%])	Person Time (subject-years)
≥ 44 weeks	687 (67.8)	683.55
≥ 48 weeks	668 (65.9)	666.66
≥ 52 weeks	541 (53.4)	544.70
≥ 60 weeks	0 (0.0)	0
Total	1014 (100.0)	837.86

[a] Primary Safety Pool (210 mg SC Q4W dose only): Studies D5180C00007 and CD-RI-MEDI9929-1146.

[b] Exposure Pool: Studies (210 mg SC Q4W dose only): D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011 and D5180C00013.

n, number of subjects; Q4W, every 4 weeks; SC, subcutaneous.

Source: ISS Table 3.1

Table II-2 Exposure by Age Group and Gender

	Patients (n [%])		Person Time (subject-years)	
Age group	**M**	**F**	**M**	**F**
Primary Safety Pool[a]				
≥ 12 to < 18 [adolescents] years	20 (3.0)	21 (3.2)	19.24	20.06
≥ 18 to < 65 years	183 (27.5)	322 (48.4)	175.55	308.67
≥ 65 years	40 (6.0)	79 (11.9)	38.59	74.44
Total	243 (36.5)	422 (63.5)	233.39	403.17
Exposure Pool[b]				
≥ 12 to < 18 [adolescents] years	35 (3.5)	30 (3.0)	26.38	24.35
≥ 18 to < 65 years	291 (28.7)	475 (46.8)	236.41	399.78
≥ 65 years	70 (6.9)	113 (11.1)	55.44	95.50
Total	396 (39.1)	618 (60.9)	318.22	519.64

[a] Primary Safety Pool (210 mg SC Q4W dose only): Studies D5180C00007 and CD-RI-MEDI9929-1146.

[b] Exposure Pool (210 mg SC Q4W dose only): Studies D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011 and D5180C00013.

F, female; M, male; n, number of subjects; Q4W, every 4 weeks; SC, subcutaneous.

Source: ISS Table 3.2

Table II-3 Exposure by Dose

Dose of Exposure	Patients (n)	Person Time (subject-years)
Primary Safety Pool[a]		
210 mg Q4W	665	636.56
Total	665	636.56

Table II-3 Exposure by Dose

Dose of Exposure	Patients (n)	Person Time (subject-years)
Exposure Pool[b]		
70 mg Q4W	138	136.5
210 mg Q4W	1014	837.9
280 mg Q2W	137	132.5
Total	1289	1106.8

[a] Primary Safety Pool (210 mg SC Q4W dose only): Studies D5180C00007 and CD-RI-MEDI9929-1146.

[b] Exposure Pool (all doses of tezepelumab studied): Studies D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011 and D5180C00013.

n, number of subjects; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

Source: ISS Tables 1.2.1 and 2.2.2.

Table II-4 Exposure by Racial Origin

Race	Patients (n [%])	Person Time (subject-years)
Primary Safety Pool[a]		
White	460 (69.2)	437.74
Black or African American	33 (5.0)	30.54
Asian	151 (22.7)	148.83
Other[b]	21 (3.2)	19.45
Total	665 (100.0)	636.56
Exposure Pool[c]		
White	745 (73.5)	603.82
Black or African American	52 (5.1)	39.18
Asian	195 (19.2)	174.87
Other[b]	22 (2.2)	20.00
Total	1014 (100.0)	837.86

[a] Primary Safety Pool (210 mg SC Q4W dose only): Studies D5180C00007 and CD-RI-MEDI9929-1146.

[b] Other: Includes Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native categories from eCRF.

[c] Exposure Pool (210 mg SC Q4W dose only): Studies D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011 and D5180C00013.

n, number of subjects; Q4W, every 4 weeks; SC, subcutaneous.

Source: ISS Table 3.3

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Known history of allergy or reaction to any component of the drug formulation

Reason for exclusion: Patients with a known allergy or reaction to any component of the drug formulation were excluded from clinical studies for safety reasons to ensure they were not exposed to product to which they had a documented allergy/reaction.

Is it considered to be included as missing information: No

Rationale: Tezepelumab is contraindicated in patients who have known hypersensitivity to tezepelumab or any of its excipients; therefore, this population is not relevant as missing information.

Patients with a history of cancer

Reason for exclusion: Specific exclusions applied to patients with a history of certain types of malignancy to ensure that the medical conditions or concomitant therapy for the condition did not confound the assessment of safety of tezepelumab. Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix were eligible to enter tezepelumab clinical studies provided that the patient was in remission and curative therapy was completed at least 12 months prior to entry into the study. Patients who have had other malignancies were eligible provided that the patient was in remission and curative therapy was completed at least 5 years prior to entry into the study.

Is it considered to be included as missing information: No

Rationale: There are no data to suggest that the safety profile for tezepelumab in patients with a history of cancer will be different than that of the general target population. Hence, use of tezepelumab in patients with a history of cancer is not considered to be missing information.

Presence of active helminth parasitic infection

Reason for exclusion: Tezepelumab has potential inhibitory effects on immune responses mediated by T helper cell type 2 (Th2) cells through blockade of TSLP and may decrease the host's protective response to helminth infection. Theoretically, this may cause a worsening of parasitic infection by interfering with the expulsion of helminthic parasites. Therefore, patients with a helminth parasite infection diagnosed within 6 months prior to Visit 1 that was not treated with, or had failed to respond to, standard of care therapy were excluded from clinical studies and those at high risk of infection were monitored during the studies for these infections per local medical practice.

Is it considered to be included as missing information: No

Rationale:

There is a theoretical potential risk that use of tezepelumab in this population could cause a worsening of an existing parasitic infection but there have been no confirmed cases of helminth infection reported in the clinical study programme to date. Should a helminth infection occur, prescribers are aware of the possible risk, which can be managed through routine clinical practice. Section 4.4 of the SmPC advises that patients should be treated for pre-existing helminth infections before initiating therapy with tezepelumab, therefore it is anticipated that use in this population will be limited. Given that exposure in this population is unlikely and there is insufficient evidence of a different safety profile in this population, patients with active helminth infection are not considered relevant for inclusion as missing information.

Receipt of live attenuated vaccines

Reason for exclusion: Patients were excluded from clinical studies if they had received any live attenuated vaccines within a short period of time (15 or 30 days) prior to the date of randomisation and were not permitted to receive such vaccines during the clinical study conduct. Patients were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data of tezepelumab and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: For some biologics, including those for rheumatologic disease (ACR 2015), there is a theoretical concern that disseminated viral shedding and infection can occur when live attenuated vaccines are given concomitantly with biologic use. Consequently, Section 4.5 of the proposed SmPC advises that use of live attenuated vaccines should be avoided in patients who are receiving tezepelumab. Given that exposure is in this population is unlikely, receipt of live attenuated vaccines is not considered relevant for inclusion as missing information.

Receipt of inactivated vaccines

Reason for exclusion/restriction: Receipt of inactivated vaccines was allowed in the 5 Phase 2 and 3 studies. In 4 of the studies (D5180C00007, D5180C00009, D5180C00011, and D5180C00013), receipt of inactivated vaccines was allowed provided they were not administered within 5 days before or after any study visit/investigational product (IP) administration. This restriction was applied in order to avoid factors that may confound a complete understanding of the safety and efficacy data of tezepelumab, and to ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: For those patients who received inactivated vaccines during clinical studies there is no apparent evidence of a different safety profile compared with those who did not receive vaccination.

Patients with a positive human immunodeficiency virus (HIV) test at screening or patients taking antiretroviral medications; patients with medical history of hepatitis B, hepatitis C, hepatitis B surface antigen positivity, or hepatitis C virus antibody serology

Reason for exclusion: Patients with positive HIV test, those taking antiretroviral medications, those with medical history of hepatitis B, hepatitis C, hepatitis B surface antigen positivity, or those with hepatitis C virus antibody serology were excluded from clinical studies to ensure that the study safety results were not confounded by the presence of pre-existing illnesses and to mitigate for a theoretical concern related to potential viral activation/re-activation.

Is it considered to be included as missing information: No

Rationale: There is no reason to suggest that the safety profile of tezepelumab when administered to patients with positive HIV test or those taking antiretroviral medications or those with medical history of hepatitis B, hepatitis C, hepatitis B surface antigen positivity, or hepatitis C virus antibody serology will differ from that characterised so far in the general target population. Clinical data from studies in the Primary Safety Pool (D5180C00007 and CD-RI-MEDI9929-1146) and from Study D5180C00009 indicate that antibody production in terms of IgA, IgG and IgM appears to be intact in patients treated with tezepelumab, thus no potential viral activation/re-activation in patients exposed to tezepelumab is expected.

Active liver disease, including jaundice or alanine aminotransferase or aspartate aminotransferase or alkaline phosphatase level ≥ 2.0 times the upper limit of normal

Reason for exclusion: To ensure patient safety during their participation in the study and to ensure the study results, specifically liver findings, were not confounded by pre-existing illnesses.

Is it considered to be included as missing information: No

Rationale: IgG monoclonal antibodies are not primarily cleared via the hepatic pathway, thus change in hepatic function is not expected to influence tezepelumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and total bilirubin) had no clinically relevant effect on tezepelumab clearance. For this reason, it is not anticipated that the safety profile will be different in patients with active liver disease compared with that characterised so far in the general target population.

Paediatric patients aged less than 12 years

Reason for exclusion: Paediatric patients less than 12 years old will not be exposed to the investigational product until after the benefit-risk profile is established for the intended adult and adolescent population.

Is it considered to be included as missing information: No

Rationale: Tezepelumab is not indicated in paediatric patients <12 years old, therefore this population is not relevant for missing information.

Elderly patients aged greater than 80 years

Reason for exclusion: Comorbid conditions may put elderly people at increased risk and may confound assessment of safety. Thus, this vulnerable population was excluded in all tezepelumab clinical studies.

Is it considered to be included as missing information: No

Rationale: Patients greater than 80 years old represent a small proportion of the population of adults with severe asthma; in the ISAR (described in Section II.1) of approximately 5000 patients, only 4.2% of were ≥ 80 years old, whereas 43.6% of subjects were 18 to 54 years old, and 52.1% of subjects were 55 to 79 years old [Wang et al 2020]. Thus, expected exposure of patients greater than 80 years old to tezepelumab for treatment of asthma in marketed use is expected to be limited.

In the Primary Safety Pool (age range 12 to 80 years old), a total 119 out of 665 (17.9%) subjects who received tezepelumab 210 mg SC Q4W were ≥ 65 years old (Table II-2). The safety profile of tezepelumab in asthma patients ≥ 65 years old was similar to that in asthma patients ≥ 18 to <65 years old and differences in tezepelumab PK exposures between age groups were small relative to the overall variability of exposures. Consequently, there is no scientific evidence to anticipate a different safety profile for tezepelumab in patients > 80 years old than that in the general target population and further characterisation in this population is thus not considered feasible or warranted. Therefore, this population is not relevant for missing information.

Pregnancy or lactation

Reason for exclusion: In order to ensure the safety of this patient population during the development phase of the medicinal product, these patients were excluded.

Is it considered to be included as missing information: Yes

II.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

II.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table II-5 Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	Although pregnant subjects were excluded from the clinical development programme, there were 7 reports of pregnancy during the trials in participating female subjects exposed to tezepelumab (details provided in Section II.7.3.2).
Breast-feeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Patients with active liver disease, including jaundice or alanine aminotransferase or aspartate aminotransferase or alkaline phosphatase level ≥ 2.0 times the upper limit of normal[a]	Not included in the clinical development programme
Patients with renal impairment[b]	7 subjects[c]
Patients with cardiovascular impairment[b]	28 subjects[c]

[a] This is the specific liver disease exclusion criterion included in the Primary Safety Pool studies.

[b] Renal, hepatic or cardiovascular impairment were subject of a general exclusion criterion as follows: 'Patients were excluded from the clinical development programme if they had renal, hepatic or cardiovascular impairment that was not stable, in the opinion of the Investigator, and could affect the safety of the patient throughout the study or influence the findings of the studies or their interpretations or impede the patient's ability to complete the entire duration of study'.

[c] The renal and cardiovascular impairment categories were based on searches of the Primary Safety Pool subject population baseline medical history MedDRA 23.1 preferred terms. The search strategy for renal impairment included the Standardised MedDRA Query (SMQ) of chronic kidney disease. The search strategy for cardiovascular impairment included SMQ (narrow) cardiomyopathy, cardiac failure, myocardial, infarction, and other ischaemic heart disease.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented here is based on tezepelumab's monthly actual ex-factory sales volume from each local affiliate. These data represent all tezepelumab formulation delivered to various distribution channels (e.g., wholesalers, pharmacies, etc) worldwide.

The sales volume is provided as the number of units distributed as of 31 August 2022. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient took 1 unit (210 mg/1.91mL) of tezepelumab every 4 weeks and 13 units in total per year (52 weeks). Therefore, a patient-year worth of exposure is calculated by dividing number of units by 13 (13 units of 210 mg/1.91mL tezepelumab per patient year).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to tezepelumab. More detailed patient-level data (eg, gender, ethnicity, age category, off-label use, specific populations etc) are not available.

II.5.2 Exposure

Cumulative global post-marketing patient exposure for tezepelumab (210◦mg/1.91mL) was estimated to be approximately 1774 patient-years, representing 100% of the exposure since launch (17 December 2021) to 31 August 2022. Approximately 0.12% of the worldwide distribution was in the European region and 99.88% was in the North American region.

The cumulative regional sales figures are presented in the table below.

Data stratified by indication, gender, age group, region are not available.

Table II-6 Exposure by tezepelumab cumulative sales, number of units by region

Formulation	Europe	North America	Japan	Rest of the world	Total
Single-dose pre-filled syringe (210 mg/1.91 mL)	27	23032	NA	NA	23059

NA Not Applicable

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

In view of the mechanism of action of tezepelumab, no potential for misuse for illegal purposes exists.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

II.7.1.1 Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised):

- **Serious hypersensitivity reactions:** Hypersensitivity and anaphylactic reactions are well-known reactions that can occur with protein-based therapies. In the Primary Safety Pool, the incidence of serious hypersensitivity reactions was low and similar in the tezepelumab and placebo treatment groups (0.2% of subjects and 0.3% of subjects, respectively); none were considered related to IP by the investigator. In the Primary Safety Pool and the wider clinical study programme, there were no events of anaphylaxis that the investigator considered to be causally related to tezepelumab. These reactions are managed as per routine clinical practice and product labelling (see Section 4.4 of the SmPC).
- **Helminth infections:** Tezepelumab has potential inhibitory effects on immune responses mediated by Th2 cells through blockade of TSLP and may decrease the host's protective response to helminth infection. There is a potential theoretical risk that use of tezepelumab could cause a worsening of an existing parasitic infection, however, there have been no confirmed cases of helminth infection reported in the clinical study programme to date. Helminth infections are usually nonserious and, should a helminth infection occur, prescribers will be aware of the possible risk which can be managed through routine clinical practice. Section 4.4 of the SmPC advises that patients with a pre-existing helminth infection should be treated before initiating therapy with tezepelumab, and that if patients become infected while receiving treatment with tezepelumab and do not respond to anti-helminth treatment, treatment with tezepelumab is to be discontinued until the infection resolves.

Known risks that do not impact the risk-benefit profile:

- Arthralgia
- Pharyngitis
- Injection Site Reactions
- Rash

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks

There are no important identified risks for tezepelumab.

Important Potential Risk: Serious Infections

Risk Benefit Impact

The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to infection. Given the potential theoretical risk, serious infections are included as an important potential risk.

Medically significant, serious infections have the potential to result in serious consequences such as hospitalisation, fatality, or a detrimental impact on patient's quality of life. Serious infection, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Important Potential Risk: Serious Cardiac Events

Risk Benefit Impact

There is no known mechanism by which blocking TSLP would lead to cardiac pathophysiology. However, a numeric imbalance in Cardiac Disorder SOC SAEs was observed in the long-term clinical study D5180C00018 (described in Section II.7.3.1), therefore, serious cardiac events are included as an important potential risk.

Serious cardiac events have the potential to result in serious consequences such as hospitalisation, loss of physical capacity due to persisting symptoms, fatality, or a detrimental impact on patient's quality of life. Serious cardiac events, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Important Potential Risk: Malignancy

Risk Benefit Impact

As described in Section II.2.1, there is some evidence from different animal models and in human translational studies linking TSLP over-expression to the promotion of tumour growth and metastasis (reviewed also by Protti and De Monte 2020 and Corren and Ziegler 2019), which would suggest that inhibition of TSLP would be more likely to have anti-tumour activity than be associated with increased cancer risk. However, given the long-term treatment intended for a chronic disease and the nature of malignancy development, malignancy is included as an important potential risk.

Malignancies have the potential to result in serious consequences such as hospitalisation, fatality, or a detrimental impact on patient's quality of life. Malignancies, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Missing Information: Use in pregnant and breastfeeding women

Severe asthma affects women of childbearing potential age; thus, it is important to further evaluate the impact of tezepelumab in pregnant or breastfeeding women as exposure is anticipated and tezepelumab is not contraindicated in this population.

Risk-Benefit Impact

Nonclinical data conclude that reproductive risks associated with tezepelumab administration are low. Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier, therefore, tezepelumab may be transmitted from the mother to the developing foetus. It is unknown whether tezepelumab is excreted in human milk, however, IgG antibodies are known to be present in human milk. Consequently, the possibility of harm to the foetus and breastfed infant cannot be excluded. The use of tezepelumab in pregnancy will be evaluated in the post-marketing setting through a non-interventional pregnancy study (Section III.2.1).

Missing Information: Long-term use (> 1 year)

Limited information is available on the long-term use (greater than 1 year) of tezepelumab 210 mg SC. In completed Phase 2 and 3 studies, subjects with severe asthma received tezepelumab for up to 52 weeks (refer to details in Section II.7.3.2). In the proposed marketed use, exposure to tezepelumab treatment for > 1 year is expected.

Risk-Benefit Impact

In order to provide data on the long-term effects of tezepelumab, a long-term extension study (D5180C00018) is currently ongoing (refer also to Table III-1). This study includes patients previously treated in Studies D5180C00007 and D5180C00009 and will further characterise the long-term safety profile of tezepelumab 210 mg SC Q4W for up to a total of 104 weeks of treatment. Summary exposure data as of the primary database lock for this study (9 December 2021) are provided in Section II.7.3.2. The final database lock for this study is planned for July 2022.

II.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

II.7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

II.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk:

There are no important identified risks for tezepelumab.

Important Potential Risk: Serious Infections

Potential Mechanisms

The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to infection.

Evidence source(s) and strength of evidence

There is a theoretical risk of infection based on the mechanism of action of tezepelumab, however there were no imbalances in the incidence of serious infections observed in the tezepelumab and placebo groups in the Primary Safety Pool or the long-term extension study D5180C00018.

In addition, nonclinical data do not suggest a potential impact of tezepelumab treatment on immune responses and no increase in infection was observed in treated animals. A relationship of inhibitory effects on immune responses mediated by Th2 cells and serious infection or infection overall has not been established with tezepelumab.

Characterisation of the risk

Clinical trial data from the Primary Safety Pool show that the incidence of subjects with SAEs reported in the Infections and infestations SOC was similar in the tezepelumab and placebo groups (13/665 subjects [2.0%] versus 15 /669 subjects [2.2%], respectively; 2.02 versus 2.35 per 100 subjects-years, respectively); of these SAEs, 2 events were considered causally related to IP by the investigator (1 subject for each event): upper respiratory tract infection (tezepelumab group [0.2%]) and lung abscess (placebo group [0.1%]).

Pooled data from Study D5180C00018 show that the incidence of subjects with SAEs reported in the infections and infestations SOC was similar in the tezepelumab and placebo groups (28/840 subjects in the All Teze group [ie, all subjects originally randomised to tezepelumab in the predecessor studies, D5180C00007 and D5180C00009, and randomised to tezepelumab in Study D5180C00018], versus 19/607 subjects in the Rand Pbo group [ie, all subjects randomised to placebo in the predecessor studies regardless of participation in D5180C00018, and excluding data post re-randomisation to tezepelumab in the extension

period for subjects that participated in D5180C00018], incidence rates per 100 subject-years of 2.18 versus 2.38, respectively). No apparent trends in serious infections were noted.

Very few fatal infection events were observed across the tezepelumab asthma programme, and the incidence of AEs of infection and SAEs of infection is similar across treatment groups. There were 5 fatal infections overall in Study D5180C00018 (4/840 subjects in the All Teze group versus 1/607 subject in the Rand Pbo group; 0.29 versus 0.12 per 100 subject-years, respectively), with no other fatal infections reported in the rest of the completed studies in the tezepelumab asthma programme. None of the fatal infection events were considered to be causally associated by the Investigator or the Sponsor and all were considered by the blinded Independent Adjudication Committee to be unlikely to be related to IP (none were considered to have certain or probable/likely causality).

Risk factors and risk groups

No specific risk factors or subgroups of patients have been identified in respect of increased potential risk of infection with tezepelumab.

Preventability

As per standard medical practice, patients should be encouraged to seek medical advice if signs or symptoms suggestive of any infection occur in order to receive early medical treatment (eg, oral antibiotics, etc) before an infection becomes serious. If infection occurs, close monitoring and early intervention can mitigate the impact.

As noted in Section 4.4 of the SmPC, patients with pre-existing serious infections should be treated before initiating therapy with tezepelumab. If patients develop a serious infection while receiving tezepelumab treatment and do not respond to treatment, therapy with tezepelumab should be discontinued until the serious infection resolves.

Impact on the risk-benefit balance of the product

Medically significant, serious infections have the potential to result in serious consequences such as hospitalisation, fatality, or a detrimental impact on patient's quality of life. Serious infection, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Further characterisation of this potential risk through pharmacovigilance activities (as described in Sections III.2 and III.3) will provide a better understanding of this risk and further define potential impact on the benefit-risk of tezepelumab.

Public health impact

As the potential impact is to the treated population of patients with severe asthma only, there is no public health impact.

Important Potential Risk: Serious Cardiac Events

Potential Mechanisms

There is no known mechanism by which blocking TSLP would lead to cardiac pathophysiology. Little or no expression of TSLP and TSLPR is detected in human cardiac tissue (Uhlén et al 2015). Studies using TSLPR deficient or knockout mice have shown no adverse CV findings (Al-Shami et al 2005, Carpino et al 2004). While there are multiple adaptive and innate pathways where TSLP activity, or the blocking of TSLPR, may influence inflammation and inflammatory mediators; mechanisms specific to the human cardiovascular system have not been identified.

Evidence source(s) and strength of evidence

A numeric imbalance in Cardiac Disorder SOC SAEs was observed in Study D5180C00018, however, there were no imbalances in overall cardiac SOC events in the Primary Safety Pool or the long-term extension study D5180C00018.

No cardiac safety signals were identified in the tezepelumab safety pharmacology study, nonclinical toxicology studies, or tissue cross-reactivity study with human and cynomolgus monkey tissues. These studies tested tezepelumab dose levels that resulted in safety margins of greater than 100-fold on an AUC and C_{max} basis to the maximum recommended human dose of a subcutaneous 210 mg dose, every four weeks.

Characterisation of the risk

In the Primary Safety Pool no imbalance in the incidence of overall Cardiac Disorder SOC events (serious and nonserious combined) was observed for tezepelumab and placebo treatment groups (20/665 [3.0%] subjects, incidence rate 3.11 per 100 subject years versus 19/669 [2.8%] subjects, incidence rate 2.98 per 100 subject-years, respectively). In Study D5180C00018, there was no imbalance in the incidence of overall AEs in the Cardiac Disorders SOC (serious and nonserious combined) observed for tezepelumab and placebo groups (40/840 subjects, 3.12 per 100 subject-years in the All Teze group versus 22/607 subjects, incidence rate of 2.75 per 100 subject-years in the Rand Pbo group).

In the Primary Safety Pool, the incidence of Cardiac Disorders SOC SAEs was low in the tezepelumab and placebo treatment groups (5/665 subjects, incidence rate 0.78 per 100 subject-years versus 2/669 subjects, incidence rate of 0.31 per 100 subject-years, respectively). However, in Study D5180C00018, an imbalance in rates of Cardiac Disorders SAEs between treatment groups was apparent at the grouped SOC level and not at the

individual PT level (17/840 subjects, incidence rate of 1.33 per 100 subject-years in the All Teze group versus 0/607 subjects, incidence rate of 0.00 per 100 subject-years in the Rand Pbo group). It is noted that 4 of the 5 events in the Primary Safety Pool in the tezepelumab 210 mg group were observed in Study D5180C00007 and are therefore also counted as part of the imbalance observed in DESTINATION. Analyses by PTs showed no apparent pattern in types or categories of cardiac events and the events were also observed across different HLGT categories (ie, cardiac arrhythmias, coronary artery disease, heart failures, and myocardial disorders).

A small number of Cardiac Disorder SOC Fatal AEs have been observed in Study D5180C00018 (3/840 subjects in the All Teze group and 1/607 subjects in the Rand Pbo group; incidence rates of 0.22 and 0.12 per 100 subject-years, respectively). None of the fatal events were considered causally related to IP by the Investigator. All were considered as unlikely to be related to IP by the blinded Independent Adjudication Committee. No other events of Cardiac Disorder SOC fatal AEs were observed within a broader pool of studies in asthma assessing 210 mg Q4W multiple dose.

Risk factors and risk groups

There is no evidence of a specific factor that would increase the risk of fatal cardiac events in subjects receiving tezepelumab, and no specific subgroup of patients who may be at an increased risk of serious cardiac events has been identified.

Preventability

As noted in SmPC Section 4.4, 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.

Impact on the risk-benefit balance of the product

Serious cardiac events have the potential to result in serious consequences such as hospitalisation, loss of physical capacity due to persisting symptoms, fatality, or a detrimental impact on patient's quality of life. Serious cardiac events, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Further characterisation of this potential risk through pharmacovigilance activities (as described in Sections III.2 and III.3) will provide a better understanding of this risk and further define potential impact on the benefit-risk of tezepelumab.

Public health impact

As the potential impact is to the treated population of patients with severe asthma only, there is no public health impact.

Important Potential Risk: Malignancy

Potential Mechanisms

As described in Section II.2.1, there is evidence from different animal models and in human translational studies linking TSLP over-expression to the promotion of tumour growth and metastasis (reviewed also by Protti and De Monte 2020, and Corren and Ziegler 2019), which would suggest that inhibition of TSLP would be more likely to have anti-tumour activity than be associated with increased cancer risk.

Evidence source(s) and strength of evidence

Malignancies have been reported in the completed asthma studies of tezepelumab. The incidence of malignancies reported was low and similar across tezepelumab and placebo treatment groups in the Primary Safety Pool and in the long-term study D5180C00018 including up to 2 years of treatment. However, longer-term exposure data are not available, and a potential theoretical risk of malignancy remains.

Data from chronic toxicity studies (summarised in Section II.2.1) did not reveal any product-specific concerns with tezepelumab regarding malignancy risk.

Characterisation of the risk

In the Primary Safety Pool, a total of 11 subjects reported a malignancy in the on-treatment period: 6 subjects (0.9%) in the tezepelumab group and 5 subjects (0.7%) in the placebo group. Malignancies in the tezepelumab group included 2 (0.3%) subjects with basal cell carcinoma, 2 (0.3%) subjects with malignant melanoma in situ, 2 (0.3%) subjects with prostate cancer, and 1 (0.2%) subject with squamous cell carcinoma (2 malignancies were reported in one subject). In the long-term study D5180C00018, a total of 12 subjects reported a malignancy on treatment, and the incidence of subjects with malignancies was similar in the tezepelumab and placebo groups (7/840 subjects in the All Teze group versus 5/607 subjects in the Rand Pbo group; incidence rates of 0.55 and 0.63 per 100 subject-years, respectively). Malignancies reported in the Rand Teze group were as follows: malignant melanoma in situ (2 subjects), basal cell carcinoma (1 subject), colon cancer stage IV (1 subject), colorectal cancer (1 subject), invasive breast carcinoma (1 subject), prostate cancer (1 subject) and squamous cell carcinoma (1 subject).

No apparent trends in malignancies were noted in either the Primary Safety Pool or Study D5180C00018 with up to 104 weeks of treatment with tezepelumab.

Risk factors and risk groups

No specific risk factors or subgroups of patients have been identified in respect of potential malignancy risk for patients treated with tezepelumab.

Preventability

The general risk of malignancy can be reduced by managing lifestyle factors such as smoking, alcohol use, and activity levels. There is currently no evidence of an increased risk of malignancy for tezepelumab specifically therefore general measures such as early detection and managing lifestyle factors are appropriate.

Impact on the risk-benefit balance of the product

Malignancies have the potential to result in serious consequences such as hospitalisation, fatality, or a detrimental impact on patient's quality of life. Malignancies, if confirmed to be causally related, would impact the benefit-risk of tezepelumab.

Further characterisation of this potential risk through pharmacovigilance activities (as described in Sections III.2 and III.3) will provide a better understanding of this risk and further define potential impact on the benefit-risk of tezepelumab.

Public health impact

As the potential impact is to the treated population of patients with severe asthma only, there is no public health impact.

II.7.3.2 Presentation of Missing Information

Missing information: Use in pregnant and breastfeeding women

Evidence source:

Pregnancy:

No adverse effects on maternal health, pregnancy outcome, embryo-foetal development, or neonatal development were observed in a prenatal and postnatal development study conducted in cynomolgus monkeys following intravenous tezepelumab administration up to 300 mg/kg/week from early gestation through delivery. The safety margins from this study (calculated using Gestation Day 139-142 exposure prior to parturition) are approximately 168 times the maximum recommended human dose (MRHD) on an area under the concentration-time curve at steady state basis, and 259 times the MRHD on a maximum observed serum concentration at steady state basis.

The exposure data on pregnancy from the clinical studies are limited and therefore insufficient to inform on drug-associated risk in this population. Human IgG antibodies, such as tezepelumab, are transported across the placenta barrier, therefore, tezepelumab may be transmitted from the mother to the developing foetus.

Eleven patients in the confirmatory asthma exacerbation studies reported pregnancies, 4 in CD-RI-MEDI9929-1146 (2 in the tezepelumab 210 mg Q4W group and 2 in the tezepelumab 280 mg Q2W group [all occurred in the on-treatment period]), and 7 in D5180C00007 (3 in the tezepelumab 210 mg Q4W group [2 during the on-treatment period] and 4 in the placebo group [2 during the on-treatment period]). Seven patients delivered healthy, full term infants. One patient in the CD-RI-MEDI9929-1146 tezepelumab 280 mg group delivered pre-term twins after experiencing an SAE of pre-eclampsia. One patient in the CD-RI-MEDI9929-1146 tezepelumab 280 mg group was reported to have a spontaneous abortion at 11 weeks into the pregnancy. Two patients in D5180C00007 were reported to have had spontaneous abortions at 6 and 9 weeks into the pregnancies, respectively, both patients were in the tezepelumab 210 mg group, of which one became pregnant during the on-treatment period. No additional information was provided for the 3 patients who had spontaneous abortions. No pregnancies were reported in any of the other completed tezepelumab asthma clinical studies.

As patients were discontinued from IP once their pregnancy was known, there are no data relating to patients taking tezepelumab throughout the entirety of their pregnancy, and there are no data relating to the effect of tezepelumab on lactating patients or their offspring.

Breastfeeding: In nonclinical species the possibility of transfer from maternal animal to the infant via milk could not be excluded. It is unknown whether tezepelumab is excreted in human milk. However, IgG antibodies are known to be present in human milk. Therefore, risk to the breastfed child cannot be excluded.

In Section 4.6 of the SmPC, it is recommended not to use tezepelumab during pregnancy unless the expected benefit to the pregnant mother is greater than any possible risk to the foetus. It is also stated that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from using tezepelumab, taking into account the benefit and risk of breast-feeding for the child and the benefit of therapy for the woman.

Population in need of further characterisation:

Use of tezepelumab in pregnant women will be studied in a post-marketing secondary data collection, observational, 2-stage study using healthcare databases (Section III.2.1).

Missing information: Long-term use (> 1 year)

Evidence source:

Limited information is available on the long-term use of tezepelumab 210 mg SC. In completed Phase 2 and 3 studies, subjects with severe asthma received tezepelumab for up to 52 weeks. In the proposed marketed use, exposure to tezepelumab treatment for > 1 year is expected.

In the Primary Safety Pool, where studies included a treatment period of up to 52 weeks, out of a total of 665 subjects who received tezepelumab 210 mg SC Q4W, 615 (92.5%) and 541 (81.4%) subjects, respectively, received treatment for ≥ 48 weeks and ≥ 52 weeks (Table II-1). In the Exposure Pool (all 5 Phase 2 and 3 studies), where the treatment period ranged from 24 to 52 weeks, out of a total of 1014 subjects who received tezepelumab 210 mg SC Q4W, 668 (65.9%) and 541 (53.4%), respectively, received treatment for ≥ 48 weeks and for ≥ 52 weeks (Table II-1). A Phase 3 clinical study is currently ongoing to characterise the long-term safety profile of tezepelumab as described below. As of the primary database lock for D5180C00018 (9 December 2021), based on pooled exposure data for subjects from both predecessor studies, a total of 839 subjects in the All Teze group were exposed to tezepelumab with an overall mean duration of exposure of 558.7 days (range: 24 to 796 days). The final database lock for this study is planned for July 2022.

Population in need of further characterisation:

The safety and tolerability of tezepelumab 210 mg Q4W SC in long-term use (> 1 year) is being evaluated in an ongoing Phase 3, double-blind, randomised, placebo controlled, parallel group, long-term extension study (D5180C00018), including adults and adolescents with severe uncontrolled asthma previously treated in Studies D5180C00007 and D5180C00009 (Table III-1). This ongoing study is not classified as a post-authorisation safety study (PASS).

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the Safety Concerns

Table II-7 Summary of Safety Concerns

Important identified risks	None
Important potential risks	Serious Infections Serious cardiac events Malignancy
Missing information	Use in pregnant and breastfeeding women Long-term use (> 1year)

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for safety concern(s):

Serious infections, serious cardiac events and malignancies will be monitored using post-marketing targeted follow-up questionnaires (see Annex 4) to obtain additional information about the patient, the underlying disease, all potential risk factors, the sequence of events, diagnostic details, and final outcome.

Other forms of routine pharmacovigilance activities for safety concerns:

Serious infections, serious cardiac events and malignancies will also continue to be monitored through collection of data in ongoing studies, including Study D5180C00024 (OCS reduction study in severe asthma; 28-week treatment period with 12-week safety follow-up; planned N = 207 randomised 2:1 tezepelumab:placebo), and Study D5180C00021 (China/Asia regional efficacy and safety study in severe asthma; 52-week treatment period with 12-week safety follow-up; planned N = 396 randomised 1:1 tezepelumab:placebo).

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

III.2.1 Tezepelumab Pregnancy Study

D5180R00010: A Database Study of the Use (and Safety) of Tezepelumab in Women with Severe Asthma During Pregnancy

Rationale and study objectives

Tezepelumab is anticipated to be a first in class biologic indicated for the treatment of severe asthma based on its mechanism of action. There are risks associated with pregnancy in women with severe asthma and there is limited data available in the tezepelumab clinical programme on pregnancy and pregnancy outcomes. The prevalence of asthma and severe asthma in women of childbearing age, coupled with the chronic nature of treatment, makes inadvertent exposure in pregnancy possible. Hence, the safety of tezepelumab in pregnancy is considered to be missing information for regulatory requirements.

To fill this important knowledge gap, AstraZeneca proposes to conduct a secondary, observational 2-stage study using a healthcare database.

The objectives of the proposed study are the following:

- Stage 1: To monitor the use of tezepelumab in pregnant women with severe asthma to inform the initiation of Stage 2.
- Stage 2:

- To describe pregnancy and delivery outcomes in pregnancies among women with severe asthma exposed to tezepelumab at any time during pregnancy. Outcomes will be assessed by trimester of exposure as a secondary objective.
- To compare frequency of outcomes in pregnant women exposed to tezepelumab with that in those not exposed to tezepelumab.

Study design:

The proposed study is a secondary data collection, observational, 2-stage study using a healthcare database. Once feasibility assessment of data sources has been completed and a data source selected [1], and tezepelumab is well established in the respective markets, Stage 1 will provide data to monitor the use of tezepelumab in pregnant women with severe asthma and is designed to inform when would be the best time to initiate Stage 2. The Stage 1 study will identify the cohort of pregnant women with severe asthma who were exposed to tezepelumab during their pregnancy and have met all the inclusion criteria for the Stage 2 study. Included patients must have background data available before the index date, which is the date of the prescription/dispensing tezepelumab and followed for up to 1 year post-delivery to assess the pregnancy outcomes.

It is anticipated that with the availability of data from Stage 1, Stage 2 will be a safety outcome study that aims to describe pregnancy and delivery outcomes among pregnant women with severe asthma who were exposed to tezepelumab during their pregnancy and compare its frequency with that of the 2 comparator cohorts: (1) Disease cohort: pregnant women with severe asthma who have not been exposed to any biologics; and (2) Non-disease cohort: healthy pregnant women with no current diagnosis of asthma and who have not been exposed to any asthma medications. Appropriate statistical methods to ensure comparability between the cohorts will be used (eg, propensity score matching) and include key known and potential confounders. Incidence rate of pregnancy outcomes will be described by study groups. The incidence rate ratios will be calculated using appropriate statistical methods to ensure comparability between the cohorts.

[1] The following are data sources that will be evaluated in the feasibility assessment but are not limited to: HealthCore Integrated Research Database (HIRD) in the United States (US); Optum Dynamic Assessment of Pregnancies and Infants (Optum DAPI) in the US; IBM MarketScan Commercial Claims and Encounters Database in the US; The Sentinel (including the Mother-Infant dataset) in the US; Clinical Practice Research Datalink (CPRD) in the UK; Swedish National Registries; Finnish National Registries; German Pharmacoepidemiological Research Database (GePaRD); French administrative health care database (SNDS).

Study population:

It is anticipated that the study population for the safety outcome study (Stage 2) will be a total of 800 women, comprising 200 women in the tezepelumab-exposed cohort, 300 women in the treated disease cohort, and 300 women in the non-disease cohort.

Milestones

- Study Protocol: Within 6 months of approval
- Study Start: To be confirmed
- Final Report Submission: To be confirmed

III.2.2 Phase 3 Efficacy and Safety Study of Tezepelumab in Reducing OCS Use in Adults with OCS Dependent Asthma (D5180C00024)

A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled, 28-week Phase 3 Efficacy and Safety Study of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma (SUNRISE)

Rationale and study objectives

The purpose of this global study is to demonstrate the ability of tezepelumab, compared with placebo, to reduce OCS use in adults with severe asthma being treated with maintenance OCS in combination with high dose ICS and LABA, with or without other asthma controller therapies, while maintaining asthma control.

The primary objective of the study is to evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA by assessment of categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control. The key secondary objective is to evaluate the effect of tezepelumab compared with placebo on pre-bronchodilator lung function by evaluation of change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV_1) at Week 28. The study will also evaluate the safety and tolerability of tezepelumab based on assessment of AEs, SAEs, clinical chemistry, haematology and vital signs.

Study design

This is a Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of tezepelumab 210 mg Q4W administered SC for 28 weeks using an accessorised pre-filled syringe, compared with placebo in reducing OCS use in OCS-dependent adult asthma participants.

Study population

The study population comprises adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, and who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.

Approximately 207 participants will be randomised in a 2:1 ratio to receive tezepelumab 210 mg or placebo SC Q4W for a total of 7 doses.

Milestones

- Study Protocol: 07 Feb 2022 (Version 1.0)
- Study Start: estimated Q3 2022
- Final Report Submission: 1H 2026

III.2.3 Phase 3 Regional (China/Asia) Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma (D5180C00021)

A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, 52-week, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma (DIRECTION)

Rationale and study objectives

The purpose of this regional (China/Asia) study is to confirm the efficacy and safety of 210 mg dose of tezepelumab administered SC Q4W in adults (18 to 80 years of age inclusive) with a history of asthma exacerbations and severe, uncontrolled asthma receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS. The study will evaluate the incidence of asthma exacerbations and other efficacy parameters such as lung function, asthma control and quality of life as well as a safety evaluation to further characterise the benefit-risk profile of the drug.

The primary objective of the study is to assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult subjects with severe uncontrolled asthma compared with placebo by evaluation of the primary outcome measure AAER ratio vs placebo over 52 weeks. Key secondary objectives include evaluation of the effect of 210 mg tezepelumab SC Q4W compared with placebo based on assessment of pulmonary function, health status/health related quality of life, asthma control and asthma symptoms, respectively. The study will also evaluate the safety and tolerability of tezepelumab based on assessment of AEs (including SAEs), vital signs, 12-lead ECG, and clinical laboratory tests (clinical chemistry,

haematology, urinalysis). Additional secondary and exploratory objectives are detailed in the study protocol.

Study design

This is a regional, multicentre, randomized, double-blind, placebo controlled, parallel group, phase 3 study designed to evaluate the efficacy and safety of tezepelumab 210 mg administered Q4W in adults with severe, uncontrolled asthma on medium to high-dose ICS and at least one additional asthma controller medication with or without OCS.

Study population

The study population comprises adults (18 to 80 years of age inclusive) with a history of asthma exacerbations and severe, uncontrolled asthma receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS.

A total of 396 subjects will be randomized in the study in a 1:1 ratio to either tezepelumab or placebo (198 per group), with approximately 70% of the subjects (278 subjects: 139 subjects per group) from China. The rest of the subjects will come from other countries. The subjects will be stratified by region (China/non-China).

Milestones

- Study Protocol: 17 May 2022 (Version 5.0)
- Study Start: first subject enrolment June 2019
- Final Report Submission: 1H2025

III.2.4 Serious Cardiac Events Post-Authorisation Safety Study

A Non-Interventional Multi-Country Post-Authorisation Safety Study (PASS) to Assess the Incidence of Serious Cardiac Events in Patients with Severe Uncontrolled Asthma Exposed to Tezepelumab

Rationale and study objectives

A numerical imbalance in serious cardiac events was observed in a single study (D5180C00018); thus to further characterise serious cardiac events AstraZeneca will conduct a non-interventional multi-country PASS to assess risk of serious cardiac events with tezepelumab treatment in patients with severe uncontrolled asthma.

The main aim of the tezepelumab non-interventional study is to evaluate possible effects of tezepelumab exposure in patients with severe uncontrolled asthma on serious cardiac events.

The overall objective of the study is to compare the incidence of serious cardiac events in patients with severe uncontrolled asthma newly exposed to tezepelumab with the incidence in comparable severe uncontrolled asthma patients exposed to other standard of care regimens. The specific objectives are to be determined following consultation with CHMP/PRAC.

Study Design

This study will be a non-interventional observational cohort study of patients with severe uncontrolled asthma receiving tezepelumab compared with comparable patients with severe uncontrolled asthma on standard of care using a tezepelumab new user design and propensity score approach. Multiple observational data sources in the EU will be analysed separately and, subsequently, a meta-analysis will be performed (where feasible). Sources in the US may also be included if required to attain desired sample size.

Potential outcomes under consideration include: MACE (Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); MACE+ (MACE + Hospitalisation for heart failure, unstable angina); individual components of MACE, Hospitalisation for heart failure, unstable angina; and a broader definition of serious cardiac events (to be determined).

Study Population

The study population will be patients with severe uncontrolled asthma, aged ≥ 12 years in-line with the current tezepelumab indication. Patients will be selected using asthma diagnosis codes and medication prescription codes in the EHR sources that are indicative of severe uncontrolled asthma. Specific inclusion/exclusion criteria will be defined in the protocol development stage.

Milestones

- Protocol submission: 1 year post-authorisation of tezepelumab
- Start of data collection: post final PRAC approval of the protocol
- Final report submission: to be determined after protocol development

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones for EMA	Due dates
Category 1 – Not applicable				
Category 2 – Not applicable				

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones for EMA	Due dates
Category 3 - Required additional pharmacovigilance activities				
Study D5180R00010: Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy Planned	To describe the use of tezepelumab in women with severe asthma during pregnancy	Use in pregnancy	Study Protocol Final study report	Within 6 months of approval To be confirmed
Study D5180C00018 (DESTINATION): Phase 3 LTE study to evaluate the safety and tolerability of tezepelumab in adults and adolescents with severe uncontrolled asthma. Ongoing (This study is not a PASS)	To evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects	Long-term use (> 1 year)	Study Protocol Final study report	Completed 20 Aug 2018 Estimated Nov 2022
Study D5180C00024 (SUNRISE): Phase 3 study to evaluate the efficacy and safety of tezepelumab in reducing OCS use in adults with OCS dependent asthma	To demonstrate the ability of tezepelumab, compared with placebo, to reduce OCS use in adults with severe asthma being treated with maintenance OCS in combination with high dose ICS and LABA with or without other asthma controller therapies, while maintaining asthma control.	Serious infections, serious cardiac events, malignancy	Study Protocol Final study report	07 Feb 2022 (Version 1.0) Estimated date: 1H 2026
Study D5180C00021 (DIRECTION): A regional Phase 3 study to evaluate the efficacy and safety of tezepelumab in adults with severe uncontrolled asthma	To evaluate the efficacy and safety of tezepelumab in adults with severe uncontrolled asthma on medium to high dose ICS and at least one additional asthma controller medication with or without OCS.	Serious infections, serious cardiac events, malignancy	Study Protocol Final study report	17 May 2022 (version 5.0) Estimated date: 1H2025

Table III-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones for EMA	Due dates
Serious cardiac events post-authorisation safety study	To compare the incidence of serious cardiac events in patients with severe uncontrolled asthma newly-exposed to tezepelumab with the incidence in comparable patients exposed to other standard of care regimens.	Serious cardiac events	Study Protocol Final study report	Within 1 year of approval To be confirmed

EMA, European Medicines Agency; ICS, inhaled corticosteroids; LABA, long-acting β2 agonists; LTE, long-term extension; OCS, oral corticosteroids; PASS, post-authorisation safety study.

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable as no post-authorisation efficacy studies are planned.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	
Important potential risks	
Serious infections	Routine risk communication: SmPC Section 4.4 and Package Leaflet Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 and Package Leaflet Section 2
Serious cardiac events	Routine risk communication: SmPC Section 4.4 and Package Leaflet Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 and Package Leaflet Section 2
Malignancy	None
Missing information	
Use in pregnancy and breastfeeding	Routine risk communication: SmPC Section 4.6 and Package Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 and Package Leaflet Section 2

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Long-term use (> 1 year)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None

SmPC, Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V: 1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Serious infections	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021 - 52-week China/Asia regional efficacy and safety study in severe asthma
Serious cardiac events	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021 - 52-week China/Asia regional efficacy and safety study in severe asthma Serious cardiac events post-authorisation safety study

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Malignancy	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Post-marketing targeted follow-up questionnaires Additional pharmacovigilance activities: Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021 - 52-week China/Asia regional efficacy and safety study in severe asthma
Missing information		
Use in pregnancy and breastfeeding	Routine risk minimisation measures: SmPC Section 4.6 and Package Leaflet Section 2	Additional pharmacovigilance activity: Study D5180R00010 - Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy
Long-term use (> 1 year)	Routine risk minimisation measures: None	Additional pharmacovigilance activity: Study D5180C00018 (DESTINATION) - Phase 3 safety extension study to evaluate the safety and tolerability of tezepelumab in adults and adolescents with severe uncontrolled asthma.

SmPC, Summary of Product Characteristics.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR TEZSPIRE™ (TEZEPELUMAB)

This is a summary of the risk management plan (RMP) for TEZSPIRE™. The RMP details important risks of TEZSPIRE, how these risks can be minimised, and how more information will be obtained about TEZSPIRE's risks and uncertainties (missing information).

TEZSPIRE's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how tezepelumab should be used.

This summary of the RMP for TEZSPIRE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TEZSPIRE's RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

The proposed indication of TEZSPIRE is as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma (see SmPC for the full indication). It contains tezepelumab as the active substance and it is given/self-administered by subcutaneous injection.

Further information about the evaluation of TEZSPIRE's benefits can be found in TEZSPIRE's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage
https://www.ema.europa.eu/en/medicines/human/EPAR/tezspire

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of TEZSPIRE, together with measures to minimise such risks and the proposed studies for learning more about TEZSPIRE's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of tezepelumab is not yet available, it is listed under 'missing information' below.

VI.2.1 List of Important Risks and Missing Information

Important risks of TEZSPIRE are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for

which there is sufficient proof of a link with the use of TEZSPIRE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	Serious infections Serious cardiac events Malignancy
Missing information	Use in pregnant and breastfeeding women Long-term use (> 1 year)

VI.2.2 Summary of Important Risks

Table VI-2 Important Potential Risk: Serious Infections

Evidence for linking the risk to the medicine	Although there is a theoretical risk of infection based on the mechanism of action of tezepelumab, there were no imbalances in the incidence of serious infections observed in the tezepelumab and placebo groups in the Primary Safety Pool or the long-term extension study D5180C00018.
Risk factors and risk groups	No specific factors or subgroups of patients have been identified in respect of increased potential risk of infection with tezepelumab.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021 - 52-week China/Asia regional efficacy and safety study in severe asthma

SmPC, Summary of Product Characteristics.

Table VI-3 Important Potential Risk: Serious Cardiac Events

Evidence for linking the risk to the medicine	A numeric imbalance in serious cardiac events was observed in Study D5180C00018, however, there were no imbalances in overall cardiac events (serious and non-serious) in the Primary Safety Pool or the long-term extension study D5180C00018.
Risk factors and risk groups	There is no evidence of a specific factor that would increase the risk of fatal cardiac events in subjects receiving tezepelumab, and no specific subgroup of patients who may be at an increased risk of serious cardiac events has been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021 - 52-week China/Asia regional efficacy and safety study in severe asthma Serious cardiac events post-authorisation safety study

SmPC, Summary of Product Characteristics.

Table VI-4 Important Potential Risk: Malignancy

Evidence for linking the risk to the medicine	Malignancies have been reported in the completed asthma studies of tezepelumab. The incidence of malignancies reported was low and similar across tezepelumab and placebo treatment groups in the Primary Safety Pool and in the long-term study D5180C00018 including up to 2 years of treatment. However, longer-term exposure data are not available, and a potential theoretical risk of malignancy remains.
Risk factors and risk groups	No specific risk factors or subgroups of patients have been identified in respect of potential malignancy risk for patients treated with tezepelumab.
Risk minimisation measures	None
Additional pharmacovigilance activities	Study D5180C00024 - 28-week OCS-reduction study in severe asthma Study D5180C00021- 52-week China/Asia regional efficacy and safety study in severe asthma

SmPC, Summary of Product Characteristics.

Table VI-5 Missing Information: Use in Pregnant and Breastfeeding Women

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 and Package Leaflet Section 2 Additional risk minimisation measures: None
Additional pharmacovigilance activities	Study D5180R00010 - Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy

SmPC, Summary of Product Characteristics.

Table VI-6 Missing Information: Long-term Use (> 1 Year)

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Study D5180C00018 (DESTINATION) - Phase 3 safety extension study to evaluate the safety and tolerability of tezepelumab in adults and adolescents with severe uncontrolled asthma.

VI.2.3 Post-Authorisation Development Plan

VI.2.3.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of TEZSPIRE.

VI.2.3.2 Other Studies in Post-authorisation Development Plan

Tezepelumab Pregnancy Study (D5180R00010)

Study title: Study of the Use (and Safety) of Tezepelumab in Women with Severe Asthma During Pregnancy

Purpose of the study: The proposed study has the following objectives:

- Stage 1: To monitor the use of tezepelumab in pregnant women with severe asthma to inform the initiation of Stage 2.
- Stage 2:
  - To describe pregnancy and delivery outcomes in pregnancies among women with severe asthma exposed to tezepelumab at any time during pregnancy. Outcomes will be assessed by trimester of exposure as a secondary objective.
  - To compare frequency of outcomes in pregnant women exposed to tezepelumab with that in those not exposed to tezepelumab.

DESTINATION - Long-term Extension Study (D5180C00018)

Study title: A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma

Purpose of the study: The primary objective of this long-term extension study is to evaluate the long-term safety and tolerability of 210 mg tezepelumab SC Q4W in severe asthma subjects. The secondary objective is to assess the long-term effect of 210 mg tezepelumab subcutaneously administered every 4 weeks on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo.

(This study is not classified as a post-authorisation safety study.)

SUNRISE – OCS reduction study in severe asthma (D5180C00024)

Study Title: A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled 28-week Phase 3 Efficacy and Safety Study of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Purpose of the study: To demonstrate the ability of tezepelumab, compared with placebo, to reduce OCS use in adults with severe asthma being treated with maintenance OCS in combination with high dose ICS and LABA, with or without other asthma controller therapies, while maintaining asthma control.

DIRECTION – China/Asia regional efficacy and safety study in severe asthma (D5180C00021)

Study Title: A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, 52-week Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma

Purpose of the study: To confirm the efficacy and safety of 210 mg dose of tezepelumab administered SC Q4W in adults (18 to 80 years of age inclusive) with a history of asthma exacerbations and severe, uncontrolled asthma receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS. The study will evaluate the incidence of asthma exacerbations and other efficacy parameters such as lung function, asthma control and quality of life as well as a safety evaluation to further characterise the benefit-risk profile of the drug.

Serious cardiac events post-authorisation safety study

Study title: A Non-Interventional Multi-Country Post-Authorisation Safety Study (PASS) to Assess the Incidence of Serious Cardiac Events in Patients with Severe Uncontrolled Asthma Exposed to Tezepelumab

Purpose of the study: To evaluate possible effects of tezepelumab exposure in patients with severe asthma on serious cardiac events. The overall objective of the study is to compare the incidence of serious cardiac events in patients with severe uncontrolled asthma newly exposed to tezepelumab with the incidence in comparable severe uncontrolled asthma patients exposed to other standard of care regimens.

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EU RMP Part VII Annex 4

Drug Substance Tezepelumab

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR TEZSPIRE™ (TEZEPELUMAB)

Part VII ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following post-marketing targeted safety questionnaires are provided in this annex:

- Serious Infections Targeted Safety Questionnaire
- Serious Cardiac Events Targeted Safety Questionnaire
- Malignancies Targeted Safety Questionnaire

AstraZeneca

MALIGNANCY Adverse Event Report Questionnaire

AZ Case ID #

Please provide the information below for the reported adverse event(s):

1. Patient details

Date of birth (*dd/mm/yyyy*): Age (*years*):	Country of origin: Gender at Birth: ☐ Male ☐ Female	Height: ____ cm ☐ in ☐ Weight:____ kg ☐ lbs☐

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian

☐ Other ☐ Refused or Unknown

Ethnic Group: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

If applicable, indigenous identity status:

2. Suspect product(s)

Tezepelumab

Dose and frequency:	Route of administration:	
Indication:	Lot/Batch number(s) Expiration date(s)	
Start date:	Stop date:	Product use ongoing:

Was tezepelumab treatment stopped due to the event(s)?

Please provide causal relationship assessment between tezepelumab and adverse event(s):

Other Suspect Drugs

Please only include other drugs you consider to be causality related to the adverse event(s)

Suspect Drug Name	Indication	Dose and frequency	Route of administration	Start date:	Stop date:	Treatment ongoing: Y/N	Causal relation with the event: Y/N

3. Adverse Event(s)

Adverse Event(s)	Start date	Stop date	Outcome * 1. No evidence of disease 2. Stable/Inactive disease 3.Active disease

* **1. No evidence of disease** (after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies. Has had a complete resection or a complete remission of their cancer). **2. Stable/Inactive disease** (Evidence of disease, but is not progressing, and no new and/or change in treatment since their previous evaluation). **3.Active disease** (Evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy)

Did any of the event(s) require hospitalization? If yes, specify:

Treatment of adverse event(s):

For fatal outcome, please provide cause of death:

Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

Please describe the malignancy

Is this a new diagnosis or a relapse/disease progression of a pre-existing condition?

Anatomical location:

MALIGNANCY Adverse Event Report Questionnaire

AZ Case ID

Histological type (e.g. cell type confirmed by biopsy):
Tumor, Node, Metastasis (TNM) classification:
Grade/Staging:
Other, specify:
Signs and symptoms in chronological order:

Diagnostic tests (provide test names, dates, results and normal ranges – provide pre-treatment results if available):

CT/ MRI/ ultrasound:
Histopathology:
Cytology:
Genetic testing:
CD marker evaluation:
Other, specify (e.g. biomarkers):

Please provide prior screening tests results if appropriate (e.g., mammogram, Pap test, colonoscopy):

4. Relevant history

(Are there any other etiological factors? Please mark with an "X" all that apply):

- Exposure to environmental factors, specify:
- Related co-morbidities, specify:
- Family history,specify:
- Occupational history:
- Smoking:
- Diet; specify:
- Chronic alcohol use:
- Chemicals exposure [asbestos, benzenes, nickel, etc.]:
- Radiation exposure [sun rays, x-rays, radioactive elements]:
- Infection (e.g., Papilloma, Cytomegalovirus, Schistosoma, hepatitis, HIV/AIDS):
- Medication-induced [e.g., hormone replacement therapy (HRT), diethylstilbestrol (DES)]:
- Immunosuppression,specify:
- Chemotherapy:
- Other, specify:

5. Concomitant medications

Drug Name	Indication	Dose and frequency	Route of administration	Start date:	Stop date:	Treatment ongoing: Y/N

7.Reporter details

Reporter's Name: Reporter's Address: Telephone #: Fax #:	Is the reporter a healthcare professional (HCP)? No ☐ Yes ☐ If yes, please provide specialty:	If no, please confirm if we can contact the HCP? No ☐ Yes ☐ If yes, please provide contact information of the HCP

Thank you for completing this form.

_____ _____

Name of the reporter Signature

AstraZeneca

Tezspire Questionnaire for Serious Cardiac Events

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name:	Is Reporter a healthcare professional? ☐ No ☐ Yes, If yes, please provide specialty:	Telephone #:
Reporter's Address:	Reporter's Signature:	Date *(DD/MM/YY)*:

2. Patient's Details

Initials: Gender at Birth: ☐ Male ☐ Female Date of Birth (*DD/MM/YYYY*): Age (*years*):

Country:
Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Unknown
Ethnic Group: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown
If applicable, indigenous identity status:

3. Adverse Event Details

Adverse Event(s)	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Outcome	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify: ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify: ☐ Patient died ☐ Unknown

In the event of Death, please provide the cause of death (*please provide copy of autopsy report, if available).*

Was the patient hospitalized for the event(s)? ☐ No ☐ Yes

Provide the date of onset of symptoms:

Diagnostic criteria and clinical diagnosis of the event(s): (include key clinical features and diagnostic test results):

What signs and symptoms did the patient experience?

☐ Dyspnoea / Breathlessness
☐ Chest pain/discomfort
☐ Palpitations
☐ Fatigue
☐ Orthopnoea/paroxysmal nocturnal dyspnea
☐ Lightheadedness / Fainting
☐ Other, please specify:

Were there any complications ? ☐ No ☐ Yes
If 'Yes', please provide a brief statement of complications from the event(s):

Was CPR required? ☐ Yes ☐ No

4. TEZSPIRE administration

Indication:	Dosage:	Start Date *(DD/MM/YY)*:	Stop Date *(DD/MM/YY)*:	Was suspect drug withdrawn? ☐ No ☐ Yes

5. How was the patient treated?

Was treatment provided? ☐ No ☐ Yes
If Yes, Please provide the details of treatment: _____

☐ Treatment details - ***please specify:*** _____

AstraZeneca

Questionnaire for Major Adverse Cardiac Events (MACE)

AZ Date of Receipt:_____
AZ Case ID#: _____

6. Other Suspect Drugs

Please only include other drugs you consider to be causally related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) reoccur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/Concomitant Vaccines

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. For vaccines, please include name and number of doses.

Name	Indication	Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

8. Relevant Medical History/Concurrent Diseases

Medical History	**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*
Previously known ischemic heart disease/ heart failure/ Valvular heart disease ☐ No ☐ Yes		
Pulmonary oedema ☐ No ☐ Yes		
Any thrombosis or embolism ☐ No ☐ Yes		
Hypertension ☐ No ☐ Yes		
Hyperlipidemia ☐ No ☐ Yes		
Diabetes mellitus ☐ No ☐ Yes		
Concomitant disease: (liver, renal, infectious, respiratory, immunological, neoplasm, etc.) ☐ No ☐ Yes		
Obesity ☐ No ☐ Yes		
Smoking ☐ No ☐ Yes		
Family medical history of cardiac diseases? Please specify ☐ No ☐ Yes		

Other, please specify:

9. Laboratory Results- Before/During/After Treatment

Please provide details of the relevant lab tests as applicable (attach test results if available).

Test	**Was the test performed?**	**Test Date (DD/MM/YY)**	**Result**
Electrocardiography (ECG)	☐ No ☐ Yes		
Echocardiography	☐ No ☐ Yes		
Coronary angiography	☐ No ☐ Yes		
Arterial Blood Gases	☐ No ☐ Yes		
Cardiac enzymes: CK-MB/ Troponin T/ Troponin N	☐ No ☐ Yes		

Blood glucose levels/ HbA1C	☐ No ☐ Yes		
Details of diagnostic test performed : Please provide details below.			

Thank you for completing this form.

AstraZeneca

Serious Infections Questionnaire
Request for Additional Information

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name:

Is Reporter a healthcare professional?
☐ ☐ Yes, If yes, please provide specialty:

Telephone #:No

Fax #:

Reporter's Address:

Reporter's Signature:

Date *(DD/MM/YY):*

2. Patient's Details

Initials:

Gender at Birth:
☐ Male ☐ Female

Date of Birth (*DD/MM/YYYY*):
Age (*years*):

Race: ☐White ☐Black or African American ☐Native American ☐Alaska Native ☐Native Hawaiian ☐Asian ☐Other ☐Refused or Unknown
Ethnic Group: ☐Hispanic or Latino ☐Not Hispanic or Latino ☐Unknown

If applicable, indigenous identity status:

3. Infection Adverse Event Details

Adverse Event(s)	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Outcome	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died

Diagnostic criteria and clinical diagnosis of the event(s): (*include key clinical features and diagnostic test results*)

Was the patient hospitalized for the event(s)?
☐ No ☐ Yes

Was treatment provided?
☐ No ☐ Yes

Were there any complications caused by the event(s)?
☐ No ☐ Yes

If 'Yes' to any of the questions to the left, please provide a brief statement of clinical course, relevant treatment (specify antiobiotics if used, timing, and dosage) and any complications from the event(s):

Site of infection: (*check all that apply*)
☐ Bone ☐ Blood ☐ Mucus membrane, specify: _____
☐ CNS ☐ Gastrointestinal ☐ Urinary tract ☐ HEENT, specify: _____
☐ Hepatobiliary ☐ Joint ☐ Kidney ☐ Lower respiratory ☐ Prostate
☐ Upper respiratory ☐ Skin ☐ Other, please specify: _____

Causal organism (*please specify*):
☐ Bacterial ☐ Fungal ☐ Mycobacterium
☐ Protozoa ☐ Viral ☐ Unknown
☐ Helminth ☐ Covid-19
☐ Other, please describe: _____

Species (*please specify if available*):

4. Tezepelumab Therapy

Indication:	Dosage:	Start Date *(DD/MM/YY)*:	Lot/Batch number:

Was tezepelumab stopped or the dosage altered due to the event(s)?
☐ Yes, permanently ☐ Yes, temporarily ☐ No ☐ Not applicable

If yes, did the event(s) improve after stopping/altering tezepelumab?
☐ Yes, Date Stopped or Dose Changed (*DD/MM/YY*):_____ ☐ No ☐ Not applicable

Was tezepelumab reintroduced? ☐ Yes, date reintroduced (*DD/MM/YY*):_____ ☐ No ☐ Not applicable

If yes, did the event(s) recur after reintroduction? ☐ Yes, date recurred (*DD/MM/YY*):_____ ☐ No ☐ Not applicable

AstraZeneca

Infections Questionnaire
Request for Additional Information

AZ Case ID#: _____

5. Other Suspect Drugs

Please only include other drugs you consider to be causality related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?

☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) recur after reintroduction?

☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

6. Concomitant Drugs and Vaccines *For vaccines, please include name and number of doses.*

Concomitant Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

7. Relevant Medical History/Concurrent Diseases

Please provide details of any other relevant medical history/concurrent diseases, including approximate dates of diagnosis and resolution if applicable. Please describe if patient has any history of a previous similar event, including timing, treatment and outcome.

Medical History/Concurrent Diseases	Comments

Does the patient possess any of the following risk factors for the event:			History		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	If yes, please provide details
Alcohol abuse	☐ No	☐ Yes	☐ Current	☐ Past			
Smoking	☐ No	☐ Yes	☐ Current	☐ Past			
Skin wound, laceration or penetration	☐ No	☐ Yes	☐ Current	☐ Past			
Animal/insect/human bite	☐ No	☐ Yes	☐ Current	☐ Past			
Organ transplant	☐ No	☐ Yes	☐ Current	☐ Past			
Recent hospitalization	☐ No	☐ Yes	☐ Current	☐ Past			
HIV	☐ No	☐ Yes	☐ Current	☐ Past			
Immune suppression	☐ No	☐ Yes	☐ Current	☐ Past			
Malignancy	☐ No	☐ Yes	☐ Current	☐ Past			
Travel to countries with endemic helminth infections	☐ No	☐ Yes	☐ Current	☐ Past			
Other, please specify:	☐ No	☐ Yes	☐ Current	☐ Past			

8. Laboratory Results- Before/During/After Treatment

Please provide details of the following relevant lab tests (attached test results if available).

Test	Reference Values (provide units) (…….to.....)	Baseline Value (pre-treatment) date *(DD/MM/YY)* and result	Event Onset Value date *(DD/MM/YY)* and result	Peak Value date *(DD/MM/YY)* and result	Post-drug withdrawal Value date *(DD/MM/YY)* and result	Return to Normal Value date *(DD/MM/YY)* and result
White blood cell count						
Absolute neutrophil count and differential (%)						
Lymphocytes Subtype:_____ Subtype:_____ Subtype: _____						
Red blood cell count						
Platelet count						
Hemoglobin						
Hematocrit						
Strongyloides Serology						
Eosinophils						
Other, please specify:						

Other investigations (serology, PCR, microscopy, biopsy, autopsy) :		Results
Urine culture	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Sputum culture	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Blood culture	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
X-ray	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Ultrasound	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
CT/MRI	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Serology (please specify titers and immunoglobulin type if available)	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
PCR	☐ Not Performed ☐ Performed, date*(DD/MM/YY):*	
Autopsy	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Other, please specify:	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	
Other, please specify:	☐ Not Performed ☐ Performed, date *(DD/MM/YY)*:	

9. Please provide any further relevant information about the Adverse Event

Include any other clinical details, diagnostic tests, key disorders ruled out, infectious disease consultation result or treatments received that have not been previously noted.

Thank you for completing this form.