| **EU RMP** | |
|---|---|
| Drug Substance | Tezepelumab |
| Version Number | 6 |
| Succession Number | 2 |
| Data lock point | 29 October 2024 |
| Date of final sign off | See e-signature page |

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

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

TEZSPIRE™ is a trademark of the AstraZeneca group of companies.

## Administrative Information

This RMP is a consolidated version including the changes approved as part of the recently finalised safety variation (RMP v5 s2, Procedure EMA/VR/0000262075), and the changes related to the extension of indication (RMP v4 s2, Procedure EMA/VR/0000245013).

## Rationale for submitting an updated RMP

Addition of CRSwNP as a new indication.

Addition of exposure and safety data from Study D5180C00021 (DIRECTION), and exposure data from Studies D5180C00018 (DESTINATION), D5180C00031 (VECTOR), and D5180C00019 (NOZOMI).

## Summary of significant changes in this RMP

| | |
|---|---|
| Part II SI | Updated Module SI Epidemiology of the Indication(s) and the Target Population with epidemiology of chronic rhinosinusitis with nasal polyps. |
| Part II SIII | Updated clinical trial exposure data with data from Study D5242C00001, D5180C00021, D5180C00018, D5180C00031, and D5180C00019 |
| Part II SV | Updated post-authorisation exposure |
| Part II SVII | Updated summary of serious infections in asthma<br>Updated summary of serious cardiac events in asthma<br>Added safety data from Study D5242C00001<br>Updated important risks with data from Study D5180C00021 |
| Part III | Study D5180C00021 was completed and removed |
| Part V | Study D5180C00021 was completed and removed |
| Part VI | CRSwNP was added as an indication for tezepelumab<br>Study D5180C00021 was completed and removed |
| Annexes | Annex 2: updated in line with Part III Pharmacovigilance Plan<br>Annex 3: Study D5180C00021 removed |

| | |
|---|---|
| **Other RMP versions under evaluation** | **Version Number**: Not applicable<br>**Submitted**: Not applicable<br>**Procedure number**: Not applicable |
| **Details of currently approved RMP** | **Version Number**: 5<br>**Approved with procedure**: EMA/VR/0000262075<br>**Date of approval:** 10 July 2025 |

# TABLE OF CONTENTS

## LIST OF TABLES

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation/Special term | Definition/Explanation |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AI | Autoinjector |
| APFS | Accessorised pre-filled syringe |
| ATC | Anatomical therapeutic chemical |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CRSwNP | Chronic rhinosinusitis with nasal polyps |
| ECG | Electrocardiogram |
| EEA | European Economic Area |
| EU | European Union |
| F | Female |
| FeNO | Fraction of exhaled nitric oxide |
| $FEV_1$ | Forced expiratory volume in one second |
| GINA | Global Initiative for Asthma |
| HIV | Human immunodeficiency virus |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| ICH | International Council for Harmonisation |
| ICS | Inhaled corticosteroids |
| Ig | Immunoglobulin |
| IL | Interleukin |
| INN | International non-proprietary name |
| IP | Investigational product |
| ISS | Integrated Summary of Safety |
| IV | Intravenous |
| KLH | Keyhole limpet hemocyanin |
| LABA | Long-acting β2 agonist |
| LAMA | Long-acting muscarinic antagonist |
| M | Male |
| mAb | Monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| n | Number of participants in analysis |
| NSAID | Non-steroidal anti-inflammatory drug |
| OCS | Oral corticosteroids |

| Abbreviation/Special term | Definition/Explanation |
|---|---|
| PASS | Post-Authorisation Safety Study |
| PT | (MedDRA) Preferred Term |
| PY | Person-years |
| Q | Quarter |
| Q2W | Every 2 weeks |
| Q4W | Every 4 weeks |
| QPPV | Qualified person responsible for pharmacovigilance |
| RMP | Risk Management Plan |
| SABA | Short-acting β2 agonist |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SD | Standard deviation |
| SmPC | Summary of Product Characteristics (EU) |
| SMQ | Standardised MedDRA Query |
| SOC | System Organ Class |
| Th2 | T helper cell type 2 |
| TSLP | Thymic stromal lymphopoietin |
| TSLPR | Thymic stromal lymphopoietin receptor |
| TSQ | Targeted safety questionnaire |
| UK | United Kingdom |
| US | United States of America |
| w/v | Weight per volume |

# 1 PART I: PRODUCT OVERVIEW

**Table 1-1 Product Overview**

| | |
|---|---|
| Active substance(s)<br>(INN or common name) | Tezepelumab |
| Pharmacotherapeutic group(s) (ATC Code) | R03DX11 |
| Marketing Authorisation Holder | AstraZeneca AB<br>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:<br>Tezepelumab is a human mAb IgG2λ directed against TSLP. |
| | Summary of mode of action:<br>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:<br>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 | Current: 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 1-1 Product Overview**

| | |
|---|---|
| | Proposed: TEZSPIRE is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids, and/or surgery do not provide adequate disease control. |
| Dosage in the EEA | Current: The recommended dose is 210 mg of tezepelumab by SC injection every 4 weeks. |
| Pharmaceutical form(s) and strengths in the EEA | Current: 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 |

# 2 PART II: SAFETY SPECIFICATION

## 2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

### 2.1.1 Asthma

**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 PY (Torén et al 2004). The incidence rate of asthma was higher among adult women (2.9 cases per 1000 PY) than adult men (1.5 cases per 1000 PY). In the 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 women (4.9/1000) than adult men (2.8/1000).

**Prevalence**

Globally, the prevalence of asthma is approximately 358 million individuals (GINA 2024, 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 2024). Data from the European National Health and Wellness Survey of 37,476 adults in France, Germany, Italy, Spain, and the 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 ICS plus LABAs or additional asthma controllers to achieve asthma control, or remaining uncontrolled despite use of these medications (GINA 2024, 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 Woolcock 1998, Busse et al 2000, O'Byrne et al 2012, Chung et al 2014), whilst based on GINA criteria, approximately 20% of patients with asthma have severe asthma, of which 20% are inadequately controlled (Peters et al 2006). A systematic literature review (Chen et al 2018) reported the prevalence of severe, uncontrolled asthma as between 8% to 87.4% of patients with severe asthma. 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).

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

The European Network for Understanding Mechanisms of Severe Asthma reported a higher proportion of women 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 patients with severe, uncontrolled asthma and patients with controlled asthma (mean age 42.4 years [SD 12.1] and 40.9 years [SD 14.3], respectively) and the mean percent $FEV_1$ among the patients with severe, uncontrolled asthma was 71.8% (ENFUMOSA 2003). The International Severe Asthma Registry, 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 patients with severe, uncontrolled asthma from UK, Germany, France, Italy, and Spain, 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%) (Demoly et al 2009).

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 2024 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 2024).

**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 2024, NAEPP 2007). GINA guidelines for patients with severe asthma recommend the following:

- GINA Step 4 treatment
  - Medium dose ICS-formoterol maintenance and reliever therapy (TRACK 1, preferred). Alternatively, medium/high dose ICS + LABA plus as needed SABA or as needed ICS + SABA (TRACK 2).
- GINA Step 5 treatment
  - Add-on LAMA, refer for phenotypic assessment, and to consider high dose ICS-formoterol ± anti-IgE, anti-IL-5/IL-5 receptor alpha, anti-IL-4 receptor alpha, anti-TSLP, with as needed low dose ICS + formoterol (rescue) (TRACK 1, preferred). If TRACK 1 is not available in the country, then TRACK 2 should be chosen, ie, add-on LAMA, refer for phenotypic assessment, and consider high-dose maintenance ICS-LABA ± biologics + as needed ICS-SABA or as needed SABA (rescue).

Many patients with asthma remain symptomatic despite treatment with ICS and LABA combinations (Rabe et al 2004). Treatment options then include the addition of other controller therapies including a leukotriene receptor antagonist, LAMA, theophylline, and OCS.

Biologic therapies can provide additional asthma control for patients with severe, uncontrolled asthma, and those targeting IgE, IL-4/IL-13, IL-5 and TSLP are now included in international treatment guidelines (GINA 2024) as an add-on treatment to patients uncontrolled with ICS/LABA treatment. Omalizumab (XOLAIR®, Genentech and Novartis) 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 (NUCALA®, GlaxoSmithKline), reslizumab (CINQAIR®, Teva Pharmaceuticals), benralizumab, and dupilumab (DUPIXENT®, Regeneron Pharmaceuticals and Sanofi), 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 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).

Tezepelumab is the only biologic approved in the US and rest of world for severe asthma without phenotypic (eg, eosinophilic or allergic) or biomarker limitations (AstraZeneca Pharmaceuticals LP 2021).

**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 patients with asthma. As part of the severe refractory definition, these patients need at least 3 steroid bursts per year (Wenzel 2005). Approximately 30% of patients with severe, refractory asthma 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 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 emergency room 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 emergency room 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 495,000 deaths worldwide every year (GINA 2024). 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 rates 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 patients with severe asthma (Engelkes et al 2020). The risk of respiratory-related mortality is approximately 8-times greater in patients with severe, uncontrolled asthma compared with patients with severe, controlled asthma (Fernandes et al 2014).

**Important co-morbidities**

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 COPD and asthma may coexist in smokers with asthma; 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 2024).

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 patients with severe asthma, 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 43,000 patients with severe asthma in Netherlands, Denmark, UK, Italy, and Spain during the study period 2008 to 2013 (Engelkes et al 2020). An Italian registry of 493 patients with severe, uncontrolled asthma 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%), gastroesophageal reflux disease (17.5%), and cardiovascular disease (37.7%).

As patients with asthma age, the comorbid diseases commonly seen in an ageing 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).

### 2.1.2 Chronic Rhinosinusitis with Nasal Polyps

#### Incidence

There is limited information on the incidence of CRSwNP in the European population. A study conducted in Germany over a 5-year period (2015 to 2019) found that 0.4% of the population were newly diagnosed with CRSwNP, with annual estimates ranging from 0.06% to 0.15% (Starry et al 2022).

Additionally, a systematic literature review of epidemiological studies published between 01 January 2008 and 08 February 2019 identified only one study that assessed the incidence of CRSwNP and reported an average incidence rate of 83 cases per 100,000 PY in Pennsylvania, US. This study included data from clinics and hospitals in a 31-county region of central and northeastern Pennsylvania (Chen et al 2020, Tan et al 2013).

#### Prevalence

Chronic rhinosinusitis affects between 3% and 27% of the adult population in Europe and the US (Hastan et al 2011, Hirsch et al 2017, Palmer et al 2019, Dietz de Loos et al 2019) and the population estimates of the prevalence of CRSwNP range from 0.6% in Spain, 1.1% in the US, to 4.4% in Finland (Sanchez-Collado et al 2022, Palmer et al 2019, Hedman et al 1999).

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

Studies conducted in Spain and Germany reported a higher proportion of men than women in the CRSwNP population (59.2% [Sanchez-Collado et al 2022] and 55.9% [Starry et al 2022]), respectively). Among commercially insured adults in the US, the standardised prevalence of nasal polyps was 215 per 100,000 in men and 158 per 100,000 in women (Benson et al 2022). Whereas this study suggests that men are more likely to have CRSwNP than women (Wautlet et al 2023), Klossek et al. found no substantial difference in the prevalence of CRSwNP between women (2.2%) and men (1.98%) in France. However, this analysis was not adjusted for possible confounders or effect modifiers (Klossek et al 2005).

CRSwNP is considered a disease of middle age, with increasing prevalence with age (Hastan et al 2011, Wautlet et al 2023). The age of onset is typically from age 40 to 60 years (Benson et al 2022, Stevens et al 2016).

No study in Europe reported race or ethnicity distribution among people with CRSwNP, and a retrospective cohort study of patients with chronic rhinosinusitis treated at a large urban tertiary care referral centre in Chicago showed no difference in the prevalence of polyposis across racial/ethnic groups (White, African American, Asian, or Latino) (Mahdavinia et al 2016).

Patients with asthma or other upper or lower airway diseases such as COPD are at an increased risk of developing CRSwNP. Individuals with NSAID-exacerbated respiratory disease and CRSwNP tend to have more severe CRSwNP disease (and lower airways disease/asthma) and recurrent disease following nasal polyp surgery in general even in the absence of acute exposure to NSAIDs (Stevens et al 2017). Smoking is also an important risk factor associated with CRSwNP (Tan et al 2013, Hedman et al 1999, Wautlet et al 2023). Genetics and nasal anatomical variations may play a role as risk factors for chronic rhinosinusitis and possibly CRSwNP (Fokkens et al 2023, Ricciardolo et al 2020). Respiratory infections and environmental factors such as exposure to pollution, dust, and chemicals have also been suggested as possible risk factors (Fokkens et al 2023, Ricciardolo et al 2020).

**The main existing treatment options**

The current standard of care for CRSwNP includes intranasal and systemic corticosteroids, long-term antibiotics, and nasal polyp removal surgery. Treatment progresses stepwise from intranasal to systemic corticosteroids, and eventually to surgical procedures such as implantation of a corticosteroid-eluting stent, polypectomy, or endoscopic sinus surgery (Dessouky and Hopkins 2015, Peters et al 2014). These treatments may provide symptomatic relief but do not address the underlying inflammatory processes, leading to frequent recurrence, and the treatments are associated with side effects.

The use of intranasal corticosteroids can be associated with nosebleeds, and delivery of intranasal corticosteroids to the site of disease may be impaired due to swollen nasal and sinus tissue, thick mucus, and ciliary dysfunction (Agarwal et al 2020, Ah-See et al 2012, Wu et al 2019). Systemic corticosteroids may be used in more severe cases, but systemic corticosteroid use is associated with serious side effects such as osteoporosis, diabetes, and high blood pressure (Bachert et al 2020, Manson et al 2009, Orlandi et al 2021). The 2014 US practice guidelines for nasal polyps indicate that the duration of clinical benefit of systemic corticosteroids is variable and may decrease with repeated courses of treatment (Peters et al 2014).

Patients who require systemic corticosteroid treatment may need to undergo surgery to reduce polyp size, recurrent chronic sinus infections, and symptom burden (Fokkens et al 2012, Hopkins 2019, Kwah et al 2020). Surgical procedures may be recommended in patients who do not respond to or are intolerant to systemic corticosteroids; however, nasal polyps recur in 40% or more patients in the years after surgery (Bai et al 2022, DeConde et al 2017).

In addition, the biologic treatments dupilumab, omalizumab, and mepolizumab are available as add-on therapy for CRSwNP with insufficient symptom control from treatments described above. However, 30% to 60% of patients do not respond to these biologics (Bachert et al 2017, Bachert et al 2019, Gevaert et al 2011) due to persistent tissue fibrosis and non-type 2

mediated disease. As a result, many patients still rely on systemic corticosteroid treatment despite the associated drawbacks.

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

Chronic rhinosinusitis is classified into 2 major phenotypes based on nasal endoscopic findings: chronic rhinosinusitis without nasal polyps and CRSwNP. CRSwNP is characterised by local (sinonasal) and systemic (lower airway) inflammation, with persistent symptoms of nasal congestion, rhinorrhoea, facial pain, and loss of smell (Bachert et al 2014).

Patients with CRSwNP are typically subdivided into 2 groups: eosinophilic and non-eosinophilic, differentiated by the type of inflammation found within the nasal cavities and sinuses and within the nasal polyps themselves. However, some patients have more than one type of inflammatory endotype (Stevens et al 2019).

Eosinophilic CRSwNP is characterised by infiltration of the nasal polyps by eosinophils, mast cells, and basophils and the presence of T2 cytokines (IL-4, IL-5, IL-13) (Avdeeva and Fokkens 2018, Dennis et al 2016, Kim and Cho 2017). Most patients with CRSwNP show evidence of type 2 airway inflammation. As a result of the shared type 2 inflammatory pathway implicated in several coexisting diseases, patients with CRSwNP often have comorbid asthma and/or NSAID-exacerbated respiratory disease (Bachert et al 2021).

Non-eosinophilic disease in CRSwNP is characterised by infiltration of the nasal polyps by neutrophils, type 1 T helper cells, type 17 T helper cells, and the presence of non-T2 cytokines (interferon-γ and IL-17) (Avdeeva and Fokkens 2018, Zhang et al 2008). Non-eosinophilic nasal polyps are typically less severe and have a lower likelihood of recurrence compared with eosinophilic nasal polyps (Bachert et al 2015, Lou et al 2018).

Patients with eosinophilic nasal polyps have the highest disease burden (Bachert et al 2016, Kim and Cho 2017, Bachert et al 2018, Fokkens et al 2019) with higher rates of recurrence following surgery than patients with non-eosinophilic CRSwNP (Bachert et al 2015, Tokunaga et al 2015, Lou et al 2018).

CRSwNP is the more debilitating of the 2 phenotypes of chronic rhinosinusitis. In one study, the mortality risk was greater in patients with CRSwNP than those without nasal polyps (hazard ratio 1.38, 95% CI 1.09, 1.77) (Alt et al 2017). CRSwNP is associated with significant morbidity and reduced health-related quality of life (Alobid et al 2011, Hastan et al 2011, Stevens et al 2016, Orlandi et al 2016, Fokkens et al 2020). Lower health-related quality of life is observed especially in patients with comorbid asthma and/or NSAID-exacerbated respiratory disease (Khan et al 2019b) and in patients who need repeated treatment with corticosteroids and/or sinonasal surgeries to alleviate its uncontrolled symptoms.

**Important co-morbidities**

Approximately 31% to 65% of individuals with CRSwNP have at least one comorbid inflammatory condition, such as asthma, allergic rhinitis, or atopic dermatitis (Khan et al 2019a, Khan et al 2023). CRSwNP often coexists with asthma, with estimates suggesting that 26% to 67% of individuals with CRSwNP also present with asthma (Chen et al 2020, Wautlet et al 2023, Stevens et al 2016, Laidlaw et al 2021, Toppila-Salmi et al 2022). When these conditions coexist, CRSwNP is more challenging to control with therapeutic interventions, and such individuals are often prone to more exacerbations and increased airway obstruction and inflammation (Sanchez-Collado et al 2022, Laidlaw et al 2021). NSAID-exacerbated respiratory disease is estimated to be present in 8% to 26% of patients with CRSwNP and has also been identified among the most severe and difficult-to-treat cases of CRSwNP (Wautlet et al 2023, Stevens et al 2016, Laidlaw et al 2021). Allergic rhinitis and allergic sensitisation are estimated to be present in 50% to 70% of patients with CRSwNP (Wautlet et al 2023) and gastroesophageal reflux disease in 30% of patients (Tan et al 2013. Other comorbidities reported in 2 studies include diabetes mellitus, hypertension, anxiety, and depression (Tan et al 2013, Sanchez-Collado et al 2022). Being overweight and having comorbid dyslipidaemia have also been associated with severe CRSwNP with odds ratios of 1.13 (95% CI 1.05, 1.21) and 1.56 (1.43, 1.70), respectively, compared with non-severe CRSwNP (Sanchez-Collado et al 2022).

## 2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

### 2.2.1 Summary of Key Safety Findings from Non-clinical Studies and Relevance to Human Usage

**Toxicity**

Cynomolgus monkeys were selected as the nonclinical toxicology species because tezepelumab binds to human and cynomolgus monkey 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 IV administration (a toxicologically relevant dose level).

*Repeat-dose toxicity studies:* In all nonclinical studies, the no observed adverse effect level was the highest dose tested (up to 300 mg/kg) for each route of administration (IV and 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 KLH. Mean anti-KLH IgG titres were mildly-to-moderately decreased at 300 mg/kg. At 50 and 100 mg/kg, IgG titres were sporadically reduced but the changes were not statistically significant. Reduced anti-KLH IgG antibody titres 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 titres were not evident in offspring in a subsequent cynomolgus enhanced pre- and postnatal development 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 no observed adverse effect level for this study was 300 mg/kg.

Genotoxicity

Tezepelumab is a 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 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 behaviour, and body temperature after a single 300 mg/kg IV tezepelumab administration.

## 2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The clinical trial exposure to tezepelumab is presented for the asthma Primary Safety Pool, the asthma Exposure Pool, and Study D5242C00001 (WAYPOINT) in participants with CRSwNP,

### 2.3.1 Asthma

The Primary Safety Pool consists of pooled data from the confirmatory asthma exacerbation studies D5180C00007 (Phase III) and CD-RI-MEDI9929-1146 (Phase IIb). 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 Q4W SC dose in participants with severe, uncontrolled asthma and to support the evaluation of risks presented in this RMP in Section 2.7.

The Exposure Pool consists of pooled data from all 9 of the tezepelumab Phase II and III asthma studies (D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011, D5180C00013, D5180C00018, D5180C00019, D5180C00021, and D5180C00031). This pool comprises 7 studies in participants with severe asthma (D5180C00007, CD-RI-MEDI9929-1146, D5180C00009 [a Phase III, OCS-reduction study], D5180C00011 [a Phase III, device functionality study], D5180C00018, D5180C00019, and D5180C00021), and 2 studies in patients with moderate to severe asthma (D5180C00013 [a Phase II mechanistic study] and D5180C00031 [a Phase IIIb study to evaluate the effect of tezepelumab on the humoral immune response]). This pool provides a broader view of the extent of patient exposure to tezepelumab in the Phase II/III clinical programme including exposure data for 4 tezepelumab treatment groups: 70 mg Q4W SC, 210 mg Q4W SC, 280 mg Q2W SC, and tezepelumab 'all doses' combined group.

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

**Table 2-1 Duration of Exposure**

| Duration of exposure | Participants (n [%]) | Person time (person-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 |

## Table 2-1 Duration of Exposure

| Duration of exposure | Participants (n [%]) | Person time (person-years) |
|---|---|---|
| ≥ 52 weeks | 541 (81.4) | 544.70 |
| ≥ 60 weeks | 0 (0.0) | 0 |
| Total | 665 (100.0) | 636.56 |
| **Exposure Pool [b]** | | |
| ≥ 4 weeks | 1547 (99.7) | 1825.15 |
| ≥ 8 weeks | 1535 (98.9) | 1823.97 |
| ≥ 12 weeks | 1525 (98.3) | 1822.21 |
| ≥ 16 weeks | 1520 (97.9) | 1820.96 |
| ≥ 20 weeks | 1470 (94.7) | 1804.59 |
| ≥ 24 weeks | 1465 (94.4) | 1802.55 |
| ≥ 28 weeks | 1242 (80.0) | 1696.11 |
| ≥ 36 weeks | 1183 (76.2) | 1662.44 |
| ≥ 44 weeks | 1162 (74.9) | 1646.71 |
| ≥ 48 weeks | 1149 (74.0) | 1635.37 |
| ≥ 52 weeks | 1118 (72.0) | 1606.06 |
| ≥ 60 weeks | 474 (30.5) | 944.73 |
| ≥ 68 weeks | 468 (30.2) | 937.43 |
| ≥ 76 weeks | 464 (29.9) | 931.96 |
| ≥ 84 weeks | 459 (29.6) | 924.36 |
| ≥ 92 weeks | 456 (29.4) | 919.31 |
| ≥ 100 weeks | 447 (28.8) | 902.67 |
| ≥ 108 weeks | 23 (1.5) | 48.34 |
| Total | 1552 (100.0) | 1825.44 |

[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, D5180C00013, D5180C00018, D5180C00019, D5180C00021, and D5180C00031.

Source: ISS Table 3.1 and root/cdar/d518/iemt/tzp754_rmp_teze_pool/dev/program/table_00_754_02.sas table_00_754_02.rtf.

## Table 2-2 Exposure by Age Group and Gender

| | Participants (n [%]) | | Person Time (person-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 |

## Table 2-2 Exposure by Age Group and Gender

| | Participants (n [%]) | | Person Time (person-years) | |
|---|---|---|---|---|
| **Age group** | **M** | **F** | **M** | **F** |
| ≥ 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 | 56 (3.6) | 48 (3.1) | 54.04 | 55.63 |
| ≥ 18 to < 65 years | 454 (29.3) | 734 (47.3) | 521.02 | 880.09 |
| ≥ 65 years | 108 (7.0) | 152 (9.8) | 124.55 | 190.11 |
| Total | 618 (39.8) | 934 (60.2) | 699.61 | 1125.83 |

[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, D5180C00013, D5180C00018, D5180C00019, D5180C00021, and D5180C00031.

Source: ISS Table 3.2 and root/cdar/d518/iemt/tzp754_rmp_teze_pool/dev/program/table_00_754_03.sas table_00_754_03.rtf.

## Table 2-3 Exposure by Dose

| Dose of Exposure | Participants (n) | Person Time (person-years) |
|---|---|---|
| **Primary Safety Pool [a]** | | |
| 210 mg Q4W | 665 | 636.56 |
| Total | 665 | 636.56 |
| **Exposure Pool [b]** | | |
| 70 mg Q4W | 138 | 141.5 |
| 210 mg Q4W | 1552 | 1825.4 |
| 280 mg Q2W | 137 | 132.5 |
| Total | 1827 | 2099.4 |

[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, D5180C00013, D5180C00018, D5180C00019, D5180C00021, and D5180C00031.

Source: ISS Table 1.2.1 and Table 2.2.2 and root/cdar/d518/iemt/tzp754_rmp_teze_pool/dev/program/table_00_754_01.sas table_00_754_01.rtf.

## Table 2-4 Exposure by Race

| Race | Participants (n [%]) | Person time (person-years) |
|---|---|---|
| **Primary Safety Pool [a]** | | |
| White | 460 (69.2) | 437.74 |
| Black or African American | 33 (5.0) | 30.54 |

**Table 2-4 Exposure by Race**

| Race | Participants (n [%]) | Person time (person-years) |
|---|---|---|
| Asian | 151 (22.7) | 148.83 |
| Other [b] | 21 (3.2) | 19.45 |
| Total | 665 (100.0) | 636.56 |
| **Exposure Pool [c]** | | |
| White | 923 (59.5) | 1119.09 |
| Black or African American | 71 (4.6) | 76.29 |
| Asian | 523 (33.7) | 581.74 |
| Native Hawaiian or Other Pacific Islander | 1 (0.1) | 2.01 |
| American Indian or Alaska Native | 2 (0.1) | 0.65 |
| Multiple | 1 (0.1) | 1.05 |
| Other | 31 (2.0) | 44.60 |
| Total | 1552 (100.0) | 1825.44 |

[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 electronic case report form.

[c] Exposure Pool (210 mg SC Q4W dose only): Studies D5180C00007, CD-RI-MEDI9929-1146, D5180C00009, D5180C00011, D5180C00013, D5180C00018, D5180C00019, D5180C00021, and D5180C00031.

Source: ISS Table 3.3 and root/cdar/d518/iemt/tzp754_rmp_teze_pool/dev/program/table_00_754_04.sas table_00_754_04.rtf.

### 2.3.2 Chronic Rhinosinusitis With Nasal Polyps

The duration of exposure, exposure by age group and sex, exposure by dose, and exposure by racial origin for tezepelumab in Study D5242C00001 are presented in Table 2-5, Table 2-6, Table 2-7, Table 2-8, respectively.

**Table 2-5 Duration of Exposure in Participants with CRSwNP**

| Duration of exposure | Participants (n [%]) | Person Time (person-years) |
|---|---|---|
| **≥ 4 weeks** | 203 (100) | 204.2 |
| **≥ 8 weeks** | 203 (100) | 204.2 |
| **≥ 12 weeks** | 203 (100) | 204.2 |
| **≥ 16 weeks** | 202 (99.5) | 204.0 |
| **≥ 20 weeks** | 202 (99.5) | 204.0 |
| **≥ 24 weeks** | 201 (99.0) | 203.6 |
| **≥ 28 weeks** | 201 (99.0) | 203.6 |
| **≥ 32 weeks** | 201 (99.0) | 203.6 |

## Table 2-5 Duration of Exposure in Participants with CRSwNP

| Duration of exposure | Participants (n [%]) | Person Time (person-years) |
|---|---|---|
| **≥ 36 weeks** | 200 (98.5) | 203.0 |
| **≥ 40 weeks** | 199 (98.0) | 202.3 |
| **≥ 44 weeks** | 198 (97.5) | 201.5 |
| **≥ 48 weeks** | 196 (96.6) | 199.8 |
| **≥ 52 weeks** | 190 (93.6) | 193.9 |
| **Total** | **203 (100)** | **204.2** |

Includes participants treated with tezepelumab 210 mg Q4W SC.

Source: \csr\dev\output\rmp\t-rmp-02-01-dur.rtf.

## Table 2-6 Age Group and Gender in Participants with CRSwNP

| | Participants (n [%]) | | Person Time (person-years) | |
|---|---|---|---|---|
| **Age group** | **M** | **F** | **M** | **F** |
| **≥ 18 to < 65 years** | 108 (85.7) | 66 (85.7) | 107.4 | 67.7 |
| **≥ 65 years** | 18 (14.3) | 11 (14.3) | 18.2 | 11.0 |
| **Total** | 126 (100) | 77 (100) | 125.5 | 78.7 |

Includes participants treated with tezepelumab 210 mg Q4W SC.

Source: \csr\dev\output\rmp\t-rmp-02-02-age-gender.rtf.

## Table 2-7 Exposure by Dose in Participants with CRSwNP

| Dose of Exposure | Participants (n [%]) | Person Time (person-years) |
|---|---|---|
| **210 mg Q4W** | 203 (100) | 204.2 |
| **Total** | 203 (100) | 204.2 |

Includes participants treated with tezepelumab 210 mg Q4W SC.

Source: \csr\dev\output\rmp\t-rmp-02-03-by-dose.rtf.

## Table 2-8 Exposure by Race in Participants With CRSwNP

| Race | Patients (n [%]) | Person Time (person-years) |
|---|---|---|
| **White** | 150 (73.9) | 151.5 |
| **Black or African American** | 3 (1.5) | 4.0 |
| **Asian** | 46 (22.7) | 45.0 |
| **Other** | 4 (2.0) | 3.8 |
| **Total** | 203 (100) | 204.2 |

Includes participants treated with tezepelumab 210 mg Q4W SC.

Source: \csr\dev\output\rmp\t-rmp-02-04-by-race.rtf.

# 2.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## 2.4.1 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 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 (Fraenkel et al 2021), 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 II and III 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/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 HIV test at screening or patients taking antiretroviral medications; patients with a 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 (alanine aminotransferase, aspartate aminotransferase, 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 were not exposed to the IP until the benefit-risk profile was 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 International Severe Asthma Registry (described in Section 2.1.1) of approximately 5,000 patients, only 4.2% of were ≥ 80 years old, whereas 43.6% of participants were 18 to 54 years old, and 52.1% of participants 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 of 119 out of 665 (17.9%) participants who received tezepelumab 210 mg SC Q4W were ≥ 65 years old (Table 2-2). The safety profile of tezepelumab in patients ≥ 65 years old was similar to that in patients with asthma ≥ 18 to < 65 years old and differences in tezepelumab pharmacokinetic 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

### 2.4.2 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.

### 2.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

**Table 2-9 Exposure of Special Populations Included or Not in Clinical Trial Development Programmes**

| Type of special population | Exposure |
|---|---|
| **Pregnant women** | Although pregnant patients were excluded from the clinical development programme, there were 7 reports of pregnancy during the trials in participating female participants exposed to tezepelumab (details provided in Section 2.7.3.2). |
| **Breastfeeding women** | Not included in the clinical development programme |
| **Patient 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 patients [c] |
| Patients with cardiovascular impairment [b] | 28 patients [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 participant population baseline medical history MedDRA 23.1 preferred terms. The search strategy for renal impairment included the SMQ of chronic kidney disease. The search strategy for cardiovascular impairment included SMQ (narrow) cardiomyopathy, cardiac failure, myocardial, infarction, and other ischaemic heart disease.

## 2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

### 2.5.1 Method Used to Calculate Exposure

The post-marketing patient exposure data presented here are 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 30 November 2024. The estimated post-marketing patient exposure data are an approximation based on the assumption that each patient took one unit (210 mg/1.91 mL) of tezepelumab every 4 weeks and 13 units in total per year (52 weeks). Therefore, a PY worth of exposure is calculated by dividing number of units by 13 (13 units of 210 mg/1.91 mL tezepelumab per PY).

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.

### 2.5.2 Exposure

Cumulative global post-marketing patient exposure for tezepelumab (210 mg/1.91 mL) was estimated to be approximately 73,425 PYs until 30 November 2024.

The cumulative regional sales figures are presented in Table 2-10.

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

**Table 2-10 TEZSPIRE Cumulative Sales, Number of Units**

| Formulation | Total |
|---|---|
| APFS (210 mg/1.91 mL) [a] | 553,413 |
| AI (210 mg/1.91 mL) | 401,116 |
| Total | 954,529 |

[a] Single-dose pre-filled syringe refers to APFS only.

## 2.6 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.

## 2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

### 2.7.1 Identification of Safety Concerns in the Initial RMP Submission

This section describes the safety concerns at the time of RMP Version 1 approval; it will not be updated.

#### 2.7.1.1 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 participants and 0.3% of participants, 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

#### 2.7.1.2 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 2.7.3.1), 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 2.2.1, there is some evidence from different animal models and in human translational studies linking TSLP overexpression 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 3.2.1).

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

Limited information is available on the long-term use (greater than one year) of tezepelumab 210 mg SC. In completed Phase II and III studies, participants with severe asthma received tezepelumab for up to 52 weeks (refer to details in Section 2.7.3.2). 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 3-1). This study includes participants 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 (09 December 2021) are provided in Section 2.7.3.2. The final database lock for this study is planned for July 2022.

## 2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable

## 2.7.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

### 2.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

**Important identified/potential 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

*Asthma*

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

Pooled data from Study D5180C00018 (extension study for D5180C00007 and D5180C00009) show that the characteristics of SAEs reported in the Infections and infestations SOC were generally similar to those in the Primary Safety Pool with incidence rates per 100 PY of 2.18 versus 2.38, respectively, in the All tezepelumab group (ie, participants randomised to tezepelumab in the predecessor studies [D5180C00007 and D5180C00009] and randomised and treated with tezepelumab in D5180C00018) and Randomised placebo group (all participants 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 participants who participated in D5180C00018). No apparent trends in serious infections were noted.

In Study D5180C00021, the incidence of participants with SAEs reported in the Infections and infestations SOC was low overall, and the proportion of participants experiencing serious infections was numerically lower in the tezepelumab group (2 of 201 [1.0%] participants) than the placebo group (10 of 199 [5.0%] participants). The incidence rates per 100 PY were 1.03 and 5.41, respectively. No apparent trends in AE category were noted in Study D5180C00021.

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 of 840 participants in the All tezepelumab group versus 1 of 607 participants in the Randomised placebo group; 0.29 versus

0.12 per 100 PY, 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 related 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).

*Chronic Rhinosinusitis With Nasal Polyps*

In Study D5242C00001 in participants with CRSwNP, the incidence of participants with SAEs reported in the Infections and infestations SOC was low. The incidence of SAEs reported in the Infections and infestations SOC was similar in the tezepelumab and placebo groups (5 of 203 [2.5%] participants and 4 of 205 [2.0%], respectively). The exposure-adjusted incidence rates per 100 PY were 2.5 and 2.3, respectively. In Study 5242C00001, there were no fatal infection events in the tezepelumab group and one fatal infection event in the placebo group. No apparent trends in serious infections were noted in this study.

The incidence of AEs of infection and SAEs of infection was similar in the tezepelumab and placebo groups.

Risk factors and risk groups

No specific risk factors or subgroups of patients have been identified with respect to 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 may 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 3.2 and Section 3.3) 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 cardiovascular 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 Disorder SOC events (serious and nonserious combined) 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 safety pharmacology and nonclinical toxicology studies tested tezepelumab dose levels that resulted in safety margins of greater than 100-fold on an area under the serum concentration curve and maximum serum concentration basis to the maximum recommended human dose of a subcutaneous 210 mg dose, every 4 weeks.

Characterisation of the risk

*Asthma*

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 of 665 [3.0%] participants, incidence rate 3.11 per 100 PY versus 19 of 669 [2.8%] participants, incidence rate 2.98 per 100 PY, 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 of 840 participants, 3.12 per 100 PY in the All tezepelumab group versus 22 of 607 participants, incidence rate of 2.75 per 100 PY in the Randomised placebo group).

In the Primary Safety Pool, the incidence of Cardiac Disorders SOC SAEs was low in the tezepelumab and placebo treatment groups (5 of 665 participants, incidence rate 0.78 per 100 PY versus 2 of 669 participants, incidence rate of 0.31 per 100 PY, 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 of 840 participants, incidence rate of 1.33 per 100 PY in the All tezepelumab group versus 0 of 607 participants, incidence rate of 0.00 per 100 PY in the Randomised placebo 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 Study D5180C00018. Analyses by PTs showed no apparent pattern in types or categories of cardiac events and the events were also observed across different high level group term 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 of 840 participants in the All tezepelumab group and 1 of 607 participants in the Randomised placebo group; incidence rates of 0.22 and 0.12 per 100 PY, respectively).

In Study D5180C00021, the incidence of participants with SAEs reported in the Cardiac Disorder SOC in the on-treatment period was low and similar in the tezepelumab and placebo groups (1 of 201 [0.5%] participants and 1 of 199 [0.5%] participants, respectively). The incidence rates per 100 PY were 0.51 and 0.54, respectively. No apparent trends in cardiac events were noted in Study D5180C00021. No Cardiac Disorder SOC fatal AEs were observed in Study D5180C00021.

No other events of Cardiac Disorder SOC fatal AEs were observed within a broader pool of completed AstraZeneca-sponsored clinical studies in asthma assessing 210 mg Q4W.

*Chronic Rhinosinusitis With Nasal Polyps*

In Study D5242C00001, the incidence of participants with SAEs reported in the Cardiac Disorders SOC was low and similar in the tezepelumab and placebo groups (2 of 203 [1.0%] participants and 3 of 205 [1.5%] participants, respectively). The exposure-adjusted incidence rates per 100 PY were 1.0 and 1.7, respectively. There were no fatal cardiac events in Study D5242C00001 and no apparent trends in cardiac events were noted in this study.

The incidence of cardiac AEs and cardiac SAEs was similar in the tezepelumab and placebo groups.

Risk factors and risk groups

There is no evidence of a specific factor that would increase the risk of fatal cardiac events in patients 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 3.2 and 3.3) 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 2.2.1, there is evidence from different animal models and in human translational studies linking TSLP overexpression 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 beyond 2 years are not available, and a potential theoretical risk of malignancy remains.

Data from chronic toxicity studies (summarised in Section 2.2.1) did not reveal any product-specific concerns with tezepelumab regarding malignancy risk.

Characterisation of the risk

*Asthma*

In the Primary Safety Pool, a total of 11 participants reported a malignancy in the on-treatment period: 6 participants (0.9%) in the tezepelumab group and 5 participants (0.7%) in the placebo group. Malignancies in the tezepelumab group included 2 (0.3%) participants with

basal cell carcinoma, 2 (0.3%) participants with malignant melanoma in situ, 2 (0.3%) participants with prostate cancer, and 1 (0.2%) participant with squamous cell carcinoma (2 malignancies were reported in one participant). In the long-term study D5180C00018, a total of 12 participants reported a malignancy on treatment, and the incidence of participants with malignancies was similar in the tezepelumab and placebo groups (7 of 840 participants in the All tezepelumab group versus 5 of 607 participants in the Randomised placebo group; incidence rates of 0.55 and 0.63 per 100 PY, respectively). Malignancies reported in the Randomised tezepelumab group were as follows: malignant melanoma in situ (2 participants), basal cell carcinoma (one participant), colon cancer stage IV (one participant), colorectal cancer (one participant), invasive breast carcinoma (one participant), prostate cancer (one participant) and squamous cell carcinoma (one participant).

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.

In Study D5180C00021, the incidence of participants with AEs of malignancy reported in the on-treatment period was low and similar in the tezepelumab and placebo groups (0 of 201 [0%] participants and 1 of 199 [0.5%] participants, respectively). The incidence rates per 100 PY were 0.00 and 0.54, respectively. There were no fatal malignancy events in Study D5180C00021.

*Chronic Rhinosinusitis With Nasal Polyps*

In Study D5242C00001, the incidence of AEs of malignancy reported in the on-treatment period was low and similar in the tezepelumab and placebo groups (2 of 203 [1.0%] participants and 1 of 205 [0.5%] participants, respectively). Malignancies in the tezepelumab group were reported in the PT invasive lobular breast carcinoma and PT malignant melanoma. The exposure-adjusted incidence rates per 100 PY in the tezepelumab and placebo groups were 1.0 and 0.6, respectively.

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 3.2 and Section 3.3) 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.

### 2.7.3.2 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 IV 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 on an area under the concentration-time curve at steady state basis, and 259 times the maximum recommended human dose 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 participants 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 participants delivered healthy, full-term infants. One participant in the CD-RI-MEDI9929-1146 tezepelumab 280 mg group delivered pre-term twins after experiencing an SAE of pre-eclampsia. One participant in the CD-RI-MEDI9929-1146 tezepelumab 280 mg group was reported to have a spontaneous abortion at 11 weeks into the pregnancy. Two participants in D5180C00007 were reported to have had spontaneous abortions at 6 and 9 weeks into the pregnancies, respectively, both participants 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 participants who had spontaneous abortions. No pregnancies were reported in any of the other completed tezepelumab asthma clinical studies and in Study D5242C00001 in participants with CRSwNP.

*Breastfeeding:* In nonclinical species, since tezepelumab was detected in milk (albeit at very low levels compared to maternal serum), the possibility of transfer from maternal animal to 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 breastfeeding or to discontinue/abstain from using tezepelumab, taking into account the benefit and risk of breastfeeding 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 PASS, non-interventional pregnancy study using secondary data (Section 3.2.1).

# 2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

## 2.8.1 Summary of the Safety Concerns

**Table 2-11 Summary of Safety Concerns**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | Serious infections<br>Serious cardiac events<br>Malignancy |
| Missing information | Use in pregnant and breastfeeding women |

# 3 PART III: PHARMACOVIGILANCE PLAN

# 3.1 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 adverse event follow-up questionnaires (TSQs; Annex 4 in Section 7.4) to obtain additional information about the patient, the underlying disease, all potential risk factors, the sequence of events, diagnostic details, and outcome.

# 3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

## 3.2.1 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 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 are 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 missing information for regulatory requirements.

The primary objective of the study is to compare the risk of major congenital malformations between pregnant women with severe asthma who were exposed to tezepelumab in their first trimester and pregnant women with severe asthma who were unexposed to tezepelumab. The secondary objective is to compare the risk of minor congenital malformations, adverse pregnancy outcomes, and adverse infant outcomes separately, between pregnant women with severe asthma who were exposed to tezepelumab during pregnancy and pregnant women with severe asthma who were unexposed to tezepelumab.

Study design

The proposed study will apply a non-interventional, longitudinal, population-based, cohort design to secondary data derived from multiple large data sources that are representative of EU Member states. Data sources in the US may also be included if required. Appropriate statistical methods will be used to ensure comparability between the cohorts (eg, propensity score method).

Study population

The target study population is pregnant women with severe asthma. Patients will be selected using a combination of diagnosis codes for asthma (ICD-10) and medications and other diagnoses that are indicative of severe asthma. The exposed group will be defined as women with severe, uncontrolled asthma who received at least one dose of tezepelumab from 16 weeks prior to conception date to the end of pregnancy. The unexposed group (control group) will be defined as pregnant women with severe, uncontrolled asthma who are unexposed to tezepelumab.

Milestones

- Submission of initial Study Protocol: 17 March 2023
- Interim Report 1: 31 March 2028

- Interim Report 2: 31 March 2031
- Final Report: March 2034

### 3.2.2 Phase III 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 $FEV_1$ 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 III, 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 APFS, 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 one 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

- Submission of initial Study Protocol: 07 February 2022
- Study Start: First participant in was on 09 August 2022
- Final abbreviated Clinical Study Report Submission: Q1 2026

### 3.2.3 Serious Cardiac Events Post-authorisation Safety Study (D5180R00024)

**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 this 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 adverse cardiovascular events in adolescent and adult patients with severe, uncontrolled asthma newly exposed to tezepelumab with the incidence in comparable patients with severe, uncontrolled asthma exposed to other standard of care regimens. The primary objective of this study is to compare the risk of a composite of major adverse cardiovascular events in tezepelumab-treated adolescent and adult patients with severe asthma with matched patients unexposed to tezepelumab. Secondary objectives are to compare the risks of a composite of serious adverse cardiovascular events, and of the individual cardiovascular events included in the composite measures, between the tezepelumab-treated patients and the matched patients unexposed to tezepelumab.

Study design

This study is 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.

Study outcomes include major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke); a composite of serious adverse cardiovascular events (arrhythmias, coronary artery disease, heart failure, or myocardial disorders); individual components of major adverse cardiovascular events and the composite of serious adverse

cardiovascular events (ie, arrhythmias, coronary artery disease, heart failure, or myocardial disorders).

Study population

The study population will consist of individuals with severe, uncontrolled asthma, aged 12 years and older on index date. Patients will be selected using asthma diagnosis codes and medication prescription codes that are indicative of severe, uncontrolled asthma in the Electronic Health Records sources.

Milestones

- Submission of initial Study Protocol: 19 September 2023
- Interim Report 1: 30 April 2026
- Interim Report 2: 30 April 2028
- Final Report: 31 May 2030

## 3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

**Table 3-1 Ongoing and Planned Additional Pharmacovigilance Activities**

| Study<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** – Not applicable | | | | |
| **Category 2** – Not applicable | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| Study D5180R00010: Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy.<br>Ongoing | To evaluate the risk of adverse pregnancy, foetal, and infant outcomes in pregnant women with severe, uncontrolled asthma taking tezepelumab compared with a suitably matched unexposed population using real-world data. | Use in pregnancy | Study Protocol submission | 17Mar2023 |
| | | | Interim Report 1 | 31Mar2028 |
| | | | Interim Report 2 | 31Mar2031 |
| | | | Final Study Report submission | March 2034 |
| Study D5180C00024 (SUNRISE): Phase III study to evaluate the efficacy and safety of tezepelumab in | To demonstrate the ability of tezepelumab, compared with placebo, to reduce OCS use in adults with severe asthma being treated | Serious infections, serious cardiac events, malignancy | Study Protocol | 07Feb2022 |

**Table 3-1 Ongoing and Planned Additional Pharmacovigilance Activities**

| Study<br>Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| reducing OCS use in adults with OCS-dependent asthma<br>Ongoing | with maintenance OCS in combination with high dose ICS and LABA with or without other asthma controller therapies, while maintaining asthma control. | | Final Study Report (abbreviated) | Q1 2026 |
| Study D5180R00024: Serious cardiac events post-authorisation safety study.<br>Ongoing | To compare the incidence of serious cardiac events between patients with severe, uncontrolled asthma who are newly exposed to tezepelumab and suitably matched patients who are unexposed to tezepelumab. | Serious cardiac events | Study Protocol submission | 19Sep2023 |
| | | | Interim Report 1 | 30Apr2026 |
| | | | Interim Report 2 | 30Apr2028 |
| | | | Final Study Report submission | 31May 2030 |

# 4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

# 5 PART V: RISK MINIMISATION MEASURES

## 5.1 ROUTINE RISK MINIMISATION MEASURES

**Table 5-1 Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Important identified risk** | |
| None | |
| **Important potential risks** | |
| Serious infections | Routine risk communication: SmPC Section 4.4 and Package Leaflet<br>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<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4 and Package Leaflet Section 2 |
| Malignancy | None |

**Table 5-1 Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety concern | Routine risk minimisation activities |
|---|---|
| **Missing information** | |
| Use in pregnancy and breastfeeding | Routine risk communication: SmPC Section 4.6 and Package Leaflet Section 2<br>Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6 and Package Leaflet Section 2 |

## 5.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of the medicinal product.

## 5.3 SUMMARY OF RISK MINIMISATION MEASURES

**Table 5-2 Summary Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern**

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| **Important identified risks** | | |
| None | Not applicable | Not applicable |
| **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 ADR follow-up questionnaires<br>Additional pharmacovigilance activities:<br>Study D5180C00024 - 28-week OCS-reduction 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 ADR follow-up questionnaires<br>Additional pharmacovigilance activities:<br>Study D5180C00024 - 28-week OCS-reduction study in severe asthma<br>Study D5180R00024 - Serious cardiac events post authorisation safety study |

**Table 5-2 Summary 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:<br>Post-marketing targeted ADR follow-up questionnaires<br>Additional pharmacovigilance activities:<br>Study D5180C00024 - 28-week OCS-reduction 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:<br>Study D5180R00010 (PASS) - Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy |

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

This is a summary of the 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 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.

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

## 6.1 THE MEDICINE AND WHAT IT IS USED FOR

TEZSPIRE is authorised for:

Asthma

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

Chronic rhinosinusitis with nasal polyps

TEZSPIRE is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids, and/or surgery do not provide adequate disease control.

TEZSPIRE contains tezepelumab as the active substance and it is given/self-administered by SC injection.

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

## 6.2 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 (eg, 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.

### 6.2.1 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 (e.g., on the long-term use of the medicine).

**Table 6-1 List of Important Risks and Missing Information**

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | Serious infections<br>Serious cardiac events<br>Malignancy |
| **Missing Information** | Use in pregnant and breastfeeding women |

### 6.2.2 Summary of Important Risks

**Table 6-2 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<br>Additional risk minimisation measures: None |
| **Additional pharmacovigilance activities** | Study D5180C00024 - 28-week OCS-reduction study in severe asthma |

**Table 6-3 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 patients receiving tezepelumab, and no specific subgroup of patients who may be at an increased risk of serious cardiac events has been identified. |

**Table 6-3 Important Potential Risk: Serious Cardiac Events**

| | |
|---|---|
| **Risk minimisation measures** | Routine risk minimisation measures: SmPC Section 4.4 and Package Leaflet Section 2<br>Additional risk minimisation measures: None |
| **Additional pharmacovigilance activities** | Study D5180C00024 - 28-week OCS-reduction study in severe asthma<br>Study D5180R00024 - Serious cardiac events post-authorisation safety study |

**Table 6-4 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 |

**Table 6-5 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 pharmacovigilance activities** | Study D5180R00010 - Database study of the use (and safety) of tezepelumab in women with severe asthma during pregnancy |

## 6.2.3 Post-authorisation Development Plan

### 6.2.3.1 Studies Which are Conditions of the Marketing Authorisation

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

### 6.2.3.2 Other Studies in Post-authorisation Development Plan

**Tezepelumab pregnancy study (D5180R00010)**

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

Purpose of the study: The primary objective of the study is to compare the risk of major congenital malformations between pregnant women with severe asthma who were exposed to tezepelumab in their first trimester and pregnant women with severe asthma who were unexposed to tezepelumab. The secondary objective is to compare the risk of minor congenital

malformations, adverse pregnancy outcomes, and adverse infant outcomes, separately, between pregnant women with severe asthma who were exposed to tezepelumab during pregnancy and pregnant women with severe asthma who were unexposed to tezepelumab.

**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.

**Serious cardiac events post-authorisation safety study (D5180R00024)**

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: The overall objective of the study is to evaluate the risk of serious adverse cardiovascular events in adolescent and adult patients with severe asthma taking tezepelumab compared with a comparable, suitably matched, unexposed population using real-world data.

# 7 PART VII: ANNEXES

## 7.1 ANNEX 1: EudraVigilance Interface – Not Applicable

## 7.2 ANNEX 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Programme

## 7.3 ANNEX 3: Protocols for Proposed, Ongoing and Completed Studies in the Pharmacovigilance Plan

### 7.3.1 Part A: Requested Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review With this Updated Version of the RMP – Not Applicable

### 7.3.2 Part B: Requested Amendments of Previously Approved Protocols of Studies in the Pharmacovigilance Plan, Submitted for Regulatory Review With This Updated Version of the RMP – Not Applicable

### 7.3.3 Part C: Previously Agreed Protocols for Ongoing Studies and Final Protocols not Reviewed by the Competent Authority

## 7.4 ANNEX 4: 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

# TEZSPIRE Questionnaire for Serious Infections

## 1. Reporter's Information

Reporter's Name:

Is Reporter a healthcare professional?
No Yes, If yes, please provide specialty:

Telephone #:

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<br>Event ongoing | Recovered with sequelae<br>Patient died |
| | | | Recovered<br>Event ongoing | Recovered with sequelae<br>Patient died |
| | | | Recovered<br>Event ongoing | Recovered with sequelae<br>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 antibiotics 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: |
|---|---|---|---|
| | | | |

Please provide causal relationship assessment between tezepelumab and adverse event(s): (Y/N and provide justification)

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

If yes, please provide details on the reoccurring event:

## 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 drugwithdrawn? |
|---|---|---|---|---|---|---|
| | | | | | | No Yes |
| | | | | | | No Yes |
| | | | | | | No Yes |

If any of the above drugs were stopped or their dosage altered, did the event(s) improve after stopping/altering?
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 drugwithdrawn? |
|---|---|---|---|---|---|---|
| | | | | | | 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 Valuedate *(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 NormalValue date *(DD/MM/YY)* and result |
|---|---|---|---|---|---|---|
| White blood cell count | | | | | | |
| Absolute neutrophil count and differential (%) | | | | | | |
| Lymphocytes<br>Subtype:_____<br>Subtype:_____<br>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)*: | |
| C-reactive protein | ☐ 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 havenot been previously noted.*

# TEZSPIRE Questionnaire for Serious Cardiac Events

## 1. Reporter's Information

Reporter's Name: Is Reporter a healthcare professional? Telephone #:
☐ No ☐ Yes, If yes, please provide specialty:

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<br>☐ Event ongoing | ☐ Recovered with sequelae<br>If yes, please specify:<br>☐ Patient died ☐ Unknown |
| | | | ☐ Recovered<br>☐ Event ongoing | ☐ Recovered with sequelae<br>If yes, please specify:<br>☐ 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

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

## 4. TEZSPIRE administration

| Indication: | Dosage: | Start Date *(DD/MM/YY)*: | Stop Date *(DD/MM/YY)*: | Was suspect drug withdrawn?<br>☐ No ☐ Yes | Lot/batch number: |
|---|---|---|---|---|---|
| | | | | | |

Please provide causal relationship assessment between tezepelumab and adverse event(s): (Y/N and provide justification)

**5. 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 or their dosage altered, did the event(s) improve after stopping/altering?

☐ 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)*: _____

If yes, please provide details on the reoccurring event:

**6. 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 |

**7. Relevant Medical History/Concurrent Diseases**

| **Medical History** | | **Start Date** *(DD/MM/YY)* | **Stop Date** *(DD/MM/YY)* | If yes, please provide details |
|---|---|---|---|---|
| Previously known ischemic heart disease/ heart failure/ Valvular heart disease. Please specify: | ☐ 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.) Please specify: | ☐ 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. | | | |

# TEZSPIRE Questionnaire for Malignancies

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

## 1. Patient details

| | | |
|---|---|---|
| Date of birth (*dd/mm/yyyy*):<br>Age (*years*): | Country of origin:<br>Gender at Birth: ☐ Male ☐ Female | Height: ____ cm ☐ in ☐<br>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)<br>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): (Y/N and provide justification)

**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 |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

## 3. Adverse Event(s)

| Adverse Event(s) | Start date | Stop date | Outcome * 1. No evidence of disease 2. Stable/Inactive disease 3. Active disease 4. Fatal outcome |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

*** 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, please specify:<br><br>Treatment of adverse event(s):<br><br>For fatal outcome, please provide cause of death and copy of the autopsy report if available: |
| **Please describe the malignancy** |
| Is this a new diagnosis or a relapse/disease progression of a pre-existing condition?<br><br>Anatomical location:<br>Histological type (e.g. cell type confirmed by biopsy):<br>Tumour, Node, Metastasis (TNM)<br>classification:<br>Grade/Staging:<br>Other, specify:<br>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:<br>Histopathology:<br>Cytology:<br>Genetic testing:<br>CD marker evaluation:<br>Other, specify (e.g. biomarkers): |
| Please provide prior screening tests results if appropriate (e.g., mammogram, Pap test, colonoscopy): |
| **4. Relevant history**<br>*(Are there any other etiological factors? Please mark with an "X" all that apply):* |
| • Exposure to environmental factors, specify:<br>• Related co-morbidities, specify:<br>• Family history, specify:<br>• Occupational history:<br>• Smoking:<br>• Diet; specify:<br>• Chronic alcohol use:<br>• Chemicals exposure [asbestos, benzenes, nickel, etc.]:<br>• Radiation exposure [sun rays, x-rays, radioactive elements]:<br>• Infection (e.g., Papilloma, Cytomegalovirus, Schistosoma, hepatitis, HIV/AIDS):<br>• Medication-induced [e.g., hormone replacement therapy (HRT), diethylstilbestrol (DES)]:<br>• Immunosuppression, specify:<br>• Chemotherapy:<br>• 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:<br>Reporter's Address:<br>Telephone #:<br>Fax #: | Is the reporter a healthcare professional (HCP)?<br>No ☐ Yes ☐<br>If yes, please provide specialty: | If no, please confirm if we can contact the HCP? No ☐ Yes ☐<br>If yes, please provide contact information of the HCP |

**Thank you for completing this form.**

## 7.5 ANNEX 5: Protocols for Proposed and Ongoing Studies in RMP Part IV – Not Applicable

## 7.6 ANNEX 6: Details of Proposed Additional Risk Minimisation Activities – Not Applicable

## 7.7 ANNEX 7: Other Supporting Data (Including Referenced Material) – Not Applicable

## 7.8 ANNEX 8: Summary of Changes to the Risk Management Plan Over Time

# LIST OF REFERENCES

**Agarwal et al 2020**
Agarwal A, Spath D, Sherris DA, Kita H, Ponikau JU. Therapeutic antibodies for nasal polyposis treatment: where are we headed? Clin Rev Allergy Immunol. 2020;59(2):141-9.

**Ah-See et al 2012**
Ah-See KL, MacKenzie J, Ah-See KW. Management of chronic rhinosinusitis. BMJ. 2012;345:e7054.

**Alobid et al 2011**
Alobid I, Antón E, Armengot M, Chao J, Colás C, del Cuvillo A, et al; Rhinoconjunctivitis Committee; Spanish Society of Allergy and Clinical Immunology; Rhinology and Allergy Commission; Spanish Society of Otorhinolaryngology. SEAIC-SEORL. Consensus document on nasal polyposis. POLINA project. J Investig Allergol Clin Immunol. 2011;21(Suppl 1):1-58.

**Al-Shami et al 2005**
Al-Shami A, Spolski R, Kelly J, Keane-Myers A, Leonard WJ. A role for TSLP in the development of inflammation in an asthma model. J Exp Med. 2005;202:829-39.

**Alt et al 2017**
Alt JA, Thomas AJ, Curtin K, Wong J, Rudmik L, Orlandi RR. Mortality risk in patients with chronic rhinosinusitis and its association to asthma. Int Forum Allergy Rhinol. 2017;7(6):591-9.

**Ambrose et al 2020**
Ambrose CS, Chipps BE, Moore WC, Soong W, Trevor J, Ledford DK, et al. The CHRONICLE study of US adults with subspecialist-treated severe asthma: objectives, design, and initial results. Pragmat Obs Res. 2020;11:77-90.

**Avdeeva and Fokkens 2018**
Avdeeva K, Fokkens W. Precision medicine in chronic rhinosinusitis with nasal polyps. Curr Allergy Asthma Rep. 2018;18(4):25.

**Bachert et al 2014**
Bachert C, Pawankar R, Zhang L, Bunnag C, Fokkens WJ, Hamilos DL, et al. ICON: chronic rhinosinusitis. World Allergy Organ J. 2014;7(1):25.

**Bachert et al 2015**
Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol. 2015;136(6):1431-40.

**Bachert et al 2016**
Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA. 2016;315(5):469-79.

**Bachert et al 2017**
Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. J Allergy Clin Immunol. 2017;140(4):1024-1031.e14.

**Bachert et al 2018**
Bachert C, Zhang N, Hellings PW, Bousquet J. Endotype-driven care pathways in patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2018;141(5):1543-51.

**Bachert et al 2019**
Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-50.

**Bachert et al 2020**
Bachert C, Marple B, Schlosser RJ, Hopkins C, Schleimer RP, Lambrecht BN, et al. Adult chronic rhinosinusitis. Nat Rev Dis Primers. 2020;6(1):86.

**Bachert et al 2021**
Bachert C, Bhattacharyya N, Desrosiers M, Khan AH. Burden of disease in chronic rhinosinusitis with nasal polyps. J Asthma Allergy. 2021;14:127-34.

**Bai et al 2022**
Bai J, Huang JH, Price CPE, Schauer JM, Suh LA, Harmon R, et al. Prognostic factors for polyp recurrence in chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2022;150(2):352-361.e7.

**Barnes and Woolcock 1998**
Barnes PJ, Woolcock AJ. Difficult asthma. Eur Respir J. 1998;12:1209-18.

**Barooei et al 2015**
Barooei R, Mahmoudian RA, Abbaszadegan MR, Mansouri A, Gholamin M. Evaluation of thymic stromal lymphopoietin (TSLP) and its correlation with lymphatic metastasis in human gastric cancer. Med Oncol 2015;32(8):217.

**Bateman et al 2008**
Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31:143–78.

**Benson et al 2022**
Benson VS, Germain G, Chan RH, Sousa AR, Yang S, Silver J, et al. Elucidating the real-world burden of chronic rhinosinusitis with nasal polyps in patients in the USA. OTO Open. 2022;6(4):2473974X221128930.

**Buelo et al 2018**
Buelo A, McLean S, Julious S, Flores-Kim J, Bush A, Henderson J, et al; ARC Group. At-risk children with asthma (ARC): a systematic review. Thorax. 2018;73:813-24.

**Busse et al 2000**
Busse WW, Banks-Schlegel S, Wenzel SE. Pathophysiology of severe asthma. J Allergy Clin Immunol. 2000;106:1033-42.

**Carpino et al 2004**
Carpino N, Thierfelder WE, Chang M-S, Saris C, Turner SJ, Ziegler SF, et al. Absence of an essential role for thymic stromal lymphopoietin receptor in murine B-cell development, Mol Cell Biol. 2004;24:2584-92.

**Chen et al 2018**
Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. Curr Med Res Opin. 2018;34(12):2075-88.

**Chen et al 2020**
Chen S, Zhou A, Emmanuel B, Thomas K, Guiang H. Systematic literature review of the epidemiology and clinical burden of chronic rhinosinusitis with nasal polyposis. Curr Med Res Opin. 2020;36(11):1897-911.

**Chung et al 2014**
Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343-73.

**CINQAERO SmPC**
CINQAERO (reslizumab) Summary of Product Characteristics. Teva Pharmaceuticals Limited, Castleford, UK. Available at: https://ec.europa.eu/health/documents/community-register/2017/20170428137621/anx_137621_en.pdf. Accessed 05 December 2024.

**Corren and Ziegler 2019**
Corren J, Ziegler SF. TSLP: from allergy to cancer. Nat Immunol. 2019:20:1603-9.

**DeConde et al 2017**
DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. Laryngoscope. 2017;127(3):550-5.

**Demoly et al 2009**
Demoly P, Paggiaro P, Plaza V, Bolge SC, Kannan H, Sohier B, et al. Prevalence of asthma control among adults in France, Germany, Italy, Spain, and the UK. Eur Respir Rev. 2009;18:105-12.

**Dennis et al 2016**
Dennis SK, Lam K, Luong A. A review of classification schemes for chronic rhinosinusitis with nasal polyposis endotypes. Laryngoscope Investig Otolaryngol. 2016;1(5):130-4.

**Dessouky and Hopkins 2015**
Dessouky O, Hopkins C. Surgical versus medical interventions in CRS and nasal polyps: comparative evidence between medical and surgical efficacy. Curr Allergy Asthma Rep. 2015;15(11):66.

**Dietz de Loos et al 2019**
Dietz de Loos D, Lourijsen ES, Wildeman MAM, Freling NJM, Wolvers MDJ, Reitsma S, et al. Prevalence of chronic rhinosinusitis in the general population based on sinus radiology and symptomatology. J Allergy Clin Immunol. 2019;143(3):1207-14.

**Doz et al 2013**
Doz M, Chouaid C, Com-Ruelle L, Calvo E, Brosa M, Robert J, et al. The association between asthma control, health care costs, and quality of life in France and Spain. BMC Pulm Med. 2013;13:15.

**DUPIXENT SmPC**
DUPIXENT (dupilumab) solution for injection. Summary of Product Characteristics. Sanofi-Aventis Groupe. Available at: https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. Accessed 09 March 2020.

**ENFUMOSA 2003**
The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J. 2003;22:470-7.

**Engelkes et al 2020**
Engelkes M, de Ridder MA, Svensson E, Berencsi K, Prieto-Alhambra D, Lapi F, et al. Multinational cohort study of mortality in patients with asthma and severe asthma. Respir Med. 2020;165:105919.

**FASENRA SmPC**
FASENRA (benralizumab) for injection. Summary of Product Characteristics. AstraZeneca AB. Revised August 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/fasenra-epar-product-information_en.pdf, Accessed 09 March 2020.

**Fernandes et al 2014**
Fernandes AGO, Souza-Machado C, Coelho RCP, Franco PA, Esquivel RM, Souza-Machado A, et al. Risk factors for death in patients with severe asthma. J Bras Pneumol. 2014;40:364-72.

**Fokkens et al 2012**
Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;23:1-298.

**Fokkens et al 2019**
Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74(12):2312-9.

**Fokkens et al 2020**
Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology. 2020;58(Suppl S29):1-464.

**Fokkens et al 2023**
Fokkens WJ, Viskens AS, Backer V, Conti D, De Corso E, Gevaert P, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. Rhinology. 2023;61(3):194-202.

**Fraenkel et al 2021**
Fraenkel L, Bathon JM, England BR, St. Clair EW, Arayssi T, Carandang K, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2021;73(7):924-39.

**GBD Collaborators 2017**
GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017;5:691-706.

**Gevaert et al 2011**
Gevaert P, van Bruaene N, Cattaert T, van Steen K, van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol. 2011;128(5):989-95.e1-8.

**GINA 2024**
Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. May 2024. Available from: http://www.ginasthma.org. Accessed 11 September 2024.

**Hastan et al 2011**
Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA(2)LEN study. Allergy. 2011;66(9):1216-23.

**Hedman et al 1999**
Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999;28(4):717-22.

**Hirsch et al 2017**
Hirsch AG, Stewart WF, Sundaresan AS, Young AJ, Kennedy TL, Scott Greene J, et al. Nasal and sinus symptoms and chronic rhinosinusitis in a population-based sample. Allergy. 2017;72(2):274-81.

**Hopkins 2019**
Hopkins C. Chronic rhinosinusitis with nasal polyps. N Engl J Med. 2019;381(1):55-63.

**Israel and Reddel 2017**
Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. N Engl J Med. 2017;377:965-76.

**Kerkhof et al 2018**
Kerkhof M, Tran TN, Soriano J, Golam S, Gibson D, Hillyer EV, et al. Healthcare Resource Use and Costs of Severe, Uncontrolled Eosinophilic Asthma in the UK General Population. Thorax. 2018;73(2):116-24.

**Khan et al 2019a**
Khan A, Vandeplas G, Huynh TMT, Joish VN, Mannent L, Tomassen P, et al. The Global Allergy and Asthma European Network (GALEN) rhinosinusitis cohort: a large European cross-sectional study of chronic rhinosinusitis patients with and without nasal polyps. Rhinology. 2019;57(1):32-42.

**Khan et al 2019b**
Khan A, Huynh TMT, Vandeplas G, Joish VN, Mannent LP, Tomassen P, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. Rhinology. 2019;57(5):343-51.

**Khan et al 2023**
Khan AH, Gouia I, Kamat S, Johnson R, Small M, Siddall J. Prevalence and severity distribution of type 2 inflammation-related comorbidities among patients with asthma, chronic rhinosinusitis with nasal polyps, and atopic dermatitis. Lung. 2023;201(1):57-63.

**Kim and Cho 2017**
Kim DW, Cho SH. Emerging endotypes of chronic rhinosinusitis and its application to precision medicine. Allergy Asthma Immunol Res. 2017;9(4):299-306.

**Klossek et al 2005**
Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: a cross-sectional, case-control study. Allergy. 2005;60(2):233-7.

**Kwah et al 2020**
Kwah JH, Somani SN, Stevens WW, Kern RC, Smith SS, Welch KC, et al. Clinical factors associated with acute exacerbations of chronic rhinosinusitis. J Allergy Clin Immunol. 2020;145(6):1598-605.

**Laidlaw et al 2021**
Laidlaw TM, Mullol J, Woessner KM, Amin N, Mannent LP. Chronic rhinosinusitis with nasal polyps and asthma. J Allergy Clin Immunol Pract. 2021;9(3):1133-41.

**Lo Kuan and Ziegler 2014**
Lo Kuan E, Ziegler SF. Thymic stromal lymphopoietin and cancer. J Immunol. 2014;193(9):4283-8.

**Lou et al 2018**
Lou H, Zhang N, Bachert C, Zhang L. Highlights of eosinophilic chronic rhinosinusitis with nasal polyps in definition, prognosis, and advancement. Int Forum Allergy Rhinol. 2018;8(11):1218-25.

**Mahdavinia et al 2016**
Mahdavinia M, Benhammuda M, Codispoti CD, Tobin MC, Losavio PS, Mehta A, et al. African American patients with chronic rhinosinusitis have a distinct phenotype of polyposis associated with increased asthma hospitalization. J Allergy Clin Immunol Pract. 2016;4(4):658-64.e1.

**Maio et al 2018**
Maio S, Baldacci S, Bresciani M, Simoni M, Latorre M, Murgia N, et al; AGAVE group. RItA: The Italian severe/uncontrolled Asthma Registry. Allergy. 2018;73(3):683-95.

**Manson et al 2009**
Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. Respir Med. 2009;103:975–94.

**NAEPP 2007**
National Asthma Education and Prevention Program Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. Summary Report 2007. Available from: https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. Accessed 20 February 2020.

**NUCALA SmPC**
NUCALA (mepolizumab) Summary of Product Characteristics. GlaxoSmithKline Trading Services Limited. Available at: https://www.ema.europa.eu/en/documents/product-information/nucala-epar-product-information_en.pdf. Accessed 09 March 2020.

**O'Byrne et al 2012**
O'Byrne PM, Naji N, Gauvreau GM. Severe asthma: future treatments. Clin Exp Allergy. 2012;42:706-11.

**Orlandi et al 2016**
Orlandi RR, Kingdom TT, Hwang PH, Smith TL, Alt JA, Baroody FM, et al. International consensus statement on allergy and rhinology: rhinosinusitis. Int Forum Allergy Rhinol. 2016;6(Suppl 1):S22-209.

**Orlandi et al 2021**
Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. Int Forum Allergy Rhinol. 2021;11(3):213–739.

**Palmer et al 2019**
Palmer JN, Messina JC, Biletch R, Grosel K, Mahmoud RA. A cross-sectional, population-based survey of U.S. adults with symptoms of chronic rhinosinusitis. Allergy Asthma Proc. 2019;40(1):48-56.

**Peters et al 2006**
Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: A review of the prevalence, disease burden and options for treatment. Respir Med. 2006:100(7);1139-51.

**Peters et al 2014**
Peters AT, Spector S, Hsu J, Hamilos DL, Baroody FM, Chandra RK, et al; Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. Diagnosis and management of rhinosinusitis: a practice parameter update. Ann Allergy Asthma Immunol. 2014;113(4):347-85.

**Price et al 2014**
Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ Prim Care Respir Med. 2014;24:14009.

**Protti and De Monte 2020**
Protti MP, De Monte L. Thymic stromal lymphopoietin and cancer: Th2-dependent and -independent mechanisms. Front Immunol. 2020;11:2088.

**Rabe et al 2004**
Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol. 2004;114(1):40-7.

**Ricciardolo et al 2020**
Ricciardolo FLM, Levra S, Sprio AE, Bertolini F, Carriero V, Gallo F, et al. A real-world assessment of asthma with chronic rhinosinusitis. Ann Allergy Asthma Immunol. 2020;125(1):65-71.

**Salpeter 2003**
Salpeter SR. Cardioselective beta blocker use in patients with asthma and chronic obstructive pulmonary disease: an evidence-based approach to standards of care. Cardiovasc Rev Rep. 2003;24(11):564-72.

**Sanchez-Collado et al 2022**
Sanchez-Collado I, Mora T, Munoz-Cano R, Ribo P, Mullol J, Valero A. Prevalence of chronic rhinosinusitis with nasal polyps in Catalonia (Spain): a retrospective, large-scale population-based study. Rhinology. 2022;60(5):384-96.

**Soong et al 2020**
Soong W, Ambrose CS, Trevor J, Lugogo N, Gawade P, Desai P, et al. Real-world asthma exacerbation and hospitalization rates by treatment among specialist-treated United States severe asthma patients Ann Allergy Asthma Immunol. 2020;125(5):S27.

**Starry et al 2022**
Starry A, Hardtstock F, Wilke T, Weihing J, Ultsch B, Wernitz M, et al. Epidemiology and treatment of patients with chronic rhinosinusitis with nasal polyps in Germany-A claims data study. Allergy. 2022;77(9):2725-36.

**Stevens et al 2016**
Stevens WW, Schleimer RP, Kern RC. Chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract. 2016;4(4):565-72.

**Stevens et al 2017**
Stevens WW, Peters AT, Hirsch AG, Nordberg CM, Schwartz BS, Mercer DG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. J Allergy Clin Immunol Pract. 2017;5(4):1061-70.e3.

**Stevens et al 2019**
Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, et al. Associations between inflammatory endotypes and clinical presentations in chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2019;7(8):2812-20.e3.

**Sullivan et al 2018**
Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. J Allergy Clin Immunol. 2018;141(1):110–6.e7.

**Tan et al 2013**
Tan BK, Chandra RK, Pollak J, Kato A, Conley DB, Peters AT, et al. Incidence and associated premorbid diagnoses of patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2013;131(5):1350-60.

**To et al 2012**
To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204.

**Tokunaga et al 2015**
Tokunaga T, Sakashita M, Haruna T, Asaka D, Takeno S, Ikeda H, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. Allergy. 2015;70(8):995-1003.

**Toppila-Salmi et al 2022**
Toppila-Salmi S, Hällfors J, Aakko J, Mannerström B, Nieminen K, Telg G, et al. The burden of chronic rhinosinusitis with nasal polyps and its relation to asthma in Finland. Clin Transl Allergy. 2022;12(10):e12200.

**Torén et al 2004**
Torén K, Gislason T, Omenaas E, Jögi R, Forsberg B, Nyström L, et al; RHINE Group. A prospective study of asthma incidence and its predictors: the RHINE Study. Eur Respir J. 2004;24(6):942-6.

**Uhlén et al 2015**
Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015;347(6220):1260419.

**Van Ganse et al 2006**
Van Ganse E, Antonicelli L, Zhang Q, Laforest L, Yin DD, Nocea G, et al. Asthma-related resource use and cost by GINA classification of severity in three European countries. Respir Med. 2006;100:140-7.

**Wang et al 2020**
Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. Chest. 2020;157(4):790-804.

**Watanabe et al 2015**
Watanabe J, Saito H, Miyatani K, Ikeguchi M, Umekita Y. TSLP Expression and high Serum TSLP level indicate a poor prognosis in gastric cancer patients. Yonago Acta Med. 2015;58(3):137-43.

**Wautlet et al 2023**
Wautlet A, Bachert C, Desrosiers M, Hellings PW, Peters AT. The management of chronic rhinosinusitis with nasal polyps (CRSwNP) with biologics. J Allergy Clin Immunol Pract. 2023;11(9):2642-51.

**Wenzel 2003**
Wenzel S. Severe asthma: epidemiology, pathophysiology and treatment. Mt Sinai J Med. 2003;70(3):185-90.

**Wenzel 2005**
Wenzel S. Severe Asthma in Adults. Am J Respir Crit Care Med. 2005;172(2);149-60.

**Winer et al 2012**
Winer RA, Qin X, Harrington T, Moorman J, Zahran H. Asthma incidence among children and adults: findings from the Behavioral Risk Factor Surveillance system asthma call-back survey – United States, 2006-2008. J Asthma. 2012;49(1):16-22.

**Wu et al 2019**
Wu EL, Harris WC, Babcock CM, Alexander BH, Riley CA, McCoul ED. Epistaxis risk associated with intranasal corticosteroid sprays: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2019;161(1):18-27.

**Xie et al 2015**
Xie F, Liu L-B, Shang W-Q, Chang K-K, Meng Y-H, Mei J, et al. The infiltration and functional regulation of eosinophils induced by TSLP promote the proliferation of cervical cancer cell. Cancer Lett. 2015;364(2):106-17.

**XOLAIR SmPC**
XOLAIR (omalizumab). Summary of Product Characteristics. Novartis Europharm Limited, Dublin, Ireland. Available at: https://www.ema.europa.eu/en/documents/product-information/xolair-epar-product-information_en.pdf. Accessed 09 March 2020.

**Zeiger et al 2016**
Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. J Allergy Clin Immunol Pract. 2016;4:120-9.e3.

**Zhang et al 2008**
Zhang N, Van Zele T, Perez-Novo C, Van Bruaene N, Holtappels G, DeRuyck N, et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. J Allergy Clin Immunol. 2008;122(5):961-8.

Signature Page for VV-RIM-09513086 System v4.0
EU Risk Management System Version 6 Succession 2

| | |
|---|---|
| Approve: Document Level Task<br>Verdict: Approved | Gemma Jimenez<br>Qualified Person Approval<br>27-Aug-2025 09:17:40 GMT+0000 |

Signature Page for VV-RIM-09513086 System v4.0
EU Risk Management System Version 6 Succession 2