Module 1.8.2

European Union Risk Management Plan (EU-RMP) for EXDENSUR (depemokimab)

RMP version to be assessed as part of this application	
RMP Version number	1.0
Data lock point for this RMP	20 September 2024
Date of final sign off	04 December 2025
Rationale for submitting an updated RMP Not Applicable	
Summary of significant changes in this RMP: Not Applicable	
Other RMP versions under evaluation Not applicable	
Details of the currently approved RMP Not applicable	

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QPPV Signature	Electronic signature on file

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
AQLQ	Asthma Quality of Life Questionnaire
BMI	Body Mass Index
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
CRS	Chronic Rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without Nasal Polyps
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ED	Emergency Department
eGFR	Estimated Glomerular Filtration Rate
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
ESS	Endoscopic sinus surgery
EU	European Union
FEV1	Forced Expiratory Volume in 1 second
FTIH	First Time in Humans
GALEN	Global Allergy and Asthma European Network
GBD	Global Burden of Disease
GDS	Global Datasheet
GERD	Gastroesophageal Reflux
GINA	Global Initiative for Asthma
ICD	International Classification of Diseases
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroids
ICU	Intensive Care Unit
IgG1	Immunoglobulin G1
IHME	Institute for Health Metrics and Evaluation

IL-5	Interleukin-5
IV	Intravenous
LABA	Long-acting Beta Agonists
mAbs	Monoclonal antibodies
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institute of Health
NP	Nasal Polyps
NSAID	Non-steroidal anti-inflammatory drug
OCS	Oral Corticosteroids
OR	Odds Ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PK	Pharmacokinetics
RMP	Risk Management Plan
SABA	Short-acting β2-Agonists
SARP III	Severe Asthma Research Program
SC	Subcutaneous
SCS	Systemic corticosteroids
SmPC	Summary of Product Characteristic
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TENOR	Outcomes and Treatment Regimens
UK	United Kingdom
US	United States

Trademark Information

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EXDENSUR

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None

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Depemokimab
Pharmacotherapeutic group(s) (ATC Code)	Not assigned
Marketing Authorization Holder/ Applicant	GlaxoSmithKline Trading Services Limited
Medicinal products to which this RMP refers	Depemokimab
Invented name(s) in the European Economic Area (EEA)	EXDENSUR
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Depemokimab is a recombinant humanized IgG1κ monoclonal antibody specific for human interleukin-5 (IL-5). The antibody consists of two kappa light chains (LC) and two IgG1 heavy chains (HC) with a total of 1338 amino acids.
	Summary of mode of action Depemokimab is a humanized monoclonal antibody (IgG1, kappa) that inhibits human interleukin 5 (IL-5) binding to its cognate receptor thereby inhibiting its bioactivity and the resultant IL-5-mediated inflammatory response.
	Important information about its composition Depemokimab is expressed as a soluble glycoprotein produced in a recombinant Chinese hamster ovary cell line.
Reference to the Product Information	Please refer to the product information (section 1.3.1 of the eCTD).

Indication(s) in the EEA	Current: **Asthma** EXDENSUR is indicated as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by blood eosinophil count in adults and adolescents 12 years and older who are inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another asthma controller. **CRSwNP** EXDENSUR 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: **Asthma** *Adults and Adolescents (12 years and older)* The recommended dose is 100 mg of depemokimab administered by SC injection once every 6 months. *Children aged less than 12 years of age* The safety and efficacy of depemokimab in children aged less than 12 years have not been established. No data are available. **CRSwNP** *Adults* The recommended dose is 100 mg of depemokimab administered by SC injection once every 6 months. *Children* There is no relevant use of EXDENSUR in the pediatric population for the treatment of CRSwNP.

Pharmaceutical form(s) and strengths	Current (if applicable): **100 mg solution for injection in pre-filled pen** Colorless, yellow to brown, clear or opalescent solution in a single-use, pre-filled pen. Each pre-filled pen delivers 100 mg depemokimab in 1 mL (100 mg/mL). **100 mg solution for injection in pre-filled syringe** Colorless, yellow to brown, clear or opalescent solution in a single-use, pre-filled syringe. Each pre-filled syringe delivers 100 mg depemokimab in 1 mL (100 mg/mL).
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Asthma

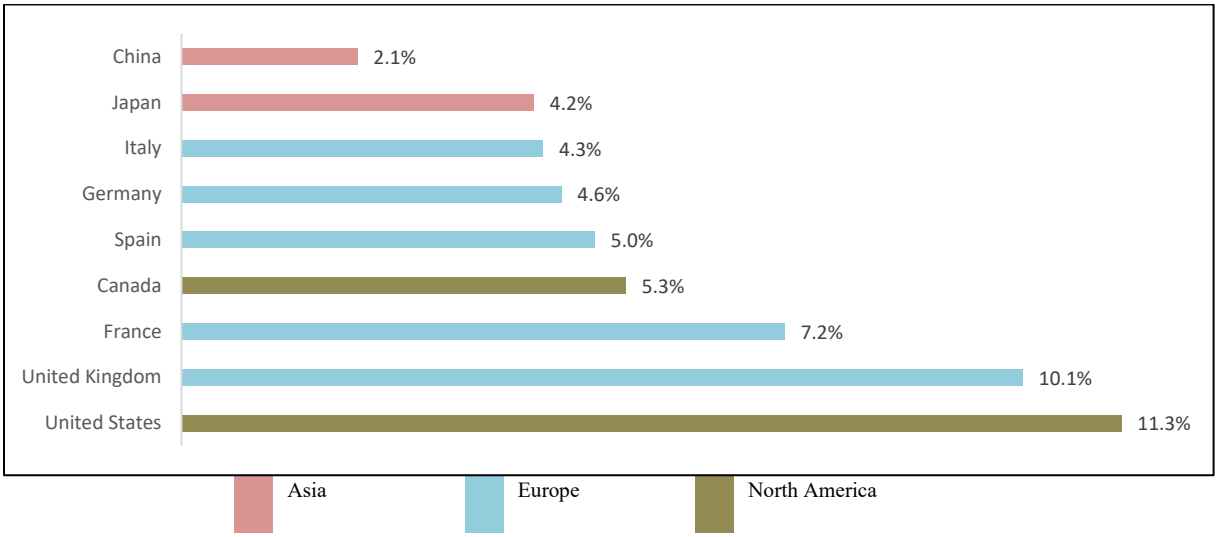
Incidence

Most patients with asthma are diagnosed in childhood. Few studies report on the incidence of asthma as it is difficult to distinguish between new and existing cases. However, recent calculations from the IHME using available data from the 2022 GBD study estimate the global incidence of asthma. Asthma incidence among adults were estimated at 2.7 and 2.1 per 1000 person-years in females and males, respectively for 2021 [IHME, 2024] with higher incidence rates observed in the US (female: 8.3; male: 4.4) [IHME, 2024]. In younger populations, global estimates of asthma incidence was 4.7 per 1000 person-years in 12 to 17-year-old age cohorts, respectively [IHME, 2024].

Prevalence

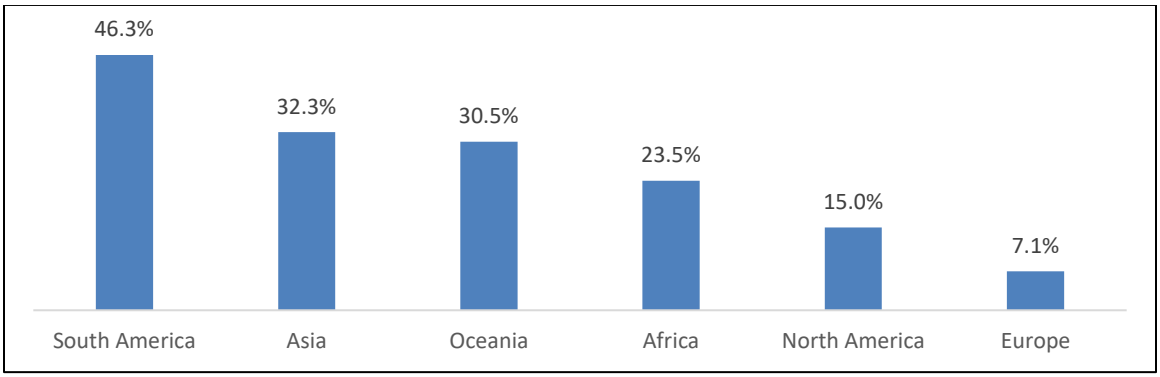
11Overall, the prevalence of asthma was estimated to be highest in the US (11.3%), UK (10.1%), Portugal (10.0%), Australia (9.7%), and Sweden (8.2%) [Rabe, 2023]. Prevalence in Europe was estimated at 5.7%. As described previously, the highest asthma prevalence in Europe was estimated in the UK, Portugal, and Sweden, followed by the Netherlands (7.7%), Ireland (7.6%), Norway (7.4%) and France (7.2%). Some European countries report prevalence less than 5%, including Serbia (3.1%), Slovakia (3.1%), Czechia (3.3%) and Ukraine (3.5%) [Rabe, 2023].

Figure 2. 2019 Asthma Prevalence Across Select Countries (%) [Rabe, 2023]



Severe asthma is heterogenous and is estimated to affect approximately 3-10% of asthmatic patients but is responsible for a disproportionate percentage of the health care costs associated with asthma in the US, Europe and Japan [Rönnebjerg 2021; Backman 2019; Nagase 2020; Song 2020]. Severe or therapy-resistant asthma is recognized as a major unmet need. Severe asthma may be defined as asthma that requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming ''uncontrolled'', or that remains ''uncontrolled'' despite this therapy [Chung, 2014; GINA, 2024]. According to the GINA, the "eosinophilic phenotype is found in the majority of people with severe asthma", suggesting a similar prevalence to severe asthma [GINA, 2024]. While there are reliable estimates for developed countries, there was limited reliable and accurate data for low-middle income countries. Global estimate from the 2019 GBD study report that approximately 26% of those with asthma are affected with severe asthma, while 7.1% are affected in Europe [Figure 3; Rabe, 2023]. The higher rates of severe asthma are driven by low-middle income countries who had the lower asthma prevalence but higher severe asthma, which may be due to underreporting of mild-moderate asthma and access to medications.

Figure 3. Global Prevalence Estimates for Severe Asthma Rates Within Asthma Populations [Rabe, 2023]



Emerging concepts for understanding severe asthma, such as the "treatable traits" approach, are being increasingly adopted, which move away from a stringent definition, towards the systematic assessment and identification of specific characteristics within respiratory, extra-respiratory, and behavioral domains, and treating traits in each domain at the individual level [Park, 2022]. Type 2 inflammation is the underlying pathology for more than 80% [Heaney, 2021] of people with severe asthma, and is driven by Th2 and ILC2 cells, which both produce IL-5 [Maspero, 2022]. IL-5 is a major cytokine responsible for the growth and differentiation of eosinophils in the bone marrow, and recruitment, activation, and survival of eosinophils in the tissue space [Pelaia, 2019]. Uncontrolled T2 inflammation, resulting in eosinophilia, is a recognized risk factor for severe disease exacerbations, airway remodeling and lung function decline in asthma [Pelaia, 2019; Green, 2002; Siddiqui, 2023].

To estimate the proportion of asthma patients eligible for treatment with depemokimab, data from a cohort of patients with prevalent asthma identified using the CPRD database was used (Data on File, RF/NLA/0149/17). This retrospective database study aimed to estimate the proportion of patients with asthma who had: 1) ≥2 exacerbations during

the previous year (i.e., an asthma-related emergency department visit or hospitalization or any use of an OCS), 2) a blood eosinophil level ≥150 cells/µL, and 3) received treatment consistent with step 4 or 5 outlined in the GINA Asthma Management Guidelines [GINA, 2018]. During 2005 to 2011, a cohort of 208,086 patients with asthma was identified in the CPRD database, among which 8,926 had experienced ≥2 exacerbations during the 12-month period prior to the index date (Table 2). Nearly 30% of asthma patients with ≥2 exacerbations had a blood eosinophil measurement recorded in the database. Based on this subset of patients, approximately 2.5%, 2.0%, and 3.3% of children (aged 6-11 years), adolescents (12-17 years), and adults (≥18 years), respectively, had both ≥2 exacerbations in the prior 12-months and a blood eosinophil level ≥150 cells/µl. Subsequent restriction of the numerator to include only those receiving treatment consistent with GINA Step 4 or 5 further reduced the estimated percentage of the desired patient profile to 0.8%, 0.7%, and 1.9% of children, adolescents, and adults with current asthma, respectively. This analysis of an electronic medical record database from a primary care setting in the UK suggests that approximately 2% of adults with asthma experienced ≥2 exacerbations in the past year, had a blood eosinophil level ≥150 cells/µl and were treated at GINA Step 4 or 5. This patient profile was significantly smaller among children and adolescents than in adults. While the population is small, this population has a disproportionately high societal and individual healthcare system burden and individual financial burden of up to 4.4 times more than the mild asthma patients [Håkansson 2023], and was estimated to account for 50% of all asthma related costs in the UK [Nunes 2017].

Table 2 Estimated frequency of asthma patients identified in the UK primary care setting with ≥ 2 exacerbations in the previous year, elevated blood eosinophilia and treated at GINA Step 4 or 5, by age group (CPRD GOLD, 2005-2011)

	Children (6 to 11 yrs)		Adolescents (12 to 17 yrs)		Adults (≥18 yrs)		Total	
	N	%‡	N	%‡	N	%‡	N	%‡
Current asthma study population	25,185	100	24,387	100	158,514	100	208,086	100
Subset with ≥2 exacerbation during 12-month period	883	3.5	692	2.8	7,351	4.6	8,926	4.3
Subset with eosinophil ≥150 cells/µl†	624	2.5	489	2.0	5,199	3.3	6,312	3.0
Subset classified as GINA Step 4&5	208	0.8	160	0.7	3,025	1.9	3,393	1.6

†Estimated based on the subset of patients with a valid blood eosinophil measurement recorded in the database; elevated blood eosinophil (≥150 cells/µL) was observed in 70.7% of subjects with ≥2 exacerbations and a blood eosinophil measurement.
‡The denominator for the percent calculations is equal to the total number of current asthma patients in each respective age group.
NOTE: Italic denote estimated figures.
SOURCE: Data on File, RF/NLA/0149/17

SI.1.1 Demographics of the population in the proposed indication and risk factors for the disease:

Patient Demographics

Data from the International Severe Asthma Registry suggest that adults receiving GINA 5 treatment or uncontrolled at GINA 4 (majority of which are Type 2 phenotype) are older (mean age: 55.0 years), predominantly female (58.3%), Caucasian (72.6%), and do not have a history of smoking (60.6%) [Wang, 2020]. Other large-scale studies have reported similar demographic distributions [Teague, 2018; Jackson, 2021; Koya, 2023]. Additionally, these patients may have higher BMI (mean BMI: 33.5 vs. 31.0 kg/m^2, $p < 0.05$), greater asthma duration (mean years since asthma diagnosis: 32.3 vs. 28.1 years, $p < 0.05$), and poorer quality of life despite treatment with increased doses of corticosteroids (mean total AQLQ scores: 4.6 vs. 5.5, $p < 0.05$) [Teague, 2018].

Demographic trends in asthma adult populations receiving GINA 5 treatment or uncontrolled at GINA 4 are not fully replicated in children and adolescents. In the US SARP III cohort for example, most patients aged <18 years with severe asthma were males, and African-Americans comprised the largest ethnicity affected with severe asthma in this age cohort (44.1%) [Teague, 2018].

An unsupervised cluster analysis in children aged 6-17 years with severe asthma in the SARP Network identified four distinct phenotypes based on 12 continuous and composite variables (Table 3) [Fitzpatrick, 2011]. However, no single phenotype corresponded well with definitions of severe asthma described in published guidelines, suggesting that severe asthma in children is highly heterogenous.

Table 3 Summary Description of Phenotypes of Childhood Severe Asthma Clusters identified in the NIH/NHLBI SARP

Cluster	Summary Description
1	Late-onset symptomatic asthma with normal lung function (n=48); age (yrs) = 9 (3)†
2	Early-onset atopic asthma with normal lung function (n=52); age = 10 (2)†
3	Early-onset atopic asthma with mild airflow limitation (n=32); age = 15 (2)†
4	Early-onset atopic asthma with advanced airflow limitation (n=29); age = 12 (2)†

†Data represent mean (SD)

Source:Fitzpatrick, 2011

Risk Factors

There are several clinical and environmental factors that can influence the severity and persistence of asthma. These include atopy, pollution, tobacco smoke, GERD, respiratory infections and genetics [GINA, 2024].

An estimated 50 to 60% of asthma cases are attributable to atopy [Chipps, 2012]. Wolfe et al reported that among 378 asthmatic children followed from age 7 up to 35 years (at 7-year intervals), the presence of any atopy in childhood was a significant risk factor for moderate-to severe asthma in later life (odds ratio = 1.66; 95% CI: 1.09-2.52) [Wolfe, 2000].

Key risk factors associated with severe asthma include sex, race, obesity, tobacco smoke and environmental tobacco smoke exposure [Jarjour, 2012]. Data from several severe asthma cohorts suggest that female sex is linked to an increased risk for severe asthma, evidenced by the female-to-male ratio of at least 2-to-1 observed in several severe asthma cohorts [Heaney, 2010; Chipps 2012; de Carvalho- Pinto, 2012; Teague, 2018]. Data from the National Hospital Discharge Survey and the US vital statistics systems suggest a greater risk for severe asthma, hospitalization and mortality in black patients with asthma compared to white patients [Teague, 2018; Gupta, 2006]. In the Epidemiology and Natural History of Asthma: TENOR study of severe or difficult to treat asthma, black patients were more likely to have a higher frequency of ED visits, poorer control, poorer quality of life and more likely to use ≥3 long-term controllers compared to white patients, even after adjustment of potential confounders [Chipps, 2012]. Obesity is another risk factor shown to be associated with increased asthma severity in adult-onset disease [Haldar, 2008; Moore, 2010]. Although current smoking prevalence is low among patients with severe asthma, tobacco smoke has been shown to be associated with lack of control of disease and hospitalizations or ED visits for asthma [Talreja, 2012]. Environmental tobacco smoke exposure, validated by urine cotinine levels, in severe asthmatics was associated among other factors with low lung function, greater airway hyperresponsiveness, and increased rescue medication use [Comhair, 2011].

With respect to asthma exacerbations, type 2 inflammatory markers including higher blood eosinophil levels and higher FeNO have been identified as risk factors for asthma exacerbations [GINA 2024]. Other risk factors for asthma exacerbations include SABA over-use, inadequate ICS use, other medical conditions (obesity, CRS, GERD, food allergy and pregnancy), harmful environmental exposures, psychosocial problems, poor lung function, and exacerbation history [GINA 2024].

SI.1.2 The main existing treatment options

ICS are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2024]. Treatment with ICS controls asthma symptoms, improves quality of life and lung function, decreases airway hyperresponsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma mortality. However, add-on therapy with another controller, in particular inhaled LABA, is preferred to increasing the dose of ICS to achieve asthma control. The addition of a LABA to an ICS improves symptom scores, decreases nocturnal asthma symptoms, improves lung function and reduces the number of asthma exacerbations [Ducharme, 2010].

In patients with severe disease or whose asthma remains uncontrolled despite treatment with ICS and LABA combination medications, the current guidelines (GINA, NAEPP and

BTS) recommend treatment with OCS and consideration of add-on type-2 targeted biologic therapies. While maintenance treatment with OCS may be used and can improve pulmonary function and reduce levels of sputum eosinophils in patients with severe refractory asthma [Dente, 2010], the use of long-term OCS is limited by the risk of significant side effects associated with it, including the following: osteoporosis, hypertension, diabetes, hypothalamic pituitary-adrenal axis suppression, obesity, cataracts, glaucoma, skin thinning leading to cutaneous striae and easy bruising, and muscle weakness; Thus, low-dose maintenance OCS is recommended as treatment of last resort, if no other options are available [GINA, 2024].

Asthma guidelines recommend add-on targeted therapy for asthma patients who have evidence of type 2 inflammation and frequent exacerbations and/or poor symptom control, despite treatment with optimized ICS-LABA [GINA, 2024]. The guidelines also state that higher blood eosinophils are predictive of good response to IL-5 inhibition [Ortega, 2016], and also recommend that dosing frequency and patient preference are taken into account when considering treatments, as these factors can affect adherence [GINA, 2024]. Six monoclonal antibodies have been approved for asthma target key cells and mediators mostly in the T2 high inflammatory pathway, including eosinophils: omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab. All have been shown to reduce asthma exacerbations and improve asthma control in patient's refractory to maintenance therapy regimens [Patadia 2024]. Phenotyping these patients are advised prior to initiating targeted type-2 biologic therapies, and this includes biomarker assessments of blood eosinophils (≥150/μL), and/or fractional concentration of exhaled nitric oxide (FeNO ≥ 20ppb), and/or sputum eosinophil (≥2%), and/or whether asthma is clinically allergen-driven [GINA 2024].

Anti-IL-5 therapies have an established efficacy and long-term safety profile in asthmatic patients with a type 2 phenotype [GINA, 2024]. Three biologics targeting IL-5 or its receptor (mepolizumab, reslizumab and benralizumab) are approved for the treatment of severe asthma with an eosinophilic phenotype, administered as an add-on treatment once every 4 to 8 weeks. All 3 biologics, by utilizing blood eosinophils as a biomarker to predict patients likely to respond to therapy, have been shown to reduce exacerbations in asthma patients with type 2 inflammation characterized by increased eosinophils [Haldar, 2009; Castro, 2011; Pavord, 2012; Bel, 2014 ; Ortega, 2014; Castro, 2015; Bleecker, 2016; FitzGerald, 2016; Chupp, 2017]. While these 3 therapies have been shown to decrease exacerbations, reduce the requirement for systemic steroids, and enhance patient outcomes [GINA, 2024], a lack of adherence to the indicated dosing schedules (SC or IV administration every 4 to 8 weeks) can increase exacerbation rates and healthcare costs [Cristancho, 2024]. In general, biologics with shorter dosing intervals have worse adherence [Ledford, 2023; Gelhorn, 2019] and there is a need for treatments that have a favorable benefit-risk profile with a prolonged dosing interval in this patient population.

Bronchial thermoplasty, with registry enrolment is also an alternative although evidence for efficacy and long-term safety is limited [GINA, 2024].

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Despite improved asthma control management and increased medication use, asthma related exacerbations remain a significant burden on the healthcare system and are the best predictive factor for future exacerbations in both children and adults [Racine 2021; Lowden, 2022; GINA 2024]. More than 40% of patients with severe asthma experience severe exacerbations [Wenzel, 2007; Trevor, 2021].

Repeat exacerbations have been associated with lung function decline [Ortega, 2018] and can lead to hospitalization and potentially death [Sado, 2023]. Exacerbations are also responsible for significant asthma-related health care expenditures, lost education/work, and can impact economic productivity [Fuhlbrigge, 2012; Burnette, 2023; Yang, 2023].

Asthma mortality is infrequent with an estimated 5.7 deaths per 100,000 among asthma persons of all ages globally [IHME, 2024]. The appropriate management of asthma, particularly the increased use of inhaled corticosteroids over the past 20 years, has resulted in a reduction in asthma mortality [Chatenoud, 2009; DiSantostefano, 2008], although these declines have plateaued more recently [Ebmeier, 2017].

Asthma mortality has been associated with over-reliance on short-acting beta-agonists, underuse of ICS and use of OCS, influenza infection, and food allergies [GINA, 2024]. Additionally, risk of death has previously been described as being associated with prior asthma-related hospital admissions or emergency care visits [Papiris, 2002]. Intubation and intensive care unit admission are also associated with an increased mortality risk [Pendergraft, 2004]. Consequently, it is reasonable to conclude that the mortality rate in patients with severe asthma is greater than that observed in mild/moderate patients, as severe asthma patients have a higher risk of exacerbations, requiring hospitalization or ICU treatment compared to mild/moderate patients [Moore, 2007; Miller, 2006]. Male sex, uncontrolled asthma within the past year, number of asthma exacerbations in the past year, and prebronchodilator FEV1 < 60% have been identified as significant risk factors for mortality for the population with severe asthma [Fernandes, 2014].

SI.1.4 Important co-morbidities

Common comorbidities reported in patients with severe asthma include rhinosinusitis (54%-72%), nasal polyps (7% to 25%), GERD (41%-60%) and obesity (55%) [de Carvalho-Pinto, 2012; Wenzel, 2007; Rabe, 2023]. In a meta-analysis that assessed the association between comorbidities and severe asthma among 1791 patients, the study found: allergic rhinitis (OR 11.71, 95% CI 5.33–26.98) and COPD (OR 19.27, 95% CI 15.87–23.41) were very strongly associated with severe asthma; obesity (OR 4.06, 95% CI 2.99–5.51), hypertension (OR 3.35, 95% CI 1.57–7.14), panic attack (OR 3.16, 95% CI 1.84–5.24), phobia (OR 3.56, 95% CI 1.37–7.96) and bipolar disorder (OR 6.16, 95% CI 2.10–15.2) were strongly associated [Rogliani, 2023]. As previously stated, the association between obesity and severe asthma is more common in women [Holguin, 2011; Holguin, 2010]. Several factors that are associated with exacerbation frequency have also been identified and include nasal disease, recurrent respiratory infections, psychological dysfunction, and obstructive sleep apnoea [Ten Brinke, 2005].

SI.2 Chronic Rhinosinusitis with Nasal Polyps

Incidence

CRSwNP is a term used to describe a phenotype and based on the increased understanding of the underlying pathophysiology, the term diffuse bilateral CRS has been adopted [Hellings, 2023]. CRS is a chronic condition characterised by inflammation of the sino-nasal cavities and is one of the most prevalent chronic diseases in developed countries. In Europe, the GALEN of epidemiological population-based studies reported a prevalence of CRS, as defined by European Position Statement criteria, of 10.9% ranging from 6.9% in Finland to 27.1% in Portugal [Hastan, 2011].

Diffuse bilateral CRS is divided into two phenotypes: CRSwNP and CRS without (sans) nasal polyps (CRSwNP). Very few studies have reported on the incidence of CRSwNP. The incidence in Denmark of symptomatic NPs was 0.63/1,000 [Larsen & Tos, 2002], in Germany it ranged from 0.60 to 1.5/1000 from 2016 to 2019 [Starry, 2022], which was similar to the US with an incidence of 0.83 per 1,000 person-years for CRSwNP [Tan, 2013].

Prevalence

The prevalence of CRSwNP using cross-sectional patient surveys of the general population ranges from 0.5% in Spain and Germany [Sanchez-Collado, 2022; Starry, 2022] to 1.1% in the US [Palmer, 2019] and China [Shi, 2015] to 2.1% in France [Klossek, 2005] and up to 8.6% in Finland [Toppila-Salmi, 2022]. The prevalence of CRSwNP continues to rise [Hedman, 1999; Johansson, 2003; Toppila-Salmi, 2022]. In general, patients with CRSwNP were more likely to be male and older with the prevalence and incidence increasing up to the 5-6th decades [Johansson, 2003; Ahn, 2016; Larsen & Tos, 2002; Khan, 2019; Klossek, 2005; Tan 2013]. The prevalence of CRSwNP does not appear to differ by race/ethnicity when compared to CRSsNP and control populations [Tan, 2013].

SI.2.1 Demographics of the population in the proposed indication and risk factors for the disease

CRSwNP is a disease of middle age with the general age of diagnosis ranging from 40 to 60 years and is typically more common in males than females, however, disease may be more severe in females than males [Stevens, 2015]. Whilst the prevalence of CRSwNP does not appear to differ by race, lower rates of surgery for NP have been reported in Black and Hispanic populations than in Caucasian populations, but this finding may reflect differing access to healthcare or behavioral differences rather than lower prevalence [Hopkins 2019; Woodard, 2016]. Risk factors for developing CRSwNP include aging, male sex, allergy, CRS-related symptoms and high serum concentrations of cytokines IL-5 or IL-13 [Chen, 2020]. However, the main risk factors for patients with CRSwNP include asthma and eosinophilia.

The degree of type 2 inflammation observed in CRSwNP patients is likely associated with disease comorbidities such as asthma. Up to 55% of patients with NPs have asthma [Philpott, 2018; Khan, 2019; Stevens, 2017] compared to 1% to 21.5% of the general population [To, 2012]. NP recurrence and repeated surgery are more frequent among

patients with CRSwNP with asthma than without asthma [Sella, 2020; Mendelsohn, 2011; Hoseini, 2012; Loftus, 2020]. NP are thought to be associated with late onset asthma (rather than early onset asthma) whether this is after aged 12 years [Khan, 2019], adult-onset (after 18 years of age) or late adult-onset asthma (onset after 40 years of age) [Won, 2018]. The prevalence of asthma in CRSwNP patients appears higher in a Caucasian than an Asian population (54% vs. 7%) complementing the slightly higher eosinophilic inflammation in a Caucasian population [Zhang, 2008].

Eosinophilia has been shown to be associated with CRSwNP, however, there is no consensus on the definition used to define eosinophilia. In Western countries, the majority of patients with CRSwNP have a type 2 inflammation characterized by eosinophilia (~80%) and elevated levels of interleukin-4, interleukin-5, and interleukin-13 cytokines [Bachert, 2017; Zhang, 2017; Wang. 2016]. In Europe, prevalence estimates for eosinophilic CRSwNP in the CRSwNP population ranged from 84-91% [Chen 2020]. While in Asia, the estimated prevalence of eosinophilic CRSwNP in CRSwNP patients ranges from 42% to 65% in China and 60% to 89% in Japan [Cao 2009; Hu 2012; Wang 2016; Nakayama 2011].

Patients with CRSwNP have higher blood eosinophil levels than patients with CRSsNP [Putman, 2018], and CRSwNP patients that additionally have asthma have higher eosinophil levels compared to CRSwNP patients without asthma [Sella, 2020]. Eosinophilia may also be associated with NP recurrence with the risk of recurrence being up to 3 times higher among CRSwNP patients with eosinophilia than without [Brescia, 2015; Wu, 2017; Hoseini, 2012], and predicted multiple recurrences of NP following functional ESS [Guo, 2018]. Eosinophilia has also been shown to be associated with more severe disease [Aslan, 2017; Lou, 2016], and worse respiratory function [Lou, 2016; Tanaka, 2014].

SI.2.2 The main existing treatment options

Management and treatment for CRSwNP varies internationally, including United States, United Kingdom, Spain, Italy, Japan, China, and Canada [Orlandi 2021; Rank 2023; Hopkins 2021; Alobid 2023; Lombardi 2021; De Corso 2022; Miwa 2019; Liu 2020; Thamboo 2021]. There has been a recent update in CRS management guidance from the EPOS 2012 to EPOS 2020 [Fokkens, 2012; Fokkens, 2020] whereby management for CRSsNP and CRSwNP are no longer differentiated [Fokkens, 2020]. Unless otherwise stated, details on treatment options for patients with CRSwNP have been summarized from the EPOS 2020 position paper [Fokkens, 2020].

The main treatment options for patients with CRSwNP include saline nasal irrigation, intranasal corticosteroids (drops, spray, rinses), short-course systemic corticosteroids, and surgery. While guidelines and position papers agree with using intranasal corticosteroids as a treatment option, there is no consensus on the dose, or duration of use. Similarly, there was no consensus on using short-course systemic corticosteroids or surgery as a treatment option. For systemic corticosteroids, all guidelines or position papers (except the US) outlined recommendations for systematic corticosteroids, while for China, it was recommended to consider contraindications and side effects. However, the dose, duration of use and number of courses of systematic corticosteroids were not outlined in the

guidelines or position papers. While surgery was mentioned within the guidelines and position papers, all except Spain do not have a prescriptive recommendation and criteria for use of surgery as a treatment option. Biological therapies have recently been approved for patients with severe disease and corticosteroid-eluting implants are available for patients post NP surgery.

Saline nasal irrigation is considered an important aspect of disease management by improving nasal mucosal function through several physiological effects including the removal of mucus and crusts. Saline irrigation with isotonic saline or Ringer's lactate is considered an effective treatment.

Intranasal corticosteroids reduce NP size and prevent NP recurrence following ESS. They also improve nasal symptoms and quality of life and are effective, safe, and well tolerated; most of the reported adverse events are mild or moderate in severity.

Short-course systemic corticosteroids (1-2 courses per year) might be a helpful add-on therapy for patients whose disease is only partially controlled or is uncontrolled by intranasal corticosteroids. With or without local corticosteroids, short-course systemic corticosteroids can significantly reduce scores for total symptoms and NP but can also have no impact on quality of life as well as potentially causing side effects. However, the use of systematic corticosteroids are associated with significant side effects (see SI.1.2).

Dupixent (anti-IL4Rα treatment) was the first biological therapy to be approved in October 2019 for the treatment of adults with inadequately controlled CRSwNP [Dupixent SmPC, 2024]. In July 2020, approval of Xolair (an anti-IgE treatment) in the EU was achieved as an add-on therapy to intranasal corticosteroids for the treatment of adults with severe CRSwNP [Xolair SmPC, 2023]. In November 2021, approval of Nucala (an anti-IL5 treatment) in the EU was achieved 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 control [Nucala SmPC, 2022].

Corticosteroid-eluting implants are an option for patients with recurrent NP following sinus surgery. Implants can reduce NP score, as well as the need for surgery and can also have a small positive effect on nasal obstruction [Fokkens, 2020].

If patients undergo surgery and polyps recur, possible options for add-on therapy include longer (tapering) treatment with systemic corticosteroids, long-term antibiotics, or biologicals when indicated. However, international position papers differ regarding whether the use of antibiotics and SCS should be used due to low quality evidence and adverse side-effects, respectively, and aspirin treatment after desensitization (ATAD) in non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease is associated with adverse effects and poor adherence due to daily administration [Fokkens, 2020; Orlandi 2021].

SI.2.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

In the most recent EPOS position paper, CRS (with or without nasal polyps) in adults is defined as the presence of two or more symptoms, one of which should be either nasal

blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): ± facial pain/pressure; ± reduction or loss of smell; for at least 12 weeks [Fokkens, 2020]. Additionally, patients with CRSwNP require evidence of NP identified by endoscope or CT scan. Polyps, which can grow in both nostrils (bilateral), greatly impact a patient's quality of life through increases in nasal obstruction, loss of smell, facial pain, facial pressure and nasal discharge. The 2020 EPOS propose classification of CRS based on autonomic distribution, whether disease is localized (often unilateral) or diffuse (always bilateral). Each of these groups can then be classified as type 2 or non-type 2 [Fokkens, 2020]. IL-5 is a key mediator of type 2 inflammation and plays a range of roles in the pathophysiology of type 2 inflammatory airway diseases. Elevated local IL-5 and tissue eosinophil counts are associated with poorer clinical performance, higher subjective and objective disease, increased risk of polyp recurrence following sinus surgery and a greater need for SCS/OCS [De Corso, 2022].

NP typically present as bilateral inflammatory lesions originating in the ethmoid sinuses and projecting into the nasal airway beneath the middle turbinate [Stevens, 2016]. NP found in patients younger than 20 years of age may raise suspicion for cystic fibrosis and unilateral nasal growths suggest a possible encephalocele (a neural tube defect). NP newly diagnosed in patients older than 80 years may suggest a neoplasm [Stevens, 2016].

In patients with mild symptoms, intranasal corticosteroids and saline irrigation should be prescribed, and patients educated on the importance on the need for long-term adherence to therapy [Hopkins, 2019]. For patients with more severe disease, additional treatment may include short-term systemic corticosteroids or biological therapy to reduce symptoms. Surgery for polyp removal is reserved for patients where symptoms are not controlled with corticosteroids, however, NPs are likely to recur [Hopkins, 2019].

Severe symptomatic CRSwNP recurrence rates, defined as patients undergoing revision ESS, are reported to be 20.6% within a 5-year period after surgery [Hopkins, 2009] but NP recurrence may be as high as 35% on endoscopic examination after 6 months, 38% after 12 months, 40% after 18 months [DeConde, 2017] and up to 79% after 12 years (of which, 47% had revision surgery) [Calus, 2019]. A recent meta-analysis of surgery revision rates among patients with CRSwNP reported a mean revision rate of 16.2% over a weighted mean follow-up of 89.6 months: rates were higher among patients with asthma than without asthma (22.6% vs. 8.0%) and among patients with multiple previous surgeries than just one (26.4% vs. 14.3%) [Loftus, 2020]. Type 2 inflammation is a strong predictor of recurrent CRSwNP disease with more than 50% of recurrences occurring in clusters with high eosinophilia [Wei, 2018; Vlaminck, 2014]. Clinical features such as nasal obstruction, total nasal symptom score, olfactory dysfunction were associated with recurrent CRSwNP [Kim, 2023].

CRSwNP patients do not die from the disease itself, however, rarely they may die from complications of surgery for NP removal; the literature is sparse and largely limited to case reports [Mayer, 2009; Čurović, 2019; Tawadros, 2008].

SI.2.4 Important co-morbidities

Important co-morbidities of patients with CRSwNP include asthma, allergies and the degree of Type 2 inflammation observed in CRSwNP patients is likely associated with these comorbidities [Kim, 2023].

A history of allergies, including aspirin intolerance, eczema, and food allergies, has been positively associated with the presence of NPs [Klossek, 2005]. The relationship between atopy and CRSwNP has been well studied with mixed findings suggesting that the prevalence of allergy may vary by phenotype [Wilson, 2014]. The prevalence of aspirin sensitivity in NP patients ranges from 10% in a UK CRSwNP cohort [Philpott, 2018] to 56% in the GALEN cohort which additionally included other NSAID hypersensitivities [Khan, 2019]. Asthma and allergic rhinitis were also a commonly reported comorbidity for CRSwNP patients [Chen, 2020].

The most frequently recorded comorbidities in adult patients with CRSwNP have reported in a recent US claims analysis (Optum Clinformatics™ Data Mart) [GSK study ID 223119]. During the most recent eligible 12 months period of continuous enrolment of 1st Jul 2021 – 30th Jun 2023, comorbidity frequencies were identified by the presence of ICD-10 3-digit level codes. The observed prevalence of the comorbidities in CRSwNP patients are detailed below. Among adults (≥18 years of age), the most frequently recorded comorbidity was disorders of lipoprotein metabolism and other lipidemias (55%), essential hypertension (49%), followed by vasomotor and allergic rhinitis (46%), other and unspecified disorders of nose and nasal sinuses (42%), and asthma (29%) (Table 4).

Table 4 Frequency of top 10 comorbidities among adults with CRSwNP (aged ≥18 years) [GSK study ID 223119]

Comorbidity	N (%)
E78 Disorders of lipoprotein metabolism and other lipidemias	20,307 (54.58%)
I10 Essential (primary) hypertension	18,375 (49.38%)
J30 Vasomotor and allergic rhinitis	17,022 (45.75%)
J34 Other and unspecified disorders of nose and nasal sinuses	15,721 (42.25%)
J45 Asthma	11,098 (29.83%)
M54 Dorsalgia	10,097 (27.14%)
M25 Other joint disorder, not elsewhere classified	10,088 (27.11%)
K21 Gastro-esophageal reflux disease	9,826 (26.41%)
J01 Acute sinusitis	9,263 (24.90%)
G47 Sleep disorders	9,056 (24.34%)

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

KEY SAFETY FINDINGS FROM NON-CLINICAL STUDIES AND RELEVANCE TO HUMAN USAGE:

Table 5 Key Safety findings (from non-clinical studies)

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including: **Single and repeat-dose toxicity**: The safety profile of depemokimab has been evaluated in 4-week single dose (10 and 100 mg/kg) and 26-week repeat dose (10 and 100 mg/kg on Day 1 and Week 14) toxicity studies followed by an off-dose period, administered by the subcutaneous route to monkeys. Adverse findings were limited to the 4-week study, where vascular-related inflammation in multiple organs of one monkey at 10 mg/kg and as a focal lesion in a single bronchial artery in one female at 100 mg/kg, which were morphologically similar to spontaneous arteritis reported in cynomolgus monkeys. While an indirect relationship to treatment with depemokimab through exacerbation of spontaneous immune complex disease cannot be excluded, similar effects were not observed in the 26-week repeat dose toxicity study.	To date, events consistent with type III hypersensitivity/immune complex disease have not been observed in patients given depemokimab.
Reproductive and Developmental toxicity: While reproductive toxicology studies have not been conducted with depemokimab, the risk for fertility and embryofetal development effects is low based on the nonclinical safety data with depemokimab, its high degree of specific binding to IL-5, the low likelihood of increased placental transfer relative to mAbs without half-life extending modifications in the Fc domain, and the absence of fertility and developmental effects with mepolizumab, homologous anti-murine IL-5 mAbs or other in-class therapies and in genetic models of IL-5 pathway inactivation.	As a precautionary measure, it is preferable to avoid the use of depemokimab during pregnancy.
Genotoxicity: As depemokimab is a large molecular weight protein, genotoxicity studies are not appropriate.	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Immunotoxicity: Depemokimab reduces circulating eosinophils in monkeys and humans. Eosinophils are believed to play a role in host defense to parasitic infections. Evaluations in mice deficient in IL-5 and/or eosinophils and treatment of wild type mice with anti-IL-5 antibodies have not shown a reduced ability to control parasitic infections.	The weight of evidence from a critical review of preclinical toxicity data and clinical trial data, and pharmacological properties of depemokimab, suggests that the risk for potential immunotoxicity is low.
Immunogenicity (ADA): ADAs were detected following single or repeat dosing in monkeys at ≥10 mg/kg/dose. Depemokimab plasma concentrations were decreased in one animal given 10 mg/kg/dose which had the highest ADA titre.	There was no identified clinically significant effect of ADA on the PK, PD, or safety of depemokimab. Study participants who were ADA positive had a generally similar profile of adverse events as those who were ADA-negative.
Carcinogenicity: Depemokimab, like other IL-5 pathway inhibitors, is not believed to possess an inherent carcinogenic potential or increase the susceptibility to tumor formation secondary to altered immune surveillance. Furthermore, there is no evidence to date that depemokimab or other IL-5 modulating agents has produced immunosuppression in animals or patients.	The similar incidence of Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC between placebo (1%) and depemokimab (1%) was observed in the placebo -controlled pool.
General safety pharmacology: **Cardiovascular:** In monkeys, increases in QTc interval were observed following the second dose of 100 mg/kg dose (administered Q3 months). The increases were of low magnitude and were not consistent with the high molecular weight of an antibody, high specificity of target interactions of depemokimab, reduction of circulating eosinophils by targeting the IL-5 pathway, limited distribution or access to cellular targets, lack of binding to monkey or human heart tissue as demonstrated in tissue cross reactivity studies, or in the absence of histological or additional functional (ECG) correlates. Therefore, these findings were considered of uncertain relationship to treatment.	Based on the mechanism of action of depemokimab and the results of chronic administration to monkeys at suprapharmacologic doses, there is a low likelihood for adverse effects on CV, renal, respiratory and CNS function. No significant ECG effects, including QTc interval, have been observed in patients given depemokimab to date and ECG parameters continue to be monitored in the Phase III clinical studies.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Respiratory, renal and central nervous system: There were no significant effects of depemokimab on respiratory functions, nor on clinical CNS signs or nervous system histopathology findings after single or repeat doses up to 100 mg/kg in monkeys.	
Other toxicity-related information **Local tolerance:** In monkeys, single and repeat SC administrations of depemokimab at 10 and 100 mg/kg/dose (highest dose administered) were well tolerated with no injection site reactions.	Injection site reactions have been reported in clinical trials and were rated as mild or moderate by investigators. Injection site reactions are a well described side effect of monoclonal antibodies and easily managed in clinical practice

In summary, the cynomolgus monkey was demonstrated to be an appropriate toxicology species due to human comparability with IL-5 protein sequence identity, depemokimab binding and activity. ADAs were detected in several monkeys; however, the ability to determine toxicity in the terminal necropsy animals was not compromised by ADAs due to the fact that robust target engagement and systemic exposure was observed. Reduced blood eosinophil counts and increases in serum total IL-5 concentrations were observed and were consistent with pharmacology and target engagement. Adverse multi-organ vascular inflammation was present in a monkey given a single dose of 10 mg/kg. Minimal focal inflammation of a bronchial artery was also present in a monkey given a single dose of 100 mg/kg. Based on the demonstration of local immune complexes, a direct effect of depemokimab is considered an unlikely cause of these arterial changes, although an indirect relationship to treatment with depemokimab cannot be excluded. Based on the weight of evidence and the absence of microscopic findings in the 26-week study at comparable doses, the vascular findings are considered to be of limited clinical relevance. Increases in QTc were observed following the second dose (Week 14) of 100 mg/kg in the 26-week toxicity study and was considered of uncertain relationship to treatment. There were no injection site reactions following single or repeat SC dosing in monkeys. Depemokimab has a low reproductive toxicity risk for fertility and embryofetal development based on the nonclinical safety data with depemokimab, its high degree of specific binding to IL-5, the low likelihood of increased placental transfer and accumulation in the fetus, and the absence of developmental effects with mepolizumab, homologous anti-murine IL-5 antibodies or other in-class therapies and in genetic models of IL-5 pathway inactivation. In addition, as with other in-class therapies, depemokimab is not believed to possess inherent carcinogenic potential or increase the susceptibility to tumor formation secondary to altered immune surveillance, since depemokimab has not produced immunosuppression in animals or participants in clinical studies. Taken together, these data support the safe use of depemokimab in the proposed patient population under the prescribed therapeutic dosage regimen.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

As of 20 September 2024, an estimated 1715 patients (1936.76 person time) have been exposed to depemokimab in ongoing and completed clinical studies. A summary of clinical trial experience is presented below.

Table 6 Duration of exposure

Cumulative for all studies (person time)	
Duration of exposure	**Persons (N=1715)**
<=6 m	332
>6 to <=12 m	597
>12 m	786
Total person time (patient years)	1936.76
Number of doses	
1	332
2	964
3	70
4	349
Asthma Indication	
Duration of exposure	**Persons (N=1283)**
<=6 m	151
>6 to <=12 m	458
>12 m	674
Total person time (patient years)	1594.84
Number of doses	
1	151
2	713
3	70
4	349
CRSwNP Indication	
Duration of exposure	**Persons (N=272)**
<=6 m	21
>6 to <=12 m	139
>12 m	112
Total person time (patient years)	262.20
Number of doses	
1	21
2	251

Table 7 Age group and gender

All Studies				
Age group	**Persons**		**Person time**	
	M	F	M	F
12 - 17 years	19	14	23.98	18.49
18 - 64 years	610	667	645	754.08
≥ 65 years	163	242	193.27	301.95
Total	792	923	862.25	1074.51
Asthma Indication				
Age group	**Persons**		**Person time**	
	M	F	M	F
12 - 17 years	19	14	23.98	18.49
18 - 64 years	369	525	452.61	651.56
≥ 65 years	132	224	164.24	283.96
Total	520	763	640.83	954.01
CRSwNP Indication				
Age group	**Persons**		**Person time**	
	M	F	M	F
18 - 64 years	156	67	150.04	65.14
≥ 65 years	31	18	29.03	17.99
Total	187	85	179.06	83.13

Table 8 Dose (All studies)

Dose of exposure	Persons	Person time
2 mg SC	6	2.99
10 mg SC	6	2.99
30 mg SC	9	4.48
100 mg SC	1678	1918.33
300 mg SC	16	7.97
Total	1715	1936.76

Table 9 Ethnic origin

Ethnic origin (All studies)	Persons	Person time
AMERICAN INDIAN OR ALASKA NATIVE	7	8.01
ASIAN	314	363.08
BLACK OR AFRICAN AMERICAN	95	85.79
WHITE	1280	1464.42
MIXED RACE	9	5.52
UNKNOWN	1	0.98
Missing	9	8.97
Total	1715	1936.76
Asthma Indication		
Ethnic origin	Persons	Person time
AMERICAN INDIAN OR ALASKA NATIVE	5	6.49
ASIAN	223	287.62
BLACK OR AFRICAN AMERICAN	52	61.34
WHITE	996	1232.39
MIXED RACE	2	2.03
UNKNOWN	0	0.00
Missing	5	4.96
Total	1283	1594.84
CRSwNP Indication		
Ethnic origin	Persons	Person time
AMERICAN INDIAN OR ALASKA NATIVE	1	1.02
ASIAN	64	62.00
BLACK OR AFRICAN AMERICAN	6	6.01
WHITE	196	188.19
MIXED RACE	0	0.00
UNKNOWN	1	0.98
Missing	4	4.01
Total	272	262.20

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

Missing information relevant for the proposed indication is included in module SVII.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 10 Exclusion criteria

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Hypersensitivity: Allergy/intolerance to a mAb or biologic	To minimize risk to the patient and to minimize the interference on both safety and efficacy data.	NO	Hypersensitivity to the active substance or to any of the excipients is included as a Contraindication in the depemokimab SmPC and this has been adequately addressed in sections 4.3, 4.4 and 4.8 of the SmPC.
Smoking status – current smoker or former smoker (only for asthma)	Current smokers or former smokers with a smoking history of ≥ 10 pack-year were excluded to assure the study population did not include patients with a possible diagnosis of COPD.	NO	Not a safety related exclusion criteria.
CV co-morbidities uncontrolled with standard therapy	Patients with clinically significant cardiovascular conditions that are uncontrolled with standard therapy are excluded to minimize risk to the patient and to minimize the interference on both safety and efficacy data.	NO	Patients with less severe and/or controlled cardiovascular conditions were not formally excluded from the program.

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Children younger than 12 years (only for asthma)	The safety and efficacy of depemokimab had not been established in this population.	NO	Product-specific waiver granted for all subsets of the pediatric population for asthma
Pregnant women	The safety and efficacy of depemokimab is not established in this population.	Yes	Female study subjects were excluded from the clinical trial program if they were pregnant or breastfeeding. Women of child bearing potential, if allowed to participate, were required to use acceptable contraceptive measures as specified in the study protocol. Non-clinical reproductive toxicity studies were not conducted with depemokimab based on a weight of evidence assessment which concluded a low risk to this population. However, the long- acting nature of depemokimab significantly increases the probability of longer pregnancy exposure.
Breastfeeding women	The safety and efficacy of depemokimab is not established in this population.	NO	It is unknown whether depemokimab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards. However, as it is a protein, it is expected to be digested in the breastfed infants' gut, thus systemic absorption of IgG is negligible.

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
Malignancy Specific exclusions applied to patients with a current malignancy or a previous history of cancer in remission for less than 12 months prior to screening. Patients who had localized carcinoma of the skin which was resected for cure were eligible to enter depemokimab clinical studies.	Patients with malignancy were excluded to minimize the interference of either the malignancy or the treatment for the malignancy with the assessment of both the efficacy and safety of depemokimab.	NO	Not a safety specific exclusion criteria for depemokimab. There are no data to suggest that the safety profile of depemokimab in patients with a history of malignancy will be different than that of the general target population. Hence, use of depemokimab in patients with a history of malignancy is not considered to be missing information.
Parasitic Infections	Eosinophils may be involved in the immunological response to some helminth infections. The safety of depemokimab in this population has not been established	NO	There are no data to support a contraindication in this population. Patients with active parasite infections should receive appropriate treatment prior to starting depemokimab. If patients become infected during treatment with depemokimab and do not respond to anti-helminth treatment, a delay of the next depemokimab dose should be considered.
Concurrent treatment with other monoclonal antibodies	Patients receiving other mAbs were excluded due to potential interference with	NO	No formal interaction studies conducted; however, low potential for drug-drug interactions because depemokimab selectively

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
	efficacy and safety data interpretation.		binds and neutralizes the cytokine IL-5.
Unstable or clinically significant liver disease uncontrolled with standard therapy	Standard exclusion criterion for developmental compound	NO	Liver effects were not observed in nonclinical toxicology studies, based on liver histopathology and clinical chemistry parameters. Additionally, in monkey and human tissue cross reactivity studies, no specific binding of depemokimab was observed in liver tissue. No formal studies have been conducted to investigate the effect of hepatic impairment on the PK of depemokimab. Since depemokimab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of depemokimab. Dosage adjustments are unlikely to be required.
Unstable or clinically significant renal disease uncontrolled with standard therapy	Standard exclusion criterion for developmental compound	NO	Renal effects were not observed in toxicology studies. No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of depemokimab. Depemokimab is a humanized IgG1 monoclonal antibody characterized by a large molecular weight of around 150 kDa that precludes its elimination by glomerular

Criterion	Reason for exclusion	Is it considered to be included as missing information? (YES/NO)	Rationale
			filtration. Consequently, changes in renal function are not anticipated to impact the elimination of depemokimab and a renal impairment study was not, therefore, conducted. Based on pooled population PK analysis no dose adjustment is required in patients with an eGFR of <60 mL/min/1.73m2. Data was however limited in patients with eGFR values <60 mL/min/1.73m2 (n=32)

SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program 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. Based on the available data and duration of exposure, there is currently no evidence to suggest concerns regarding these adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 11 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	As of 20 September 2024, 11 pregnancies and one pregnancy for the partner of a male subject were reported receiving investigational product in the completed and ongoing depemokimab studies (all indications). Of the 11 pregnancies, two were reported in subjects who received placebo, two were in subjects that received an active comparator and seven in

Type of special population	Exposure
	subjects that received depemokimab The male subject received depemokimab.
Breastfeeding women	Not included in clinical development program
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in clinical development program
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other	None

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

There is no data for this section as Depemokimab has not been marketed in any country.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Due to the mechanism of action of depemokimab, the potential for illegal use or misuse is considered to be very low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

Identification of safety concerns was based on the analysis of data from the randomized treatment group of the integrated safety analysis and on risks reported for other anti-IL5s.

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

REASON FOR NOT INCLUDING AN IDENTIFIED OR POTENTIAL RISK IN THE LIST OF SAFETY CONCERNS IN THE RMP:

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

Allergic reactions

Allergic reactions to anti-IL5s, with anaphylaxis being the most severe form, are understood in clinical practice. Warnings related to both acute and delayed systemic reactions, including hypersensitivity reactions, are included in the warnings and precautions section of the depemokimab SmPC. Hypersensitivity to the active substance or to any of the excipients is also listed as a contraindication. No events of anaphylaxis were reported from placebo-controlled pool of 4 placebo-controlled studies across two indications of asthma (206713, 213744) and CRSwNP (217095, 218079), or the asthma OLE study (212895) and asthma non-inferiority study (206785) at interim analysis, or in any of the phase 1 studies (205722, 208021, 214099). Given that this is a known risk for all mAbs, and it can be managed as per standard clinical practice, additional plans to further characterize this risk are not warranted.

Other reasons for considering the risks not important:

Immunogenicity

In the repeat dose nonclinical toxicology study, ADAs were detected at ≥10 mg/kg/dose. Depemokimab plasma concentrations were decreased only in one animal given 10 mg/kg/dose which had the highest ADA titre. Immunogenicity (incidence or consequences) in animals is not predictive of outcome in humans. In patients who received at least one 100 mg dose of depemokimab administered SC every 26 weeks, 9% (44/499) asthma study participants (206713, 213744) and 8% (21/272) CRSwNP study participants (217095, 218079) were positive for ADA during the 52-week studies. For asthma study participants enrolled in a 1-year OLE study (212895) the ADA incidence at interim analysis was 7% (43/588). For asthma study participants enrolled in a study with prior use of mepolizumab or benralizumab (206785), the ADA incidence at interim analysis was 3% (17/531). Immunogenicity data was collected in study participants with asthma for up to 104 weeks (n = 214) and in study participants with CRSwNP for up to 52 weeks (n = 272). Across asthma and CRSwNP indications (206713, 213744, 217095, 218079, and 212895), there were <1% (5/963) NAb positive study participants: 4 in asthma study participants (206713, 213744 and 212895) and 1 CRSwNP study participant (217095, 218079). No NAbs have been detected in asthma non-inferiority study (206785).

Anti-depemokimab antibodies did not discernibly impact the PK of depemokimab and there was no evidence of a correlation between antibody titres and changes in eosinophil level. Study participants who were ADA positive had a generally similar profile of adverse events as those who were ADA-negative. There was no identified clinically significant effect of ADA on the PK, PD, or safety of depemokimab.

QTc prolongation

In the repeat dose nonclinical toxicity study, increases in QTc were observed following the second dose (Week 14) of 100 mg/kg. The increases were of low magnitude and were not consistent with the high specificity of target interactions of depemokimab, reduction of circulating eosinophils by targeting the IL-5 pathway, limited distribution or access to cellular targets, lack of binding to monkey or human heart tissue as demonstrated in tissue cross reactivity studies, or in the absence of histological or additional functional (ECG) correlates. Therefore, these findings were considered of uncertain relationship to treatment.

Cardiac safety was comprehensively assessed in the depemokimab clinical development program. No treatment effect on the QT interval was observed in patients treated with depemokimab across both asthma and CRSwNP programs at the recommended clinical dose of 100 mg SC. This included an ECG assessment at Tmax, approximately 14 days post-dose, when depemokimab reached peak plasma concentration. Based on the analysis of AEs including those derived from SMQ Torsade de Pointes/ QT prolongation, there was no indication of depemokimab affecting the QT interval. No severe clinical outcomes such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, ventricular flutter, or sudden deaths were reported.

PK-QTcF analysis based on data from FTIH study (205722), China PK study (208021), relative bioavailability study (214099) and from placebo-controlled pool of 4 placebo controlled studies across two indications of asthma (206713, 213744) and CRSwNP (217095, 218079), also demonstrated no trends of concern in QTcF change from baseline with increasing depemokimab concentration, following depemokimab SC administration up to 300 mg.

There is no clinical scientific evidence from the completed studies to suggest depemokimab has an effect on QTc interval.

Type III Hypersensitivity (immune complex disease/ vasculitis)

In the single dose 4-week toxicology study in monkeys, vascular-related inflammation in multiple organs of one female at 10 mg/kg, and as a focal lesion in a single bronchial artery in one female at 100 mg/kg, were observed, which were morphologically similar to spontaneous arteritis reported in cynomolgus monkeys. While an indirect relationship to treatment with depemokimab through exacerbation of spontaneous immune complex disease cannot be excluded, similar effects were not observed in the repeat dose toxicity study.

No events of Type III Hypersensitivity (immune complex disease/ vasculitis) were reported from placebo-controlled pool of 4 placebo-controlled studies across two indications of asthma (206713, 213744) and CRSwNP (217095, 218079) and from asthma OLE study

(212895) and asthma non-inferiority study (206785) at interim analysis or in any of the phase 1 studies (205722, 208021, 214099). As such, there is no evidence of a causal association between depemokimab and Type III Hypersensitivity.

Malignancy

Genotoxicity studies have not been conducted with depemokimab as in vitro and in vivo assays to assess the genotoxic potential of monoclonal antibodies are not generally considered to be of relevance to identify genotoxic hazards [ICH S6(R1)]. Depemokimab is not believed to possess an inherent carcinogenic potential since monoclonal antibodies are not considered to be associated with cancer risks unless they cause significant immunosuppression, which depemokimab does not.

Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Consequently, the necessity of IL-5 and eosinophils for immune surveillance on neoplasia is unclear [Jackson, 2023].

A low incidence of malignancy events was observed across the depemokimab clinical studies, with cumulative exposure of 1936.76 patient years. Similar incidence of events under Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC was observed between placebo (6/517 [1%]) and depemokimab (10/773 [1%]) in a pool of 4 placebo-controlled studies, across two indications of asthma (206713, 213744) and CRSwNP (217095, 218079). Of these, 7 were SAEs (2/517 [<1%] in the placebo group; 5/773 [<1%] in the depemokimab group). In asthma OLE study (212895) at interim analysis, events under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC were reported by 6/629 (<1%) participants. Of these, 3 were SAEs (3/629 [<1%]). Of note, 201 participants who received depemokimab in both parent study (206713, 213744) and in the OLE study (212895) received 4 doses of depemokimab 100 mg SC in total and were followed for 104 weeks i.e. completed the OLE study (212895). In asthma non-inferiority study (206785) at interim analysis, events under the Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC were reported by 22 participants (7/538 [1%] in the mepolizumab/benralizumab group; 15/538 [3%] in the depemokimab group). Of these, 7 were considered SAEs (3/538 [<1%] participants in the mepolizumab/benralizumab group; 4/538 [<1%] in the depemokimab group).

Across all studies, the types of malignancies reported varied and were those that are common in the general population and included breast cancer, adenocarcinoma of the colon, ovarian cancer, prostate cancer, bronchial carcinoma, thyroid cancer, basal cell carcinoma, squamous cell carcinoma and malignant melanoma. There were no participants that received depemokimab who reported a malignancy that resulted in a fatal outcome.

The weight of evidence from a critical review of nonclinical toxicology data and clinical trial data with depemokimab along with other drugs in this class, as well as literature regarding IL-5 pathway inhibition does not support an association between anti-IL-5 therapies and malignancy [Mota, 2023; Pavord, 2024].

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

IMPORTANT IDENTIFIED RISK

None

IMPORTANT POTENTIAL RISK

None

MISSING INFORMATION: USE IN PREGNANT PATIENTS

Risk-benefit impact: As clinical experience with use of depemokimab during pregnancy is limited, it is not possible to define the risk in this patient population. The long- acting nature of depemokimab is expected to significantly increase the probability of longer pregnancy exposure if the patient becomes pregnant during routine use.

As a result, the SmPC states it is preferable to avoid the use of EXDENSUR during pregnancy.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified/potential risks associated with Depemokimab.

SVII.3.2 Presentation of the missing information

Use in pregnant patients:

Evidence Source:

Non-clinical reproductive toxicity studies were not conducted with depemokimab. There are no fertility data available in humans and the effect of depemokimab on human pregnancy is unknown. A Maternal-fetal antibody distribution modelling study was developed to investigate if the enhanced FcRn affinity of depemokimab alters fetal exposure. This model predicted only minor increases (up to 2-fold) in PK parameters in the fetus with depemokimab which were not considered clinically significant.

Population in need of further characterization:

Pregnant women were excluded from clinical studies with depemokimab. Female subjects of childbearing potential participating in the studies were required to commit to use of a contraceptive method, as specified in the protocol. Pregnancy testing was done prior to each dose and at the final study contact; subjects were withdrawn from study medication if a pregnancy occurred.

As of the 20 September 2024, 11 pregnancies were reported for 10 female subjects and one pregnancy for the partner of a male subject receiving investigational product in the completed and ongoing depemokimab studies (all indications). Of the 11 pregnancies, 2 were reported in subjects who received placebo, 2 subjects received an active comparator, and 7 received depemokimab. There were 3 reports of a spontaneous abortion at less than 22 weeks gestation, 1 live birth, 2 elective terminations: all with no apparent congenital anomalies present and 1 ongoing pregnancy on depemokimab. The partner of the male participant reported a live birth with no apparent congenital anomaly present.

Anticipated risk/consequence of the missing information:

There is insufficient knowledge to determine whether the safety profile differs in this population. Pregnancy is known risk factor for asthma exacerbations [GINA 2024]. The long-acting nature of depemokimab significantly increases the probability of longer pregnancy exposure if the patient becomes pregnant during routine use.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 12 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant patients

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

There are no activities beyond adverse reaction reporting and signal detection

Specific adverse reaction follow-up questionnaires

None

Other forms of routine pharmacovigilance activities

None

III.2 Additional pharmacovigilance activities

Not proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There is no post-authorization efficacy study proposed for this product.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table 13 Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Missing Information: Use in pregnant patients	**Routine risk communication:** SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available relating to EXDENSUR which states that there are no or limited amount of data from the use of depemokimab in pregnant women. As a precautionary measure, it is preferable to avoid the use of EXDENSUR during pregnancy. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Not applicable **Other routine risk minimization measures beyond the Product Information:** Not applicable

V.2. Additional Risk Minimization Measures

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

V.3 Summary of risk minimization measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Missing Information: Use in pregnant patients	**Routine risk minimization measures:** SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available relating to EXDENSUR which states that there are no or limited amount of data from the use of depemokimab in pregnant women. **Additional risk minimization measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for EXDENSUR

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

EXDENSUR's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EXDENSUR should be used.

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

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

I. The medicine and what it is used for

EXDENSUR is authorized for asthma and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) (see SmPC for the full indication). It contains depemokimab as the active substance and it is given by subcutaneous route.

Further information about the evaluation of EXDENSUR’s benefits can be found in EXDENSUR’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize 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 authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of EXDENSUR are risks that need special risk management activities to further investigate or minimize 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 EXDENSUR. 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).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant patients

II.B Summary of important risks

Missing information	
Risk minimization measures	Routine risk minimization measures: The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available relating to EXDENSUR which states that there are no or limited amount of data from the use of depemokimab in pregnant women. Additional risk minimization measures: None

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of EXDENSUR.

II.C.2 Other studies in post-authorization development plan

There are no studies required for EXDENSUR

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.