Module 1.8.2

European Union Risk Management Plan (EU-RMP) for NUCALA (mepolizumab)

RMP version to be assessed as part of this application	
RMP Version number	15.1
Data lock point for this RMP	09 July 2025
Date of final sign off	31 October 2025

Rationale for submitting an updated RMP

EU RMP v15.1 is being submitted on EMA request

•To remove the missing information 'Safety of mepolizumab in patients with organ- or life-threatening EGPA,' from the summary of safety concerns.

•To add an Enhanced data collection to further investigate the missing information “Limited data in pregnant and lactating patients” in Part V of the RMP as a routine pharmacovigilance activity.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in the present EU-RMP
Part II: Safety specification	Module SIV - Populations not studied in clinical trials	In section SIV.1- The status of the missing information regarding the exclusion criteria "Organ-threatening or life-threatening EGPA" was changed to “No”, and the rationale for this change was provided.
Part II: Safety specification	Module SVII - Identified and Potential Risks	Section SVII.2 was updated with Summary of changes to the list of safety concerns In section SVII.3.2 The details of the missing information "Safety of mepolizumab in patients with organ- or life-threatening EGPA" was removed In section SVII.3.2 for the missing information “limited data in pregnant and lactating patients” the wording has been updated to reflect the current status of an enhanced data collection activity.

Part II: Safety specification	Module SVIII - Summary of the safety concerns	Missing information "Safety of mepolizumab in patients with organ- or life-threatening EGPA" was removed as a safety concern
Part III: Pharmacovigilance plan (including post authorisation safety studies)	III.1 Routine pharmacovigilance activities	As enhanced data collection has now been implemented, the wording has been updated to reflect the current status of the activity for mepolizumab pregnancy exposure
PART V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	V.1 Routine Risk Minimization Measures V.3 Summary of risk minimisation measures	Section V.1 -The missing information, "Safety of mepolizumab in patients with organ- or life-threatening EGPA," was removed as a safety concern. Section V.3: was updated to reflect enhanced data collection as part of routine pharmacovigilance activities for the missing information, "Limited data in pregnant and lactating patients." Additionally, the missing information, "Safety of mepolizumab in patients with organ- or life-threatening EGPA," was removed as a safety concern.
Part VI: Summary of the risk management plan	II A List of important risks and missing information II.B Summary of important risks	Section II A and Section II B The missing information "safety of mepolizumab in patients with organ- or life-threatening EGPA" was removed.

Other RMP versions under evaluation		
RMP Version number	**Submitted on**	**Procedure number**
Version 14	06 March 2025	EMA/VR/0000257645
Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval**
Version 13	EMEA/H/C/003860/II/0071	10 April 2025

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QPPV Signature	Electronic signature on file

ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
ANCA	Antineutrophil cytoplasmic antibodies
ATAD	Aspirin treatment after desensitization
ATS	American Thoracic Society
AUC	Area Under the Curve
BMI	Body Mass Index
BTS	British Thoracic Society
CEL	Chronic eosinophilic leukaemia
CHCC	Chapel Hill Consensus Conference
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
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
CVT	Cardiac, vascular and thromboembolic
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medicines Agency
ESS	Endoscopic sinus surgery
ENFUMOSA	European Network For Understanding Mechanisms Of Severe Asthma
ERS	European Respiratory Society
EU	European Union
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps
FEV1	Forced expiratory volume in 1 second
GALEN	Global Allergy and Asthma European Network
GBD	Global Burden of Disease
GERD	Gastroesophageal reflux disease
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
EOE	Eosinophilic esophagitis
EPAR	European Public Assessment Report
hERG	human Ether-à-go-go-Related Gene
HES	Hypereosinophilic syndrome
ICD	International Classification of Diseases
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INF-A	Interferon-α
kDa	kiloDaltons

LABA	Long acting beta agonists
L-HES	Lymphocytic HES
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
M-HES	Myeloproliferative hypereosinophilic syndrome
MPO-ANCA	Myeloperoxidase anti-antineutrophil cytoplasmic antibodies
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institute of Health
NP	Nasal polyps
NSAID	Nonsteroidal anti-inflammatory drug
OCS	Oral corticosteroid
OLE	Open label extension
PASS	Post-authorisation safety study
PCSA	Placebo controlled severe asthma
PD	Pharmacodynamic
PIP	Paediatric investigation plan
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
QTc	Corrected QT interval
RCT	Randomized controlled trial
RMP	Risk management plan
SARP	Severe Asthma Research Program
SAE	Serious Adverse Event
SC	Subcutaneous
SCS	Systemic corticosteroids
SGA	Small for gestational age
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
TNF-□	Tumor necrosis factor alpha
TSLP	Thymic Stromal Lymphopoietin
UK	United Kingdom
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

TRADEMARK INFORMATION

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Mepolizumab
Pharmacotherapeutic group(s) (ATC Code)	R03DX09
Marketing Authorisation Holder/ Applicant	GSK Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Co. Dublin, Ireland
Medicinal products to which this RMP refers	Mepolizumab
Invented name(s) in the European Economic Area (EEA)	Nucala
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class** Mepolizumab is a humanized IgG monoclonal antibody (IgG1, kappa) with human heavy and light chain frameworks. The functional protein is a disulfide-linked $\alpha 2 \beta 2$ tetramer consisting of two light (kappa) and two heavy (IgG1) chains. There is a single glycosylation site on each heavy chain. The complementarity determining regions were grafted from the murine antibody, 2B6, by molecular genetic techniques.
	Summary of mode of action Mepolizumab is specific for human IL-5 and blocks binding of human IL-5 to the alpha chain of the IL-5 receptor complex present on the eosinophil cell surface.
	Important information about its composition Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology

Reference to the Product Information	Please refer to the approved product information
Indication(s) in the EEA	**Current:** **Severe Asthma** NUCALA is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older. **EGPA** Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA. **HES** Nucala is indicated as an add-on treatment for adult patients with inadequately controlled HES without an identifiable non-haematologic secondary cause. **CRSwNP** Nucala is indicated as an as add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with SCS and/or surgery do not provide adequate disease control.
	Proposed: None
Dosage in the EEA	**Current:** **Severe Asthma** Adults and adolescents aged 12 years and older: The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. Children aged 6 to 11 years old: The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

	EGPA Adults and adolescents aged 12 years and older The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks. Children aged 6 to 11 years old: Children weighing ≥ 40 kg The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks. Children weighing < 40 kg The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks. **HES** Adults The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks. **CRSwNP** Adults The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.
	Proposed: None
Pharmaceutical form(s) and strengths	**Current:** Each vial contains 100 mg mepolizumab. After reconstitution, 1 ml of solution contains 100 mg mepolizumab. Powder for solution for injection. Lyophilised white powder. Nucala 100 mg solution for injection in pre-filled pen. Nucala 100 mg solution for injection in pre-filled syringe.

	Nucala 40 mg solution for injection in pre-filled syringe A clear to opalescent, colourless to pale yellow to pale brown solution.
	Proposed**:** None
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

SI.1 Severe Asthma

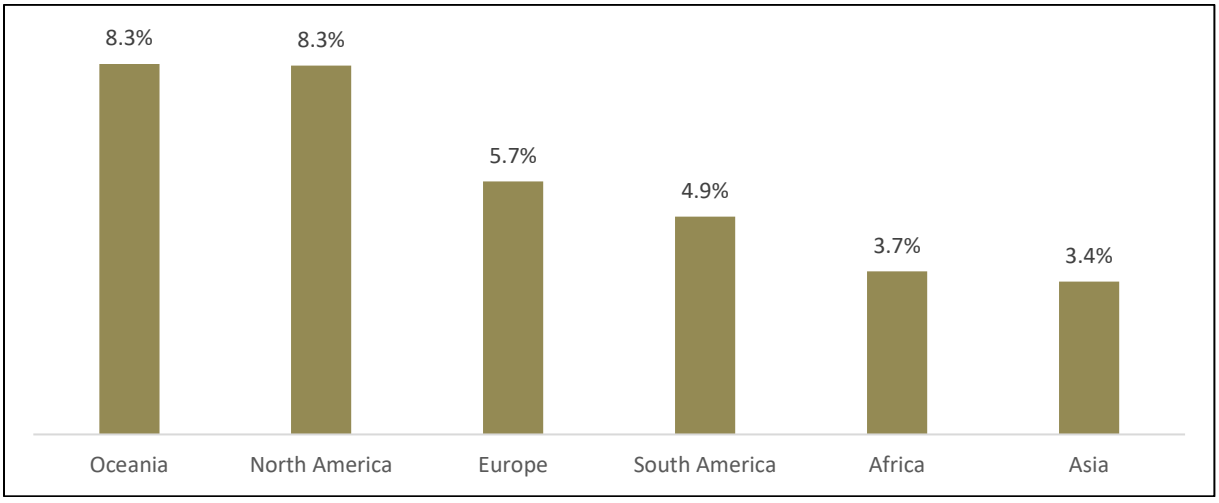
INCIDENCE

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 Institute for Health Metrics and Evaluation using available data from the 2022 Global Burden of Disease (GBD) study estimate the global incidence of asthma. Across all severities, 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 across all severities were 9.5 and 4.7 per 1000 person-years in 6 to 11 and 12 to 17-year-old age cohorts, respectively [IHME, 2024].

Prevalence

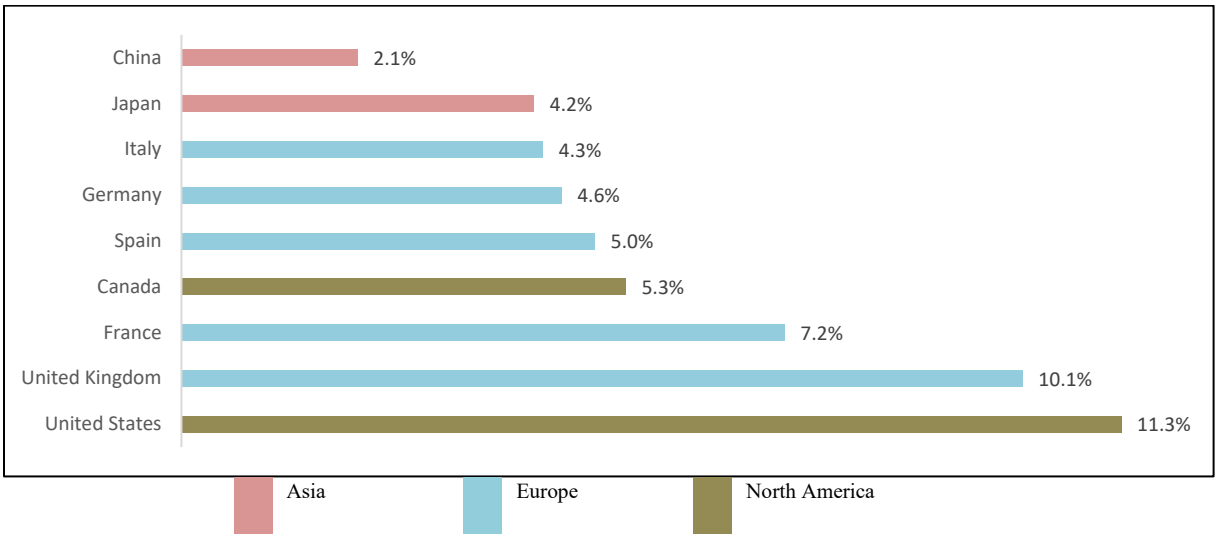
Globally, asthma prevalence varies across populations and based on definitions used to describe the condition (e.g. symptoms, patient/physician reported, lung function). Recent calculations utilizing data from 69 countries included in the 2019 GBD estimated asthma prevalence to range between 1.4% in Bangladesh to 11.3% in the US [Rabe, 2023]. Rates were observed to be highest in more developed regions (Oceania: 8.3%, North America: 8.3%, Europe: 5.7%), compared to lesser developed regions (Asia: 3.4%, Africa: 3.7%) [Figure 1; Rabe, 2023]. However, it is possible that differences in prevalence rates between the regions may be attributable to limitations in the health system and care delivery in lesser developed regions, resulting in lower asthma diagnosis and reporting in those regions [Rabe, 2023].

Figure 1 2019 Asthma Prevalence Across Geographic Regions (%) [Rabe, 2023]



Overall, 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]. Asthma prevalence rates should be interpreted with caution as there is no universally accepted definition and asthma presentation and diagnosing practices are heterogenous globally.

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

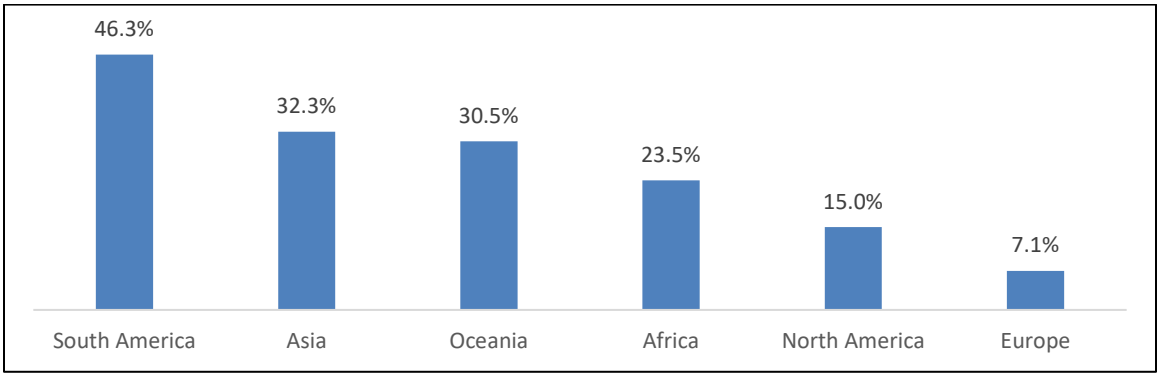


Although the majority of patients with asthma can be effectively treated with available controller medications, a subset of patients requires additional controller therapy and may still be uncontrolled. This subset of severe asthma is a heterogenous disease that affects approximately 3-10% of asthmatic patients but is responsible for a disproportionate percentage of the health care costs associated with asthma [Moore, 2007; Godard, 2002; Antonicelli, 2004; Song, 2020]. Severe or therapy-resistant asthma is recognized as a major unmet need. A task force, supported by the ERS and ATS, provided recommendations and guidelines on the evaluation and treatment of severe asthma in children and adults [Chung, 2014]. Severe asthma is defined as asthma that requires treatment with high dose ICS plus a second controller and/or SCS to prevent it from becoming ‘‘uncontrolled’’ or that remains ‘‘uncontrolled’’ despite this therapy.

Although figures of 3 to 10% of the total asthma population are often estimated as the global prevalence of severe asthma [Chung, 2014; GINA 2023], larger prevalence ranges (up to 39% of asthma patients) have been reported [Chen, 2018]. Estimates from the 2019 GBD study report that approximately 26% of those with asthma, are affected with severe asthma, with greater burden observed in South America (46.3%) and Asia (32.3%) compared to 15% in North America and 7.1% in Europe [Figure 3; Rabe, 2023]. However,

many of these studies had small patient numbers and inconsistent definitions. According to the GINA, the "eosinophilic phenotype is found in the majority of people with severe asthma", suggesting similar prevalence rates to severe asthma [GINA, 2023].

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



As noted previously, precise estimates of the prevalence and incidence of severe asthma are difficult to determine as severe asthma is characterized by a wide variation in clinical symptoms, healthcare resource utilization, treatments received, and natural history [Chen, 2018]. Consequently, the definition for severe asthma has evolved over the time with several distinct sub-phenotypes being described: uncontrolled asthma, difficult to control asthma, severe refractory asthma, and problematic asthma (Table 2). Today, 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 behavioural domains, and treating traits in each domain at the individual level [Park, 2022].

Table 2 Evolution of the definition of "severe" asthma

Organisation, year	Term	Definition
ERS, 1999	Difficult asthma	Asthma remaining uncontrolled despite high-dose inhaled glucocorticosteroids with or without systemic glucocorticosteroids
	Uncontrolled asthma	Persistent asthma symptoms or recurrent exacerbations
ATS, 2000	Severe refractory asthma	According to an ERS Task Force including criteria that specifies asthma control
WHO, 2010		Addition of responsiveness to treatment and future risk as a marker for asthma control
IMI, 2011	Poorly controlled asthma	Algorithm to distinguish difficult-to-control asthma from severe refractory asthma
ATS/ERS, 2013		Latest recommendations on the identification, evaluation and treatment of patients with severe refractory asthma

ERS: European Respiratory Society; ATS: American Thoracic Society; WHO: World Health Organization; IMI: Innovative Medicines Initiative.

Source: Wener, 2013

To estimate the proportion of asthma patients eligible for treatment with mepolizumab, an analysis was conducted in a cohort of patients with prevalent asthma identified using the CPRD database (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 3). 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.

Table 3 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 on the basis of the subset of patients with a valid blood eosinophil measurement recorded in the database; elevated blood eosinophilia (≥150 cells/ul) 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: Italics denote estimated figures.

SOURCE: Data on File, RF/NLA/0149/17

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

Severe asthma is generally characterized by frequent exacerbations, irreversible airway obstruction, and the need for treatment with high doses of ICS, OCSs, and/or anti- IgE. Data from the SARP suggest that subjects with severe asthma are older with a longer duration of disease compared with subjects with mild or moderate disease [Moore, 2007]. Although there were more females in all severity groups, there was no difference in race or sex distribution among the groups. Other large-scale studies in severe asthma have reported similar age and sex distributions (Table 4). Data from the International Severe Asthma Registry suggest that adults with severe asthma (receiving GINA 5 treatment or uncontrolled at GINA 4) are mostly Caucasian (72.6%), and do not have a history of smoking (60.6%) [Wang, 2020]. Data from the SARP III cohort demonstrated that compared to subjects with non-severe asthma (N = 213), adults with severe asthma (N = 313) are significantly older (49.7 vs. 44.5 years, $p < 0.05$q), have a higher BMI (mean BMI: 33.5 vs. 31.0 kg/m2, $p < 0.05$), 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 asthma quality of life questionnaire scores: 4.6 vs. 5.5, $p < 0.05$) [Teague, 2018]. However, both populations were observed to have similar distributions in sex (female distribution: non-severe (66.7%), severe (67.1%)) and ethnicity (Caucasian distribution: non-severe (66.7%), severe (62.0%)) [Teague, 2018].

Table 4 Age and gender reported in severe asthma cohorts

Characteristic	TENOR Study [Dolan, 2004]	SARP [Moore, 2007]	ENFUMOSA [E.N.F.U.M.O.S.A., 2003]	de Carvalho-Pinto Severe Asthma Cohort [de Carvalho, 2012]	BTS Difficult Asthma Registry [Heaney, 2010]
Sample size	770	204	163	74	382
Female (%)	62.2%	64.0%	81.5%	77.0%	63.1%
Mean age (yrs)	38.9 ± 20.9	41 ± 13	42.4 ± 12.1	44.5 ± 10.7	44.9 ±13.7

NOTE: Data presented as mean ± SD

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 5) [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 5 Childhood 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 demographic and environmental factors that can influence the severity and persistence of asthma. These include genetics, atopy, pollution, tobacco smoke, GERD, obesity, and respiratory infections [GINA, 2023]. Although some factors such as viral infections are related to asthma exacerbations, there is no evidence to suggest that they cause asthma.

Childhood-onset asthma has a strong association with atopy. Atopy occurs in 30 to 50% of the population in developed countries and frequently occurs in the absence of asthma. 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]. In addition, allergen-specific sensitization (particularly multiple early-life sensitizations) are one of the most important risk factors in the development of asthma [GINA, 2023].

Environmental exposures related to asthma symptoms include dust mites, pets, cockroach dander, fungi, molds, yeasts, tobacco smoke, and air pollution [GINA, 2023]. There is also good evidence to suggest that asthma is a heritable disease. Family studies have compellingly shown an increased prevalence of asthma among offspring of subjects with asthma compared to the offspring of subjects without asthma [GINA, 2023].

Key risk factors associated with severe asthma include sex, race, obesity, tobacco smoke and environmental tobacco smoke exposure [Jarjour, 2012]. Eosinophilic airway inflammation has also been suggested to increase the risk of severe or difficult-to-control asthma [Desai, 2010]. 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 [Dolan, 2004; Moore, 2007; E.N.F.U.M.O.S.A, 2003; de Carvalho-Pinto, 2012; Heaney, 2010]. Severe asthma has also been shown to be more prevalent in women after puberty compared to men [Farha 2009; Tantisira, 2008]. Although no difference in race distribution by asthma severity was

observed in SARP, 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 subjects with asthma compared to white subjects [Moore, 2007; Gupta, 2006]. In black subjects, biologic factors, including IgE levels, skin test reactivity, and family history were associated with severe asthma [Gamble, 2010]. In unsupervised cluster analyses, obesity appeared to be associated with increased asthma severity in adult-onset disease [Haldar, 2008; Moore, 2010]. The increased risk observed in obese women has been attributed to sex hormones or obesity-related inflammation [Holguin, 2011; Holguin, 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 emergency department visits for asthma [Talreja, 2012]. Environmental tobacco smoke exposure, validated by urine cotinine levels, in severe asthmatics was associated among other factors to low lung function, greater airway hyperresponsiveness, and increased rescue medication use [Comhair, 2011].

SI.1.2 The main existing treatment options

ICS are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2023]. Treatment with ICS controls asthma symptoms, improves quality of life and lung function, decreases airway hyper-responsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma mortality. The dose of ICS is selected based on the severity of the patient's asthma. 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]. Among asthma patients 6-11 years (children), GINA recommends increasing ICS dose over combination ICS/LABA therapy.

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 high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications (such as tiotropium, anti-IgE, or anti-IL-5/anti-IL-5R therapies). Severe asthma is also able to be treated with non-pharmacological interventions including bronchial thermoplasty and high-altitude treatment [Cox, 2006; Rijssenbeek-Nouwens, 2011].

Maintenance treatment with OCS can improve pulmonary function and reduce levels of sputum eosinophils in patients with severe refractory asthma [Dente, 2010]. However, 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; medium and high dose OCS is also associated with increased risk for emergency department visits and inpatient visits [GINA, 2023; Lefebvre, 2015]. Among paediatrics, the most frequently observed side effects were weight gain, growth retardation, and cushingoid features [Aljebab, 2017]. Thus, there is an important unmet need due to the frequent exposure to repeated intermittent or long-term continuous use of SCS and as such are at risk of the long-term side effects. According to

data from the Healthcare Cost and Utilization Project, corticosteroids were among the most common cause of drug-related AEs prior to hospital admission, accounting for 9.6% of all pre-admission drug-related AEs in the US in 2011 [Weiss, 2013]. Despite these risks for significant AEs, studies in the published literature have reported that between 20% and 60% of patients with severe or uncontrolled asthma have been reported to be taking long-term or maintenance OCS [Bleecker, 2020].]. Among children, reports of long-term or maintenance OCS range from 10% to 24% [Fleming, 2015; Phipatanakul, 2017]. There is also considerable variation in the proportion of patients with severe asthma who receive long-term OCS, including regional variation, differences in physician practices, and patient variability within the severe asthma subgroup.

A recent call-to-action article, endorsed by the World Allergy Organization and the Respiratory Effectiveness Group, reviewed the evidence on the burden of SCS on patients with asthma and provided an overview of potential strategies for implementing SCS Stewardship [Bleecker, 2022]. As per OCS, the most common AEs include osteoporosis, cardiovascular disease, and metabolic complications. The impact of acute use of SCS used for treatment of exacerbations is often underestimated by patients and physician. Previous evidence has shown that cumulative effects of treatment of SCS courses over time increases the risk of AEs, including gastrointestinal bleeding, sepsis, venous thromboembolism, fracture, and heart failure [Bleecker, 2022]. Long term SCS is also associated with a higher risk of mortality when compared to no SCS use [Bleecker, 2022].

Six monoclonal antibodies have been approved for asthma which 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].

Omalizumab, a monoclonal antibody directed against IgE, is used as an add-on treatment in patients with moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. Omalizumab has been shown to reduce exacerbations (~26%) in patients inadequately controlled on high-dose ICS and LABA with reduced lung function and a recent history of clinically significant exacerbations [Humbert, 2005].

Mepolizumab and reslizumab are anti-IL-5 monoclonal antibody therapies and benralizumab is an anti-IL-5 receptor monoclonal antibody therapy that are recommended for use as add-on treatment in patients with severe asthma with an eosinophilic phenotype. All anti-IL-5 treatments reduced clinically significant asthma exacerbations by approximately half in patients with severe eosinophilic asthma on standard of care with poorly controlled disease [Farne, 2017].

Dupilumab is an anti-IL-4Rα monoclonal antibody, approved for use in patients with severe eosinophilic/type 2 asthma, or adults requiring treatment with maintenance OCS [GINA, 2023]. In patients with severe asthma, dupilumab reduces severe exacerbations and improves quality of life [Agache, 2020]. In a phase 3 RCT, dupilumab has also demonstrated ability to reduce OCS, while decreasing the rate of severe exacerbations

and increasing the FEV1 in patients with glucocorticoid-dependent severe asthma [Rabe, 2018].

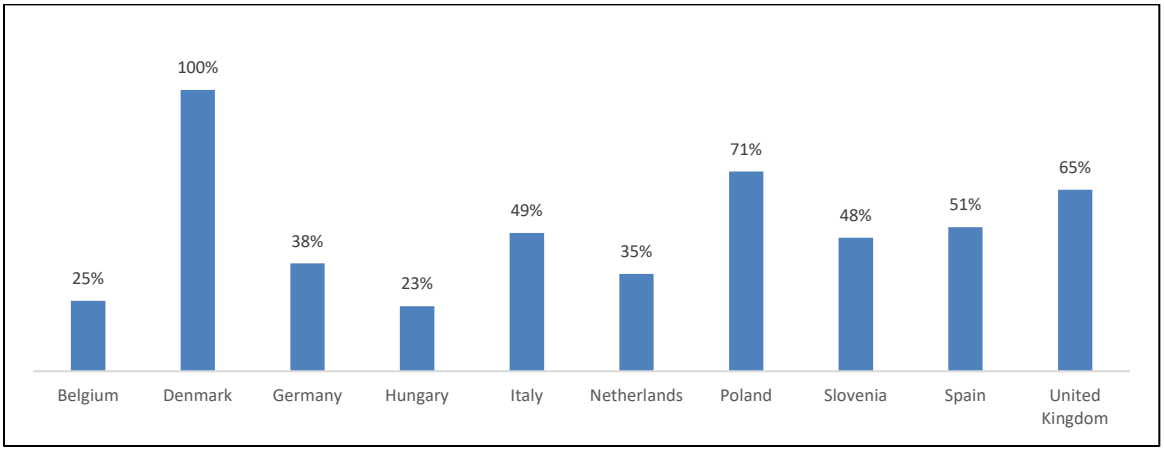
Tezepelumab is an anti-thymic stromal lymphopoietin (anti-TSLP) for patients with severe asthma [GINA, 2023]. It binds specifically to TSLP, blocking it from interacting with its heterodimeric receptor [Menzies-Gow, 2021]. As demonstrated in a phase 3 RCT, patients with severe, uncontrolled asthma who received tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life than those who received placebo [Menzies-Gow, 2021].

Bronchial thermoplasty is a non-pharmacological therapy for patients with severe asthma who continue to be symptomatic despite maximal treatment [Cox, 2006]. By diminishing bronchial constriction through reducing airway smooth muscle mass using thermal energy, treatment with bronchial thermoplasty has demonstrated a safe and effective response, including a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work [Pavord, 2007; Castro, 2010]. However, this invasive procedure is still considered in development and further research is needed to determine which subgroups of patients with severe asthma will benefit most from this intervention following long-term observation.

Across Europe, biologics are widely used for the treatment of severe asthma (23% to 100%), with anti-IgE treatment more frequently used in most included countries [van Bragt, 2020; Figure 4]. In the UK, however, a greater proportion of patients with severe asthma are receiving anti-IL-5 therapies [Jackson, 2021; van Bragt, 2020], with more patients on mepolizumab (50.3%) compared to reslizumab (0.6%) [Jackson, 2021]. Thermoplasty use in Europe for severe asthma is low (<1.5%) [van Bragt, 2020].

In the US, insights from the CHRONICLE study reveal that biologics are used by 66% of patients with severe asthma, with similar rates of use for anti-IgE and anti-IL-5 treatments, 46% vs 45%, respectively [Panettieri Jr., 2022]. However, use of anti-IL-4Rα treatment, dupilumab, is increasing with dupilumab being the most frequently initiated biologic between October 2018 and February 2021 [Panettieri Jr., 2022].

Figure 4 Proportion of Patients with Severe Asthma Across Europe Receiving Biologic Treatment [van Bragt, 2020]



From a cross-sectional, retrospective analysis of aggregated registry data of the ERS Severe Heterogeneous Asthma Research collaboration, Patient-centred (SHARP) Clinical Research Collaboration. ERS SHARP includes 11 different European national registries for severe asthma, and the current study comprises 3236 patients [van Bragt, 2020].

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

Severe asthma is a heterogenous disease that is commonly characterized by frequent severe exacerbations, irreversible airway obstruction, maintenance SCS treatment, obesity and persistent eosinophilia (Table 6). 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 [Rodrigo, 2004; Ten Brinke, 2005]. More than 40% of patients with severe asthma experience severe exacerbations [Wenzel, 2007]. A retrospective cohort study using a US healthcare claims database showed that 44% of asthma patients treated at GINA step 5 experienced at least one exacerbation during a 12-month follow-up period compared to 17.0-21.9% of asthmatic patients treated at GINA steps 1-4 [Suruki, 2012]. Among paediatrics aged 6-17 years with severe asthma, approximately 55% experience a hospitalization within a year and 10-15% have a lifetime history of intubation [Fitzpatrick, 2012].

Some observational studies of severe asthma have shown that patients with severe asthma have lower FEV1 and a ratio of FEV1 to forced vital capacity (FEV1/FVC) of ≤65% [de Carvalho-Pinto, 2012; Moore, 2007; Heaney, 2010]. Campo et al reported in their review that between 23% and 60% of patients diagnosed with severe asthma experience fixed airflow obstruction [Campo, 2013].

The range of reported long-term use of OCS in patients with severe or uncontrolled asthma was between 20% and as high as 60% in some studies [Bleecker, 2020]. Among children, reports of long-term or maintenance OCS range from 10% to 24% [Fleming, 2015; Phipatanakul, 2017]. The variation in the use of long-term OCS was attributed to both the heterogeneity of severe asthma and the variability in physician prescribing patterns. Data from several severe asthma cohorts suggest that approximately one-third of patients with severe asthma report receiving maintenance OCS treatment (Table 6).

A review of the literature reveals few studies that examine the impact of SCS on the development of AEs in a severe asthma population. The most commonly reported AEs in the literature were gastric discomfort which occurred in up to 16% of patients, hyperglycaemia, changes in white blood cell count, and cardiac-related events [Marquette, 1995; Morell, 1992; Rizzato, 1998; Wen, 2005]. A review of the use of corticosteroids in the UK revealed approximately 40% of the use of SCS is for respiratory diseases [van Staa, 2000]. As asthma treatment guidelines indicate SCS use in severe asthma, it is expected that a significant proportion of SCS use for respiratory disease in the UK is within this population.

Eosinophilia has been shown to be associated with severe asthma and poor asthma control [Desai, 2010; Hastie, 2010; Just, 2012; Shiota, 2011]. Although the proportion of asthma associated with elevated eosinophils is not known, studies of mild and severe asthma suggest that it may be approximately 50% [Wenzel, 1999; Woodruff, 2009]; in one study of severe asthma patients, up to 79% of patients with severe asthma were determined to have induced sputum eosinophils ≥3% [de Carvalho-Pinto, 2012].

Table 6 Patient and disease characteristics reported in severe asthma cohorts

Characteristic	TENOR Study [Dolan, 2004]	SARP [Moore, 2007]	ENFUMOSA [E.N.F.U.M.O.S.A., 2003 Holgate, 2004]	Carvalho-Pinto Severe Asthma Cohort [de Carvalho-Pinto, 2012]	BTS Difficult Asthma Registry [Heaney, 2010]
Sample size	770	204	163	74	382
Atopy (≥1 positive skin test)	52.3%*	71%	<60%	64%	57.3%
Chronic OCS use	NA	32%	32.5%	27%	41.7%
BMI	28.3 ± 8.59	-	M: 26.5 ± 4.2 F: 27.2 ± 6.0	30.0 ± 6.2	28 (24.3-32.4)
Blood eosinophils	NA	(-0.75 ± 0.51)§	4.4% ± 5.0	NA	0.3 x 10^9cells/l
Sputum eosinophils	NA	NA	NA	16.5% ± 16.4%	NA

*Percent of patients with IgE ≥100IU/mL
§ Log-transformed value for mean number of eosinophil cells per mL
NOTE: Data presented as mean ± SD

Through the research of SARP it has been determined that one of the main differentiating clinical factors of severe versus mild/moderate asthma is the significantly greater frequency and severity of high-risk outcomes, such as emergency department visits, hospitalizations, intensive care admissions, and intubations. Following the application of unsupervised cluster analysis methodology to analyse the SARP cohort, SARP investigators reported that nearly 70% of subjects in Cluster 4 (n= 120, mean age 38 years old) and 80% of subjects in Cluster 5 (n=116, mean age 49 years old) met the ATS workshop criteria for severe asthma. Health care utilization was similar in both clusters with nearly half of

subjects reporting ≥ 3 oral steroid bursts and an additional 25% reporting inpatient hospitalization in the past year for a severe exacerbation. Nearly 40% of these subjects reported a history of a prior ICU admission for asthma in their lifetime ($p<0.0001$). These two clusters had elevated sputum eosinophils. In contrast, a milder sub-group (Cluster 1) was characterized by younger (mean age 27 years old), predominantly female subjects with childhood onset/atopic asthma and normal lung function. Forty percent of subjects in Cluster 1 were receiving no controller medications. These patients did not have elevated sputum eosinophils [Moore, 2010].

Asthma mortality is relatively rare, with an estimated 0.19 deaths per 100,000 among persons aged 5-34 years globally [Ebmeier, 2017]. The appropriate management of asthma, particularly the increased use of ICS over the past 20 years, has resulted in a reduction in asthma mortality, although these declines have plateaued more recently [Chatenoud, 2009; DiSantostefano, 2008; Ebmeier, 2017]. In Europe, asthma mortality rates steadily declined from their peak in 1994 with the highest asthma mortality rates in Germany (4.7/100,000 in men and 2.7/100,000 in women) and the lowest in Italy (1.4/100,000 in men and 0.9/100,000 in women) and Spain (1.3/100,000 in men and 1.2/100,000 in women) declining to less than 1.5/100,000 throughout Europe (France, Germany, Italy, Spain, and the UK) by 2002-2004, including Germany (1.3/100,000 in men and 1.0/100,000 in women) [Chatenoud, 2009]. Deaths due to asthma in the paediatric population are rare, but measurable (range 0.0-0.7/100,000), and prevalence of disease is correlated with hospital admissions and mortality [Asher, 2014; Anderson, 2008].

Asthma mortality has been associated with over-reliance on short-acting beta-agonists, under use of ICS and use of OCS, and psychosocial problems (drinking/substance abuse, family problems) [GINA, 2018]. 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 ICU 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].

SI.1.4 Important co-morbidities

Patients with asthma suffer from a variety of comorbidities. The presence of comorbidities are linked with poorer outcomes in asthma including increased exacerbations, poorer asthma control, and adverse impacts on quality of life [Tay, 2016]. A meta-analysis analysing the strength of association between comorbidities in asthma, including 878,224 patients, identified having COPD (odds ratio (OR) = 6.23, 95% CI 4.43– 8.77) and having other chronic respiratory diseases (OR 12.85, 95% CI 10.14–16.29) were very strongly associated with having asthma; while having allergic rhinitis (OR 4.24, 95% CI 3.82–4.71), allergic conjunctivitis (OR 2.63, 95% CI 2.22–3.11), bronchiectasis (OR 4.89, 95% CI 4.48–5.34), hypertensive cardiomyopathy (OR 4.24, 95% CI 2.06–8.90), and nasal congestion ((OR 3.30, 95% CI 2.96–3.67) were strongly associated with having asthma [Rogliani, 2023].

Common comorbidities reported in patients with severe asthma include rhinosinusitis (54%-72%), GERD (41%-60%) and obesity (55%) [de Carvalho-Pinto, 2012; Wenzel, 2007]. Severe 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]. Allergic and non-allergic rhinosinusitis have been shown to be associated with asthma outcomes, especially when present in conjunction with aspirin-exacerbated respiratory disease [Mascia, 2005].

Gastro-oesophageal disease has been associated with severe disease and implicated in exacerbating disease control through direct effects on airway responsiveness or aspiration-induced inflammation. A study assessing clinical characteristics of patients with severe asthma and involving 438 patients (204 with severe asthma, 70 moderate, and 164 mild) found that GERD was reported more often in patients with severe asthma (41%) than in those with mild or moderate disease (12%-16%) ($P < 0.0001$) [Moore, 2007]. Obesity has been shown to be associated with an increased risk for asthma, persistence and severity of disease, and loss of control [Camargo, 1999; Nystad, 2004; Chen, 2009; Liu, 2009]. One study has demonstrated that weight loss can result in improved asthma control and reduction in asthma severity [Ford, 2005]. As previously stated, the association between obesity and severe asthma is more common in women [Holguin, 2011; Holguin, 2010].

The 20 most frequently recorded comorbidities in children, adolescent and adult patients with severe asthma, respectively, were identified in the previously described analysis of the CPRD GOLD database [GlaxoSmithKline Study ID PRJ3177, 2017]. The methodology was the same as described above, and comorbidities identified in 2016 were reported at Level 2 Read description in CPRD.

The observed prevalence of the comorbidities in severe asthma patients detailed below were generally lower among patients with non-severe asthma (defined as GINA Step 1-3).

The 10 most frequently reported comorbidities in 2016 among children with severe asthma (6-11 years of age), were: respiratory conditions (29.9%, including acute respiratory infections (24.5%) and other upper respiratory tract diseases (5.4%)), skin and subcutaneous tissue conditions (15.5%, including other skin and subcutaneous tissue inflammatory conditions (7.7%), skin and subcutaneous tissue infections (4.0%), and other skin and subcutaneous tissue disorders (3.8%)), diseases of the ear and mastoid process (10.6%), viral diseases (9.7%, including other viral and chlamydial diseases (7.1%) and viral diseases with exanthem (2.6%)), disorders of the eye and adnexa (3.8%), rheumatism excluding the back (3.1%), mycoses (2.6%), mental and behavioural disorders (2.3%), male genital organ diseases (1.9%), and neurotic, personality and other nonpsychotic disorders (1%).

The 10 most frequently reported comorbidities in 2016 among adolescents with severe asthma (12-17 years of age) were: respiratory conditions (28.2%, including acute respiratory infections (22.1%) and other upper respiratory tract diseases (6.1%)), skin and subcutaneous tissue conditions (23.7%, including other skin and subcutaneous tissue inflammatory conditions (10.9%), other skin and subcutaneous tissue disorders (9.2%) and skin and subcutaneous tissue infections (3.6%)), diseases of the ear and mastoid process (7.5%), rheumatism excluding the back (6.1%), viral diseases (4.6% including other viral

and chlamydial diseases (3.6%) and viral diseases with exanthema (1.0%)), disorders of the eye and adnexa (3.9%), neurotic, personality and other nonpsychotic disorders (3.2%), vertebral column syndromes (2.4%), arthropathies and related disorders (2.2%), other central nervous system disorders (2.2%), and other female genital tract disorders (2%).

The top 10 most frequently reported comorbidities in 2016 among adults (≥18 years of age) with severe asthma were: respiratory conditions (29.4%, including acute respiratory infections (25.4%) and other upper respiratory tract diseases (4.0%)), skin and subcutaneous tissue conditions (22.9%, including other skin and sub-cutaneous tissue disorders (9.3%), other skin and sub-cutaneous tissue inflammatory condition (7.2%), and skin and subcutaneous tissue infections (6.4%)), rheumatism excluding the back (17.2%) arthropathies and related disorders (8.7%), vertebral column syndromes (7.4%), diseases of the ear and mastoid process (6.8%), disorders of eye and adnexa (5.8%), mycoses (5.4%), other urinary system diseases (4.9%) and neurotic, personality and other nonpsychotic disorders (4%).

SI.2 Eosinophilic Granulomatosis with Polyangiitis

INCIDENCE AND PREVALENCE

EGPA is a rare HES characterised by small vessel vasculitis in association with asthma, sinusitis and pulmonary infiltrates [Dunogué, 2011; Keogh, 2006; Holle, 2009; Vaglio, 2012].

A systematic review of published literature, to June 2019, identified 35 studies (published in 40 manuscripts) that described frequency of disease [Gonzalez-Gay, 2003; Kanecki, 2017; Mohammad, 2009; Nesher, 2016; Nilsen, 2017; Ormerod, 2008; Pamuk, 2016; Reinhold-Keller, 2002; Rodriguez-Muguruza, 2016; Romero-Gomez, 2015; Vinit, 2011; Dadoniene, 2005; Herlyn, 2017; Fujimoto, 2011; Pearce, 2016; Bell, 2018; Haugeberg, 1998; Herlyn, 2014; Mahr, 2004; Sada, 2014; Wójcik, 2018; Gokhale, 2018; Pamuk, 2013; Jaffe, 2014; Jaffe, 2012; Watts, 2009; Herlyn, 2008; Mohammad, 2007; Watts, 2001; Watts, 1995; Watts, 2000; Martin, 1999; Reinhold-Keller, 2000; Mohammad, 2011; Berti, 2017; Pearce, 2014; Pearce, 2015; Romero-Gómez, 2013; Watts, 2008]. Twenty-three of these studies were conducted in European countries, with the remaining studies from the US, Israel, Turkey Australia, Japan or multiple countries. Amongst these studies there was apparent heterogeneity in the criteria used to diagnose EGPA, including ACR 1990 criteria, CHCC 1994, CHCC 2012 or the Lanham criteria.

Incidence ranged from 0.18 (Spain) to 4.00 (US) cases per 1,000,000 person-years. In studies from Europe incidence ranges from 0.18 (Spain) to 2.5 (Norway) cases per 1,000,000 person years.

Nine (8 European countries) of thirteen studies reported period prevalence between 2 and 24 cases per 1,000,000 individuals and 4 of thirteen studies reported point prevalence estimates between 8.1 and 30.4 cases per 1,000,000 individuals.

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

Most studies reported the mean age at presentation of EGPA to fall between the 40-60 years of age, although some studies report EGPA cases as young as 10 years [Gendelman, 2013] and as old as 89 years [Herlyn, 2014]. Several studies have reported an equal proportion of males and females presenting with EGPA in the adult population [Martin, 1999; Comarmond, 2013; Conron, 2000; Detoraki, 2016; Haugeberg, 1998; Romero-Gomez, 2015]. However, some studies have reported a higher proportion of females presenting with EGPA ranging from 58% based on inpatient records [Hasegawa, 2015] to 89% in the paediatric population [Gendelman, 2013].

There are limited data to suggest there may be race/ethnic differences in disease burden, and it is unclear whether these observations may be related to an underlying genetic predisposition or differences in diagnosis and management. Gibelin et al. reported that in New Zealand, EGPA was 2-4 times more common in people of European ancestry compared to Maoris, Asians and Pacific Islanders [Gibelin, 2011]. Sreih et al. reported in a US study that prevalence of EGPA amongst Hispanics was twice the prevalence of EGPA in Caucasians [Sreih, 2015].

SI.2.2 The main existing treatment options

Treatment options for EGPA patients, both paediatric and adult, are limited. Treatment aims to improve symptoms, suppress/reduce eosinophil count to prevent peripheral tissue/neurological infiltration and damage by inflammation leading to a more severe disease progression. The treatment options for EGPA described below include guidance from the British Society for Rheumatology, the British Health Professionals in Rheumatology and the EGPA Consensus Task Force recommendations for EGPA evaluation and management [Ntatsaki, 2014; Groh, 2015].

OCSs such as prednisolone are the primary treatment for EGPA patients. For more severe patients, immunosuppressants including cyclophosphamide can be given in addition to OCS to help suppress eosinophil levels. For patients with life/organ threatening disease, maintenance therapy with azathioprine or methotrexate is recommended. Second line therapy for patients who fail to taper OCS include IVIg where flares become refractory. For select patients, second and third line therapy of Interferon-alpha can be considered.

Other treatments reported to have been used in EGPA patients include plasma exchange [Conron, 2000], rituximab [Gendelman, 2013] and omalizumab. Plasma exchange is only effective in select patients [Groh, 2015]. Rituximab is approved for the treatment of patients with other forms of vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis). In a study of 5 EGPA patients, anti-IgE omalizumab helped patients to reduce OCS use and improve asthma symptoms and lung function [Detoraki, 2016].

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

EGPA typically develops in three phases. The first, prodromic, phase is characterized by asthma, allergic rhinitis and sinusitis. The second, eosinophilic, phase involves an increase in the eosinophilic count and organ infiltration. In the third, vasculitic, phase patients suffer from the consequences of necrotizing vasculitis [Gioffredi, 2014].

Extrapulmonary organ involvement is a common problem that is associated with morbidity and sometimes even mortality among EGPA patients. The commonly affected systems are skin, sinuses, cardiovascular system, kidneys, peripheral nervous system and the gastrointestinal tract. Kidney, heart and/or gastrointestinal involvements are associated with poor prognoses among EGPA patients and require treatment with immunosuppressive therapy [Groh, 2015; Comarmond, 2013; Gioffredi, 2014]. Cardiac involvement is further associated with EGPA patient deaths [Gioffredi, 2014]. It is therefore recommended that once EGPA is diagnosed, organ involvement should be evaluated via organ specific tests (renal function tests or urine analysis to evaluate kidney function, and chest imaging and electrocardiography to evaluate cardiac involvement). Additional diagnostic procedures should also be considered depending on the symptoms or physical examination findings [Groh, 2015]. Guillevin et al. in a prospective study of 96 EGPA patients reported poor prognosis of patients with gastrointestinal or central nervous system involvement or cardiac failure [Guillevin, 1999].

According to the EGPA Consensus Task Force recommendations for evaluation and management of EGPA, remission can be defined as the absence of clinical symptoms and biologic abnormalities in patients on minimal prednisone and/or immunosuppressant dose. This group defined EGPA relapse as the new appearance or recurrence or worsening of clinical EGPA manifestations (excluding asthma and/or Ear, nose and throat), requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants [Groh, 2015]. Due to a lack of consensus on the definition of a relapse, the reported proportion of relapses in EGPA patients ranges from 18%-81.1% [Eleftheriou, 2016; Durel, 2016; Comarmond, 2013; Zwerina, 2009; Samson, 2013; Ribi, 2008; Mukhtyar, 2008; Guillevin,1999; Pavone, 2006; Baldini, 2010]. Of the reported proportion of relapse, paediatric relapse ranges between 18%-46% [Eleftheriou, 2016; Zwerina, 2009] and was attributable to ineffectiveness of treatment. In the adult population, the lowest reported proportion of relapse was 20%, gastrointestinal involvement and ANCA persistent positivity were reported as risk factors for EGPA relapse [Baldini, 2010]. Like the paediatric population, relapse in the adult population was also largely a result of long-term ineffectiveness of treatment [Durel, 2016].

Due to the rarity of this condition, obtaining accurate numbers for survival of EGPA patients in the general population is difficult. Samson et al. in a study of 115 patients captured across two prospective randomised trials reported overall survival at 1-, 3-, 5- and 7-years at 98%, 94%, 92% 90% respectively [Samson, 2013]. Sinico et al. also highlight the clinical significance of ANCA in 93 EGPA patients and found that 5-year survival and relapse rates were similar for both groups (91.8% and 46.3% for ANCA-positive patients versus 97.1% and 35.4% for ANCA-negative patients, respectively) [Samson, 2013; Sinico, 2005]. Conron et al. reported a 10-year survival rate of 72-75% in an English study

[Conron, 2000]. In Japan, Hasegawa et al. reported a mortality rate of 4.4% with mortality being much higher in patients aged >65 [Hasegawa, 2015]. The presence of ear, nose and throat disease was associated with lower mortality in EGPA patients [Hasegawa, 2015]. A systematic literature review describes mortality in 6/33 (19%) children, all related to underlying disease [Zwerina, 2009]. Overall, the survival did not seem to be significantly affected by baseline anti-MPO–ANCA status, or eosinophil count, or the occurrence of relapses. Age greater than 65 years was associated with a higher risk of death during follow-up [Samson, 2013]. EGPA patients have reported significant impact to their daily life including reduced mobility, significant fatigue and a general reduction in their overall quality of life as a result of EGPA pathogenesis. Additionally, treatment with immunosuppressants, notably cyclophosphamide showed improved clinical response and patient survival [Conron, 2000; Samson, 2013].

SI.2.4 Important co-morbidities

EGPA patients can suffer from numerous comorbidities as a result of the underlying disease itself or as a result of treatments. Comorbidities reported in EGPA patients are often manifestations of pulmonary and non-pulmonary organ involvement. These include asthma, mono/poly neuritis, infections, osteoporosis, allergies, pulmonary disease, cardio-cerebrovascular disease, digestive disease, sepsis and cancers [Conron, 2000; Hasegawa, 2015; Comarmond, 2013; Gendelman, 2013].

SI.3 Hypereosinophilic Syndrome

INCIDENCE AND PREVALENCE

HES refers to a group of rare hematologic disorders characterized by peripheral blood eosinophil count of 1.5 × 10^9 cells/L or higher for at least two occasions in an interval ≥ 1 month, lack of evidence on secondary causes, and eosinophilic organ involvement [Wang, 2019].

The incidence and prevalence of HES is not well characterized. One of the challenges that affect the accurate determination of incidence and prevalence of HES is its diagnosis. A complete evaluation of the patient is needed to exclude other disorders as the major reason for hypereosinophilia and organ damage. After exclusion of secondary causes of eosinophilia, diagnostic evaluation of primary eosinophilia requires a combination of morphologic analysis of the blood and bone marrow, standard cytogenetics, and T-cell clonality assessment to detect histopathologic or clonal evidence for an acute or chronic myeloid or lymphoproliferative disorder [Gotlib, 2017; Shomali, 2019].

In one study using the International Classification of Diseases (ICD) for Oncology, under the general category of chronic myeloproliferative disorders, an age-adjusted incidence rate of the m-HES variant/ CEL, of 0.036 per 100,000 person-years was reported [Crane, 2010]. Extrapolating this result, based on that M-HES accounted for 10-20% of all HES, an overall annual age-adjusted incidence rate for all HES was estimated between 0.018-0.036 as lower bounds and 0.18-0.36 per 100,000 person-years as upper bounds and a prevalence rate between 0.3 and 6.3 per 100,000 [Crane, 2010]. These estimates were derived using the Surveillance, Epidemiology, and End Results database from 2001-2005. This is a

collection of population-based cancer registries in the US, therefore estimates may not be generalizable to the broader population.

In a study performed by GSK using the CPRD GOLD and Aurum databases, using specific READ codes for HES, the overall annual estimated incidence rate of HES ranged between <0.04 and 0.17 per 100,000 person-years from 2010-2018 [Requena, 2021]. The overall annual estimated prevalence of HES ranged between 0.15 and 0.89 cases per 100,000 persons over the 9-year study period. CPRD encompasses data from the network of general practitioners in the UK and given that diagnosis and treatment of HES involve specialized care, the true burden might be underestimated.

SI.3.1 Demographics of the population in the authorised indication and risk factors for the disease:

Currently, little is known about the etiology and risk factors for HES. It is usually diagnosed between the ages of 20 and 50, and exhibits similar gender distribution, except for the myeloproliferative variants of HES, where the majority of the patients are male [Shomali, 2019]. The most common presenting signs and symptoms are weakness and fatigue (26%), cough (24%), dyspnea (16%), myalgias or angioedema (14%), rash or fever (12%), and rhinitis (10%) [Shomali, 2019]. Organ damage may occur in HES irrespective of the underlying subtype. The most commonly affected organ systems are dermatologic, pulmonary, and gastrointestinal systems, seen in roughly 40-70% of patients Cardiac and neurological systems are relatively less commonly impacted and seen in roughly 20-30% of patients [Williams, 2016; Ogbogu, 2009; Kuang, 2018].

SI.3.2 The main existing treatment options

There are limited treatment options approved for HES, however, there are numerous treatment modalities to control symptoms and mitigate eosinophil-mediated organ damage. Corticosteroids are the first line of therapy for all HES variants due to their ability to induce eosinophil apoptosis although Khoury et al. recently demonstrated that M-HES and L-HES have worse corticosteroid response compared to other variants [Khoury, 2018; Shomali, 2019; Iurlo, 2019]. For M-HES (F/P+) imatinib has been recognized as first line treatment [Klion, 2015; Butt, 2017; Roufosse, 2015]. Corticosteroid therapy can be complicated by side effects in patients that require long-term treatment. In a retrospective chart review of 188 HES patients at US and European centers, 75% received corticosteroids as initial monotherapy and 85% of these individuals achieved complete or partial response within a month of treatment [Ogbogu, 2009]. The proportion of HES patients receiving corticosteroids and responding to treatment was similar in Williams et al. at 80% and 83%, respectively. In another study of 33 idiopathic HES patients all treated with corticosteroids, 64% exhibited complete resolution of elevated eosinophils within a week and 21% were either resistant or intolerant [Helbig, 2013].

Hydroxyurea is an antineoplastic agent that is usually used as second line therapy in combination with corticosteroids and among corticosteroid non-responders [Shomali, 2019; Iurlo, 2019]. In Ogbogu et al., 34% of the 188 patients were treated with hydroxyurea, 18 of whom received it as monotherapy. Among these 18, 6 achieved complete response and 7 achieved partial response. Hydroxyurea had to be discontinued in roughly 77% of the patients were administered because of low efficacy and side effects.

Interferon-α (INF-A) is an immune system modulator that functions by boosting the immune system and regulating expression of genes critical to cell growth [Shomali, 2019; Iurlo 2019]. INF-A isn't a first line therapy but has been used in combination with corticosteroids or hydroxyurea in non-responding HES patients (primarily CEL). In Ogbogu et al., 46 of the 188 patients were treated with INF-A, 12 as monotherapy. Only 2 of the 12 achieved a complete response while 4 of the 12 achieved partial response. Drug intolerance was more highly reported compared to first line therapies.

Imatinib is a tyrosine kinase inhibitor that is effective in treating disorders involving activation of the tyrosine kinase family of genes [Shomali, 2019; Iurlo, 2019]. Historically, imatinib has been effective in treating myeloid leukemias and FIP1L1-PDGFRA (F/P+) patients. In a prospective study of 19 HES patients, imatinib produced remission in all 8 patients that were F/P+ [Arefi, 2012]. In comparison, studies among F/P- HES patients showed 50% response and 0% response [Helbig, 2012; Jain, 2009]. In Ogbogu et al. imatinib was initiated in 68 of 188 patients and 88% of the F/P+ and 23% of the F/P- responded, which is in line with prior findings.

SI.3.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

The natural history and prognosis of HES depends on the HES variant. The ability to distinguish different HES variants is critical for optimal patient management because the clinical manifestations and response to treatment vary considerably depending on the aetiology of eosinophilia. Variants of HES include M-HES, CEL, NOS, L-HES, and idiopathic HES [Roufosse, 2009, Klion, 2015].

Mortality in HES patients have improved markedly over time. A 1989 study of 40 patients reported a 20% 5-year mortality rate [Lefebvre, 1989]. By comparison, a 2013 Mayo Clinic study reported a 9-10% mortality rate over a 19-year period of follow-up among 247 patients [Podjasek, 2013]. Of the 23 deaths, the cause of death was identified in 15 patients: 5 from cardiac dysfunction (33%), 3 from infection (20%), 3 from unrelated malignancy (20%), 2 from thromboembolic phenomena (13%), and 2 from vascular disease (13%). This is similar to the mortality rates of 8% and ~10-15% in two other large-scale epidemiological investigations [Williams, 2016; Kuang 2018]. Another smaller study reported no mortality among five individuals with HES over a span of 2 to 6 years of follow-up [Ang, 2012].

SI.3.4 Important co-morbidities

In the same cited study performed by GSK, the most common comorbidities defined as having a diagnostic code in the year prior diagnosis revealed a high proportion of patients with diseases of white blood cells (41%) and respiratory conditions such asthma (16%), acute bronchitis and bronchiolitis (13%). This fact is consistent with the diagnosis criteria for this disease [Requena, 2021].

SI.4 Chronic Rhinosinusitis with Nasal Polyps

INCIDENCE AND PREVALENCE

NPs are benign, soft, inflammatory masses of sinonasal tissue and are considered to be a subgroup of CRS termed CRSwNP [Hopkins, 2019]: in the literature the terms NP and CRSwNP are generally considered synonymous. 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].

CRS is divided into two phenotypes: CRSwNP and CRSsNP. Very few studies report on the incidence of CRSwNP. The incidence in Denmark of symptomatic NPs was 0.63/1,000 [Larsen & Tos, 2002], which was similar to the US with an incidence of 0.83 per 1,000 person-years for CRSwNP [Tan, 2013].

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 4.3% in Finland [Hedman, 1999]. 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 CRS without NP (CRSsNP) and control populations [Tan, 2013].

SI.4.1 Demographics of the population in the authorised 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 behavioural differences rather than lower prevalence [Hopkins 2019; Woodard, 2016]. Risk factors 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 CRSwNP patients 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 characterised by eosinophilia (~80%) and elevated levels of interleukin-4, IL-5, and interleukin-13 cytokines [Bachert, 2017; Zhang, 2017; Wang. 2016]. Patients with CRSwNP have higher blood eosinophil levels than patients with CRSsNP, and CRSwNP patients that additionally had asthma had 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, 2016; 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.4.2 The main existing treatment options

There has been a recent update in CRS management guidance from the EPOS 2012 to EPOS 2020 guidelines [Fokkens, 2012; Fokkens, 2020] whereby the guidelines no longer differentiate between management of CRSsNP and CRSwNP [Fokkens, 2020]. Unless otherwise stated, details on treatment options for patients with CRSwNP have been summarised from the EPOS 2020 guidelines [Fokkens, 2020].

The main treatment options for patients with CRSwNP include saline nasal irrigation, nasal corticosteroids (drops, spray, rinses), and short-course SCS. 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.

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

Short-course SCS (1-2 courses per year) might be a helpful add-on therapy for patients whose disease is only partially controlled or is uncontrolled by nasal corticosteroids. With or without local corticosteroids, short-course SCS can significantly reduce scores for total symptoms and NP but can also have no impact on quality of life and can cause substantial side effects.

Dupilumab (anti-IL4 treatment) is the first biological therapy to be approved for the treatment of adults with inadequately controlled CRSwNP [Hoy, 2020]. On 31st 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 SPC 2020].

Mepolizumab (anti-IL5 treatment) is also approved for treatment of adult patients with CRSwNP at a dose of 100 mg in the US, in all EEA countries, the UK as well as 20 further countries.

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.

If patients undergo surgery and polyps recur, possible options for add-on therapy include ATAD, longer (tapering) treatment with SCS, long term antibiotics, or biologicals when indicated. However, international guidelines differ regarding whether the use of antibiotics and OCS should be used due to low quality evidence and adverse side-effects, respectively, and ATAD is associated with adverse effects and poor adherence due to daily administration.

SI.4.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

In the most recent EPOS guidelines, CRS (with or without NPs) 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 EPOS 2020 guidelines 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. Unfortunately, no reliable biomarkers that define type 2 inflammation can yet predict response to medication [Fokkens, 2020].

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, nasal steroids 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 SCS 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 disease 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.4.4 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.

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].

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

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

Key Safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat-dose toxicity: Single IV doses up to 300 mg/kg and monthly repeat IV doses up to 100 mg/kg resulted in continuous exposure of the monkeys to mepolizumab for as long as 6 months and were not associated with toxicological findings. In the 6-month toxicity study, consistent with the pharmacology, peripheral blood eosinophil counts were decreased >80% for the duration of the study with no evidence of adverse effects. Circulating eosinophil counts recover following clearance of mepolizumab; there were no effects on eosinophil precursors in the bone marrow. **Reproductive and Developmental toxicity:** No effects of antagonism of IL-5 on reproductive function, pregnancy or immune development in offspring have been observed in either monkeys given mepolizumab or mice given a homologue anti-IL5 antibody. **Genotoxicity:** As mepolizumab is a large molecular weight protein, genotoxicity studies are not appropriate. **Immunotoxicity:** Treatment with mepolizumab 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 mepolizumab, suggests that the risk for potential immunotoxicity is low. **Immunogenicity (ADA):** Administration of mepolizumab by IV or SC routes to monkeys has	Toxicology studies conducted with mepolizumab in monkeys have not identified any adverse findings. Consistent with the expected pharmacology, there were significant, prolonged reductions in circulating eosinophils, which recover upon clearance of mepolizumab. This pharmacology was not associated with adverse effects on the immune system or on reproductive function and developmental toxicity. A critical review of the scientific literature does not indicate that neutralization of IL-5 with subsequent reductions in circulating eosinophils would be associated with alterations of immune system function in host defense or tumor surveillance.

Key Safety findings (from non-clinical studies)	Relevance to human usage
had a low incidence of immunogenic responses (antibodies to mepolizumab). **Carcinogenicity:** Mepolizumab is not believed to possess an inherent carcinogenic potential or increase the susceptibility to tumor formation secondary to significant immunosuppression, and there is no evidence to date that mepolizumab has produced immunosuppression in animals or patients.	
General Safety pharmacology: (as applicable) **Cardiovascular:** There were no effects of mepolizumab on cardiovascular (including QTc), respiratory and renal function or body temperature after single and repeat IV doses up to 100 mg/kg in monkeys. **Nervous system:** There were no effects of mepolizumab on clinical signs or nervous system histopathology findings after single and 7-monthly repeat IV doses up to 100 mg/kg in monkeys.	Based on the mechanism of action of mepolizumab and the results of chronic administration to monkeys at suprapharmacologic doses, there is a low likelihood for adverse effects on cardiovascular, renal, respiratory, and central nervous system function.
Other toxicity-related information or data (as applicable) **Mechanisms for drug interactions:** No drug interaction studies have been conducted as mepolizumab is cleared through cellular catabolism following nonspecific uptake by pinocytosis and is not metabolized by the cytochrome P450 system. **Local tolerance:** In monkeys, 7-monthly repeat IV and SC administrations of 100 and 10 mg/kg, respectively, were well tolerated with no injection or infusion site reactions.	In the population PKs analyses conducted during the clinical development of mepolizumab, there is no evidence to suggest an effect of commonly co-administered small molecule drugs on mepolizumab exposure. There is also no evidence of dose adjustments being required for the small molecule drugs commonly co-administered in the clinical studies There have been reports of systemic (i.e. both IgE and non-IgE-mediated) and local site reactions in patients; however, the overall risk is low based on the overall data to date.

In summary, the pharmacological, toxicokinetic and toxicological properties of mepolizumab have been well characterized, within the constraints normally applicable to the development a monoclonal antibody. Mepolizumab binds to human lymphoid tissues in vitro, and is pharmacologically active (decreased eosinophils) in monkeys at doses ≥0.5 mg/kg. Intravenous doses up to 300 mg/kg and subcutaneous doses up to 40 mg/kg have been well tolerated by monkeys. The principal effect observed in toxicology studies up to 6 months duration was related to the pharmacology of mepolizumab and these pharmacologic effects reversed following the cessation of treatment. Administration of mepolizumab to monkeys has had a low incidence of immunogenic responses. No effects

of antagonism of IL-5 on reproductive function, pregnancy or immune development in offspring have been observed. Antagonism of IL-5 did not affect host defenses to parasitic infection. Taken together, these data support the safe use of mepolizumab in the proposed patient population under the prescribed therapeutic dosage regimen.

In conclusion, there are no important identified risk or important potential risks from the nonclinical data. Direct assessment of immunotoxic (e.g., host defense to infectious agents and host surveillance of neoplasia) effects of mepolizumab could not be undertaken in animals as test systems are not established in monkeys, the only pharmacologically responsive preclinical species (GSK document number 2014N217317_01). To address these potential effects of mepolizumab, a critical review of clinical safety data across all clinical programmes was undertaken and is summarized in the integrated summary of safety for the initial severe eosinophilic asthma submission.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Table 7 Clinical Trial Exposure: Duration of Exposure

Cumulative for all indications[1]	
Duration of exposure (at least)	**Persons**
≥1 m	4357
≥3 m	3835
≥6 m	3056
≥12 m	2454
≥24 m	947
Total person time (patient years)	7204.61
Severe Asthma (Mepolizumab All Doses)	
Duration of exposure (at least)	**Persons**
≥1 m	1850
≥3 m	1803
≥6 m	1549
≥12 m	1116
≥24 m	650
Total person time (patient years)	3791.76
EGPA	
Duration of exposure (at least)	**Persons**
≥1 m	127
≥3 m	125
≥6 m	125
≥12 m	118
≥24 m	88
Total person time (patient years)	365.89
HES	
Duration of exposure (at least)	**Persons**
≥1 m	456
≥3 m	429
≥6 m	355
≥12 m	306
≥24 m	209
Total person time (patient years)	1910.44
Nasal Polyps	
Duration of exposure (at least)	**Persons**
≥1 m	259
≥3 m	250
≥6 m	233
≥12 m	182
≥24 m	0

Total person time (patient years)	216.44
Note: For 6 subjects in the HES expanded access program, exposure duration was not recorded. Includes exposure from completed studies and ongong studies with interim report [1] Cumulative exposure for all indications across the mepolizumab program	
Source: Nasal Polyps ISS (mid213570/iss_02), Table 3.75 and Table 3.76	

Table 8 Clinical Trial Exposure: By Age Group and Gender

Cumulative for all indications[1]				
Age group	**Persons**		**Person time (patient years)**	
	M	**F**	**M**	**F**
2-5 years	11	2	2.41	0.48
6-11 years	43	15	34.24	25.39
12-17 years	55	47	92.38	55.04
18-64 years	1624	1734	2625.00	3336.34
≥ 65 years	493	326	585.15	432.88
Unknown	0	1	0	5.96
Total	2226	2125	3339.18	3856.09
Severe Asthma (Mepolizumab All Doses)				
Age group	**Persons**		**Person time (patient years)**	
	M	**F**	**M**	**F**
2-5 years	1	0	0.24	0
6-11 years	24	10	25.52	10.42
12-17 years	21	27	26.65	35.08
18-64 years	638	925	1375.24	1970.17
≥ 65 years	88	116	143.61	204.83
Total	772	1078	1571.26	2220.50
EGPA (Mepolizumab All Doses)				
Age group	**Persons**		**Person time (patient years)**	
	M	**F**	**M**	**F**
2-5 years	0	0	0	0
6-11 years	0	0	0	0
12-17 years	0	0	0	0
18-64 years	45	67	138.01	180.19
≥ 65 years	7	8	23.45	24.25
Total	52	75	161.46	204.44
HES (Mepolizumab All Doses)				
Age group	**Persons**		**Person time (patient years)**	
	M	**F**	**M**	**F**
2-5 years	1	0	0.08	0
6-11 years	1	2	4.51	14.27
12-17 years	14	13	61.14	18.35
18-64 years	168	190	709.24	917.67

≥ 65 years	40	20	104.47	65.42
Unknown	0	1	0	5.96
Total	224	226	879.44	1021.67
Nasal Polyps (Mepolizumab All Doses)				
Age group	**Persons**		**Person time (patient years)**	
	M	**F**	**M**	**F**
2-5 years	0	0	0	0
6-11 years	0	0	0	0
12-17 years	0	0	0	0
18-64 years	155	69	129.24	57.80
≥ 65 years	24	11	20.81	8.59
Total	179	80	150.05	66.39
Note: For 6 subjects in the HES expanded access program, exposure duration was not recorded. In addition, six subjects with exposure data in the HES expanded access program have unknown age and gender. Includes data from completed studies and ongoing studies with interim report [1] Cumulative exposure for all indications across the mepolizumab program				
Source: Nasal Polyps ISS (mid213570/iss_02), Table 3.5, Table 3.85				

Table 9 Clinical Trial Exposure: By Dose

Cumulative for all indications[1]		
Dose of exposure	**Persons**	**Person time (patient years)**
40 mg SC	26	21.12
100 mg SC	2722	4035.87
40/100 mg SC	4	4.04
300 mg SC	458	641.06
75 mg IV	361	257.25
250 mg IV	294	171.87
750 mg IV	446	517.69
Other[2]	575	1557.55
Total[3]	4357	7204.61
Severe Asthma		
Dose of exposure	**Persons**	**Person time (patient years)**
40 mg SC	26	21.12
100 mg SC	1613	3227.37
40/100 mg SC	4	4.04
300 mg SC	0	0
75 mg IV	344	254.25
250 mg IV	152	142.19
750 mg IV	156	143.50
Other[2]	0	0
Total[3]	1850	3791.76
EGPA		
Dose of exposure	**Persons**	**Person time (patient years)**

100 mg SC	0	0
300 mg SC	127	365.89
75 mg IV	0	0
250 mg IV	0	0
750 mg IV	0	0
Other[2]	0	0
Total[3]	127	365.89
HES		
Dose of exposure	**Persons**	**Person time (patient years)**
100 mg SC	0	0
300 mg SC	106	71.41
75 mg IV	0	0
250 mg IV	0	0
750 mg IV	81	320.04
Other[2]	353	1520.12
Total[3]	456	1910.44
Nasal Polyps		
Dose of exposure	**Persons**	**Person time (patient years)**
100 mg SC	206	194.79
300 mg SC	0	0
75 mg IV	0	0
250 mg IV	0	0
750 mg IV	53	21.65
Other[2]	0	0
Total[3]	259	216.44

Note: For 6 subjects in the HES expanded access program, exposure duration was not recorded.
Includes data from completed studies and ongoing studies with interim report.
Subjects exposed to more than one dose are counted in each dose. For 4 subjects in the 200363 asthma paediatric study who received 40 SC in Part A and changed their dose from 40 SC to 100 SC at some point during part B of the study, their exposure in part A is recorded under 40 SC and their exposure in part B is recorded under 40/100 SC.

[1] Cumulative exposure for all indications across the mepolizumab program
[2] Includes IV doses: 10mg, 750mg/1500mg, 0.05, 0.5, 0.55, 2.5 and 10mg/kg, SC doses: 12.5, 125 and 250mg and IM: 250mg. In addition, includes all subjects enrolled in the HES Expanded Access Program.
[3] Subjects/persons exposed to more than one dose of mepolizumab are counted once in the Total row.
Source: Nasal Polyps ISS (mid213570/iss_02), Table 3.75 and Table 3.76, (mid213570/postcsr_2022_01) Table 3.100 and Table 3.101.

Table 10 Clinical Trial Exposure: By Ethnic or Racial Origin

Ethnic/racial origin	Persons	Person time (patient years)
Severe Asthma (Mepolizumab All Doses)		
African American/African Heritage	86	103.35
White	1579	3277.70
Asian	160	382.57
Other	24	27.92
Not recorded	1	0.22
Total	1850	3791.76
EGPA (Mepolizumab All Doses)		
African American/African Heritage	0	0
White	118	339.47
Asian	8	21.57
Other	1	4.85
Total	127	365.89
HES (Mepolizumab All Doses)		
African American/African Heritage	29	104.59
White	391	1736.05
Asian	18	26.18
Other	13	41.63
Not recorded	5	2.00
Total	456	1910.44
Nasal Polyps (Mepolizumab All Doses)		
African American/African Heritage	5	4.49
White	243	203.48
Asian	11	8.47
Other	0	0
Total	259	216.44

Note: For 6 subjects in the HES expanded access program, exposure duration was not recorded.

Source: Nasal Polyps ISS (mid213570/iss_02), Table 3.6 and Table 3.76

Table 11 Clinical Trial Exposure: Paediatrics (By Indication)

	Persons	Person time (patient years)
Severe Asthma (Mepolizumab All Doses)		
2-5 years	1	0.24
6-11 years	34	35.94
12-17 years	48	61.73
Eosinophilic Esophagitis (Mepolizumab All Doses)	**Persons**	**Person time (patient years)**
2-5 years	11	2.57
6-11 years	21	4.91
12-17 years	27	6.21
Hypereosinophilic Syndrome (Mepolizumab All Doses)	**Persons**	**Person time (patient years)**
2-5 years	1	0.08
6-11 years	3	18.78
12-17 years	27	79.49

Source: EGPA Paediatric ISS (mid213570/iss_05), Table 2.8

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

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

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Hypersensitivity: a hypersensitivity reaction related to mepolizumab or its excipients	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 mepolizumab SmPC
Children younger than 12 years	The safety and efficacy of NUCALA had not been established in this population during the initial severe asthma clinical development programme and was subject to a PIP in the EU. Similarily, there is a PIP in place for HES indications and a product specific waiver for CRSwNP. The PIPs cover paediatric age range from 6-17 years old.	YES	Children younger than 12 (age 6-11) were enrolled in a the completed paediatric study (200363; Part A PK/PD phase, Part B long-term safety/PD phase) (Part A N=36; Part B N=30). The safety profile in paediatric patients is similar to the known safety profile of mepolizumab. No new safety concerns unique to paediatric patients have been identified. However, at the request of CHMP during the Type II variation to extend the indication to include EGPA to mepolizumab (procedure EMEA/H/C/003860/II/0036/G), GSK was requested to include safety of mepolizumab in children with EGPA as missing information. As per CHMP request, a PASS is ongoing to generate safety and efficacy data for mepolizumab in the post-

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			marketing setting in EGPA pediatric patients aged 6 to 17 years (study 218065). The study protocol has been formally approved by EMA, and there is 1 patient enrolled as of 22 July 2024 HES has a PIP in the EU, which is a 52-week open label study 215360 investigating the efficacy and safety of mepolizumab in participants 6-17 years old.
Children younger than 6 years	The agreed PIPs consisted of a waiver for this age group.	NO	NUCALA is not indicated for children < 6 years of age.
Organ-threatening or life-threatening EGPA	Subjects with organ- and/or life threatening EGPA were excluded from study MEA115921 because of the logistics of their disease management but not for safety concerns. In summary, patients with organ and/or life threatening EGPA are medically unstable and require repeated admission to an ICU, surgical intervention, transplantation or imminent remission induction. Regarding the latter, cyclophosphamide, which is commonly	NO	There is no evidence for a different safety profile of mepolizumab in patients with severe organ or life-threatening EGPA

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	used as induction therapy for such patients, was prohibited in study MEA115921 since its associated toxicity precluded its use at a stable dose for the 52-weeks duration of the study.		
Pregnant or lactating women	The safety and efficacy of mepolizumab is not established in this population.	YES	Female study subjects were excluded from the clinical trial programme 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.
Malignancy	Patients with malignancy were excluded to minimize the interference of either the malignancy or the treatment for the malignancy on the assessment of both efficacy and safety of mepolizumab.	NO	Not a safety specific exclusion criteria for mepolizumab.
Parasitic Infections	Eosinophils may be involved in the immunological response to some helminth infections.	NO	During the phase III severe asthma programme, two cases of parasitic infection were reported: an event of parasitic gastroenteritis which was unconfirmed, non-serious, treated with albendazole and resolved within 10 days with continued

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			mepolizumab treatment; a case of cutaneous larvae migrans that resolved promptly with treatment while mepolizumab was continued. In the phase III placebo-controlled studies in patients with EGPA, HES or CRSwNP no parasitic infections were reported. One patient with HES reported a non-serious AE of parasite stool test positive in the OLE study 205203. The event was of moderate intensity and was considered resolving at the time of reporting. Reported treatment for infection with blastocystis was oral 400 mg albendazole every 12 hours. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of mepolizumab can be considered.
Concurrent treatment with other monoclonal antibodies	Patients receiving other monoclonal antibodies were excluded due to potential interference with efficacy and safety data interpretation.	NO	No formal interaction studies conducted; however, low potential for drug-drug interactions because selectively binds and neutralizes the cytokine IL-5.
Unstable or clinically significant liver	Standard exclusion criterion for	NO	No formal studies have been conducted to investigate the effect of hepatic impairment

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
disease uncontrolled with standard therapy	developmental compound		on the PK of mepolizumab. Since mepolizumab 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 mepolizumab. Dosage adjustments are unlikely to be required.
Unstable or clinically significant renal disease uncontrolled with standard therapy	Standard exclusion criterion for developmental compound	NO	No formal studies have been conducted to investigate the effect of renal impairment on the PKs of mepolizumab. Based on population PK analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min. However, mepolizumab is not cleared renally. Dosage adjustments are unlikely to be required.
Smoking status – current smoker (adult and adolescent severe asthma studies)	Current smokers and smokers with ≥ 10 pack-year history were excluded to assure the study population did not include patients with a possible diagnosis of COPD.	NO	Not a safety related exclusion criteria.
Cardiovascular co-morbidities	Patients with severe comorbid cardiovascular	NO	Patients with less severe and/or controlled cardiovascular conditions

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
uncontrolled with standard therapy	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.		were included in the clinical studies.

SIV.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, or adverse reactions with a long latency.

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

Table 12 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure Total number of subjects and person time
Pregnant women Pregnant and breast-feeding women were excluded from clinical studies with mepolizumab. Female subjects of childbearing potential participating in the studies were required to commit to consistent and correct use of a contraceptive method with a <1% failure rate. 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 data cut-off date 22 July 2024 42 pregnancies were reported from the completed and ongoing mepolizumab studies (all indications).

Type of special population	Exposure Total number of subjects and person time
Breastfeeding women Breast feeding women were excluded from clinical studies with mepolizumab.	Not included in clinical development programme
Patients with relevant comorbidities: • **Patients with hepatic impairment** No formal studies have been conducted to investigate the effect of hepatic impairment on the PKs of mepolizumab. However, since mepolizumab 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 mepolizumab. No dose adjustment is required in patients with hepatic impairment.	Not included in clinical development programme.
• **Patients with renal impairment** Mepolizumab is a humanized IgG1 monoclonal antibody characterized by a large molecular weight of 149.2 kDa that precludes its elimination by glomerular filtration. Consequently, changes in renal function are not anticipated to impact the elimination of mepolizumab and a renal impairment study was not, therefore, conducted. No dose adjustment is required in patients with renal impairment.	Not included in clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Severe Asthma The majority of subjects in severe asthma studies included in the initial application were White (85%) with smaller contingents of Asian (11%), African Heritage (3%), and other races (<1%). The majority of children in study 200363 were white (56%), with smaller contingents of Asian (22%), African Heritage (19%), and other races (3%). EGPA

Type of special population	Exposure Total number of subjects and person time
	The majority of subjects in EGPA study MEA115921 were white (92%), with smaller contingents of Asian (6%) and multiple races (1%). HES The majority of subjects in the placebo controlled HES studies were White (90%), with smaller contingents of African Heritage (5%) and Asian (3%). CRSwNP The majority of subjects in the placebo-controlled NP studies were White (94%), with smaller contingents of Asian (4%) and Black or African American (2%).
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other: **Paediatric Patients (<18 years of age)** Children under 6 years of age were not enrolled in the mepolizumab development programme for severe asthma, EGPA, HES and CRSwNP. The waiver was granted to the paediatric population from birth to less than 6 years of age, on the grounds that the medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible due to none or low prevalence of diseases in this age group.	Severe asthma Nineteen mepolizumab-treated adolescents aged 12-17 years were enrolled in the Phase III studies in severe asthma. In an additional study (200862), 6 mepolizumab treated adolescents were enrolled. Thirty-six children (6-11 years) were treated with mepolizumab in Part A (PK/PD phase) of paediatric study 200363, of which 30 were treated with mepolizumab in Part B (long-term safety/PD). EGPA Only adult patients with EGPA were enrolled in clinical study MEA115921. Efficacy and safety in the paediatric age group is supported by a full extrapolation approach. HES

Type of special population	Exposure Total number of subjects and person time
Elderly No formal studies have been conducted in elderly patients	Four adolescent patients were enrolled into Phase III study 200622 of which 1 received mepolizumab. All 4 adolescents enrolled into OLE study 205203 and received mepolizumab. CRSwNP Only adult patients with NP were enrolled in clinical studies 205687 and MPP111782. Severe asthma A total of 82 mepolizumab treated subjects ≥65-year-old in the pivotal severe asthma studies included in the initial application. EGPA In study MEA115921 a total of 8 mepolizumab treated subjects ≥65-year-old were enrolled. HES In the HES placebo-controlled studies a total of 12 mepolizumab treated subjects ≥65-year-old were enrolled. CRSwNP In the NP placebo-controlled studies a total of 35 mepolizumab treated subjects ≥65-year-old were enrolled.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The algorithm used to derive post- approval exposure data from IQVIA data is based on 1 patient receiving 13 doses (one 100 mg vial or 40 mg, pre-filled pen, or pre-filled syringe for SC injection every 4 weeks) per year.

SV.1.2 Exposure

Cumulative post-marketing exposure to mepolizumab till 31 December 2023 is estimated to be 438 477 patient-years (based on the total number of unit doses sold cumulatively of 5 700 198). A detailed breakdown of patient exposure data by indication, sex, age, dose, formulation and region is presented in Table 13.

Table 13 Exposure table by indication, gender, age group, dose, formulation and region

01 October 2015 To 31 December 2023 (PRESCRIPTIONS SHOWN IN THOUSANDS)																	
INDICATION	**SEX**			**AGE (YEARS)**						**DOSE**			**FORMULATION**	**REGION**				
	Male	**Female**	**UNKNOWN**	**<2**	**2 to 11**	**12 to 17**	**18 to 65**	**65+**	**Unknown**	**100 MG**	**144 MG**	**100 MG/1 ML**	**VIALS (ALL)**	**Region 1**	**Region 2**	**Region 3**	**Region 4**	**OTHERS**
Asthma or Pulmonary Eosinophilia	913.55	1570.96	37.86	0.00	14.81	8.58	1504.14	977.65	17.20	1641.31	6.77	874.30	2522.37	320.90	1690.46	30.22	414.82	65.98
EGPA	147.95	226.69	0.00	0.00	0.00	0.00	267.59	107.05	0.00	95.05	0.00	279.59	374.64	0.73	371.71	0.00	1.12	1.08
Others	157.97	230.53	0.22	0.00	0.11	0.04	213.49	175.08	0.00	187.30	0.00	201.42	388.72	59.72	260.97	3.69	47.18	17.17
HES	0.45	0.69	0.00	0.00	0.00	0.00	0.66	0.48	0.00	0.82	0.00	0.32	1.14	0.20	0.00	0.00	0.94	0.00
Nasal polyps	22.15	6.00	0.00	0.00	0.00	0.00	20.79	7.36	0.00	15.53	0.00	12.63	28.15	8.98	0.00	8.16	3.96	7.05
TOTAL	1242.08	2034.87	38.08	0.00	14.92	8.62	2006.66	1267.62	17.20	1940.00	6.77	1368.25	3315.02	390.52	2323.13	42.07	468.02	91.27

Note: The demographic data segregated by indication in Table 13 is based on the disease classification codes from WHO ICD-10. Codes for HES were selected pertaining to eosinophil counts and treatments. 'Others' includes those indications which are not asthma or pulmonary eosinophilia, EGPA, HES or NP.

The data in Table 13 is sourced from IQVIA's "MIDAS Diagnosis Insights (detailed medical data)". This covers office-based prescribing in over 11 key countries, and it covers patient demographics as well as diagnosis specific prescribing information. Diagnosis Insights data is limited to data from the last 3 years, and it does not include hospital-based doctors, with the exception of Region 2, where hospital data is also covered. Medical audits reflect country prescribing practices and care should be taken when comparing countries or analyzing on a regional or global basis. The data reflects prescriptions that are written. Information regarding prescriptions dispensed and refills are not included..

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

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

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

POTENTIAL FOR TRANSMISSION OF INFECTIOUS AGENTS

In reference to CHMP guidance on reporting of suspected transmission of any infectious agent via a medicinal product [EMA/410/01 Rev 3], GSK can confirm that it complies with the requirements of this guidance document. Nucala 100 mg (lyophilized or liquid drug product) and Nucala 40mg liquid drug product do not contain excipients derived from animals. Raw materials used in the manufacturing process that are derived directly or indirectly from animal sources were assessed to have a negligible risk of Transmissible spongiform encephalopathy contamination and comply with (EMA/410/01 Rev. 3). In addition, adventitious agent testing, as well as process design and validation provide assurance that mepolizumab (lyophilized or liquid drug product) is free from non-virus and virus adventitious agents. Therefore, GSK does not consider that these products represents a risk to humans. The potential for transmission of infectious agents is expected to be very low for mepolizumab lyophilized or liquid drug product.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

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

This section is not applicable.

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

This section is not applicable.

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

This section is not applicable.

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

The table below summarizes the changes to the list of safety concerns

Table 14 Summary of changes to the list of safety concerns

EU-RMP version number	Changes to the list of safety concerns
EU-RMP 15.1	Removal of “Safety of mepolizumab in patients with organ- or life-threatening EGPA” as a missing information

In study MEA115921 (study to investigate the efficacy and safety of mepolizumab in the treatment of EGPA), participants with organ- or life-threatening EGPA were excluded. This exclusion was not due to concerns about potential difference in the safety profile in this patient population, but partly due to the multiple definitions of the severity of EGPA and organ- or life-threatening EGPA. The CHMP recommended, as part of procedure No. EMEA/H/C/003860/II/0036/G during the extension of the indication to include EGPA, that the “safety of mepolizumab in patients with organ- or life-threatening EGPA” to be included in the RMP as missing information.

Safety data from routine reviews of this missing information have not indicated any emerging safety trends or concerns.

While the SmPC provides guidance in Sections 4.2, 4.4, and 5.1 for prescribers regarding the exclusion of patients with organ- or life-threatening EGPA from the study, it also emphasizes the need for clinical judgment in determining whether mepolizumab treatment should be discontinued if life-threatening EGPA develops. Furthermore, there is no known reason to expect that the safety profile of mepolizumab would differ in patients with severe

organ or life-threatening EGPA and there is no specific approach to such patients while on mepolizumab treatment.

Given that there are no additional pharmacovigilance activities or risk minimization measures in place to further characterize this missing information, and in line with the PRAC recommendation as part of Procedure No. EMEA/H/C/003860/II/0071, the "Safety of mepolizumab in patients with organ- or life-threatening EGPA" has been removed as a missing information from the summary of safety concerns.

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

Mepolizumab data from the integrated PCSA studies (MEA112997, MEA115588, and MEA115575) includes both the 100 mg SC and the 75 mg IV dose, which is the corresponding dose based on the absolute bioavailability with similar PDs and efficacy. Data presented is from Integrated Summary of Safety for severe asthma submission.

In the completed severe asthma OLE studies (MEA115661, MEA115666, and 201312), the only dose of mepolizumab evaluated was the 100 mg SC dose. Data presented is from individual study reports.

Paediatric severe asthma data includes open label study 200363 (Parts A and B) in children ages 6- 11 years, and integrated data in adolescents, ages 12- 17 years from 4 placebo-controlled studies (MEA112997, MEA115575, MEA115588, and 200862). Data presented is from 200363 final study report and Mepolizumab paediatric extrapolation report GSK document 2017N323587_00.

For EGPA study MEA115921 that evaluated 300mg SC dose of mepolizumab the data presented is from the final study report.

For HES study 200622 and OLE study 205203 that evaluated 300mg SC dose of mepolizumab and study MHE100185 that evaluated 750mg IV dose the data presented is from the final study reports and Summary of Clinical Safety for HES submission.

For NP study 205687 that evaluated 100mg SC dose of mepolizumab and study MPP111782 that evaluated 750mg IV dose the data presented is from the final study reports and Summary of Clinical Safety for the CRSwNP submission.

The liquid drug product program investigating mepolizumab 100mg SC dose consisted of 3 open label studies: Study 204958 (PK comparability study) in adult healthy subjects, studies 204959 and 205667 (Real World Use studies) in subjects with severe asthma. No new safety concerns to those already identified with lyophilized drug product were identified with 100mg SC mepolizumab liquid drug product. Therefore, there are no updates to Section SVII.3. Detailed summary of the safety data from the mepolizumab liquid drug product program is provided in module M.2.7.4 Summary of Safety Procedure number EMEA/H/C/3860/X/0018.

Mepolizumab 40mg liquid drug product in safety syringe has not been evaluated in clinical studies since the formulation is identical to the 100mg liquid product, which has been

extensivity studied and therefore no clinical data is available for inclusion under Part II: Module SVII section.

SVII.3.1.1 Important Identified Risk: Systemic Reactions including anaphylaxis

A prospective targeted assessment of systemic reactions was implemented throughout the severe asthma clinical development programme. Investigators/site personnel were prospectively trained and provided reference materials on reaction definitions and differentiating characteristics. Additionally, a case report form -specific data collection form was used to collect signs and symptoms associated with these reactions and to ask the Investigator specifically if the reaction met the criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis [Sampson, 2006].

Over the course of the programme, the route of drug administration transitioned from intravenous to subcutaneous, which resulted in the implementation of the following modifications regarding the reporting and recording of systemic reactions:

- During study MEA112997, mepolizumab was administered intravenously. Investigators were trained to record the term 'infusion-related reaction' for systemic non-allergic reactions. If the reaction was assessed as 'allergic/hypersensitivity', the event was to be recorded as 'hypersensitivity reaction'. If a delayed hypersensitivity reaction occurred, investigators were trained to record the most appropriate descriptive term of the type of reaction (i.e., delayed or Type IV).
- For the remaining severe asthma studies MEA115588, MEA115575, MEA115666, MEA115661, 201312, 200862, 200363 and EGPA study MEA115921, mepolizumab was administered subcutaneously for the majority or all of the participating subjects; therefore, investigators were trained to report and record systemic reactions (which included systemic allergic/hypersensitivity reactions and systemic non-allergic reactions). Reporting and recording of delayed reactions was consistent with study MEA112997.
- In the HES study 200622 and 205203, and NP study 205687, mepolizumab was administered subcutaneously for all of the participating subjects; investigators were trained to record the most appropriate descriptive term or diagnosis for the event considered systemic reaction and to determine and record whether the reaction was either a 'systemic allergic/Type I hypersensitivity reaction' or a 'systemic other reaction'.
- In the HES study MHE100185, mepolizumab was administered intravenously for all the participating subjects and information for hypersensitivity/anaphylaxis was collected via targeted forms. Since data collection was different than in study 200622, it was not integrated with systemic reaction data from study 200622.
- In the NP study MPP111782 mepolizumab was administered intravenously for all the participating subjects and events were retrospectively evaluated by GSK to identify events considered to represent potential hypersensitivity reaction. Since

data collection was different than in study 205687, it was not integrated with systemic reaction data from study 205687.

Potential mechanisms:

Biopharmaceutical products may elicit ADA responses in patients treated with the drug. ADAs have the potential to elicit hypersensitivity reactions, though in most circumstances ADAs are of no clinical significance [Barbosa, 2007]. Such reactions are reported to be less common with humanized monoclonal antibodies [Campi, 2007] than with other biologicals/monoclonal antibodies. Potentially life-threatening reactions have occurred in patients receiving biologics, but are said to be rare [Campi, 2007].

Hypersensitivity reactions (Type 1) occur when upon initial exposure to a drug, specific IgE is produced which sensitizes mast cells located on cutaneous and mucosal surfaces, as well as on circulating basophils. The initial drug exposure generally does not trigger symptoms. However, upon re-exposure, the drug binds to the cell-bound IgE to stimulate release of inflammatory mediators (e.g., histamine, leukotrienes, prostaglandins). Mast cells also have the capacity to release cytokines, including TNF-α, via an IgE-dependent mechanism, which can further intensify the symptoms of a hypersensitivity reaction. Rarely, IgE-mediated hypersensitivity reactions have been reported on the first exposure to a biological agent (e.g., cetuximab) mediated by a pre-existing IgE that cross reacts [Chung, 2008]. While acute, serious hypersensitivity reactions typically occur within the first few hours of drug exposure, in up to 20% of cases (ranges reported in the literature of <1% to 20%), serious acute anaphylactic symptoms can have a biphasic nature. The onset of events of serious acute hypersensitivity reactions can range from 1-78 hours after the initial event, although most occur within 8 hours. In some cases, the initial event is too mild and/or non-specific to be identified as a hypersensitivity reaction. The second response may be less severe, similar to, or more severe than the original episode, and fatalities have been reported. There is no consensus as to whether therapeutic measures affect the incidence of a delayed reaction. There is also no consensus on the etiology of delayed acute hypersensitivity reactions, which are not fully understood [Tole, 2007]. Delayed-type, non-acute hypersensitivity reactions resembling serum-sickness-type reactions are also known to occur during treatment with monoclonal antibody therapies [Hansel, 2010], with infliximab [Grosen, 2013; Miheller, 2007; Gamarra, 2006], rituximab [Todd, 2007; Hellerstedt, 2003], and natalizumab [Hellwig, 2008] making up the majority of the reports in the literature. Serum-sickness type drug reactions are type III immune-complex reactions that generally occur 4-10 days following exposure to serum proteins or monoclonal antibodies [Hansel, 2010]. Acute urticaria and angioedema occur more commonly than morbilliform or scarlatiniform eruptions; polyarthritis, myalgias, polysnovitis, fever, and neuritis may occur. Symptoms are generally self-limited with discontinuation of offending agent, typically lasting 1-2 weeks [Porter, 19th edition].

Evidence source(s) and strength of evidence:

There have been reports of systemic allergic and allergic-like reactions including anaphylaxis in patients who received mepolizumab. Allergic reactions (including swelling of the face, lips, mouth or tongue; wheezing, difficulty in breathing or shortness of breath; low blood pressure with fainting, dizziness or light headedness; rash; and itchy raised

bumps or hives) have been reported in clinical trials with mepolizumab but these reactions have also been reported in people who received an injection of placebo.

Characterisation of the risk:

SEVERE ASTHMA

Severe Asthma PCSA Studies

Systemic Reactions:

Across all PCSA, the frequency of subjects with any 'systemic reaction' was 20/412 (5%) in the placebo group, 7/263 (3%) in the mepolizumab 100 mg SC group and 12/344 (3%) in the mepolizumab 75 mg IV group. Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 0.78 (95% CI: 0.42, 1.45) was calculated for overall 'systemic reactions'.

Across all PCSA studies, all systemic reactions (allergic/hypersensitivity and non-allergic) were reported as non-serious. Additionally, all reactions were reported as resolved with the exception of 2 subjects in the mepolizumab 75 mg IV group: 1 report of an infusion-related reaction and 1 report of Type IV hypersensitivity were both reported as unresolved at the final contact.

In the PCSA studies there have been no reports of fatal systemic reactions. The majority of 'systemic reactions' reported from the PCSA studies (55/74) were experienced on the day of dosing. Over time, the probability of experiencing a systemic (allergic and non-allergic) reaction was similar in the mepolizumab treatments compared with placebo. The estimated hazard ratio for all mepolizumab doses compared with placebo was 1.08 (95% CI 0.64, 1.81).

Across all PCSA studies, the majority of subjects reported any 'systemic reaction' as mild or moderate intensity.

Systemic Allergic/Hypersensitivity Reactions (HSR):

Across PCSA studies the frequency of subjects with any 'systemic allergic/hypersensitivity reaction' was 7/412 (2%) in the placebo group, 3/263 (1%) in the mepolizumab 100 mg SC group and 4/344 (1%) in the mepolizumab 75 mg IV group. As described previously in this section, a CMH adjusted relative risk of 0.62 (95% CI: 0.20, 1.88) was calculated for 'systemic allergic/hypersensitivity reactions'.

Across PCSA studies, 'systemic allergic/hypersensitivity reactions' were reported with mild to moderate intensity. There were no reports of severe 'systemic allergic/hypersensitivity reactions'.

Spontaneous post marketing reports of anaphylaxis have been received and anaphylaxis was included in the Special Warnings and Precautions section and in the Undesirable Effects section in the SmPC.

Systemic Non-Allergic Injection/Infusion Reactions:

Across PCSA studies the frequency of subjects with any 'systemic non-allergic reaction' was 14/412 (3%) in the placebo group, 4/263 (2%) in the mepolizumab 100 mg SC group and 9/344 (3%) in the mepolizumab 75 mg IV group. As described previously in this section, a CMH adjusted relative risk of 0.84 (95% CI: 0.40, 1.75) was calculated for 'systemic non-allergic reactions'.

Across PCSA studies, a small proportion of subjects across all groups reported mild to moderate intensity systemic non-allergic reactions. Systemic non-allergic reactions of severe intensity were reported in 2/344 (<1%) subjects in the mepolizumab 75 mg IV group and no subjects in either the placebo or mepolizumab 100 mg SC group.

Severe Asthma OLE Studies

In general, the nature and severity of systemic (allergic/non-allergic) reactions from the OLE studies were similar to that observed in the PCSA studies. All were non-serious, with the exception of one serious Type IV delayed hypersensitivity reaction from MEA115661. There were no reports of fatal systemic reactions, and no reports of anaphylaxis considered related to mepolizumab treatment from the OLE studies.

Paediatric Severe Asthma

200363 Part A

On- treatment AEs of Special Interest	Number (%) of Subjects		
	Mepo SC 40 mg (weight <40 kg) (N=26)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC (N=36)
Systemic reactions[1,2]	1 (4)	0	1 (3)
Allergic/ hypersensitivity	1 (4)	0	1 (3)
Non-allergic	0	0	0
Anaphylaxis	0	0	0

Source: 200363 Part A - CSR Table 25

1- Subjects may have more than one type of reaction.

2- As identified by the investigator in the electronic case report form designed for collecting data on systemic reactions.

One subject in the 40 mg group experienced an on-treatment systemic reaction which was a hypersensitivity reaction with the symptom of pruritus. The event was non-serious, mild in intensity, and resolved with continued mepolizumab treatment.

200363 Part B

On treatment AEs of Special Interest	Number (%) of Subjects			
	Mepo SC 40 mg (weight <40 kg) (N=16)	Mepo SC 100 mg (weight ≥40 kg) (N=10)	Mepo SC 40/100 mg[1] (N=4)	Mepo SC (N=30)
Systemic reactions[2,3]	1 (6)	1 (10)	0	2 (7)
Allergic hypersensitivity	1 (6)	1 (10)	0	2 (7)
Anaphylactic shock	1 (6)[4]	0	0	1 (3)
Rash generalized	0	1 (10)	0	1 (3)
Non-allergic	0	0	0	0

Source Data: 200363 Part B- CSR Table 42

- Subjects enrolled to <40 kg at Visit 9 are summarised in the 40/100 mg SC group if they had weight ≥40 kg at any subsequent visit.
- Subjects may have more than one type of reaction.
- As identified by the investigator in the electronic case report form designed for collecting data on systemic reactions.
- Considered by the investigator to represent systemic reaction meeting Sampson's criteria for anaphylaxis [Sampson, 2006]; this event was not considered to be related to mepolizumab treatment and was considered related to peanut allergy.

One subject in the 100 mg group experienced an on-treatment hypersensitivity reaction of rash generalized, with the associated symptoms of rash and pruritis. The event was non-serious, moderate in intensity, and considered related to mepolizumab treatment. The event resolved without mepolizumab interruption.

Integrated Adolescent Data

On- treatment AEs of Special Interest	Number (%) of Subjects	
	Placebo N=12	Mepolizumab All Doses N=25
Systemic reactions	0	1 (4)
Hypersensitivity reactions	0	0
Non-allergic reactions	0	1 (4)
Anaphylaxis	0	0

Source: Integrated adolescent data Table 2.39

One subject in the 100 mg SC group experienced an on-treatment systemic non-allergic reaction, with the reported symptom of headache. The event was non-serious, mild in intensity and resolved with continued mepolizumab treatment.

EGPA

Study MEA115921

SAEs/AEs of Special Interest	Number (%) of Subjects		Mepolizumab vs. Placebo	
	Placebo N=68	Mepolizumab 300 mg SC N=68	Relative Risk (95% CI)	% Risk Difference (95% CI)
Anaphylaxis considered related to study treatment by the investigator	0	0	---	---
Systemic Reactions Hypersensitivity Non-allergic	1 (1) 1 (1) 0	4 (6) 3 (4) 1 (1)	4.00 (0.46, 34.87) 3.00 (0.32, 28.13) ---	4.4 (-13.0, 21.7) 2.9 (-14.5, 20.2) ---

Note: A relative risk of 1 = no difference in risk between treatments, <1 favors mepolizumab, and >1 favors placebo

Of the 5 subjects reported systemic reactions, in the mepolizumab 300mg SC group, one reported a serious event of systemic hypersensitivity reaction. The event was considered related to study treatment by the investigator. Mepolizumab was discontinued. The investigator did not consider this event to have met the criteria for anaphylaxis.

All systemic reactions (allergic/hypersensitivity and non-allergic reactions) reported across both treatment groups were of mild intensity except for one severe event on mepolizumab of hypersensitivity, which was also serious and lead to treatment discontinuation.

Symptom of injection-related reaction (non-allergic) reported 18 days after the first dose of mepolizumab was angioedema.

HES

Study 200622

SAEs/AEs of Special Interest	Number (%) of Subjects		Mepolizumab vs. Placebo	
	Placebo N=54	Mepolizumab 300mg SC N=54	Relative Risk (95% CI)	% Risk Difference (95% CI)
Anaphylaxis considered related to study treatment by the investigator	0	0	---	---
Systemic Reactions Allergic/Type I Hypersensitivity Other systemic	0 0 0	1 (2) 0 1 (2)	---	1.9 (-17.7, 21.3) --- 1.9 (-17.7, 21.3)

Note: A relative risk of 1 = no difference in risk between treatments, <1 favors mepolizumab, and >1 favors placebo

There were no reports of anaphylaxis in the mepolizumab group and one subject on placebo reported two serious events of anaphylaxis (considered unrelated to study treatment by the investigator).

One subject in the mepolizumab group had an event considered by the investigator to represent systemic reactions and classified as other systemic reaction.

Study 205203

Study 205203 was an OLE study to study 200622 with 102 subjects who received mepolizumab 300mg SC every 4 weeks for up to 20 weeks.

There were no reports of anaphylaxis in this study. Three (3%) subjects reported events considered by the investigator to represent systemic reactions. All events were non-serious and considered to be drug related by the investigator.

Study MHE100185

There were no reports of anaphylaxis in this study.

There were 2 subjects (both on mepolizumab 750 mg IV) with reported hypersensitivity reactions.

NP

Study 205687

SAEs/AEs of Special Interest	Number (%) of Subjects		Mepolizumab vs. Placebo	
	Placebo N=201	Mepolizumab 100mg SC N=206	Relative Risk (95% CI)	% Risk Difference (95% CI)
Anaphylaxis considered related to study treatment by the investigator	0	0	---	---
Systemic Reactions	1 (<1%)	2 (<1%)	1.95 (0.18, 21.35)	0.5% (-9.3, 10.2)
Allergic/Type I Hypersensitivity	0	2 (<1%)	---	1.0% (-8.8, 10.7)
Other systemic	1 (<1%)	0	---	-0.5% (-10.2, 9.3)

Note: A relative risk of 1 = no difference in risk between treatments, <1 favors mepolizumab, and >1 favors placebo

There were no events of systemic reactions meeting Sampson's criteria for anaphylaxis, and no other events of anaphylaxis during the study.

All events of systemic reactions were non-serious, mild or moderate in intensity, considered related to study treatment by the investigator, resolved, and did not lead to discontinuation of study treatment and all subjects completed the study.

Study MPP111782

There were no events of anaphylaxis reported in this study. One event was considered to represent a potential hypersensitivity reaction. It was a non-serious event of toxic skin eruption after the 2nd dose of mepolizumab and was moderate in intensity, considered related to the study treatment by the investigator and led to permanent discontinuation of study treatment.

Risk factors and risk groups:

No risk groups or risk factors were identified during clinical trials in the severe asthma, EGPA, HES and CRSwNP populations.

Preventability:

The SmPC describes dosage and administration procedures in Section 4.2 (Posology and method of administration). Section 4.3 (Contraindication) states that hypersensitivity to mepolizumab or any of excipients is contraindicated. Section 4.4 (Special warnings and precautions for use) describes reports of systemic reactions received to date. Section 4.8 (Undesirable effects) lists "hypersensitivity reactions (systemic allergic)" and "administration-related reactions (systemic non allergic)" as common adverse reactions, and anaphylaxis with frequency rare and indicated that identified from spontaneous post-marketing reporting. The Patient Information Leaflet also describes possible reactions and advises patients when to notify their doctor.

Premedication was not required or recommended and was left to the discretion of the investigator.

Impact on the risk-benefit balance of the product:

Based on the current evidence the impact on risk-benefit balance is considered to be low.

Public health impact:

The potential public health impact is considered to be low.

SVII.3.1.2 Important Potential Risk: Alterations in immune response (malignancies)

Potential mechanisms:

The preclinical experience with mepolizumab does not support a pro-oncogenic effect. Given the targeted mechanism of action, the probability that mepolizumab confers a direct risk of malignancy mediated through general immunosuppression appears low.

Evidence source(s) and strength of evidence:

Certain white blood cell types have been implicated in tumor immune surveillance and the body's ability to fight cancer. The role of eosinophils in this process is unclear. However, since mepolizumab lowers eosinophils, which are a component of innate immunity, cancer is of potential concern in patients taking mepolizumab. The frequency of cancer was monitored in clinical studies with mepolizumab and to date was similar between the patients who received mepolizumab and those who received placebo. The types of cancer reported in clinical studies were similar to those occurring in general population.

Characterisation of the risk:

SEVERE ASTHMA

Severe Asthma PCSA Studies

Across all PCSA studies, neoplasms (both benign and malignant) were reported by 16 subjects with a similar frequency across treatment groups [9/412 (2%) in the placebo group; 7/915 (<1%) in the all doses of mepolizumab combined group]. Malignancies were reported by 3 subjects (<1%) in the placebo group and 1 subject each (<1%) in the mepolizumab 75 mg IV and 250 mg IV groups. The types of malignancies reported were those that are common in the general population and include basal cell carcinoma, basosquamous carcinoma, prostate cancer, squamous cell carcinoma, and uterine cancer. None of the types of malignancies were reported in more than one subject. There was no evidence of an increased probability of occurrence with increased exposure to mepolizumab treatments compared with placebo. The estimated hazard ratio for all mepolizumab doses compared with placebo was 0.40 (95% CI 0.06, 2.57).

Across all PCSA, there were 0 subjects in the placebo or any of the mepolizumab dose groups who reported a malignancy that resulted in a fatal outcome. The frequency of subjects with a non-fatal serious malignancy was 2/412 (<1%) in the placebo group (i.e., 1 basosquamous carcinoma and 1 prostate cancer) and 1/915 (<1%) in the mepolizumab all doses combined group (i.e., 1 uterine carcinoma).

Across all PCSA, the frequency of subjects in the placebo group with a malignancy reported an outcome of Resolved (3/412; <1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0). The frequency of subjects in the mepolizumab all doses combined group with a malignancy reported an outcome of Resolved (1/263; <1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (1/263; <1%) and Fatal (0).

Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 0.33 (95% CI: 0.04, 3.05) was calculated for overall malignancies. When all doses of mepolizumab that were evaluated in the PCSA program were combined (i.e., 100 mg SC, 75 mg IV, 250 mg IV and 750 mg IV) a CMH adjusted relative risk of 0.33 (95% CI 0.03, 3.50) was calculated for overall malignancies.

Across all PCSA, the frequency of subjects in the placebo group reporting a malignancy of mild intensity was 0 in the placebo group and 0 in the mepolizumab all doses combined group. Subjects reporting a malignancy of moderate intensity were 2/412 (<1%) in the placebo group and 1/915 (<1%) in the mepolizumab all doses combined group. Subjects reporting a malignancy of severe intensity were 1/412 (<1%) in the placebo group and 1/915 (<1%) in the mepolizumab all doses combined group.

Severe Asthma OLE Studies

In the three OLE studies, malignancies were similar in frequency (approximately 2% in each study) and type to those reported from the PCSA studies.

Paediatric Severe Asthma

No events of malignancy were reported in children in 200363 Parts A and B or in adolescents in the integrated PCSA study data.

EGPA

Study MEA115921

SAEs/AEs of Special Interest	Number (%) of Subjects		Mepolizumab vs. Placebo	
	Placebo N=68	Mepolizumab 300 mg SC N=68	Relative Risk (95% CI)	% Risk Difference (95% CI)
Neoplasms[1]	3 (4)	1 (1)	0.33 (0.04, 3.13)	-2.9 (-20.2, 14.5)
Malignancies[2]	2 (3)	0	---	---

[1]Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC
[2]Defined based on the pre-specified list of MedDRA preferred terms
Note: A relative risk of 1 = no difference in risk between treatments, <1 favors mepolizumab, and >1 favors placebo

Treatment emergent neoplasms (both benign and malignant) were colon adenoma in the mepolizumab group and lipoma, Bowen's disease, and testis cancer in the placebo group.

There were no malignancy events reported in the mepolizumab group.

One of the two malignancy events (testis cancer) reported in the placebo group was a serious AE. Both events of malignancy were reported as resolved during the study and none were fatal.

HES

Studies 200622 and MHE100185

SAE/AESI	Number (%) of Subjects						Mepolizumab vs Placebo	
	200622		MHE100185		Both studies			
	PBO N=54	Mepo 300 mg SC N=54	PBO N=42	Mepo 750 mg IV N=43	PBO N=96	Mepo all doses N=97	CMH-Adjusted Relative Risk (95% CI)[3]	%Risk Difference (Exact 95% CI)
Neoplasms [1]	2 (4)	0	0	2 (5)	2 (2.1)	2 (2.1)	0.99 (0.14, 7.10)	0.0 (-14.0, 14.0)
Malignancies [2]	1 (2)	0	0	1 (2)	1 (1.0)	1 (1.0)	0.99 (0.06, 16.06)	0.0 (-14.0, 14.0)

[1]Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC
[2] Identified from SMQs prespecified by the GSK Safety Review Team
[3]Calculated using the CMH method.

Treatment emergent neoplasms (both benign and malignant) were T-cell lymphoma and uterine leiomyoma in the placebo group, and basal cell carcinoma and skin papilloma in the mepolizumab group.

The malignancy reported in the mepolizumab group was basal cell carcinoma; the event was non-serious, of moderate intensity, resolved and did not lead to treatment discontinuation. In the placebo group it was T-cell lymphoma; the event was serious, of severe intensity, not resolved and led to permanent discontinuation from study treatment and withdrawal from the study.

OLE Study 205203

Malignancies were reported for 2 (2%) subjects. A non-serious event of Bowen's disease of moderate intensity and a serious event of peripheral T-cell lymphoma unspecified of severe intensity. Both events were considered not related to study treatment by the investigator, resolved and both occurred after last scheduled dose.

NP

Studies 205687 and MPP111782

SAE/AESI	Number (%) of Subjects						Mepolizumab vs Placebo	
	205687		MMM111782		Both studies			
	PBO N=201	Mepo 100 mg SC N=206	PBO N=52	Mepo 750 mg IV N=53	PBO N=253	Mepo all doses N=259	CMH-Adjusted Relative Risk (95% CI)[3]	% Risk Difference (Exact 95% CI)
Neoplasms [1]	3 (1)	5 (2)	0	0	3 (1.2)	5 (1.9)	1.63 (0.39, 6.72)	0.7% (-8.0, 9.4)
Malignancies [2]	2 (<1)	0	0	0	2 (0.8)	0	---	-0.8% (-9.5, 7.9)

[1]Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC
[2] Identified from SMQs prespecified by the GSK Safety Review Team
[3]Calculated using the CMH method.

Treatment emergent neoplasms (both benign and malignant) were basal cell carcinoma, rectal adenoma and renal neoplasm on placebo, and skin papilloma, benign vulval neoplasm, and uterine leiomyoma on mepolizumab.

Malignancies were reported in 2 subjects in the placebo group in Study 205687 (renal neoplasm and basal cell carcinoma), both were non-serious, not considered unrelated to study treatment by the investigator, and did not lead to discontinuation of study treatment.

Risk factors and risk groups:

No risk groups or risk factors were identified during clinical trials in the severe asthma, EGPA, HES and CRSwNP populations.

Preventability:

Patients with severe asthma typically may receive treatment concurrent immunosuppressive agents (e.g. corticosteroids) which may confer an increased risk of developing malignancy. There is no evidence that add-on treatment with Nucala altered the underlying risk.

Impact on the risk-benefit balance of the product:

Based on the current evidence the impact on the risk-benefit balance is considered to be low.

Public health impact:

Potential public health impact is considered to be low.

SVII.3.1.3 Important Potential Risk: Alterations in cardiovascular safety

Potential mechanisms:

Because of the size of most biologics, such as antibodies or other large molecule therapeutics (usually >140,000 d), cardiotoxicity resulting from direct hERG channel blockade is generally not a concern. As a result, their off-target electrophysiologic liabilities are limited and there is low risk for QT-mediated pro-arrhythmia.

No acute effects on cardiovascular function after single IV doses up to 100mg/kg in monkeys.

No adverse effects on cardiac conduction or repolarization were evident on single and repeat doses studies in cynomolgus monkeys at doses at least 50-fold in excess of the clinical dose (corresponding to 70-fold higher exposures in Cmax and AUC when compared to humans dosed at 2 mg/kg or 1000 mg.

Evidence source(s) and strength of evidence:

Effects on the heart and blood vessels were monitored during the studies with mepolizumab.

Overall, the effects on the heart and blood vessels were similar between patients receiving mepolizumab and those who received placebo. In one dose-ranging study in patients with severe asthma, effects on the heart occurred more often in patients receiving mepolizumab than those who received placebo. The finding from this study was not seen in other studies in patients with severe asthma or other diseases to date.

Characterisation of the risk:

SEVERE ASTHMA

Severe Asthma PCSA Studies

Cardiac Adverse Events:
Across all PCSA studies, the frequency of subjects with a cardiac AE (i.e., MedDRA Cardiac SOC) was 12/412 (3%) in the placebo group, 6/263 (2%) in the mepolizumab 100 mg SC group and 8/344 (2%) in the mepolizumab 75 mg IV group.

Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing

the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 0.82 (95% CI: 0.38, 1.77) was calculated for all cardiac AEs.

Serious Cardiac Adverse Events:

Across all PCSA, there were 0 subjects in the placebo, mepolizumab 100mg SC and mepolizumab 75 mg IV groups who reported a serious cardiac event that resulted in a fatal outcome. The proportion of subjects with a non-fatal serious cardiac event (reported in the MedDRA SOC of cardiac events) was 1/412 (<1%) in the placebo group, 1/263 (<1%) in the mepolizumab 100 mg SC group and 2/344 (<1%) in the mepolizumab 75 mg IV group.

Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 2.69 (95% CI: 0.25, 28.58) was calculated for serious cardiac events.

Serious Cardiac, Vascular and Thromboembolic Adverse Events:

Across all PCSA, there were 3/412 (<1%) subjects in the placebo group, 1/263 (<1%) subjects in the mepolizumab 100mg SC group and 4/344 (1%) subjects in the mepolizumab 75 mg IV group who reported an event categorized as serious CVT event through medical review of all SAEs.

Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 1.57 (95% CI: 0.25, 28.58) was calculated for serious cardiac events.

Across all PCSA, there were 0 subjects in the placebo, mepolizumab 100mg SC group and mepolizumab 75 mg IV group who reported a serious CVT or ischemic event that resulted in a fatal outcome.

Across all PCSA, the frequency of subjects in the placebo group with a serious CVT event reporting an outcome of Resolved (3/412; <1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0). The frequency of subjects in the mepolizumab 100 mg SC group with a serious CVT event reporting an outcome of Resolved (1/263; <1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0). The frequency of subjects in the mepolizumab 75 mg IV group with a serious CVT event reporting an outcome of Resolved (4/344; 1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0).

Across all PCSA, the frequency of subjects in the placebo group reporting a serious CVT event of mild intensity was 0 in the placebo group and 0 in both the mepolizumab 100mg and mepolizumab 75 mg IV groups. Subjects reporting a serious CVT event of moderate intensity were 1/412 (<1%) in the placebo group, 0 in the mepolizumab 100mg SC group

and 2/344 (<1%) in the mepolizumab 75 mg IV group. Subjects reporting a serious CVT event of severe intensity were 2/412 (<1%) in the placebo group, 1/263(<1%) in the mepolizumab 100mg SC group and 2/344 (<1%) in the mepolizumab 75 mg IV group.

Serious Ischemic Adverse Events:

Across all PCSA, there were 2/412 (<1%) subjects in the placebo group, 0 subjects in the mepolizumab 100mg SC group and 2/344 (<1%) subjects in the mepolizumab 75 mg IV group who reported an event categorized as a serious ischemic event.

Because the systemic exposure of mepolizumab 100 mg SC and mepolizumab 75 mg IV are similar, the doses were combined to evaluate relative risk. The relative risk comparing the frequency of events for the combined mepolizumab doses (i.e., 100 mg SC and 75 mg IV) to placebo was calculated using the CMH method together with 95% CIs. A CMH adjusted relative risk of 1.01 (95% CI: 0.14, 7.10) was calculated for serious ischemic events.

Across all PCSA, the frequency of subjects in the placebo group with a serious ischemic event reporting an outcome of Resolved (0), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0). The frequency of subjects in the mepolizumab 100 mg SC group with a serious ischemic event reporting an outcome of Resolved (0), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0). The frequency of subjects in the mepolizumab 75 mg IV group with a serious ischemic event reporting an outcome of Resolved (2/344; <1%), Resolving (0), Resolved with Sequelae (0), Not Resolved (0) and Fatal (0).

Severe Asthma OLE Studies

In the three OLE studies, the nature and exposure adjusted rates of cardiac events were similar to those reported from the PCSA studies.

Paediatric Severe Asthma

200363 Part A

No on- treatment events in the Cardiac Disorders SOC, or Serious CVT or ischaemic events were reported in Parts A or B of this study.

Integrated Adolescent Data

No on-treatment serious events in the Cardiac Disorders SOC, or Serious CVT or ischaemic events were reported by adolescent subjects. One subject in the placebo group (1/12, 8%) reported an on-treatment non-serious event in the Cardiac Disorders SOC (palpitations) of mild intensity and with an outcome of recovered/resolved.

EGPA

Study MEA115921

SAEs/AEs of Special Interest	Number (%) of Subjects		Mepolizumab vs. Placebo	
	Placebo N=68	Mepolizumab 300 mg SC N=68	Relative Risk (95% CI)	% Risk Difference (95% CI)
Cardiac disorders[1]	6 (9)	4 (6)	0.67 (0.20, 2.26)	-2.9 (-20.2, 14.5)
Serious cardiac disorders	2 (3)	1 (1)	0.50 (0.05, 5.39)	-1.5 (-18.8, 15.9)
Serious CVT events[2]	2 (3)	2 (3)	1.00 (0.15, 6.90)	-0.0 (-17.4, 17.4)
Serious ischemic events[2]	2 (3)	1 (1)	0.50 (0.05, 5.39)	-1.5 (-18.8, 15.9)

[1]Cardiac disorders SOC
[2]Defined based on the pre-specified list of MedDRA preferred terms
CVT = cardiac, vascular, and thromboembolic
Note: A relative risk of 1 = no difference in risk between treatments, <1 favors mepolizumab, and >1 favors placebo

Serious CVT events:

All events reported across both treatment groups were of severe intensity except for an event of lacunar infarction reported in mepolizumab 300mg SC group which was considered of moderate intensity. All four subjects who experienced serious CVT AEs had a cardiovascular history or risk. All events except one (fatal event described below) reported across both treatment groups resolved during the study while continuing treatment.

One event in mepolizumab 300mg SC group had fatal outcome in subject with past medical history of coronary artery disease and supraventricular tachycardia. The underlying cause of death was coronary artery disease.

Independent adjudication of the fatal case was completed

HES

Studies 200622 and MHE100185

SAE/AESI	Number (%) of Subjects						Mepolizumab vs Placebo	
	200622		MHE100185		Both studies			
	PBO N=54	Mepo 300 mg SC N=54	PBO N=42	Mepo 750 mg IV N=43	PBO N=96	Mepo all doses N=97	CMH-Adjusted Relative Risk (95% CI)[4]	% Risk Difference (Exact 95% CI)
Cardiac Disorders [1]	2 (4)	4 (7)	3 (7)	3 (7)	5 (5.2)	7 (7.2)	1.38 (0.46, 4.20)	2.0 (-12.0, 16.1)
Serious Cardiac Disorders	1 (2)	1 (2)	0	1 (2)	1 (1.0)	2 (2.1)	1.99 (0.18, 21.75)	1.0 (-13.0, 15.0)
Serious CVT Events [2]	2 (4)	2 (4)	0	1 (2)	2 (2.1)	3 (3.1)	1.49 (0.26, 8.74)	1.0 (-13.0, 15.0)
Serious Ischemic Events [3]	0	0	0	0	0	0	---	---

1. Cardiac Disorders SOC
2. Identified from SMQs prespecified by the GSK Safety Review Team.
3. Subset of serious CVT events identified through SMQs prespecified by the GSK Safety Review Team.
4. Calculated using the CMH method.

Serious CVT events:

In the mepolizumab group 2 events were of severe and one of mild intensity, two events resolved and one had fatal outcome (described below) and two subjects did not discontinue treatment due to the event. In the placebo group one event was of moderate and one of severe intensity, both events resolved and did not lead to treatment discontinuation.

One subject (mepolizumab 750mg IV) had a fatal cardiac arrest 110 days after the 1st dose, which was not considered drug-related by the investigator.

OLE Study 205203

No serious CVT were reported in this study.

NP

Studies 205687 and MPP111782

SAE/AESI	Number (%) of Subjects						Mepolizumab vs Placebo	
	205687		MPP111782		Both studies			
	PBO N=201	Mepo 100mg SC N=206	PBO N=52	Mepo 750 mg IV N=53	PBO N=253	Mepo all doses N=259	CMH-Adjusted Relative Risk (95% CI)[4]	% Risk Difference (Exact 95% CI)
Cardiac Disorders [1]	3 (1)	1 (<1)	2 (4)	1 (2)	5 (2.0)	2 (0.8)	0.39 (0.08, 1.99)	-1.2% (-9.9,7.5)
Serious Cardiac Disorders	0	1 (<1)	0	0	0	1 (0.4)	---	0.4% (-8.3, 9.1)
Serious CVT Events [2]	2 (<1)	1 (<1)	0	0	2 (0.8)	1 (0.4)	0.49 (0.04, 5.34)	-0.4% (-9.1,8.3)
Serious Ischemic Events [3]	1 (<1)	1 (<1)	0	0	1 (0.4)	1 (0.4)	0.98 (0.06, 15.49)	0.0% (-8.7, 8.7)

1. Cardiac Disorders SOC
2. Identified from SMQs prespecified by the GSK Safety Review Team.
3. Subset of serious CVT events identified through SMQs prespecified by the GSK Safety Review Team.
4. Calculated using the CMH method.

Serious CVT Events:

On-treatment serious CVT events were reported in 3 subjects (2 subjects with one event each in the placebo group and 1 subject with 6 events in the mepolizumab group), all in Study 205687.

In the mepolizumab group 6 events were reported for 1 subject: two of severe and four of moderate intensity, all events resolved and one (PT of myocardial infarction) resulted in treatment interruption due to the event. None of the events were considered related to study treatment by the investigator.

In the placebo group both events were of severe intensity, resolved and did not lead to treatment discontinuation.

One subject in the placebo group had a post treatment fatal event of myocardial infarction reported (99 days after last placebo administration).

Risk factors and risk groups:

No risk groups or risk factors were identified during clinical trials in the severe asthma, EGPA, HES and CRSwNP populations.

Preventability:

There is no evidence to support that treatment with mepolizumab would have an additive or synergistic effect on pre-existing cardiovascular disease.

Impact on the risk-benefit balance of the product:

Based on the current evidence the impact on the risk-benefit balance is considered to be low.

Public health impact:

Potential public health impact is considered to be low.

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing Information: Limited data in pregnant and lactating patients

Evidence Source:

Non-clinical studies showed no effects of antagonism of IL-5 on reproductive function, pregnancy, or embryo-foetal or postnatal development. Mepolizumab was excreted into the milk of cynomolgous monkeys at concentrations that were less than 0.5% of those detected in plasma. There are no fertility data in humans and effect of mepolizumab on human pregnancy is unknown. There are also no data regarding the excretion of mepolizumab in human milk.

The Mepolizumab Pregnancy Exposure Study (a VAMPSS post marketing surveillance study of Mepolizumab safety in pregnancy) completed on 22 July 2024. It was a

prospective, observational, exposure cohort study of pregnancy outcomes in women exposed to mepolizumab during pregnancy compared to pregnancy outcomes in women with a diagnosis of asthma who have not used mepolizumab during pregnancy but have used other anti-asthmatic medications (treated disease comparison group), and pregnancy outcomes in women not diagnosed with asthma (non-disease comparison group). The study aimed to further evaluate the safety profile of mepolizumab during pregnancy.

Key Results

Of the 291 participants enrolled in this prospective cohort study, 23 were enrolled in the mepolizumab exposed cohort, 136 in the disease-matched unexposed cohort, and 132 in the non-diseased unexposed cohort.

Among the mepolizumab-exposed pregnancies that were enrolled in the cohort, excluding those lost to follow-up, there were 2/17 with a major birth defect (relative to 8/111 in the disease-matched unexposed cohort and 8/109 in the non-diseased matched unexposed cohort), one spontaneous abortion (relative to 2/63 in the diseased-matched unexposed cohort and none in the non-diseased unexposed cohort), and among pregnancies ending in liveborn singletons, no preterm deliveries (relative to 8/105 in the diseased-matched unexposed cohort and 7/96 in the non-diseased unexposed cohort). By definition, approximately 10% of infants were expected to meet the criteria for SGA at delivery due to the normal distribution of infant size. In the mepolizumab-exposed cohort, >10% of liveborn singletons were SGA on weight and head circumference: 2/15 infants SGA on weight and 1/6 on head circumference. In the disease-matched unexposed cohort, >10% of liveborn singletons were SGA on head circumference: 10/81 infants SGA on head circumference. In the non-diseased unexposed cohort, no infants were >10% SGA on weight, length or head circumference measurements. There were no stillbirths in the mepolizumab-exposed cohort (1 in the non-diseased unexposed cohort). There was 1 elective termination in the mepolizumab-exposed cohort (compared to none in either the diseased unexposed cohort or the non-diseased unexposed cohort).

Adverse Events/Adverse Reactions

Two study AEs with possible causality with exposure to mepolizumab were reported (defined per the patient population and study period specified in the protocol). One participant went to the emergency room for irregular breathing and influenza. A second participant reported migraines, which were assessed to have possible causality with exposure to mepolizumab.

Conclusion

Based on very small numbers in this prospective safety study, there was no evidence of a pattern of major structural birth defects in the mepolizumab-exposed cohort. There were no stillbirths, one spontaneous abortion, one elective termination, and no preterm deliveries. Data were limited but not suggestive of an increased risk for growth deficiency. In summary, no patterns were detected; however, the sample size was too small to draw conclusions about the safety of mepolizumab in pregnancy.

The VAMPSS external Scientific Advisory Board reviewed the final analysis report and concurred with the conclusions of the investigators.

Population in need of further characterisation:

Pregnant and breast-feeding women were excluded from clinical studies with mepolizumab. 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 22 July 2024, 42 pregnancies were reported from the completed and ongoing mepolizumab studies (all indications). Of the 42 pregnancies, two pregnancies were reported for the female partners of study participants: 1 on placebo which resulted in a spontaneous abortion (Study SB-240563/035), 1 on mepolizumab 100 mg SC which resulted in live birth with congenital anomaly (Study 201312). Of the remaining 40 pregnancies, 4/40 subjects were blinded, and 3/40 subjects were on placebo.

Pregnancy exposures and outcomes is monitored through routine pharmacovigilance with enhanced data collection (see Part III.1). No new significant information from post-marketing reports of exposure during pregnancy have been identified that would allow further characterization of mepolizumab use in pregnant or lactating patients.

SVII.3.2.2 Missing Information: Safety of mepolizumab in children with EGPA

Evidence Source:

In GSK studies in EGPA participants, MEA115921 and the long-term access program (MEA116841 and 201607), subjects less aged 17 or under were not included.

Paediatric EGPA, or childhood-onset EGPA defined as EGPA cases with an age <18 years at diagnosis, is rare, with only about 100 cases identified in the literature between 1951 and 2020.

Population in need of further characterisation:

Subjects less aged 17 or under were not included in GSK studies in EGPA participants: MEA115921 and the long-term access program (MEA116841 and 201607; for participants who had taken part in study MEA115921).

As discussed in the paediatric extrapolation report for EGPA indication (GSK document number 2017N313864_01), a total of 173 paediatric patients with severe asthma, HES and Eosinophilic esophagitis (EoE) have been exposed to mepolizumab, at doses equivalent to, or higher than, doses proposed for paediatric patients with EGPA. The clinical trial data show that the safety profile of mepolizumab in children and adolescents with severe eosinophilic asthma was similar to that of the overall adolescent and adult population. The safety profile of mepolizumab in paediatric patients is further informed by the experience in HES and EoE. To date, no new safety issues have been identified in paediatric patients

in any indication compared to adults. Non-clinical toxicology studies showed no evidence of reproductive or postnatal developmental effects of mepolizumab.

A post-marketing study is ongoing to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 15 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Systemic Reactions including anaphylaxis
Important potential risks	Alterations in immune response (malignancies) Alterations in cardiovascular safety
Missing information	Limited data in pregnant and lactating patients Safety of mepolizumab in children with EGPA

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required.

Specific adverse reaction follow-up questionnaires for:

Identified Risk of Systemic Reactions including anaphylaxis

A standard targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis.

Potential Risk of Alterations in cardiovascular safety:

Targeted follow-up questionnaires to collect data on Myocardial infarction /Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism.

Routine pharmacovigilance supplemented with enhanced data collection for mepolizumab pregnancy exposure

Pregnancy exposures and outcomes are continually monitored through routine pharmacovigilance. As of 22 July 2024, based on data from clinical studies and post-marketing reports, there are approximately 461 exposures to mepolizumab during pregnancy, with 159 documented pregnancy outcomes. Based on pre-clinical data, and the available clinical and post-marketing data to date, no safety signal in pregnancy has been observed.

In light of the closure of study 200870, GSK has added enhanced data collection to the routine pharmacovigilance process. The routine pharmacovigilance process aims to collect key maternal pregnancy information (e.g. relevant maternal medical history) and pregnancy outcome information. For pregnancies with mepolizumab exposure, the enhanced data collection will allow additional important variables and confounding factors specified in study 200870, as well as other key information, to be collected (e.g. relevant maternal lifestyle factors; see table below). Importantly, as done in study 200870, the enhanced data collection process will aim to collect infant information at 12 months post-partum, with requests for medical records from healthcare provider(s).

Per the routine pharmacovigilance process, any in-stream data collected for pregnancies and outcomes will be evaluated for signals on an ongoing basis, and any confirmed risks will be actioned and summarised in the PSUR as appropriate.

Variables for collection for pregnancies with mepolizumab exposure

Maternal demographic details	Prenatal imaging and aneuploidy screening/testing
Maternal medical history	Previous pregnancies and their outcomes
Relevant family history	Pregnancy outcome
Maternal pre-natal medications	Neonate parameters (e.g. weight)
Maternal adverse events	Medications given to neonate
Relevant maternal lifestyle factors	Infant/foetal adverse events
Relevant maternal pre-specified medical conditions	Infant follow-up at 12 months (including development progress and medical conditions)

The above enhanced data collection for pregnancies and outcomes following mepolizumab exposure aims to collect additional data compared to conventional spontaneous reports and to collect some important variables similar to those specified in study 200870.

III.2 Additional pharmacovigilance activities

Study 218065 (PASS: Real-World Safety and Effectiveness of NUCALA in Paediatric EGPA Patients in Europe)

Title: A post-authorisation safety study (PASS) to describe real-world safety and effectiveness of NUCALA (mepolizumab) in paediatric EGPA patients in Europe.

RATIONALE AND STUDY OBJECTIVES:

To address a request from EMA's CHMP to generate data for mepolizumab in the post-marketing setting in paediatric patients aged 6 to 17 years in Europe, this study aims to collect information on the real-world safety and effectiveness in paediatric EGPA patients treated with mepolizumab from sites across Europe in a case-series.

The primary objective of this study is to describe the real-world safety of mepolizumab treatment in paediatric EGPA patients aged 6 to 17 years in terms of AEs, SAEs, pregnancy exposures and medical device incidents.

The secondary objectives of this study are:

• To describe the real-world effectiveness of mepolizumab treatment in terms of the effect of mepolizumab on OCS dosage.

• To describe paediatric EGPA patients treated with mepolizumab per routine clinical care in terms of demographics, clinical characteristics, medical and treatment history.

STUDY DESIGN:

This multinational, multi-site, case-series will aim to collect data on real-world safety and effectiveness up to 24 months after the initiation of mepolizumab treatment in paediatric EGPA patients in Europe. In addition, demographic and relevant medical history data will be collected up to 12 months prior to the first dose of mepolizumab.

STUDY POPULATION:

Evaluable paediatric EGPA patients aged 6-17 years who already initiated mepolizumab treatment in the 12 months prior to the enrolment start date or who will initiate mepolizumab treatment after enrolment start date as part of routine clinical care from specialised centres and hospitals known to treat paediatric EGPA patients in Europe.

MILESTONES:

Milestone	Planned date
Final report of study results	31 Dec 2029

III.3 Summary Table of additional Pharmacovigilance activities

Table 16 On-going and planned additional pharmacovigilance activities

StudyStatus	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances				
None				
Category 3- Required additional pharmacovigilance activities				
218065 A post-marketing study to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA	To evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA	Use in children aged 6 – 17 years	Final Report	31 Dec 2029

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None proposed.

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 17 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Safety concern 1 Systemic reactions including anaphylaxis	**Routine risk communication:** The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions and Section 4.8 (Undesirable effects). Equivalent wording is included in the patient leaflet Section 2 and Section 4.
Safety concern 2 Potential Risk of Alterations in immune response (malignancies)	**Routine risk communication:** None
Safety concern 3 Potential Risk of Alterations in cardiovascular safety	**Routine risk communication:** None
Safety concern 4 Limited data in pregnant and lactating 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 on NUCALA.
Safety concern 5 Safety of mepolizumab in children with EGPA	**Routine risk communication:** SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children.

V.2. Additional Risk Minimisation Measures

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

V.3 Summary of risk minimisation measures

Table 18 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety concern 1 Systemic reactions including anaphylaxis	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects). Equivalent wording is included in the patient leaflet Section 2 and Section 4. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: A targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis. **Additional pharmacovigilance activities**: None
Safety concern 2 Potential Risk of Alterations in immune response (malignancies)	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Safety concern 3 Potential Risk of Alterations in cardiovascular safety	**Routine risk minimisation measures:** None proposed **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** To further evaluate this potential risk targeted follow-up questionnaires to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		Additional pharmacovigilance activities: None
Safety concern 4 Limited data in pregnant and lactating patients	**Routine risk minimisation measures:** The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available on NUCALA. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Enhanced data collection aimed at capturing key variables for further characterization **Additional pharmacovigilance activities:** None.
Safety concern 5 Safety of mepolizumab in children with EGPA	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** A post-marketing study to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Nucala (mepolizumab)

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

Nucala's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Nucala should be used.

This summary of the RMP for Nucala 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 EPAR.

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

I. The medicine and what it is used for

Nucala is authorised as an add-on treatment for severe refractory eosinophilic asthma in adult, adolescents and children aged 6 years and older.

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory EGPA.

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled HES without an identifiable non-haematologic secondary cause.

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

See SmPC for further indication information, dose and method of administration.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

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

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

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Nucala is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nucala 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 Nucala. 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	Systemic Reactions including anaphylaxis
Important potential risks	Alterations in immune response (malignancies) Alterations in cardiovascular safety
Missing information	Limited data in pregnant and lactating patients Safety of mepolizumab in children with EGPA

II.B Summary of important risks

Important identified risk: Systemic Reactions including anaphylaxis	
Evidence for linking the risk to the medicine	There have been reports of systemic reactions including anaphylaxis in patients who received mepolizumab. Allergic reactions (including swelling of the face, lips, mouth or tongue; wheezing, difficulty in breathing or shortness of breath; low blood pressure with fainting, dizziness or light headedness; rash; and itchy raised bumps or hives) have been reported in clinical trials with mepolizumab but these reactions have also been reported in people who got an injection of placebo.
Risk factors and risk groups	No risk groups or risk factors were identified during clinical trials in the severe asthma, EGPA, HES and NPs population.
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects). Equivalent wording is included in the patient leaflet Section 2 and Section 4. **Additional risk minimisation measures:** None

Important potential risk: Alterations in immune response (malignancies)	
Evidence for linking the risk to the medicine	Certain white blood cell types have been implicated in tumor immune surveillance and the body's ability to fight cancer. The role of eosinophils in this process is unclear. However, since mepolizumab lowers eosinophils, which are a component of innate immunity, cancer is of potential concern in patients taking mepolizumab. The frequency of cancer was monitored in clinical studies with mepolizumab and to date was similar between the patients who received mepolizumab and those who received placebo. The types of cancer were similar to those occurring in general population.
Risk factors and risk groups	No risk groups or risk factors were identified during clinical trials in the severe asthma EGPA, HES and NPs population.
Risk minimisation measures	No risk minimisation measures
Important potential risk: Alterations in cardiovascular safety	

Evidence for linking the risk to the medicine	Effects on the heart and blood vessels were monitored during the studies with mepolizumab. Overall, the effects on the heart and blood vessels were similar between patients receiving mepolizumab and those who received placebo. In one dose-ranging study in patients with severe asthma, effects on the heart occurred more often in patients receiving mepolizumab than those who received placebo. The finding from this study was not seen in other studies in patients with severe asthma, EGPA, HES or NPs.
Risk factors and risk groups	No risk groups or risk factors were identified during clinical trials in the severe asthma EGPA, HES and NPs population.
Risk minimisation measures	No risk minimisation measures

Missing information: Limited data in pregnant and lactating patients	
Risk minimisation measures	**Routine risk minimisation measures:** The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises prescribers on the non-clinical reproductive toxicity data available on NUCALA. **Additional risk minimisation measures:** None

Missing information: Safety of mepolizumab in children with EGPA	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** A post-marketing study to evaluate the safety and effectiveness of mepolizumab in children aged 6 – 17 years with EGPA.

II.C Post-authorisation development plan

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

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

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

Study 218065 (PASS: Real-World Safety and Effectiveness of NUCALA in Paediatric EGPA Patients in Europe)

The purpose of this study is to address a request from EMA's CHMP to generate data for mepolizumab in the post-marketing setting in paediatric patients aged 6 to 17 years in Europe, this study aims to collect information on the real-world safety and effectiveness in paediatric EGPA patients treated with mepolizumab from sites across Europe in a case-series.

The primary objective of this study is to describe the real-world safety of mepolizumab treatment in paediatric EGPA patients aged 6 to 17 years in terms of AEs, SAEs, pregnancy exposures and medical device incidents.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following Targeted Follow-up Questionnaires are provided:

Hypersensitivity/Anaphylaxis (Brighton) targeted follow up form

Mepolizumab Cerebrovascular events, stroke (CVA) and transient ischemic attack (TIA) targeted follow up form

Mepolizumab Deep vein thrombosis (DVT), pulmonary embolism (PE) targeted follow up form

Mepolizumab Myocardial infarction (MI), unstable angina (UA) targeted follow up form

Mepolizumab Peripheral arterial thromboembolism targeted follow up form

GSK

Targeted Follow Up Questionnaire for
Mepolizumab
HYPERSENSITIVITY/ANAPHYLAXIS (Brighton)

Patient age, gender, initials:	**Sex/weight (is patient obese if weight unknown):**	**GSK CASE No:**
Lot Number & Expiration date:		

Does the event fall under the following:

	Yes	**No**
Did it suddenly develop? If yes, please provide the time from administration of the suspect drug to the onset (sec/min/hr/day):	☐	☐
Did signs and symptoms rapidly progress? If yes, please provide the time from the onset to the final outcome (sec/min/hr/day):	☐	☐
Were the following organ system symptoms involved? (please tick all that apply)	☐	☐

Major criteria (tick all that apply)	**Minor criteria (tick all that apply)**

[Cutaneous symptom/mucosal symptom]

☐ Generalized urticaria (hives)
☐ Generalized erythema
☐ Localized angioedema (excluding hereditary)
☐ Generalized angioedema
☐ Generalized pruritus with skin rash

[Cardiovascular symptom]

☐ Decreased blood pressure
(☐ Blood pressure measured, ☐ Not measurable)
☐ Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
- ☐ Tachycardia
- ☐ Capillary refill time >3 s
- ☐ Reduced central pulse pressure (femoral artery, carotid artery, etc.)
- ☐ Decreased level of consciousness (JCS: digits)
- ☐ Loss of consciousness

[Respiratory symptom]

☐ Bilateral wheezing
☐ Bronchospasm
☐ Stridor
☐ Upper airway swelling (lip, tongue, throat, uvula, larynx)

Respiratory distress—2 or more of the following:
- ☐ Tachypnoea
- ☐ Increased use of accessory respiratory muscles (sternocleidomastoid, intercostal, etc.)
- ☐ Retractive breathing
- ☐ Cyanosis
- ☐ Grunting (hoarse voice, creaky voice)

[Cutaneous symptom/ mucosal symptom]

☐ Generalized pruritus without skin rash
☐ Generalized prickle sensation
☐ Injection site urticaria
☐ Painful red eyes

[Cardiovascular symptom]

☐ Reduced peripheral circulation as indicated by the combination of at least 2 of the following:
- ☐ Tachycardia and
- ☐ Capillary refill time of >3 s without hypotension
- ☐ Depressed level of consciousness (JCS: digit)

[Respiratory symptom]

☐ Persistent dry cough
☐ Hoarseness
☐ Wheezing
☐ Difficulty breathing without stridor
☐ Sensation of throat closure
☐ Sneezing
☐ Nasal discharge

[Gastrointestinal symptom]

☐ Diarrhea
☐ Abdominal pain
☐ Nausea
☐ Vomiting

Source: Rüggeberg JU et al. Brighton Collaboration Anaphylaxis Working Group. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007 Aug 1;25(31):5675-84. Epub 2007 Mar 12.

Please tick all allergy-related symptoms observed in the patient other than the above (Tick all that apply).

☐ Facial edema	☐ Hypotension causing dizziness	☐ Hypotension causing collapse	☐ Coombs positive hemolytic anemia
☐ Evidence of bone marrow suppression (☐ Agranulocytosis; ☐ Fever; ☐ Thrombocytopenia; ☐ Anemia)			
☐ Arthropathy	☐ Lymphadenopathy	☐ Proteinuria	☐ Eosinophilia
☐ Skin rash	☐ Contact dermatitis	☐ Other, please specify:	

History (Please attach a copy of the patient's medication history):

	Yes	No
Status of allergic reaction to other drugs (please provide the details below)	☐	☐

Drug history (orally	<Name of drug>	Start date of treatment (YYYY/MM/DD)	Date of final/last dose (YYYY/MM/DD)

administered and/or injected dugs in the past several months			
Any other relevant information:			

Diagnostic Tests: (Please tick all that apply and provide the test results in detail, and/or provide a copy of clinical laboratory test results)

☐ Laboratory tests including full blood count/ Coombs Test	Attached ☐
☐ ECGs- baseline and after onset of adverse event	Attached ☐
☐ Bone marrow aspiration	Attached ☐
☐ De-challenge/Re-challenge results	Attached ☐
☐ Skin biopsy	Attached ☐
☐ Other: please list	Attached ☐

<Test content>	<Date/Test Results>

Outcome of the Event:

	Yes	No
Did the patient make a full recovery? (If no, please provide the details below)	☐	☐

Please fill in the below regarding the details, including the clinical course from the start of medication to the onset of the event(s), the final outcome, and any procedures/treatments given.

	Details/Date/Time (YYYY/MM/DD; XX:XX)
Date and time, amount of the last dose (all drugs)	
Date and time of onset of the event	
Duration/course of the event	

Course until the final outcome	
Treatment: ☐ No ☐ Yes	

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

Targeted Follow Up Questionnaire for

Mepolizumab
CEREBROVASCULAR EVENTS STROKE (CVA) AND TRANSIENT ISCHEMIC ATTACK (TIA)

Patient/Subject ID: DOB/Initials:	Sex/weight (is patient obese if weight unknown): Sex: Female ☐ Male ☐ Obese? Yes ☐ No ☐ Weight	Safety Database CASE No:

Lot Number & Expiration date (*for post-marketing reports only*):

History and/or clinical examination which clearly defines the new onset of focal or global Neurological deficit?		Yes ☐	No ☐
Newly defined brain lesion consistent with signs and symptoms? *If Yes, describe:*	Unknown ☐	☐	☐

DESCRIPTION OF EVENT:

Date of Onset of Symptoms: ☐☐ ☐☐ ☐☐ (Day Month Year)

Date of Resolution of Symptoms: ☐☐ ☐☐ ☐☐ (Day Month Year)

Was event related to occurrence of arrhythmia(s)?	☐	☐
Was event due to trauma?	☐	☐

SYMPTOMS:	Yes	No
Motor and/or sensory loss in face, arm, leg <u>right</u> side?: *If Yes record details::*	☐	☐
Motor and/or sensory loss in face, arm, leg <u>left</u> side *If Yes record details:*	☐	☐
	Yes ☐	No ☐

Dysphasia/Aphasia (difficulty with language) *If Yes record details:*		
Dysarthria/Dysphagia (difficulty with speech and swallowing) *If Yes record details:*	☐	☐
Hemianopsia/Dizziness/Vertigo *If Yes record details:*	☐	☐
Ataxia *If Yes record details:*	☐	☐
Nystagmus *If Yes record details:*	☐	☐
Diplopia *If Yes record details:*	☐	☐
Acute confusion/cognitive change *If Yes record details:*	☐	☐
Decreased consciousness *If Yes record details:*	☐	☐

Did subject have abnormal neurologic exam or history prior to event? *If Yes record details:*	Yes ☐	No ☐

BRAIN IMAGING

	Yes	No
Was a CT Scan performed	☐	☐
If *Yes*, date of the CT scan: ☐☐ ☐☐ ☐☐ (Day Month Year)		
	Yes	**No**
Evidence of hemorrhage?	☐	☐
Evidence of hemorrhage conversion?	☐	☐
Evidence of Infarction?	☐	☐
Evidence of tumor?	☐	☐
Evidence of aneurysm?	☐	☐
Was a MRI scan performed?	☐	☐
If *Yes*, date of the MRI scan: ☐☐ ☐☐ ☐☐ (Day Month Year)		
Result of MRI scan ✓ one — Normal ☐ Abnormal ☐		
If Abnormal, evidence of acute/sub acute event?	☐	☐
If Abnormal, evidence of chronic event?	☐	☐
Was an MRA scan performed?:	☐	☐
If *Yes*, date of the MRA scan: ☐☐ ☐☐ ☐☐ (Day Month Year)		
Result of MRA scan ✓ one — Normal ☐ Abnormal ☐		
If Abnormal, evidence of acute/sub acute event?	☐	☐
If Abnormal, evidence of chronic event?	☐	☐

If no CT, MRI or MRA examination was performed, what was the clinical diagnosis of the cause of the event (e.g., cerebral thrombosis, hemorrhage, embolus)?

OUTCOME

	Yes	No
Were there any long-term sequelae	☐	☐

If *Yes*, complete the following:		
Able to perform ADL's (activities of daily living) without assistance?	☐	☐
Was the subject confined to bed?	☐	☐

FINAL DIAGNOSIS

✓ only one:

- ☐ Ischemic stroke
- ☐ Hemorrhagic stroke, intracerebral
- ☐ Hemorrhagic stroke, subarchnoid
- ☐ Stroke – type uncertain
- ☐ TIA

v.2 (11Oct2018)

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GSK	**Targeted Follow Up Questionnaire for** **Mepolizumab** **DEEP VEIN THROMBOSIS (DVT)/** **PULMONARY EMBOLISM (PE)**	
Patient/Subject ID: DOB/Initials:	Sex/weight (is patient obese if weight unknown): Female ☐ Male ☐ Obese? Yes ☐ No ☐ Weight	Safety Database CASE No:

Lot Number & Expiration date (*for post-marketing reports only*):

EVENT DETAILS

	Yes	No
Was subject hospitalized due to event?	☐	☐

If *Yes*, admission date: ☐☐ ☐☐ ☐☐ (Day Month Year)

Deep Vein Thrombosis (DVT)

Date of onset: ☐☐ ☐☐ ☐☐ (Day Month Year)

	Yes	No
Calf tendernes	☐	☐
Calf swelling	☐	☐
Femoral vein signs	☐	☐
Surgical procedures within the past 12 weeks	☐	☐
Other typical signs and symptoms of DVT	☐	☐

Pulmonary Embolism (PE)

Date of onset: ☐☐ ☐☐ ☐☐ (Day Month Year)

	Yes	No
Surgical procedures within the past 12 weeks:	☐	☐
Hypotension	☐	☐
Requiring vasopressor support	☐	☐
Shortness of breath	☐	☐

If Yes, complete the following:

- ☐ Mild
- ☐ Moderate
- ☐ Severe

	Yes	No
Pleuritic chest pain	☐	☐
Tachycardia, Heart Rate >100/minute	☐	☐
Other typical signs and symptoms consistent with PE	☐	☐

RISK FACTORS	Yes	No

Known hypercoagulable state	☐	☐
Prolonged immobilization	☐	☐
Postoperative	☐	☐
Recent severe trauma	☐	☐
History of prior DVT or PE	☐	☐

DIAGNOSTIC TESTS

Diagnostic Test Name	**Test Performed** Y=Yes N=No	**Consistent with DVT** Y=Yes N=No	**Date of Test** *Day Month Year*
	e.g., Y	*Y*	***01 JAN 09***
Impedance plethysmography			
Lower extremity compression ultrasonography			
Venography			
MRI Scan			
CT Scan			
Angiography			
Ventilation – Perfusion Scan			
D-dimer			

MEDICATIONS AND PROCEDURES		
Did the subject require the following treatment?	Yes	No
Thrombolytics	☐	☐
Thrombectomy	☐	☐
Anticoagulation	☐	☐

v.2 (11Oct2018)

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GSK	**Targeted Follow-Up Questionnaire for** **Mepolizumab** **MYOCARDIAL INFARCTION (MI)/UNSTABLE ANGINA (UA)**

Patient/Subject ID: DOB/Initials:	Sex/weight (is patient obese if weight unknown): Sex: Female ☐ Male ☐ Obese? Yes ☐ No ☐ Weight:	GSK CASE No:

Lot Number & Expiration date (*for post-marketing reports only*):

Description of the Event and medical history:

Myocardial Infarction (MI) / Unstable Angina (UA) date of onset:

☐☐ ☐☐ ☐☐
Day Month Year

Duration of symptoms at time of presentation: ☐☐:☐☐
Hrours: Minutes

ANGINA SYMPTOMS

	YES	NO
New onset of severe angina or accelerated angina	☐	☐
Angina at rest	☐	☐
Exertional angina	☐	☐
Atypical symptoms	☐	☐
Did the angina/infarction occur after medical or surgical procedure	☐	☐

URGENT CARE AND/OR HOSPITALISATION

Did the subject/patient visit the emergency room/chest pain center?	☐	☐
If yes, date of the emergency /chest pain center visit: ☐☐ ☐☐ ☐☐ Day Month Year		
Was subject/patient admitted to the hospital? *If yes, admission date (day/month/year):* ☐☐ ☐☐ ☐☐ Day Month Year	☐	☐
Was the subject/patient on any of the following medications anti-angina, antithrombotic agents, anti-arrhythmics, or other relevant drugs at the time the event occurred?	☐	☐
If yes, specify:		

ECG STANDARD 12 LEAD

	NON-EVALUABLE	YES	NO
Was an ECG performed?	☐	☐	☐
If "Yes," complete the following:			

Date of ECG: *[day month year]*

☑ all that apply		
Conduction		
☐ Left bundle branch block		
ECG Findings		
☐ Myocardial infarction, old		
☐ Non-specific ST-T changes		
☐ ST elevation		
☐ ST depression		
☐ T-wave flattening/inversion		
☐ Pathological Q waves		
Is there a ECG prior to current event available for comparison?	☐	☐
If 'yes,' complete the following:		
Date of ECG: *[day month year]*		
Were there any changes from the previous ECG Result?	☐	☐
☑ all that apply		
Previous ECG Findings		
☐ Non-specific ST-T changes		
☐ ST elevation		
☐ ST depression		
☐ T-wave flattening/inversion		
LABORATORY DATA		

Date Sample Taken	**Test**	**Result**	**Normal Ranges**		
			Unit	**High**	**Low**
Day Month Year					
e.g., 05 JUN 09	***Peak total bilirubin***	***8.0***	***mmol/L***	***17.0***	***2.0***
	Peak Creatine Kinase				

	Peak Creatine Kinase MB – mass (concentration)				
	Peak Creatine Kinase MB – mass (percentage)				
	Peak Creatine Kinase MB – Activity (concentration)				
	Peak Troponin I				
	Peak Troponin T				

IMAGING REPORTS

Test	Test Done Y=Yes N=No	Date of Test Day Month Year		What is the interpretation of result? 1=Normal 2=Abnormal	Is there evidence of ischemia? Y=Yes N=No	Is there evidence of infarction? Y=Yes N=No
	e.g., Y	***05 Jun 09***		***1***	***N***	***N***
Stress Test						
Echo						
Nuclear						
MRI						

SURGICAL/MEDICAL PROCEDURES

Test	Procedure Done Y=Yes N=No ***e.g., Y***	Date of Surgery/Procedure Day Month Year ***05 JUN 09***		What is interpretation of the result? 1=Normal 2=Abnormal ***1***	Is there evidence of significant lesion in any major epicardial (50% Left main Coronary Artery or 70% in any vessel)? Y=Yes N=No ***N***
Coronary Angiogram					
	Number of Vessels Affected	**Is there evidence of stent?**	**Is there evidence of stent thrombosis?**	**Has ejection fraction been evaluated?**	**If Yes, percentage of ejection fraction?**

		Y=Yes N=No NA=Not applicable	Y=Yes N=No NA=Not applicable	Y=Yes N=No	%
	e.g., X	**N**	**N**	**N**	**X%**
Coronary Angiogram (Cont.)					

SURGICAL/MEDICAL PROCEDURES Continued

Surgical/Medical Procedure	**Procedure Done**	**Date of Surgery/Procedure Day Month Year**
	e.g., Y	***09 JUN 09***
Angioplasty		
Coronary Artery Bypass Graft		

FINAL DIAGNOSIS

☑ *only one:*

- ☐ Unstable angina
- ☐ Myocardial Infarction – ST segment elevation
- ☐ Myocardial Infarction – Non-St segment elevation
- ☐ Non-cardiac chest pain

v.2 (11Oct2018)

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GSK	Targeted Follow Up Questionnaire for **Mepolizumab** **PERIPHERAL ARTERIAL THROMBOEMBOLISM**	
Patient/Subject ID: DOB/Initials:	Sex/weight (is patient obese if weight unknown): Female ☐ Male ☐ Obese? Yes ☐ No ☐ Weight	GSK CASE No:
Lot Number & Expiration date (*for post-marketing reports only*):		

Date of onset of thromboembolism: ☐☐ ☐☐ ☐☐
Day Month Year

SYMPTOMS

If Yes, complete the following:

	Yes	No
Loss of palpable pulse	☐	☐
Acute signs and symptoms	☐	☐
Chronic + subchronic signs and symptoms	☐	☐

RISK FACTORS

	Yes	No
Risk factors present?	☐	☐
If *Yes,* complete the following:		
Afib/Flutter	☐	☐
Hypercoagulable state	☐	☐
Malignancy	☐	☐
Known atherosclerotic process	☐	☐
Other risk factors	☐	☐

INTERVENTION REQUIRED OR GIVEN FOR THIS EVENT

Medication	☐	☐
Percutaneous	☐	☐
Surgical	☐	☐

Diagnostic Test Name	**Test Performed** *Y=Yes* *N=No*	**Consistent with peripheral arterial thromboembolism** *Y=Yes* *N=No*	**Thromboem-bolism within a stent?** *Y=Yes* *N=No*	***Location*** 1=Upper Extremity 2=Lower Extremity 3=Renal 4=Mesentric 5=Splenic 6=Hepatic 7=Occular/Retinal 8=Stent thrombosis OT=Other	**Other Location. Specify**	**Date of Test** *Day Month Year*
Ultrasound						
CT						
MRI						
Angiography						

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

Not applicable.