EU RMP

Drug Substance	Benralizumab
Version Number	7
Succession Number	1
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EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for FASENRA™ (benralizumab)

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

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

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Administrative Information

Rationale for submitting an updated RMP:

- Removal of malignancy from the list of safety concerns following completion of the additional pharmacovigilance activity; the post authorisation safety study (PASS) D3250R00042.

Summary of significant changes in this RMP:

Part I

- None

Part II SI

- None

Part II SII

- None

Part II SIII

- None

Part II SIV

- Updated reference to the post authorisation safety study from exclusion criteria of 'Patients with history of cancer'.

Part II SV

- Updated post autorisation exposure data.

Part II SVI

- None

Part II SVII

- Updates to remove malignancy from the list of safety concerns

Part II SVIII

- Updates to remove malignancy from the list of safety concerns

Part III

- Updates to remove study D3250R00042 as an additional pharmacovigilance activity.
- Removal of follow-up questionnaire.

Part IV

- Not applicable

Part V

- Updates to remove malignancy from the list of safety concerns.

Part VI

- Updates to remove malignancy from the list of safety concerns.
- Updates to remove malignancy PASS from the post-authorisation development plan. Minor correction: adding in missing information 'Use in pregnancy and lactating women' in section 6.2.2.

Part VII

- Annex 2: Moved malignancy PASS D3250R00042 from 'Planned and Ongoing Studies' to 'Completed Studies'. Minor amendment: Added the previously completed Benralizumab Pregnancy Exposure Study D3250R00026.
- Annex 3: Removed malignancy PASS D3250R00042 from 7.3.3 Part C 'Previously Agreed Protocols for Ongoing Studies and Final Protocols Not reviewed by Competent Authority'
- Annex 4: Removed the Adverse Reaction Follow-up Form for Malignancy.
- Annex 8: Administrative updates.

Other RMP versions under evaluation	**Version Number**: Not applicable. **Submitted**: Not applicable. **Procedure number**: Not applicable
Details of currently approved RMP	**Version Number**: 6 **Approved with procedure**: EMEA/H/C/004433/II/0052 **Date of approval:** 24 October 2024

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	**Definition/Explanation**
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
EGPA	Eosinophilic granulomatosis with polyangiitis
ENFUMOSA	European Network for Understanding Mechanisms of Severe Asthma
EU	European Union
Fc	Fragment crystallisable region
FEV1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroid
Ig	Immunoglobulin
IL	Interleukin
IL-5Rα	Interleukin-5 receptor alpha subunit
IP	Investigational product
IV	Intravenous
LABA	Long acting β2 agonists
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
PRAC	Pharmacovigilance Risk Assessment Committee
PT	(MedDRA) Preferred Term
Q	Quarter
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics (EU)
UK	United Kingdom
US	United States
VT	Venous thromboembolism

1 PART I: PRODUCT OVERVIEW

Table 1-1 Product Overview

Active substance(s) (INN or common name)	Benralizumab
Pharmacotherapeutic group(s) (ATC Code)	R03DX10
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	1 (Benralizumab)
Invented name(s) in the EEA	FASENRA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: IL-5Rα-directed mAb
	Summary of mode of action: Benralizumab is a humanised, afucosylated, monoclonal antibody (Ig1, kappa). Benralizumab binds to the alpha subunit of the human IL-5Rα with high affinity (16 pM) and specificity. The IL-5R is expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity (45.5 nM) for FcγRIII receptors on immune effectors cells such as natural killer cells leading to apoptosis of eosinophils and basophils through enhanced ADCC. Eosinophilic inflammation is an important component in the pathogenesis of asthma and EGPA, and eosinophils are a rich source of pro-inflammatory mediators (e.g., eicosanoids, leukotrienes, and cytokines) and granule proteins (e.g., eosinophil cationic protein, eosinophil peroxidase, eosinophil neurotoxin, and major basic protein). Benralizumab, by ADCC, reduces eosinophilic inflammation.

Table 1-1 Product Overview

	Important information about its composition: Accessorised prefilled syringe Each accessorised prefilled syringe contains 30 mg benralizumab in 1 mL. Autoinjector Each autoinjector contains 30 mg benralizumab in 1 mL. Benralizumab is a humanised, afucosylated, mAb selective for IL-5Rα. Benralizumab is of the IgG1/κ-class produced in Chinese hamster ovary cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa.
Hyperlink to the Product Information	FASENRA Summary of Product Characteristics
Indication(s) in the EEA	**Current:** Asthma: FASENRA is indicated as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients. EGPA: FASENRA is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis.
Dosage in the EEA	**Current:** Asthma: 30 mg of benralizumab by SC injection Q4W for the first 3 doses, and then Q8W thereafter. EGPA: The recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks.
Pharmaceutical form(s) and strengths in the EEA	**Current:** Solution for injection in accessorised prefilled syringe (injection) Solution for injection in autoinjector (injection) (FASENRA PEN)
Is/will the product be subject to additional monitoring in the EU?	No

ADCC = antibody dependent cell-mediated cytotoxicity; ATC = Anatomic Therapeutic Chemical; eCTD = electronic common technical document; EEA = European Economic Area; EGPA = eosinophilic granulomatosis with polyangiitis; Fc = fragment crystallizable region; FcγRIII = Fcγ receptor III; Ig = immunoglobulin; IL-5R = interleukin-5 receptor; IL-5Rα = interleukin-5 receptor alpha subunit; INN = International Non-proprietary Name; mAb = monoclonal antibody; Q4W = every 4 weeks; Q8W = every 8 weeks; RMP = Risk Management Plan; SC = subcutaneous

2 PART II: SAFETY SPECIFICATION

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

2.1.1 Severe Asthma with Eosinophilic Phenotype

Incidence:

In an Asthma Call-back Survey of children and adults in the United States (US), the average 12-month incidence of asthma from 2006 through 2008 was 12.5 per 1000 children and adolescents (0 to 17 years old) and 3.8 per 1000 adults (Winer et al 2012). Asthma incidence was over five times higher among 0 to 4-year-old children (23.4/1000) than 12- to 17-year-old adolescents (4.4/1000) (Winer et al 2012). In a national registry study of children and adolescents born in Denmark (1997 through 2011) or Sweden (2006 through 2010), asthma incidence was 17.3 per 1000 persons in the Danish cohort (0 to 15 year-old) and 43.4 in the Swedish cohort (0 to 4 year-old) (Henriksen et al 2015). The incidence of severe asthma with eosinophilic phenotype is largely unknown; however, eosinophilic inflammation is common in asthma (Garcia et al 2013, Schleich et al 2013), with approximately 50% of all patients with asthma having eosinophilic inflammation (Zhang and Wenzel 2007). Although more common in adults, severe asthma can present in children (Porcaro et al 2020).

Prevalence:

The prevalence of asthma range from 1% to 18% in different countries, with rates increasing over time in some while stable in others (Global Initiative for Asthma GINA 2022). The reported prevalence within the EU ranges from 1.5% in Romania to 18.4% in Scotland (Masoli et al 2004). Data from the European National Health and Wellness Survey of 37,476 adults in France, Germany, Italy, Spain and the United Kingdom (UK) reported a prevalence of diagnosed asthma of 5.8% throughout the EU (Demoly et al 2009). Worldwide, approximately 300 million individuals are living with asthma (Masoli et al 2004). It is estimated that approximately 6 million children have asthma in the US (Zahran et al 2018). Data from national and state surveillance systems administered by the US Centers for Disease Control and Prevention (CDC) show that 8.4% of adults and 5.8% of children and adolescents in the US had asthma in 2020 (CDC 2020).

Severe asthma is characterised by difficulty in achieving disease control despite use of high-dose inhaled corticosteroids (ICS) plus long acting β2 agonists (LABAs). The prevalence of severe asthma is estimated at 5% to 10% of the total asthmatic population (Barnes and Woolcock 1998, Busse et al 2000, O'Byrne et al 2012). Some studies have estimated that approximately 50% of severe asthmatics or 5% to 10% of the total asthma population have exacerbations and symptoms with the presence of persistent eosinophilia despite taking high-dose ICS (Woodruff et al 2009, Chung et al 2014, Wenzel et al 2005). Among

adolescents, the estimated prevalence of severe asthma is 6.9% globally, ranging from 3.8% in Asia-Pacific and Northern and Eastern Europe to 11.3% in North America (Lai et al 2009).

Demographics of the population in the severe asthma with eosinophilic phenotype indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

According to a cohort study sponsored by AstraZeneca, using 2 primary care databases in the UK among severe, uncontrolled eosinophilic (blood eosinophilia, defined as ≥0.3 x 109/L) asthma, 66.4% of this patient population were females, 66.8% were either overweight (body mass index [BMI] 25 to <30 kg/m2) or obese (≥30 kg/m2) and roughly half were current or ex-smokers (AstraZeneca Internal Data 2016a). The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) reported more females and higher BMI in severe uncontrolled asthma patients than those with mild to moderate asthma; mean percent predicted forced expiratory volume in 1 second (FEV1) among the severe uncontrolled patients was 71.8% (ENFUMOSA 2003). In an AstraZeneca- sponsored study in France of severe, uncontrolled eosinophilic asthma, 67.6% of patients were female, 79.6% were Caucasian, and the mean (standard deviation) BMI for the population was 27.2 (6.0) kg/m2. Nearly 40% were current or past smokers (AstraZeneca Internal Data 2016b). Factors that influence the risk of asthma, including severe presentations, are divided by GINA into factors that cause development of the disease (mainly host factors, such as genetic predisposition) and factors that trigger symptoms (environmental factors, such as allergens).

The main existing treatment options:

The current approach to anti-inflammatory controller therapy in asthma is based on a step wise intensification of a daily maintenance regimen primarily centred around ICS or ICS/LABA. Add- on therapies including long-acting muscarinic antagonist should be considered for patients with more severe asthma and poor symptom control and/ or exacerbations despite medium or high dose ICS-LABA. In GINA step 5 there are different population level recommendations depending on the inflammatory phenotype. Type 2-targeted biologics should be considered for patients with exacerbations or poor symptom control on high dose ICS-LABA who have eosinophilic or allergic biomarkers, or need maintenance OCS (GINA 2022).

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

Many patients with eosinophilic asthma suffer significant morbidity and loss of quality of life as increased eosinophils are associated with higher severity, exacerbations, decreased lung function, and mortality in patients with asthma (Garcia et al 2013, Hospers et al 2000, Price et al 2016, Talini et al 2015). In a study by Hospers et al, eosinophilia was associated with an increased risk (relative risk = 1.4 [95% confidence interval (CI) 1.2-1.7]) of all-cause mortality independent of other risk factors. Price et al reported that blood eosinophil counts >400/µL (compared with ≤400/µL) increased the likelihood of having 2 or more

exacerbations by more than 1.4 times (odds ratio 1.48, 95% CI 1.39-1.58). Talini et al examined the relationship between sputum eosinophils and FEV1 and noted that patients with higher eosinophils (>3%) at baseline had a significantly greater decline in FEV1 (-52.5 vs -18.6 mL/year, p=0.012). Finally, in another study of patients with severe asthma, those with eosinophilic inflammation despite treatment with systemic corticosteroids had nearly 20 times higher odds of being intubated compared to those without eosinophilic inflammation (Wenzel et al 1999).

Important co-morbidities:

Concomitant allergies are commonly reported underlying conditions associated with the development of asthma; thus, the clinical presentation of asthma often includes seasonal exacerbation or exacerbations related to exposures to recognised allergens. Concomitant allergic rhinitis or other allergic disease, and eczema have been identified as risk factors, particularly in younger patients. Urticaria and nasal polyposis are also commonly reported conditions seen in patients with asthma (Bateman et al 2008, Salpeter 2003).

2.1.2 Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Incidence:

Eosinophilic granulomatosis with polyangiitis is a rare disease associated with vascular inflammation and subsequent multisystem organ damage if untreated (Jakes et al 2021). The reported incidence of EGPA per million person-years in European countries ranged from 0.18 cases in Barcelona, Spain, to 2.50 cases in Norway in a systematic review of the epidemiology of EGPA in Europe and globally (Jakes et al 2021). In non-European countries, EGPA incidence ranged from 0.80 cases in Turkey to 4.00 cases in the United States (Jakes et al 2021). Across Europe, the pooled estimate of EGPA incidence per million person-years was 1.07 cases, and the pooled estimate was 0.18 cases across non-European countries (Jakes et al 2021). Globally, the pooled estimate of EGPA incidence per million person-years was 1.22 cases (Jakes et al 2021). In another review of published literature from 1990 to 2020, the incidence of EGPA per million person-years ranged from 0.50 in Germany (1998 through 1999) to 2.2 and 2.70 in Germany (1998 through 2002) and the UK, respectively (Mohammad 2020).

Prevalence:

It is estimated that the global prevalence of EGPA per million individuals ranges from 2.0 cases in Germany (in 1994) to 30.4 cases in Norway, with a pooled estimate of 15.27 cases and 12.13 cases globally and in Europe, respectively (Jakes et al 2021). In northern Germany, the prevalence of EGPA per million inhabitants increased by 3-fold from 7 cases in 1994 to 24 cases in 2006 (Herlyn et al 2014). Evidence suggests that the prevalence of EGPA per

million patients is comparable in many European countries, ranging from 10.7 cases in Paris to 13 cases in Norway, and 14 cases in Sweden (Mohammad 2020).

Demographics of the population in the EGPA indication and risk factors for the disease:

In a systematic review of the epidemiology of EGPA in Europe and globally, there were no strong trends in incidence or prevalence of EGPA by sex (Jakes et al 2021). The annual incidence per million person-years reported for male populations ranged from 0.6 cases to 7.0 cases, whilst the incidence in female subgroups ranged from 0.9 cases to 3.1 cases (Jakes et al 2021). Gender-specific prevalence per million patients ranged from 1.6 cases to 14.0 cases for males and 6.0 cases to 14.0 cases for females (Jakes et al 2021).

Several exogenous risk factors have been associated with the development of vascular inflammation, including EGPA. Environmental factors, infections, vaccinations, allergy, and farming have been implicated in the development of EGPA (Vaglio et al 2013, Watts et al 2005). Evidence suggests that immunogenetic factors such as the HLA-DRBI*04 and *07 alleles and the related HLA-DRB4 gene may confer susceptibility to EGPA, and medications such as macrolide antibiotic, leukotriene receptor antagonists, and steroid-sparing drugs used for asthma (e.g theophylline, cromolyns, anti-IgE antibody omalizumab) have been implicated in the development of EGPA (Vaglio et al 2007, Vaglio et al 2013).

The main existing treatment options:

Systemic corticosteroids, immunosuppressants, and biologics (rituximab and mepolizumab) are currently recommended in treatment guidelines for EGPA, with mepolizumab being the only therapy approved on the basis of a randomised controlled clinical trial (Chung et al 2021, Hellmich et al 2023).

A key therapeutic goal in treatment of EGPA is to induce and maintain remission whilst reducing the burden of corticosteroids and immunosuppressants because these therapies are often associated with significant adverse events, including toxicity, and a high relapse rate (Chung et al 2021, Poetker and Reh 2010).

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

EGPA is a potentially life-threatening systemic disease (Jackson et al 2022, Noth et al 2003) and usually follows a chronic relapsing course, which increases the risk of permanent tissue and/or organ damage secondary to the vasculitic process (Robson et al 2014). A relapse rate of ≥ 40% is reported and there is a substantial morbidity and healthcare burden associated with the high relapsing risk in patients with EGPA (Jakes et al 2021).

Patients with EGPA have reduced health-related quality of life scores across all dimensions of the Short Form-36 Item Health questionnaire: general health, physical functioning, emotional role limitations, physical role limitations, social functioning, mental health, bodily pain, and vitality (Sokolowska et al 2013).

The cumulative survival rates at 5 and 10 years from the disease onset are 88% to 97% and 78% to 89%, respectively (Furuta et al 2019). The primary causes of mortality have changed over time from cardiac manifestations to treatment-related causes, including infection and toxicity (Doubelt et al 2021).

Important co-morbidities:

EGPA is associated with vascular inflammation and subsequent multisystem organ damage, suggesting its potential comorbidity with diseases of multiple organ systems. Research shows that pulmonary involvement is often significant among EGPA patients, with up to 40 – 70% of them having pulmonary infiltrates (Trivioli et al 2020; White and Dubey 2023). Venous thromboembolism (VT) is also estimated to have a prevalence of about 10%, with most VT events occurring in periods of active disease, such as the months preceding or following EGPA diagnosis (Allenbach et al 2009, Novikov et al 2014, Trivioli et al 2020). Comorbid cardiovascular disease has also been associated with EGPA, and it is suggested that comorbid heart disease is a prognosticator of frequent disease relapse; the leading precipitating factor for intensive care admission; responsible for around one-third of EGPA deaths and a 14% reduction in five-year survival, compared to those without heart disease (Comarmond et al 2013, Tsurikisawa et al 2017, White and Dubey 2023). Furthermore, it is estimated that 25–30% of EGPA patients have renal disease (Durel et al 2021), and 50 – 75% to develop peripheral neuropathy (White 2023). EGPA patients also had a two-fold risk of overall malignancy than the general population in a multicentre study of 303 patients (Padoan et al 2022).

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

Key safety findings from non-clinical studies and relevance to human usage:

2.2.1 Toxicity

The cynomolgus monkey was the species selected for non-clinical safety evaluation based on the close similarity of the human and cynomolgus monkey tissue cross-reactivity profiles, binding of benralizumab to cynomolgus eosinophils, pharmacological activity of benralizumab in an interleukin (IL)-5-induced model of eosinophilia in cynomolgus monkeys and demonstrated anti-asthmatic activity of benralizumab in a cynomolgus monkey asthma model. Since benralizumab does not bind to murine interleukin-5 receptor alpha subunit

(IL-5Rα), rodents are not a suitable species for benralizumab non-clinical safety assessment; therefore, rodent benralizumab toxicology studies were not conducted.

Key issues identified from acute or repeat-dose toxicity studies

Findings from single and repeat-dose toxicity studies in cynomolgus monkeys indicated that benralizumab was generally well tolerated. Marked reductions in eosinophil counts were observed in all benralizumab-treated animals throughout the dosing and recovery periods (blood and/or bone marrow depletion). In a 9-week repeated-dose intravenous (IV) study, transient decreases in leukocytes, resulting from differential decreases in neutrophil counts, were seen in 2 of 10 animals (1 male and 1 female) treated with the highest dose (30 mg/kg; not observed in other non-clinical safety studies of longer duration) resulting in a no-observed-adverse-effect level (NOAEL) of ≤30.0 mg/kg.

Reproductive/developmental toxicity

Fertility parameters were evaluated by using sexually mature cynomolgus monkeys in the 9-month IV and subcutaneous (SC) toxicity study. No adverse benralizumab-related effects on menses, testicular volume/size, or semen analysis parameters were observed. Reproductive organ weights (epididymides, ovaries, prostate, seminal vesicle, testes, and uterus), and histopathology of reproductive tissues (testes, prostate, epididymides, seminal vesicles, ovaries, oviducts, uterus, cervix, and vagina) were not impacted by benralizumab administration. Fertility parameters were not impacted following repeated administration of benralizumab for 9 months at doses up to 25 mg/kg for IV and 30 mg/kg for SC administration.

No adverse effects of benralizumab on pregnant, neonatal, or juvenile cynomolgus monkeys were observed in an enhanced peri- and post-natal developmental and reproductive toxicology study. In the offspring, growth and development of the infants were not impacted by benralizumab exposure during pregnancy and no immunotoxicity was observed. The NOAEL was considered 30 mg/kg/dose, the highest dose tested.

Nephrotoxicity:

In the non-clinical safety studies, there were no benralizumab-related adverse effects on urinalysis or clinical chemistry parameters to suggest nephrotoxic effects. There were no adverse effects on kidney weights, or adverse macroscopic or microscopic findings in kidneys at doses up to 30 mg/kg/dose IV or SC.

Hepatotoxicity:

In the non-clinical safety studies, there were no benralizumab-related adverse effects on clinical chemistry parameters to suggest hepatotoxic effects. There were no adverse effects on

liver weights, or adverse macroscopic or microscopic findings in livers at doses up to 30 mg/kg/dose IV or SC.

Genotoxicity

Benralizumab is a monoclonal antibody (mAb) composed entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Thus, it is highly unlikely that benralizumab would react directly with DNA or other chromosomal material, and since benralizumab is a large protein molecule, it is not expected to cross the nuclear or mitochondrial membranes. According to the current guidelines on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (International Council for Harmonisation S6 R1, 2011), the range and type of standard studies evaluating genotoxicity routinely conducted for pharmaceuticals are not applicable for biotechnology-derived pharmaceuticals such as benralizumab.

Carcinogenicity

No evidence of proliferative or pre-neoplastic changes was observed in toxicology studies following repeated administration of benralizumab at doses up to 30 mg/kg/dose. Since benralizumab does not bind to murine IL-5Rα, direct assessment of carcinogenic risk of benralizumab in a validated 2-year rodent bioassay is not appropriate. Alternative models to evaluate carcinogenic risk for benralizumab were considered; however, based on differences in IL-5Rα and fragment crystallisable region (Fc)γ receptor biology between mice and humans, and liabilities noted for the IL-5- and IL-5Rα-deficient mouse models, the Sponsor considered alternative carcinogenicity models using transgenic rodents or surrogate molecules unlikely to inform carcinogenic risk.

2.2.2 Safety Pharmacology

No standalone studies were conducted; safety pharmacology endpoints are included in repeat-dose toxicity studies.

2.2.3 Other Toxicity-Related Information or Data

There is no additional non-clinical study-related information.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

2.3.1 EGPA Exposure

The benralizumab clinical development programme for EGPA consists of 1 ongoing Phase III study D3253C00001 (MANDARA) and data is presented with a cut-off date of 10 August 2023.

Table 2-1 Duration of Exposure in EGPA Studies

Duration of Exposure to benralizumab (at least)	Patients	Person Time (years) (cumulative)
All EGPA pool*		
<1 month	132	224.4
1 month	131	224.3
3 months	128	223.8
6 months	123	221.9
12 months	105	208.0
Overall	132	224.4

*All completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

Note: Month is calculated for each subject as: days/365.25/12.

EGPA = eosinophilic granulomatosis with polyangiitis; RMP = Risk Management Plan

Source: Benralizumab RMP 2023 EGPA Tables (Table II-1 Duration of exposure).

Table 2-2 Age Group and Gender in EGPA Studies

	Patients		Person Time (years)	
Age Group	**M**	**F**	**M**	**F**
All EGPA pool*				
2-11 years	0	0	0.0	0.0
12-<18 years	0	0	0.0	0.0
18-64 years	40	65	60.6	118.1
≥65 years	12	15	21.6	24.1
≥75 years	3	4	5.0	7.1

*All completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

EGPA = eosinophilic granulomatosis with polyangiitis; RMP = Risk Management Plan

Source: Benralizumab 2023 EGPA Tables (Table II-2 Exposure by age group, and gender).

Table 2-3 Dose in EGPA Studies

Dose of Exposure	Patients	Person Time (years)
All EGPA pool*		
30 mg Q4W	132	224.4
Overall	132	224.4

*All completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

EGPA = eosinophilic granulomatosis with polyangiitis; RMP = Risk Management Plan

Source: Benralizumab RMP 2023 EGPA Tables (Table II-3 Exposure by dose).

Table 2-4 Race in EGPA Studies

Ethnic Origin	Patients	Person Time (years)
All EGPA pool*		
White	103	172.6
Asian	17	34.2
Other**	5	6.9
Unknown	7	10.7

*All completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

**'Other' includes eCRF race categories 'Native Hawaiian or other Pacific Islander', 'American Indian or Alaska Native', and 'Other'.

eCRF = electronic Case Report form; EGPA = eosinophilic granulomatosis with polyangiitis; RMP = Risk Management Plan

Source: Benralizumab RMP 2023 EGPA Tables (Table II-4 Exposure by race).

2.3.2 Asthma Exposure

The benralizumab clinical development programme for asthma consists of the following completed clinical studies: 3 Phase I studies, 3 Phase II studies, 15 Phase III studies, and 1 Phase IV studies. Two Phase I studies are not included in the RMP analyses as 1 study (MI-CP158) was a single administration dose escalation study and the other study (MI-CP166) contained both single administration IV dosing and multiple SC dosing. The remaining studies are within the scope of this section.

Exposure data from ongoing studies are not presented in the exposure tables.

Table 2-5 Duration of Exposure in Asthma Studies

Duration of Exposure to benralizumab (at least)	Patients	Person Time (years) (cumulative)
All asthma pool*		
<1 month	5180	6538.3
1 month	5131	6535.1
3 months	4701	6467.8
6 months	3821	6109.6
12 months	2468	4909.1
Overall	5180	6538.3

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE).

Note: Month is calculated for each subject as: days/365.25/12.

RMP = Risk Management Plan

Source: Benralizumab RMP 2023 Asthma Tables (Table II-1 Duration of exposure).

Table 2-6 Age Group and Gender in Asthma Studies

	Patients		Person Time (years)	
Age Group	**M**	**F**	**M**	**F**
All Asthma Pool*				
2-11 years	19	9	17.8	8.3
12-<18 years	83	58	129.9	90.3
18-64 years	1631	2669	1944.7	3457.6
≥65 years	275	436	358.2	531.6
≥75 years	19	31	17.8	33.7

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE).

RMP = Risk Management Plan

Source: Benralizumab RMP 2023 Asthma Tables (Table II-2 Exposure by age group, and gender).

Table 2-7 Dose in Asthma Studies

Dose of Exposure	Patients	Person Time (years)
All Asthma Pool*		
10 mg Q8W	15	14.0
30 mg Q4W	1673	2468.2
30 mg Q8W	2836	3678.3
Benra SC 200 mg	6	1.9
Benra SC 100 mg	229	196.5
Benra SC 30 mg	180	28.1
Benra SC 25 mg	7	1.9
Benra SC 20 mg	81	68.8
Benra SC 2 mg	81	69.6
Benra IV 0.3 mg/kg	36	5.6
Benra IV 1.0 mg/kg	36	5.6
Overall	5180	6538.3

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE).

Some subjects treated with 30 mg Q4W in studies D3250C00017 (SIROCCO) and D3250C00018 (CALIMA) were treated with 30 mg Q8W in study D3250C00021 (BORA) according to their initial randomisation. These subjects are counted in 30 mg Q8W group.

Q4W = every 4 weeks; Q8W = every 8 weeks; RMP = Risk Management Plan

Source: Benralizumab RMP 2023 Asthma Tables (Table II-3 Exposure by dose).

Table 2-8 Race in Asthma Studies

Ethnic Origin	Patients	Person Time (years)
All Asthma Pool*		
White	3774	5039.6
Black or African American	264	213.5
Asian	746	894.3
Other**	288	323.3
Unknown	108	67.6

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE).

**'Other' includes eCRF race categories 'Native Hawaiian or other Pacific Islander', 'American Indian or Alaska Native', and 'Other'.

eCRF = electronic Case Report form; RMP = Risk Management Plan.

Source: Benralizumab RMP 2023 Asthma Tables (Table II-4 Exposure by race).

2.3.3 EGPA and Asthma Pooled Exposure

Exposure data from ongoing asthma studies are not presented in the exposure tables.

Table 2-9 Duration of Exposure in Pooled EGPA and Asthma Studies

Duration of Exposure to benralizumab (at least)	Patients	Person Time (years) (cumulative)
EGPA and Asthma Pool*		
<1 month	5312	6762.7
1 month	5262	6759.4
3 months	4829	6691.5
6 months	3944	6331.5
12 months	2573	5117.2
Overall	5312	6762.7

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE); and completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

Note: Month is calculated for each subject as: days/365.25/12.

Source: Benralizumab RMP 2023 Asthma & EGPA Tables (Table II-1 Duration of exposure).

Table 2-10 Age Group and Gender in Pooled EGPA and Asthma Studies

	Patients		Person Time (years)	
Age Group	**M**	**F**	**M**	**F**
EGPA and Asthma Pool *				
2-11 years	19	9	17.8	8.3
12-<18 years	83	58	129.9	90.3
18-64 years	1671	2734	2005.3	3575.7
≥65 years	287	451	379.7	555.7
≥75 years	22	35	22.7	40.8

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE); and completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

Source: Benralizumab RMP 2023 Asthma & EGPA Tables (Table II-2 Duration of exposure).

Table 2-11 Dose in pooled EGPA and asthma studies

Dose of Exposure	**Patients**	**Person Time (years)**
EGPA and Asthma Pool *		
10 mg Q8W	15	14.0
30 mg Q4W	1805	2692.6
30 mg Q8W	2836	3678.3
Benra SC 200 mg	6	1.9
Benra SC 100 mg	229	196.5
Benra SC 30 mg	180	28.1
Benra SC 25 mg	7	1.9
Benra SC 20 mg	81	68.8

Table 2-11 Dose in pooled EGPA and asthma studies

Dose of Exposure	Patients	Person Time (years)
EGPA and Asthma Pool *		
Benra SC 2 mg	81	69.6
Benra IV 0.3 mg/kg	36	5.6
Benra IV 1.0 mg/kg	36	5.6
Overall	5312	6762.7

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE); and completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

Some subjects treated with 30 mg Q4W in studies D3250C00017 (SIROCCO) and D3250C00018 (CALIMA) were treated with 30 mg Q8W in study D3250C00021 (BORA) according to their initial randomisation. These subjects are counted in 30 mg Q8W group.

Source: Benralizumab RMP 2023 Asthma & EGPA Tables (Table II-3 Duration of exposure).

Table 2-12 Race in Pooled EGPA and Asthma Studies

Ethnic Origin	Patients	Person Time (years)
EGPA and Asthma Pool*		
White	3877	5212.2
Black or African American	264	213.5
Asian	763	928.5
Other**	293	330.2
Unknown	115	78.3

*All completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MI CP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), ANDHI (D3250C00045, Main study), D3250C00021 (BORA), D32350C00037 (MELTEMI), D3250C00040 (ARIA), D3250C00065 (PONENTE, including Long-term Follow-up), D3250C00036 (MIRACLE), Phase IV: D3250C00072 (SHAMAL), Pediatric study: D3250C00025 (TATE); and completed stud(ies) for the EGPA indication: Phase III: D3253C00001 (MANDARA, including Open-label period).

**'Other' includes eCRF race categories 'Native Hawaiian or other Pacific Islander', 'American Indian or Alaska Native', and 'Other'.

Source: Benralizumab RMP 2023 Asthma & EGPA Tables (Table II-4 Duration of exposure).

2.4 MODULE SIV: Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

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

Reason for exclusion: To ensure patient safety during participation in the study. The patients with known allergy or reaction to any component of the drug formulation were excluded from clinical trials to ensure they were not exposed to product to which they had a documented allergy.

Is it considered to be included as missing information: No

Rationale: Benralizumab is contraindicated in patients who have known hypersensitivity to benralizumab or any of its excipients; therefore, this population is not relevant for the approved indication.

Patients with history of cancer:

- Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix were eligible to enter the study provided that the patient was in remission and curative therapy was completed at least 12 months prior to entry into the study.
- Patients who have had other malignancies were eligible provided that the patient was in remission and curative therapy was completed at least 5 years prior to entry into the study.

Reason for exclusion: To ensure patient safety during participation in the study and to ensure that the medical conditions due to the history of cancer or concomitant therapy for the condition did not confound the assessment of safety of benralizumab.

Is it considered to be included as missing information: No.

Rationale: There has been no evidence of a risk of malignancy from the clinical development programme and no preclinical data to suggest an increased risk. There are no data to suggest that the safety profile for patients with a history of cancer is different than that of the general population. Hence, use in patients with a history of cancer is not considered to be missing information. A malignancy Post Authorisation Safety Study (PASS) did not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non biologic therapy.

A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent, and assent when applicable, was obtained that has not been treated with, or had failed to respond, to standard of care therapy.

Reason for exclusion: There is a theoretical risk that depleting eosinophils interferes with the expulsion of helminthic parasites; therefore, to ensure patient safety during their participation in the study, those at high risk were monitored for these infections per local medical practice.

Is it considered to be included as missing information: No

Rationale: There have been no confirmed cases of helminth infections reported in benralizumab asthma Phase III clinical studies. Caution should be exercised when prescribing benralizumab to patients who have had a helminth infection as disclosed in Summary of Product Characteristics (SmPC) Section 4.4, Special warnings and precautions for use. Since the use of benralizumab in patients with existing, untreated helminth infection is not anticipated, it is not relevant for consideration as missing information.

Patients who were positive for hepatitis B surface antigen, or hepatitis C virus antibody serology, or with a positive medical history for hepatitis B or C. Patients with a history of hepatitis B vaccination without history of hepatitis B were allowed to enrol.

Reason for exclusion: To ensure patient safety during their participation in the study and to ensure that study results were not confounded by disease that may affect liver function.

Is it considered to be included as missing information: No

Rationale: Benralizumab is not expected to have an effect on liver function and benralizumab clearance is unlikely to be affected by hepatic disease. Since IgG mAbs are not primarily cleared via the hepatic pathway, benralizumab is not expected to have an effect on the safety profile in patients with prior history of hepatitis B or C or in those positive for hepatitis B surface antigen or hepatitis C virus antibody serology.

Receipt of live attenuated vaccines 30 days prior to the date of randomisation.

Reason for exclusion: To comply with vaccination guidance and/or standard medical practice in asthmatic patients, which may vary with region. Not based on a priori safety concerns.

Is it considered to be included as missing information: No

Rationale: There are no mechanistic reasons to consider that vaccination would alter response to treatment with benralizumab. There are no such concerns, contraindications or warnings for similar approved biologics for the treatment of severe asthma in adults.

Alanine aminotransferase or aspartate aminotransferase level ≥2.5 times the upper limit of normal confirmed during screening period.

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

Is it considered to be included as missing information: No

Rationale: There is no non-clinical or other a priori knowledge to suggest that benralizumab would be associated with liver toxicity. There were no findings suggestive of liver toxicity within the clinical development programme. For this reason, it is not anticipated that the safety profile will be different in patients with alanine aminotransferase or aspartate aminotransferase level ≥2.5 times the upper limit of normal.

Women who were pregnant or nursing.

Reason for exclusion: Benralizumab has not been studied in pregnant/lactating women. In order to protect this patient population during the development phase of the medicinal product, these patients were excluded.

Is it considered to be included as missing information: Yes

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

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

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

Table 2-13 Exposure of Special Populations Included or Not In Clinical Trial Development Programmes

Type of special population	**Exposure** *Total number of patients and person time*	
Pregnant women	Not included in the clinical development programme*	
Breast-feeding women		
Patient with relevant comorbidities:	Patients	Person Time (year)
Patients with hepatic impairment**	57	94.6
Patients with renal impairment**	25	34.9
Patients with cardiovascular impairment**	219	330.1

Data from all completed studies for the asthma indication: Phase I: D3250C00030 (AMES), Phase II: MI-CP 186, MI-CP 197, MICP 220, Phase III: D3250C00016 (PAMPERO), D3250C00017 (SIROCCO), D3250C00018 (CALIMA), D3250C00020 (ZONDA), D3250C00029 (GREGALE), D3250C00031 (GRECO), D3250C00032 (BISE), D3250C00033 (ALIZE), D3250C00045 (ANDHI), D32350C00037 (MELTEMI), D3250C00040 (ARIA), and D3250C00021 (BORA).

*Although pregnant subjects were excluded in the clinical development programme, there were reports of pregnancy during the trials in participating female subjects and female partners of participating male subjects) from completed benralizumab asthma studies. No safety concerns in pregnant women were identified as of the clinical cut-off date.

**The hepatic, renal and cardiovascular impairment categories were based on the Baseline medical history searched for MedDRA (Version 23.0) preferred terms.

The search strategy for hepatic impairment included Standardised MedDRA Query (SMQ) (narrow) Hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions.

The search strategy for cardiac impairment included SMQ (narrow) cardiomyopathy, SMQ (narrow) cardiac failure, SMQ (narrow) myocardial infarction and SMQ (narrow) Other ischaemic heart disease.

The search strategy for renal impairment included SMQ chronic kidney disease.

Patients were excluded from the study if they had comorbid hepatic, renal, and/or cardiovascular impairment that was not stable in the opinion of the Investigator and could affect the safety of the patient throughout the study or influence the findings of the studies or their interpretations or impede the patient's ability to complete the entire duration of study.

MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query

Source: Benralizumab RMP 2020 Asthma Tables (Table II-5 Exposure by special population).

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method Used to Calculate Exposure

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

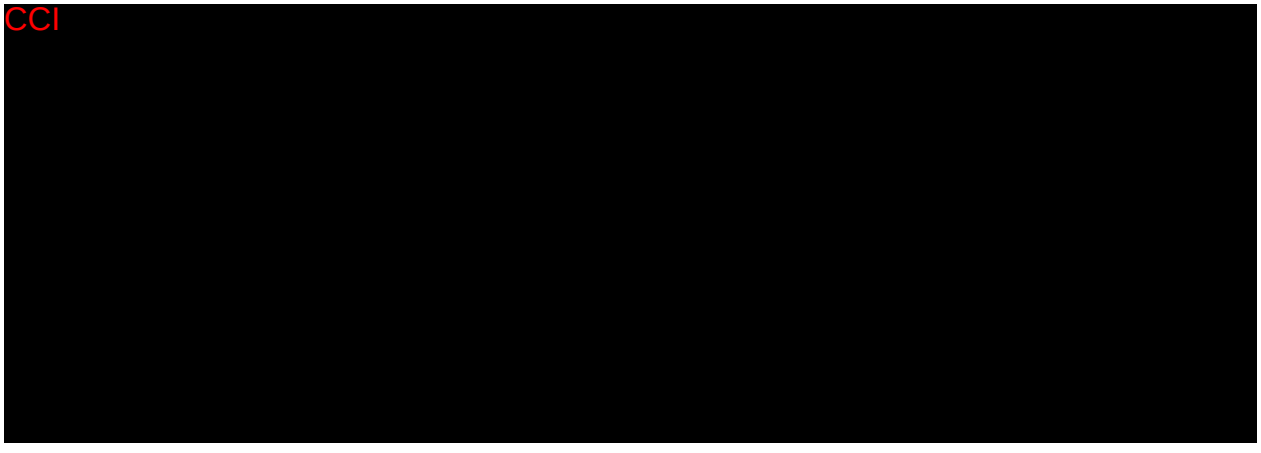
The sales volume is provided as the number of single-dose accessorised prefilled syringes and autoinjectors each containing 30 mg/ml. The estimated post-marketing patient exposure data is an approximation based on the assumption that each patient received 1 SC injection Q4W for the first 3 doses and Q8W thereafter. Therefore, a patient-year worth of exposure is estimated to be 8 doses.

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

2.5.2 Exposure

Cumulative global post-marketing patient exposure for FASENRA CCI single-dose accessorised prefilled syringes and single-dose autoinjectors - each 30 mg in 1 mL), since launch to April 2024, has been estimated to be approximately 331,764 patient-years.

CCI



2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

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

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

2.7.1.1 Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reasons for not including an identified or potential risk in the list of safety concerns in the initial (version 1) EU RMP.

Not applicable.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

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

Malignancy was included as a safety concern with an associated Post Authorisation Safety Study (PASS) commitment based on the putative effect of eosinophils in neoplastic disease.

Based on the results from the completed PASS (D3250R00042: Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorisation Safety Study), malignancy, previously classified as an important potential risk, is removed from the list of safety concerns. The removal is supported by the totality of available data, including non-clinical, clinical data from controlled studies, and post-marketing data.

The PASS was a real-world, observational cohort study conducted using data from eligible severe asthma patients enrolled in the International Severe Asthma Registry (ISAR) and AstraZeneca-sponsored United States Severe Asthma Study (CHRONICLE) databases. The objectives were to assess the incidence rates and clinical characteristics of new malignancy cases in 3 severe asthma cohorts: patients receiving benralizumab, patients receiving non-benralizumab biologics, and patients not receiving biologics. The data, which accrued during the study period of 01 November 2017 (index date) to 31 December 2023, were analysed in the primary analysis for the final report. This report builds upon previous results from the last 3 interim analyses, with more precise incidence rate estimates due to the increase in sample size.

The study identified 75 patients with new malignancies. Results for the propensity score-adjusted main analysis (after adjustments for propensity score weighting, age, sex, body

mass index, region, and smoking status) were as follows: in the benralizumab and non-benralizumab biologic cohorts, the adjusted incidence rates per 1000 PY (95% CI) were 1.3 (0.88, 1.87) and 1.1 (0.74, 1.56), respectively. In the benralizumab and non-biologic cohorts, the adjusted incidence rates per 1000 PY (95% CI) were 1.8 (1.28, 2.57) and 1.7 (1.18, 2.51), respectively. The primary result of this study demonstrated no observed increase in the risk of malignancies associated with benralizumab use.

The secondary objective of this study was to describe the clinical characteristics of new malignancies that develop in severe asthma patients and relevant subgroups. The most common cancers observed in the cohorts of interest were those of the digestive system (benralizumab cohort), melanoma and other malignant neoplasms of the skin (non-benralizumab biologic cohort), and breast (non-biologic cohort). Given the relatively low total number of new malignancies, the observed differences among cohorts in the most frequent types of cancer are not considered meaningful.

The final results do not indicate an increased risk for malignancy among benralizumab cohorts. These final results are consistent with those of the previous interim analyses. Furthermore, the observed crude and adjusted incident rates in the cohorts are consistent with the background incidence of malignancy among severe asthma patients reported in published literature (Long et al 2014, Salameh et al 2021).

No significant safety findings concerning malignancies have been identified from available data within non-clinical studies, clinical trials, postmarketing use, or periodic review of published literature. The incidence of malignancies reported in clinical trials was low and similar across treatment groups and the reporting rates of malignancies in post-marketed use remain low and without trends in patterns or time to onset (relative to drug exposure). The evaluation of cumulative data of malignancies in approximately 300,000 patient-years of exposure from postmarketing experience and 10,000 patients who have been treated with benralizumab in clinical trials has not established any causal relationship between malignancies and benralizumab.

In conclusion, the pre-defined analyses in the malignancy PASS, which included both crude and adjusted analyses, do not show evidence of a difference in the underlying risk of malignancies in patients receiving benralizumab compared to those receiving non-benralizumab biologics or non-biologic therapy. Furthermore, the clinical characteristics of the new malignancies observed in this study are consistent with what has been reported in previous publications.

No significant safety findings concerning malignancies have been identified from available data within non-clinical studies, clinical trials, or postmarketing use.

There are no further additional pharmacovigilance activities following completion of the PASS, and no additional pharmacovigilance activities are considered necessary to evaluate the potential for differences in the incidence or clinical characteristics of new malignancies. There are no clinical measures or additional risk minimisation measures related to the risk of malignancy in place, and is subsequently removed as a safety concern from the EU RMP.

As part of AstraZeneca's routine pharmacovigilance processes, malignancies will continue to be monitored, and relevant new safety information will be included in the Periodic Safety Reports.

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

2.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: There are no important identified risks for benralizumab.

Important Potential Risk: There are no important potential risks for benralizumab.

2.7.3.2 Presentation of Missing Information

Missing information: Use in pregnant and lactating women

Evidence source:

Pregnancy: The exposure data on pregnancy from the clinical studies and from the post authorisation safety study (i.e., D3250R00026) are limited and therefore insufficient to inform on drug-associated risk in this population. Monoclonal antibodies, such as benralizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential exposure to a foetus is likely to be greater during the second and third trimester of pregnancy.

Lactation: It is unknown whether benralizumab or its metabolites are excreted in human or animal milk; therefore, risk to the breastfed child cannot be excluded.

Population in need of further characterisation:

Pregnant and lactation women: Use of benralizumab in pregnant women was evaluated in the study D3250R00026 (titled 'The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study'). Due to poor recruitment, the study was prematurely discontinued and it was not feasible to characterize the safety profile of benralizumab in this population. AstraZeneca will continue to monitor the safety of benralizumab in pregnant and lactating patients as part of routine safety surveillance activities.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the Safety Concerns

Table 2-15 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant and lactating women

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

There are no additional pharmacovigilance activities.

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Not applicable				
Category 2 – Not applicable				
Category 3 – Not applicable				

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None	None
Important potential risks	
None	None
Missing Information	
Use in pregnant and lactating women	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.6

SmPC = summary of product characteristics

5.2 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.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	No risk minimisation measures	None
Important potential risks		
None	No risk minimisation measures	None
Missing information		
Use in pregnant and lactating women	Routine risk minimisation measures: SmPC Section 4.6	None

SmPC = summary of product characteristics

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR FASENRA (BENRALIZUMAB)

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

FASENRA™'s prescribing information and its package leaflet give essential information to healthcare professionals and patients on how FASENRA™ should be used.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

FASENRA™ is authorised for an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients and is authorised for the add-on treatment of adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (EGPA). It contains benralizumab as the active substance. For the treatment of severe asthma it is given by SC injection Q4W for the first 3 doses, and then Q8W thereafter. For the treatment of EGPA it is given by SC injection Q4W.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of FASENRA™, together with measures to minimise such risks and the proposed studies for learning more about FASENRA™'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 prescribing information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

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

6.2.1 List of Important Risks and Missing Information

Important risks of FASENRA™ 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 FASENRA™. 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.

Table 6-1 List of Important Risks and Missing Information

Important identified risks	None
Important potential risks	None
Missing Information	Use in pregnant and lactating women

6.2.2 Summary of Important Risks

Table 6-2 Missing information: Use in pregnant and lactating women

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6

6.2.3 Post-authorisation Development Plan

6.2.3.1 Studies Which are Conditions of the Marketing Authorisation

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

6.2.3.2 Other Studies in Post-authorisation Development Plan

There are no studies required for FASENRA™.

LIST OF REFERENCES

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