19 September 2024
EMA/598631/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fasenra

International non-proprietary name: Benralizumab

Procedure No. EMEA/H/C/004433/II/0052

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

ACQ-6	Asthma Control Questionnaire (6-item version)
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse Event
AI	Autoinjector
ANCA	Anti-neutrophil cytoplasmic antibody(ies)
ANCOVA	Analysis of covariance
APFS	Accessorised pre-filled syringe
BVAS	Birmingham Vasculitis Activity Score
CI	Confidence interval
CL	Clearance
COVID-19	Coronavirus disease – 2019
CSR	Clinical Study Report
CV	Coefficient of variation
CYC	Cyclophosphamide
DB	Double-blind
EBEs	Empirical Bayes estimates
ECG	Electrocardiogram
ECL	Electrochemiluminescence
EGPA	Eosinophilic granulomatosis with polyangiitis
EoE	Eosinophilic esophagitis
EoI	Extension of the indication
EULAR	European alliance of associations for rheumatology
F	Bioavailability
FDA	US Food and Drug Administration
IIV	Inter-individual variability
FAS	Full Analysis Set
Fc	Fragment crystallisable
FcγR	Fc-gamma receptor
GCP	Good Clinical Practice
GI	Gastrointestinal

HES	Hypereosinophilic syndrome
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IIV	Inter-individual variability
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor subunit alpha
IP	Investigational product
IPD	Important protocol deviation
IRB	Institutional Review Board
IV	Intravenous(ly)
LLOQ	Lower limit of quantification
LPC	Low positive control
mAb	Monoclonal antibody
MRD	Minimum required dilution
nAb	Neutralizing antibody
NI	non-inferior/non-inferiority
NK	Natural killer
NYHA	New York Heart Association
OCS	Oral corticosteroids (i.e., prednisone/prednisolone or equivalent dose of prednisone/prednisolone)
OLE	Open label extension
PD	Pharmacodynamic
PDGFRA	Platelet-derived growth factor receptor alpha
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PK	Pharmacokinetic
PPK	Population pharmacokinetic
PT	Preferred term

Q4W	Every 4 weeks
RoW	Rest of World
RUV	Residual unexplained variability
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SF-36v2	Short Form 36 Item Health Survey (Version 2, Acute Recall)
SNOT-22	Sino-Nasal Outcomes Test 22
SOC	System organ class
SSQ	Sino-nasal Symptoms Questionnaire
Vc	Central volume of distribution
VDI	Vasculitis Damage Index
Vp	Peripheral volume of distribution
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-GH	Work Productivity and Activity Impairment Questionnaire - General Health
WT	Body weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 22 November 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of eosinophilic granulomatosis with polyangiitis for Fasenra, based results from study D3253C00001 (Mandara); this was a randomised, double-blind, multicentre, parallel group, active-controlled, non-inferiority study that evaluated the efficacy and safety of benralizumab compared with mepolizumab in treatment of patients with EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.1 of the RMP has also been submitted. In addition, the MAH took this opportunity to introduce editorial changes. As part of the application, the MAH is requesting a 1-year extension of the market protection.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The MAH withdrew the request during the procedure.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: N/A

Timetable	**Actual dates**
Submission date	22 November 2023
Start of procedure:	23 December 2023
CHMP Rapporteur Assessment Report	20 February 2024
PRAC Rapporteur Assessment Report	21 February 2024
PRAC members comments	28 February 2024
PRAC Outcome	7 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 March 2024
Request for supplementary information (RSI)	21 March 2024

Timetable	Actual dates
CHMP Rapporteur Assessment Report	3 June 2024
PRAC Rapporteur Assessment Report	3 June 2024
PRAC members comments	5 June 2024
Updated PRAC Rapporteur Assessment Report	6 June 2024
PRAC Outcome	13 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	21 June 2024
Request for supplementary information (RSI)	27 June 2024
CHMP Rapporteur Assessment Report	4 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	13 September 2024
Opinion	19 September 2024

2. Scientific discussion

2.1. Introduction

Benralizumab is currently indicated "as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists". The Applicant is seeking an extension of the marketing authorization (MA) for the following indication: "Fasenra is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis".

2.1.1. Problem statement

Disease or condition

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) is a rare disease characterised by potentially life-threatening systemic eosinophilic vasculitis of small and medium sized vessels in association with asthma, sinusitis, transient pulmonary infiltrates, and neuropathy. The mean age at diagnosis of EGPA is 50 (± 14) years, with a gender ratio of approximately 1:1. The EGPA is a part of group of vasculitis associated with Anti-neutrophil cytoplasmic antibody(ies) (ANCAs). Eosinophils play a pathological role across the spectrum of EGPA regardless of ANCA status.

State the claimed therapeutic indication

Authorised: Fasenra is indicated as an add on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long acting β agonists (see section 5.1).

Claimed:

Eosinophilic granulomatosis with polyangiitis (EGPA)

Fasenra is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (see section 5.1).

Epidemiology and risk factors, screening tools/prevention

The incidence and prevalence of EGPA, respectively, is 1.22 per million and 15.27 per million globally, 1.07 per million and 12.13 per million in the EU, and 4.0 per million and 17.0-18.0 per million in the US (Jakes et al 2021). The prevalence of ANCAs in patients with EGPA varies widely (30–47% EGPA patients are ANCA positive) and their clinical significance remains uncertain. The prevalence of EGPA has increased over recent years likely due to an improvement in diagnostic methods, disease recognition, and improved survival. The cumulative survival rates at 5 and 10 years from the disease onset are 88-97% and 78-89%, respectively. Despite the primary causes of mortality changing over time from cardiac manifestations to treatment-related causes, including infection and toxicity, the morbidity remains high. Patients with EGPA experience a relapsing, remitting disease course, with a reported relapse rate of 20% to 30% despite standard of care treatment.

Biologic features

Eosinophils are the key effector and immunoregulatory cells in all stages of EGPA. Eosinophilia and vessel inflammation are hallmarks of EGPA and main effectors of organ damage. Eosinophils induce pathogenesis by means of tissue and vascular infiltration and inflammation through various mediators; it is therefore hypothesized that direct or indirect depletion of eosinophils through blockade of IL-5 or the IL-5R could be efficacious in the treatment of EGPA.

Clinical presentation, diagnosis

Published classification criteria highlight the importance of blood eosinophilia, asthma, and nasal polyps to classify EGPA among other forms of vasculitis. Almost all patients with EGPA have asthma, which is typically severe, corticosteroid dependent, and precedes the onset of systemic disease by several years. Multiple organs can be affected by EGPA, including the heart, upper and lower airways, skin, vasculature, gastrointestinal system, kidneys, and nervous system. Patients with EGPA have reduced Health-related quality of life (HRQoL) compared with the general population, with decreased scores across all dimensions of the SF-36v2 questionnaire: general health, physical functioning, emotional role limitations, physical role limitations, social functioning, mental health, bodily pain, and vitality.

Patients with EGPA experience a relapsing, remitting disease course, with a reported relapse rate of 20% to 30% despite standard of care treatment. Recurrent relapse is considered to place the patient at risk of permanent tissue and/or organ damage, secondary to the vasculitis process.

Vasculitis damage index (VDI) records organ damage related to chronic changes or scarring that has occurred since the onset of vasculitis, either as a result of the disease itself, the side effects of treatment, or any other comorbidity occurring after the diagnosis of vasculitis. Higher VDI scores are associated with disease burden and mortality and have been reported in older EGPA patients, those with longer duration of corticosteroid use, and those with a history of disease relapse.

Management

Systemic corticosteroids, immunosuppressants, and biologics (rituximab and mepolizumab) are currently recommended in treatment guidelines for EGPA, with mepolizumab being the only approved therapy. Systemic corticosteroids and immunosuppressants are widely used for the treatment of patients with

EGPA despite a paucity of evidence supporting their efficacy in this disease. A key therapeutic goal in the treatment of EGPA is to induce and maintain remission while reducing the burden of corticosteroids and immunosuppressants often associated with significant adverse events, including toxicity, and a high relapse rate. Rituximab has limited evidence to support efficacy in EGPA, particularly in controlling airway manifestations and reducing corticosteroid dependency. A high proportion of EGPA patients treated with mepolizumab either do not achieve remission and/or relapse, with limited reduction in corticosteroid dependency. Therefore, a significant unmet medical need remains for patients with EGPA.

2.1.2. About the product

Benralizumab is a humanized, afucosylated mAb (IgG1, IgG1κ) that binds to the human IL-5Rα on the target cell and induces direct, rapid, and nearly complete depletion of eosinophils through antibody-dependent cellular cytotoxicity. Benralizumab was approved by the FDA and by the EMA for the add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype. AstraZeneca is pursuing the development of benralizumab for the treatment of patients with EGPA. Benralizumab is a sterile liquid solution presented in accessorised pre-filled syringe (APFS) or autoinjector (AI) intended for subcutaneous administration. Each APFS contains a nominal label claim of 30 mg of benralizumab in a 1.0 mL volume. Drug Product contains a target of 30 mg/mL benralizumab in histidine/histidine-HCl, trehalose dihydrate, polysorbate 20. There were no formulation changes to the commercial Drug Product (APFS presentation) used in the MANDARA study. For the EGPA indication, the applicant proposes to use the currently approved 30 mg Drug Product formulation and presentations (APFS and AI).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

There were no formal or informal interactions with EMA regarding MANDARA study design. Furthermore, the PDCO reviewed the MANDARA study design in relation to the paediatric study design and requested efficacy outcomes for the paediatric study to be similar to the adult (MANDARA) study (P/0173/2023).

Key points of the regulatory advice obtained from FDA in formal interactions regarding MANDARA study design are summarised below:

- The applicant initially proposed a single Phase III, randomised, placebo-controlled study to support registration in EGPA. Given the severity of disease, the applicant proposed an event-driven study design that would permit patients who discontinue to be allowed to go onto best available therapy.
- The FDA found a single pivotal study acceptable in orphan/rare disease. However, the FDA expressed ethical concerns with a placebo-controlled study design due to the existence of an available treatment for this serious disease and recommended an active controlled design against mepolizumab. The Division (Pulmonary, Allergy and Rheumatology Products) also expressed concern with the proposed dosing regimen (60 mg first dose followed by 30 mg Q8W) due to a lack of initial intensive dosing (i.e., 30 mg Q4W x 3) and at minimum recommended the asthma approved dose and dosing regimen in the EGPA study.
- The objective of the meeting was to gain FDA's agreement on 1) the revised Phase III active-controlled, NI study design, 2) the selected NI margin and statistical approach, and 3) the plans for registration upon completion of the DB treatment period.
- In the preliminary meeting comments, FDA confirmed agreement with the NI study design, primary and secondary endpoints, and the 30 mg Q4W dosing regimen. It was suggested there may be some flexibility in the sample size and NI margin if the applicant could provide adequate

justification in the setting of a rare disease, a well conducted study, and inclusion of indirect comparison to the placebo rate seen in the mepolizumab study (MIRRA).

- The applicant requested clarification on methods for comparing benralizumab remission rate to the placebo remission rate seen in the mepolizumab study. As this is a novel approach, the FDA responded that validity needs to be established and demonstrated to support the indirect comparison. The FDA suggested the applicant to provide a detailed justification in the protocol and submit the SAP proposal for FDA review.
- The SAP and detailed justification for the selection of NI margin and historical comparison were submitted to the FDA on 3 Sep 2019.

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has also provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Benralizumab is a humanized, afucosylated, monoclonal antibody of relative molecular weight 150 kilodaltons. As per the ERA Guideline (EMEA/CHMP/SWP/4447/00 Rev1, 2006), vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of benralizumab. Considering the above data, benralizumab is not expected to pose a risk to the environment

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial D3253C00001 (Mandara) was performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1. Tabular overview of clinical studies

Type of study	Study identifier	Location of study report in Module 5	Objectives of the study	Study design and type of control	Test products, Dosage regimen, Route of administration	No. of subjects rand/treated	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Controlled Clinical Studies									
Efficacy and safety	D3253C00001 (MANDARA)	5.3.5.1	Evaluate the efficacy and safety of benralizumab compared to mepolizumab in the treatment of EGPA in patients receiving standard of care therapy	Randomised, DB, active-controlled, parallel group, multicentre	1 x benralizumab 30 mg plus 3 placebo to mepolizumab SC injections Q4W 3 x mepolizumab 100 mg plus 1 placebo to benralizumab SC injections Q4W	Benralizumab: 70/70 Mepolizumab: 70/70	Adults with relapsing or refractory EGPA	52 weeks of randomised treatment (DB period) followed by optional OLE period of at least 1 year	DB period complete, OLE period ongoing; Full report for primary database lock

DB = double-blind; EGPA = eosinophilic granulomatosis with polyangiitis; No. = number; OLE = open-label extension; Q4W = every 4 weeks; rand = randomised; SC = subcutaneous

2.3.2. Pharmacokinetics

Data from the pivotal MANDARA study were used for the evaluation of PK, PD and immunogenicity profile of benralizumab in EGPA:

Table 2. Overview of Benralizumab Clinical Studies with PK, PD and Immunogenicity Assessments

Study Name (Study Number)	Study Type and Design	Study Population	Dosing Regimen	Overall Objectives	PD Markers	PK, PD, and ADA Assessment Points
MANDARA (D3253C00001)	Phase III, randomised, active-controlled, parallel group, multicentre, 52-week double-blind study with an OLE	Patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy; A total of 140 eligible patients were randomised	<u>DB period:</u> 1 x benralizumab 30 mg plus 3 placebo to mepolizumab by SC injections Q4W or 3 x mepolizumab 100 mg plus 1 placebo to benralizumab by SC injections Q4W <u>OLE period:</u> benralizumab 30mg by SC injection Q4W	To compare the efficacy and safety of benralizumab 30 mg versus mepolizumab 300 mg administered by SC injection Q4W in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy	Blood (serum) eosinophils	<u>DB period:</u> PK: Pre-dose at Weeks 0, 4, 12, 24, 36, 48, and 52; post-dose at Weeks 1 and 25 ADA/nAb: Pre-dose at Weeks 0, 12, 24, 36, 48, and 52 PD: Pre-dose at Screening and Weeks 0, 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 44, 48, and 52

ADA = anti-drug antibody; DB = double-blind; EGPA = eosinophilic granulomatosis with polyangiitis; nAb = neutralising antibody; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; Q4W = every 4 weeks; SC = subcutaneous

No new biopharmaceutical studies were conducted in support of the proposed EGPA indication.

Serum samples for the assessment of benralizumab concentrations, Anti-drug antibodies (ADA) and neutralizing activity of ADA from patients with EGPA who enrolled in the MANDARA study were collected according to the schedule of activities described in the clinical protocol of the study. Benralizumab concentrations were measured using a validated Electrochemiluminescence (ECL) immunoassay which utilises a sandwich format with capture and detection mAbs recognizing 2 distinct epitopes on the benralizumab molecule. The assay was initially validated by MedImmune in both human plasma and serum and subsequently transferred to PPD where it was partially validated for use in EGPA patient serum. The results of the partial validation of the immunoassay (assay performance: accuracy and precision, electivity, and specificity) supported the validity of the method to quantify benralizumab accurately and precisely in EGPA patient serum, with an LLOQ of 3.86 ng/mL, quantitative range of 3.86 to 1250 ng/mL, and MRD of 1:50.

Assessment of Anti-Drug Antibodies to Benralizumab -Assessment of Neutralising Activity of Anti-Drug Antibody Responses: Assessment of ADA responses to benralizumab followed a 3-tiered testing approach, which consisted of validated assays for detection (screening assay), specificity (confirmatory assay), and semi-quantification (titre assay). Confirmed ADA positive samples from the Phase III study were subsequently tested for *in vitro* neutralising activity, as assessed by a ligand-binding nAb assay. ADA screening and ligand-binding neutralizing antibody assays were validated at PPD. Sensitivity and drug tolerance were estimated for both assays. Selectivity and specificity were also investigated in EGPA patient sera. The performance of both assays was shown to be stable and reliable when monitored during the MANDARA study.

In general, bioanalytical methods used have been appropriately described and validated, and deemed fit for purpose, as commented by the CHMP.

Pharmacokinetic analysis was performed only on samples from EGPA patients who received benralizumab 30 mg Q4W during the 52-week DB period. Geometric mean benralizumab trough serum concentrations reached steady state by Week 12 (1797.94 ng/mL) during the DB period (Table 3). Serum samples from week 1 and 25 were collected following benralizumab administration.

Table 3. Benralizumab Serum Concentration (ng/mL) (PK Analysis Set)

Time point	Statistic	Benralizumab 30 mg (N = 67)
Baseline	n	65
	n < LLOQ	64
	Geometric mean (CV[%])	6.09 (NC)
	Median	0
	Minimum, Maximum	0, 6.09
Week 1	n	63
	n < LLOQ	0
	Geometric mean (CV[%])	2154.93 (33.60)
	Median	2182.65
	Minimum, Maximum	989.91, 4094.65
Week 4	n	67
	n < LLOQ	0
	Geometric mean (CV[%])	1118.88 (48.82)
	Median	1140.58
	Minimum, Maximum	419.65, 6999.28
Week 12	n	66
	n < LLOQ	0
	Geometric mean (CV[%])	1797.94 (50.33)
	Median	1996.48
	Minimum, Maximum	676.03, 4268.72

Time point	Statistic	Benralizumab 30 mg (N = 67)
Week 24	n	53
	n < LLOQ	0
	Geometric mean (CV[%])	2009.30 (63.63)
	Median	2019.7
	Minimum, Maximum	383.36, 6961.92
Week 25	n	60
	n < LLOQ	0
	Geometric mean (CV[%])	2992.87 (59.00)
	Median	3222.53
	Minimum, Maximum	623.14, 6897.36
Week 36	n	66
	n < LLOQ	0
	Geometric mean (CV[%])	1829.28 (67.35)
	Median	2094.4
	Minimum, Maximum	212.22, 6512.35
Week 48	n	63
	n < LLOQ	0
	Geometric mean (CV[%])	1868.93 (59.34)
	Median	1792.87
	Minimum, Maximum	322.46, 5124.64
Week 52	n	62
	n < LLOQ	0
	Geometric mean (CV[%])	1837.16 (58.46)
	Median	1933.985
	Minimum, Maximum	339.97, 5608.26

All < LLOQ values were substituted with the value of 0.
Baseline is the last non-missing value prior to administration of the first dose of study treatment.
CV = coefficient of variation; LLOQ = lower limit of quantification (3.86 ng/mL); N = number of patients in treatment group; n = number of patients in analysis; PK = pharmacokinetics
Source: Table 14.2.4.1

Population Pharmacokinetic Analyses: Population PK modelling was conducted to characterise the PK properties of benralizumab in patients with EGPA. The benralizumab PK analysis data set consisted of 67 subjects and 516 benralizumab PK observations. Previously established two-compartment model (legacy model) with first-order absorption and elimination developed during the severe asthma clinical development programme for adult and adolescent patients was used to establish the PK profile of benralizumab in EGPA patients (final model) by comparing the PK parameter estimates from the MANDARA study with the population pharmacokinetic (PPK) estimates from the legacy model. The starting point model was originally proposed to be the model developed for the eosinophilic esophagitis (EoE) population, which was itself a model derived based on the priors of the asthma indication. It was considered more appropriate to use the model developed in the asthma indication as a starting point, for which there were extensive rich and sparse data from nine clinical trials available. Associated inter-individual variability (IIV) and residual unexplained variability (RUV) were included in the PPK analysis (Table 4):

Table 4. Comparison of the Parameter Estimates Between the Final Benralizumab PK Model and the Legacy Benralizumab PK Model

	Final Model		Legacy Model	
Parameter	**Value**	**RSE (%)**	**Value**	**RSE (%)**
PK Parameters				
CL (L/day)	0.218	4.29	0.289	2.25
V_c (L)	3.14	3.22	3.13	3.22
Q (L/day)	0.739	5.28	0.739	5.09
V_p (L)	2.50	4.27	2.52	4.44
k_a $t_{1/2abs}$ (day)	3.26	6.19	3.56	7.22
F	0.589	(FIX)	0.589	2.51
Covariate Effect on PK Parameters				
WT on CL	0.799	4.19	0.807	4.24
ADA on CL	1.25	8.28	2.24	1.52
Injection location 'thigh' on F	1.25	3.30	NA	NA
WT on V_c	0.789	13.3	0.803	13.3
WT on V_p	0.518	20.5	0.528	20.5
Inter-Individual Variability of PK Parameters				
IIV CL (CV)	0.300	9.55	0.242	3.73
IIV V_c (CV)	0.239	8.02	0.244	8.40
IIV Q (CV)	0.0894	(FIX)	0.0894	(FIX)
IIV V_p (CV)	0.439	5.22	0.447	5.42
IIV k_a (CV)	0.796	5.42	0.831	5.33
IIV F (CV)	0.171	(FIX)	0.171	11.3
RUV (CV)	0.175	11.7	0.250	2.76

Due to rounding, the values for the legacy model in this table might be slightly different from the values reported in the publication from Yan et al 2019.

The RSE for IIV and RUV parameters were reported on the approximate SD scale.

ADA = anti-drug antibody; CL = clearance; CV = coefficient of variation; F = bioavailability; IIV = inter-individual variability; k_a = first-order absorption rate constant; NA = not applicable; PK = pharmacokinetic(s); Q = inter-compartmental clearance; RSE = relative standard error; RUV = residual unexplained variability; SD = standard deviation; $t_{1/2}$ = half-life; V_c = central volume of distribution; V_p = peripheral volume of distribution; WT = weight

Source: Table A3-2, D3253C00001 PPK Report, Module 5.3.3.5

In line with the legacy model data, body weight was a significant covariate on CL, Vc, and Vp, ADA was a significant covariate on CL and injection location was a significant covariate on F (1.25, RSE: 3.30). This finding is consistent with results from the AMES study where exposure after administration in the thigh was approximately 15% to 30% higher compared to abdomen and upper arm. No other covariate-parameter relationships were identified. Overall, the parameter estimates were similar between the two models, however Clearance (CL) was predicted to be approximately 25% lower in patients with EGPA, compared to patients with asthma/severe asthma.

Exposure metrics of benralizumab were compared between the 2 models: simulated benralizumab concentrations resulting from current final PK model compared with simulated benralizumab concentrations from the legacy model and sampled population (n = 1000). For both simulations 30 mg Q4W dosing was assumed, and subjects were assumed to be ADA negative and to have received the administered dose in any other location than the thigh. Based on the summary statistics of the exposure metrics from the models/populations, the simulated benralizumab concentrations and exposure metrics for the final model

are higher compared to those simulated for the legacy model. This is attributed to the lower clearance estimated for the current final model. In addition, the variability in exposure metrics and benralizumab concentrations simulated with the current final model is higher compared to the legacy model. However, the results of these simulations should be considered with caution, in light of the relatively high shrinkage observed for the empirical Bayes estimates (EBEs) from both the current final model and legacy model, especially when evaluating the outer percentiles of the data.

The final population PK model for benralizumab in adult patients with EGPA provided a good description of the observed data overall and in ADA status and body weight (WT) subgroups.

- While the estimated parameter values were similar between the two patient populations, CL was found to be lower in patients with EGPA compared to patients with asthma.
- The final model included the covariate effects of ADA status on CL, injection location on F, and WT on CL, Vc and Vp. CL was approximately 25% higher when ADA status was positive, compared to a negative ADA status, F was also around 25% higher when doses were administered in the thigh compared to other injection locations, and CL, Vc and Vp increased with increasing WT. No additional covariate-parameter relationships were identified.
- Model simulations demonstrated higher benralizumab concentrations and a decreased WT adjusted CL when simulated with the current final model or simulated using the legacy model. As a result, the exposure parameters $t_{1/2}$, $C_{min,ss}$, $C_{av,ss}$, $C_{max,ss}$, and $AUC_{t,ss}$ were moderately increased (22-37%) for the current final model compared to the legacy model. These results should be considered with care, in light of the relatively high shrinkage observed for the EBEs from both the current final model and legacy model, especially when evaluating the outer percentiles of the data.

Assumptions directly related to the final results and conclusions of the current analysis are listed in Table 5:

Table 5. Important assumptions related to the final results and conclusions

Assumption	**Reasons for the assumption**	**Justification**	**Limitations/Risk mitigation**
The PK characteristics of benralizumab are similar in adolescents/adults with asthma/- severe asthma and in patients with EGPA (current data).	The structure of the legacy model as well as priors were built based on the parameter estimates from the legacy model were used for model development.	Available data in the MANDARA study was limited and sparse.	A different model might be obtained when developing from scratch based on rich data in patients with EGPA.
Omitting observations below the LLOQ has no impact on the parameter estimates of the final model.	A number of observations were below the LLOQ.	Omitting a small number of BLQ observations usually does not impact the parameter estimates of the final model and is a common practice	The conclusions of the analysis are not dependent on this assumption.
The predictions of the individual parameters can be used to generate individual exposure metrics even if the	Shrinkage is a property of the data and not of the model, implying that model modifications will	Without additional knowledge to inform the estimation of the EBEs, the individual estimates cannot be estimated with	A high shrinkage may complicate the detection of a possible exposure-response relationship. In the exposure-response

associated shrinkages are above what is usually considered as a high threshold (30%).	not have a large effect on shrinkage	less shrinkage. However, the population parameters are not affected by the shrinkage and no modeling decision was taken based on EBE-based diagnostics.	analysis this may be tested by estimating individual PK parameters simultaneously with the pharmacodynamic (PD) model.

Absorption and Distribution

In patients with EGPA, the estimated Vc and Vp of benralizumab were 3.14 L (RSE%: 3.22) and 2.50 L (RSE% 4.27), respectively. The IIV on Vc and Vp (%CV) were 23.9% and 43.9%, respectively.

Elimination

The estimated CL of benralizumab was 0.218 L/day (RSE%: 4.29), and IIV on CL (%CV) was 30.0% (Table 2) in patients with EGPA. CL was predicted to be approximately 25% lower in patients with EGPA compared to patients with severe asthma.

Since from the current PopPK model it cannot be concluded that the PK findings in EGPA patients are consistent with that of asthma. The interpretation of the model results is hampered due to the mainly sparse sampling data included in the model and high shrinkage values. Although, the individual estimates of exposure metrics are hampered by the high shrinkage, population parameters are not affected. Thus, the applicant included the lower CL in EGPA patients of 0.22 L/day from the final model in section 5.2 of the SmPC. Furthermore, the Applicant should remove the phrase that findings in EGPA patients were consistent with those in asthma (see comment on SmPC 5.2).

Special populations

The effect of race, sex, age, and baseline eosinophil count on benralizumab CL were evaluated.

	Overall N=67
Sex	
Male	25 (37%)
Female	42 (63%)
Race	
Asian	9 (13%)
White	50 (75%)
Multiple or other	3 (4.5%)
(Missing)	5 (7.5%)
ADA status	
ADA negative	61 (91%)
ADA positive	6 (9.0%)
Concomitant paracetamol use	
No concomitant paracetamol	51 (76%)
Concomitant paracetamol	16 (24%)
Concomitant PPI use	
No concomitant PPI	34 (51%)
Concomitant PPI	33 (49%)

Numbers represent the number of subjects in each category; percentages represent the corresponding percentage of total number of subjects, specified in the column header.

Body weight: Body weight was identified as a relevant covariate, with significant effects on CL, Vc, and Vp

ADA status: Clearance was predicted to be approximately 25% higher when patients were ADA positive (allometric coefficient: 1.25)

Injection Location: Administering the benralizumab doses in the thigh resulted in an approximately 25% increase in F compared to other injection locations (arm or abdominal wall).

Pharmacokinetics using human biomaterials

In previous severe asthma studies, human biomaterial studies showed that benralizumab binds to the interleukin-5 receptor alpha subunit with high affinity on the surface of human eosinophils and basophils and binds selectively to eosinophils in a mixed leucocyte population.

2.3.3. Pharmacodynamics

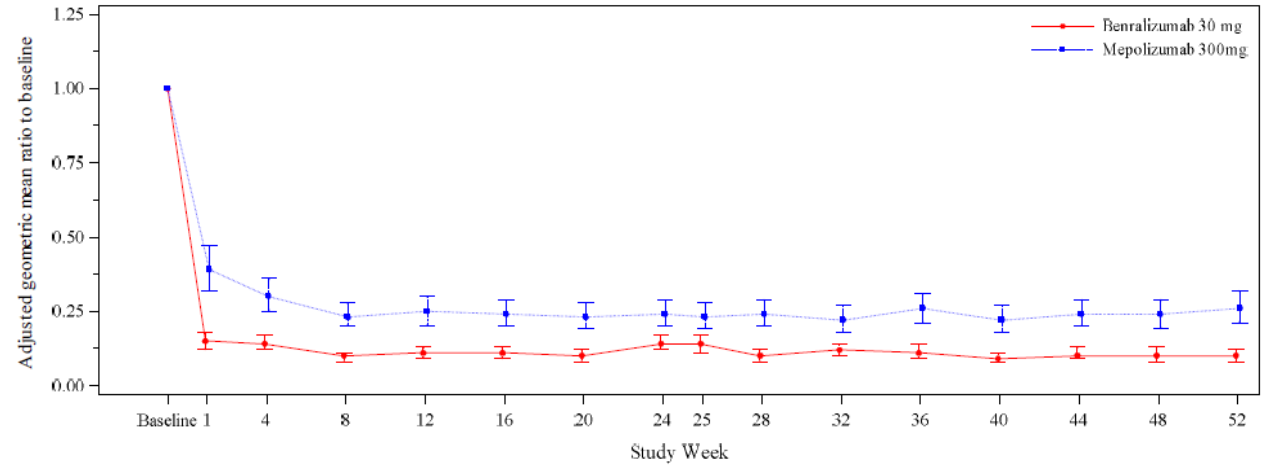
Mechanism of action

The mechanism of action of benralizumab involves depletion of eosinophils through enhanced antibody-dependent cellular cytotoxicity (ADCC). Benralizumab binds to IL-5Rα on eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIIIa, the main activating FcγR expressed on the immune effector cells, NK cells, and macrophages. The higher affinity for FcγRIIIa results in the recruitment and activation of NK cells and macrophages leading to apoptosis of eosinophils and basophils through enhanced ADCC. Depletion of blood eosinophils with benralizumab is rapid, with a 50% reduction in 1.7 ± 0.7h (mean ± SD, following a single dose, near complete, and sustained depletion of eosinophils in blood and in tissue, including airways, bone marrow, and gastrointestinal tract.

Primary and secondary pharmacology

Changes in Blood Eosinophils Over Time: A reduction in blood eosinophil count from baseline was observed in both treatment groups from Week 1, the first time point assessed, through Week 52, with greater reductions in benralizumab group compared with mepolizumab group at all time points (Figure 1). The proportion of patients with a ≥ 90% reduction in blood eosinophil count from baseline and those with an absolute blood eosinophil count of ≤ 30 cells/μL at Week 1 was higher in the benralizumab group compared with the mepolizumab group (51.5% *vs* 12.1%) with differences maintained through Week 52.

Figure 1. Absolute Eosinophil Count, Least Square Mean Change from Baseline by Timepoint, Line Plot (Full Analysis Set)



Sample Size at Timepoint (n)														
Benralizumab 30 mg: 63	68	67	65	63	64	56	56	62	61	68	64	65	64	62
Mepolizumab 300 mg: 66	63	67	64	65	66	51	60	64	66	65	64	59	60	65

The absolute eosinophil count is log-transformed. Where a result of 0 was recorded, a small value (ie, minimum of all non-missing results/2) was added prior to log transformation.
The error bars are the upper bounds and the lower bounds of the 95% CIs.
CI = confidence interval
Source: Figure 14.2.1.14.2

The proportion of patients with an absolute eosinophil count ≤ 30 cells/µL at Week 1 was higher in the benralizumab group compared with the mepolizumab group (adjusted rates of 51.5% *vs* 12.1%, p < 0.0001). This difference was maintained through Week 52 (adjusted rates at Week 52 of 69.4% *vs* 16.5%, p < 0.0001).

Greater reduction for benralizumab compared to mepolizumab was also demonstrated across all time points based on the 90% reduction threshold (p < 0.001), and at Week 1 only (p = 0.001) based on the < 150 cells/µL threshold.

Benralizumab Immunogenicity: Immunogenicity variables were summarized over DB period for all patients in the safety analysis set with at least one available ADA result. The following immunogenicity conclusions were made from MANDARA study:

In benralizumab group, both the prevalence and the incidence of ADA was 9.0% (6/67 patients). All ADA responses were treatment-induced with half of the ADA positive patients (3/67) being transiently ADA positive and the other half being persistently ADA positive (3/67). One of the persistently positive patients was also nAb positive (1/67).

Regarding the kinetics of ADA response, the percentage of ADA positive patients observed over time generally increased through Week 36 and then remained relatively constant through Week 52. Seroconversion generally occurred by Week 36. There was one nAb positive patient with positive results detected at Weeks 36 and Week 48.

In patients with positive ADA results, the median ADA titre increased until Week 48; however, because 3 out of 6 patients were transiently ADA positive, the number of ADA positive patients at each time point only ranged from 1 to 3. There was one nAb positive patient. This patient was consistently ADA positive from Week 24 through Week 52 with *in vitro* neutralising activity detected at Weeks 36 and Week 48. The detection of *in vitro* neutralizing activity coincided with the measurement of the highest titre at Week 36 and was still detectable at Week 48 although the ADA titre had decreased.

No consistent effect of ADA on mean trough benralizumab serum concentrations was observed. There was one transiently ADA positive patient with trough serum concentrations consistently (Weeks 24 to 52) below the minimum of ADA negative patients; however, the low serum concentrations occurred for this patient during time points of either ADA positive or ADA negative results. Thus, the data do not suggest an association between the low serum concentrations and ADA detection.

2.3.4. Discussion on clinical pharmacology

The interpretation of the PPK model results is hampered due to the mainly sparse sampling data included in the model and high shrinkage values. Although, the individual estimates of exposure metrics are hampered by the high shrinkage, population parameters are not affected. As the legacy model, the final benralizumab PK model was a two-compartment model with first-order absorption from the dosing site and first-order elimination from the central compartment. Both the legacy and the final benralizumab PK model included the effect of WT on CL, Vc and Vp, as well as the effect of ADA on CL. Overall, the parameter estimates were similar between the two models, although CL was predicted to be approximately 25% lower in patients with EGPA, compared to patients with asthma/severe asthma. This observation may be attributed to more frequent benralizumab dosing regimen in EGPA patients (Q4W) versus patients with severe asthma (Q4W for the first 3 doses followed by Q8W thereafter). Thus, the lower CL in EGPA patients of 0.22 L/day from the final model was included in section 5.2 of the SmPC. Furthermore, the Applicant removed the phrase that findings in EGPA patients were consistent with those in asthma. This is agreed.

Depletion of eosinophils in peripheral blood is an important marker of biological activity of benralizumab. The PD effect of benralizumab in patients with EGPA was consistent with its effect observed in patients with severe asthma, showing rapid and near complete depletion of blood eosinophils.

In benralizumab group, the percentage of patients with positive ADA result at any time and the percentage of patients who were treatment-emergent ADA positive was 9% (6/67 patients). All ADA responses were treatment-induced. Half of the patients were transiently ADA positive, and the other half were persistently ADA positive. One of the persistently ADA positive patients was also nAb positive. No consistent effect of ADA on PK, efficacy, PD and safety was observed.

2.3.5. Conclusions on clinical pharmacology

Geometric mean benralizumab trough serum concentrations reached steady state by Week 12 (1797.94 ng/mL) during the DB period. From the PPK modelling it cannot be concluded that PK findings for benralizumab in EGPA (30 mg Q4W) is overall consistent with the benralizumab PK properties in severe asthma (30 mg Q4W for the first 3 doses followed by Q8W thereafter). Based on the assessment of changes in blood eosinophil count over time and proportion of patients who reached certain thresholds of eosinophil count reduction over time, PD effect of benralizumab in patients with EGPA was consistent with its effect observed in patients with severe asthma, showing rapid and near complete depletion of blood eosinophils. The clinical pharmacology profile of benralizumab was sufficiently described and there are no outstanding issues.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose-response studies have been performed because of the rarity of EGPA. The currently approved dosing regimen of benralizumab in severe asthma is 30 mg administered SC Q4W for the first 3

doses and Q8W thereafter. According to the applicant's justification, a more frequent dosing regimen (30 mg SC Q4W) was selected for benralizumab in EGPA following discussions with FDA on: 1) the severity of the disease, 2) the extensive database of benralizumab from asthma studies, and 3) the approval of a higher dose of mepolizumab in EGPA compared with its approved dose in asthma (MIRRA). EGPA is a more severe disease than asthma often with vasculitic involvement of other organs, and the eosinophil load in patients with EGPA is often higher than in patients with asthma with an eosinophilic phenotype. In addition, clinical trial in Hypereosinophilic syndrome (HES) described in the literature also supported the use of Q4W dosing regimen of benralizumab in EGPA on the grounds that eosinophil burden in EGPA is similar to that observed in HES, with both diseases also sharing some clinical and histological feature. Benralizumab 30 mg Q4W was well tolerated and was effective in reducing blood and tissue eosinophilia in patients with several clinical subtypes of HES.

Nevertheless, while the severity of EGPA disease and approval of a higher dose of mepolizumab in EGPA compared with asthma (MIRRA) is noted by the CHMP, the applicant's decision to use the Q4W dosing regimen for benralizumab in EGPA is not driven by data specific for the proposed indication. In the responses to the CHMP's request, information on patients with EGPA controlled during the first 3 months of treatment with the loading dose of Q4W and uncontrolled disease when moved to the Q8W maintenance dose was provided, which justified the proposed dosing regimen.

2.4.2. Main study

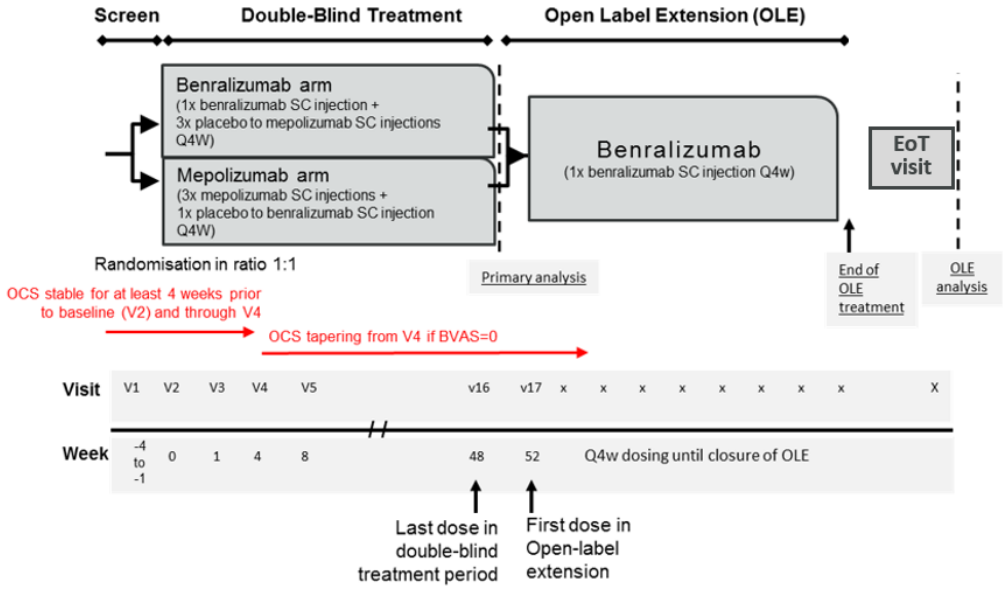
Title of Study

MANDARA study: A Randomised, Double-blind, Active-controlled 52-week Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab Compared to Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in Patients Receiving Standard of Care Therapy.

Methods

MANDARA study included a 52-week DB period in which the efficacy and safety of benralizumab were compared with an active comparator, mepolizumab (Figure 2). Eligible patients were randomized 1:1 at baseline (Visit 2) to receive benralizumab 30 mg every 4 weeks (Q4W) or mepolizumab 300 mg Q4W. The study has an ongoing Open label extension (OLE) period to assess long-term safety and tolerability of benralizumab.

Figure 2. Flow Chart of Study Design



BVAS = Birmingham Vasculitis Activity Score; EoT = End of treatment; OCS = oral corticosteroids; OLE = open-label extension; Q4W = every 4 weeks; SC = subcutaneous; V = Visit (number).

The rationale for using the Full Analysis Set (FAS) as primary analysis is that all patient data is used in this rare disease setting and the approach allows comparability with the previous mepolizumab placebo-controlled study in patients with EGPA. The analysis of safety endpoints was based on the safety analysis set. The analysis of the primary and secondary efficacy endpoints, as well as, secondary safety endpoints included all data captured during the 52-week DB treatment period, defined as the period after administration of randomised IP at Visit 2 (Week 0) and the conclusion of Visit 17 (Week 52), inclusive.

The primary database lock occurred after all randomised patients were followed up for the 52-week DB period. The study remained blinded until the primary database lock. Data from the DB period of the study (intention-to-treat approach) were included in the primary analysis. Furthermore, exposure and Adverse Event (AE) data from the OLE period available at the time of the primary database lock were also reported. Additional analyses may be performed after the primary database lock to analyze the data that were not available in the primary analysis. The final database lock occurs after the last patient has completed at least one year in the OLE period and the end of the study has been declared.

Study participants

Inclusion criteria

- Provision of signed and dated, written Informed consent form (ICF) prior to any mandatory study specific procedures, sampling, and analyses.
- Patients: males and females 18 years of age and older at the time of signing the ICF.
- Patients who have been diagnosed with EGPA for at least 6 months before screening visit (Visit 1) date based on the history or presence of: asthma plus documented eosinophilia (> 1.0 × 10^9/L and/or > 10% of leukocytes) plus documentation of at least 2 of the following additional features of EGPA:
  - (a) A biopsy showing histopathological evidence of eosinophilic vasculitis, OR perivascular eosinophilic infiltration, OR eosinophil-rich granulomatous inflammation
  - (b) Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)

(c) Pulmonary infiltrates, non-fixed

(d) Sino-nasal abnormality

(e) Cardiomyopathy (established by echocardiography or magnetic resonance imaging)

(f) Glomerulonephritis (hematuria, red cell casts, proteinuria)

(g) Alveolar hemorrhage (by bronchoalveolar lavage)

(h) Palpable purpura

(i) Positive test for ANCA immunofluorescence and/or positive test for MPO and/or PR3 antibodies

- History of relapsing OR refractory disease defined as:

  Relapsing disease: Patients should have a history of at least one confirmed EGPA relapse (i.e., requiring increase in investigator-initiated oral corticosteroids (OCS) dose, initiation/increased dose of immunosuppressive therapy or hospitalization) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 milligram per day (mg/day).

  Japan-only definition of relapsing disease: patients should have a past history of at least one confirmed EGPA relapse (i.e. requiring increase in investigator-initiated OCS dose, initiation of IV prednisolone [or equivalent], initiation/increased dose of immunosuppressive therapy, initiation/increased dose of IV Ig or hospitalization), within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day.

  Refractory disease:

  EITHER: Failure to attain remission within the 6 months prior to Visit 1 (BVAS [scale 0-63] = 0 and OCS dose ≤ 7.5 mg/day prednisolone or equivalent) following induction treatment with a standard regimen, administered for at least 3 months; OR: Within 6 months prior to screening (Visit 1), recurrence of symptoms of EGPA (not necessarily meeting the protocol definition of relapse) while tapering OCS, occurring at any dose level ≥ 7.5 mg/day prednisolone or equivalent.

- Therapy with corticosteroids: The prescribed dose of oral prednisolone or prednisone had to be stable (i.e., no adjustment of the dose), ≥ 7.5 mg/day but not > 50 mg/day) for at least 4 weeks prior to baseline (Visit 2). Stable doses of OCS other than prednisolone or prednisone could be acceptable but should be discussed with the applicant's study physician.
- Immunosuppressive therapy: If receiving immunosuppressive therapy (excluding CYC), the dosage should have been stable for the 4 weeks prior to baseline (Visit 2). Note: The dose of immunosuppressive therapy should not exceed the maximal doses used in clinical practice.
- ECG evaluation at screening (Visit 1): QTcF < 450 msec or QTcF < 480 msec for patients with bundle branch block.

Reproduction

- Negative serum pregnancy test for women of childbearing potential (WOCBP) at screening (Visit 1)
- WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomization throughout the study duration and for at least 12 weeks after last dose of Investigational product (IP). Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly).
- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal.

Women will be considered postmenopausal if they have been amenorrhoeic for ≥ 12 months prior to the planned date of randomization without an alternative medical cause.

Exclusion criteria

- Granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) or microscopic polyangiitis.
- Organ-threatening EGPA: organ-threatening EGPA as per the European League against Rheumatism criteria (Yates et al 2016), i.e., organ failure due to active vasculitis, creatinine > 5.8 mg/dL (> 513 µmol/L) within 3 months prior to screening (Visit 1) and through randomization (Visit 2).
- Life-threatening EGPA: imminently life-threatening EGPA disease defined as any of the following within 3 months prior to screening (Visit 1) and through randomization (Visit 2).
  - Intensive care required
  - Severe alveolar haemorrhage or haemoptysis requiring transfusion or ventilation or haemoglobin < 8 g/dL (< 80 g/L) or drop in haemoglobin > 2 g/dL (> 20 g/L) over a 48-hour period due to alveolar haemorrhage
  - Rapidly progressive glomerulonephritis with creatinine > 2.5 mg/dL (> 221 µmol/L) or rise in creatinine > 2 mg/dL (> 177 µmol/L) over a 48-hour period Severe gastrointestinal involvement, for example, gangrene, bleeding requiring surgery
  - Severe central nervous system involvement
  - Severe cardiac involvement, for example, life-threatening arrhythmia, cardiac failure: ejection fraction < 20%, NYHA Class III/IV (NYHA 2012), acute myocardial infarction.
- Malignancy: current malignancy, or history of malignancy, except:
  - Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix were eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to screening (Visit 1).
  - Patients with other malignancies were eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained
- Liver disease: unstable liver disease, cirrhosis, and known biliary abnormalities
- Cardiovascular: patients who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment including but not limited to:
  - Known ejection fraction < 30%, OR
  - Severe heart failure that meets NYHA Class IV (NYHA 2012), OR
  - Hospitalized in the 12 months prior to screening (Visit 1) for severe heart failure meeting NYHA Class III (NYHA 2012), OR
  - Angina diagnosed within 3 months prior to screening (Visit 1) and through randomisation (Visit 2).
- Infectious disease, Parasitic infection, Hepatitis status, Immunodeficiency History of known allergy, intolerance, or anaphylaxis to any biologic therapy or vaccine, known history of allergy or reaction to any component of the IP formulation, or other specific concurrent medical conditions or prior/concomitant/prohibited therapy or laboratory findings .

Treatments

Table 6 summarises the treatments used in the clinical study.

Table 6. Study Treatments

	Treatment 1		Treatment 2	
Study treatment name	**Benralizumab**	**Placebo to mepolizumab [a, b] (0.9% sodium chloride)**	**Mepolizumab [a b]**	**Placebo to benralizumab**
Dosage formulation	30 mg/mL solution for injection in APFS; 1 mL fill volume	Matching placebo: solutions for injection in 1 mL polypropylene syringes (3 syringes were used on each dosing occasion). Injection volume per syringe was 1 mL.	3 × 100 mg vials of powder for solution for injection reconstituted into 3 separate 1 mL polypropylene syringes for administration on each dosing occasion. Injection volume per syringe was 1 mL.	Matching placebo solution for injection in APFS; 1 mL fill volume.
Route of administration	SC injection	SC injection	SC injection	SC injection
Dosing instructions	Benralizumab active solution was administered to patients by healthcare professionals, patients, or their caregivers SC using an APFS in this clinical study.	Placebo solution was administered to patients by healthcare professionals SC using a syringe in this clinical study.	Mepolizumab active solution was administered to patients by healthcare professionals SC using a syringe in this clinical study.	Placebo solution was administered to patients by healthcare professionals SC using an APFS in this clinical study.
Packaging and labelling	Refer to pharmacy manual	Refer to pharmacy manual	Refer to pharmacy manual	Refer to pharmacy manual
Provider	Sponsor	Study site	Sponsor	Sponsor

[a] Mepolizumab was sourced locally in Japan.

[b] Mepolizumab/placebo to mepolizumab in Japan was administrated with a 2 to 3 mL polypropylene syringe and a 21 to 27 gauge needle.

APFS = accessorised pre-filled syringe; SC = subcutaneous(ly).

Objectives

Primary objective:

- To assess the durability of response to treatment with benralizumab compared with mepolizumab in patients with relapsing or refractory EGPA who were receiving standard of care therapy, assessed by the proportion of patients in remission at both Weeks 36 and 48.

Secondary objectives:

- To assess the efficacy of benralizumab compared with mepolizumab on duration of clinical remission, defined as accrued duration in weeks where a patient achieved remission.
- To assess the efficacy of benralizumab compared with mepolizumab on time to first relapse
- To assess the effect of benralizumab on corticosteroid dose required during Week 48 through Week 52 compared to mepolizumab.
- To assess the clinical benefit of benralizumab compared to mepolizumab.
- To assess the annualised relapse rate in patients receiving benralizumab compared to mepolizumab.
- To assess the proportion of patients who achieved remission within the first 24 weeks and remained in remission for the remainder of the double-blind treatment period in patients receiving benralizumab compared to mepolizumab.
- To assess additional measures of the efficacy and health status/health-related quality of life in patients receiving benralizumab compared to mepolizumab.
- To assess the safety and tolerability of benralizumab compared to mepolizumab.
- To assess the pharmacokinetics and immunogenicity of benralizumab.

Exploratory objectives:

- To assess the cumulative OCS use in response to treatment with benralizumab compared to mepolizumab.
- To evaluate the effect of benralizumab compared to mepolizumab on healthcare resource utilisation due to EGPA.
- To evaluate the effect of benralizumab compared to mepolizumab on biomarkers of inflammation[a]
- To evaluate the effect of benralizumab compared to mepolizumab on biomarkers related to the MoA, eosinophilic inflammation, and EGPA disease pathogenesis, as well as baseline predictors of response to benralizumab or mepolizumab [a]
- To characterise the patient-reported experience and treatment benefits of benralizumab compared with mepolizumab through patient interviews[a].

[a] *The following endpoints (except for CRP/ESR and IgE) related to the objective above will be reported outside of the clinical study report: biomarkers of inflammation; exploratory biomarkers in serum, nasal secretions, tissue biopsies and sputum (Mechanistic sub-study only); patient interviews to characterize patient-reported experience and treatment benefits (sub-study).*

Outcomes/endpoints

Primary endpoint: Proportion of patients with relapsing or refractory EGPA, achieving remission defined as BVAS = 0 and OCS dose ≤ 4 mg/day (main remission definition) at both Weeks 36 and 48.

Supportive endpoint: Proportion of patients who have achieved remission defined by BVAS = 0 and OCS dose ≤ 7.5 mg/day (supportive remission definition) at both Weeks 36 and 48.

Secondary endpoints:

- Total accrued duration of remission for the following categories: 0 wk, > 0 to < 12 wk, 12 to < 24 wk, 24 to < 36 wk, ≥ 36 wk. Analysis was repeated based on main and supportive remission definitions.
- Time from randomisation to first EGPA relapse, where relapse was defined as any of the following:
  - Active vasculitis (BVAS > 0); OR
  - Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR
  - Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions;

  warranting **any** of the following:
  - An increased dose of OCS therapy to 4 mg/day prednisolone total daily dose; OR
  - An increased dose or addition of immunosuppressive therapy; OR
  - Hospitalisation related to EGPA worsening.
- Based on the average daily OCS dose during Week 48 through Week 52:
  - Proportion of patients in each category: 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg and > 7.5 mg

- Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25% reduction; 25% to < 50% reduction; 50% to < 75% reduction; 75% to < 100% reduction; 100% reduction
- Proportion of patients with ≥ 50% reduction from baseline
- Proportion of patients with 100% reduction from baseline
- Proportion of patients with ≤ 4 mg in average daily dose

- Proportion of patients who had achieved any clinical benefit when meeting any of the criteria below.
- Proportion of patients who had achieved complete response when meeting all of the criteria below.
  - Remission (defined as BVAS = 0 and OCS dose ≤ 4 mg/day) at any time during the double-blind treatment period
  - ≥ 50% reduction in average daily OCS dose during Weeks 48 through 52
  - EGPA relapse free during the double-blind treatment period.

  Analysis was repeated for the supportive remission definition.
- Annualised relapse rate.
- Proportion of patients who had achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period. Analysis was repeated based on main and supportive remission definitions.
- BVAS, VDI, pulmonary function testing, asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT 22 questionnaire), health-related quality of life (SF-36v2), PGIS, WPAI-GH and blood eosinophil counts were assessed as change from Baseline over the 52-week double-blind treatment period.

  PGIC was assessed as response proportions at each weekly assessment between Visits 2 and 4.
- Safety and tolerability were evaluated based on AEs, vital signs, physical exam, clinical laboratory, and ECG.
- Serum benralizumab concentrations
- Anti-benralizumab antibodies and neutralizing antibodies.

Exploratory Endpoints:

- Cumulative OCS use, as measured by AUC for daily OCS dose, over the 52-week double-blind treatment period.
- Number of EGPA-related hospitalizations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test)
  - Biomarkers of inflammation, e.g., CRP and ESR, Exploratory biomarkers
  - Patient interviews to characterise patient-reported experience and treatment benefits (sub-study).

ACQ-6 = Asthma Control Questionnaire (6-item version); AE(s) = adverse event(s); AUC = area under the curve; BVAS = Birmingham Vasculitis Activity Score; CRP = C-reactive protein; ECG = electrocardiogram; EGPA = eosinophilic granulomatosis with polyangiitis; ER = emergency room; ESR = erythrocyte sedimentation rate; ICU = intensive care unit; IP = investigational product; MoA = mechanism of action; OCS = oral corticosteroid; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SF- 36v2 = Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22 = Sino-nasal Outcome Test-22; VDI = Vasculitis Damage Index; wk = week(s); WPAI-GH = Work Productivity and Activity Impairment Questionnaire (general health version 2.0).

Sample size

The sample size and the feasibility of completing the study were considered in the determination of the NI margin for MANDARA. Substantial evidence of mepolizumab efficacy in EGPA was demonstrated in MIRRA study with 22/68 patients (32%) treated with mepolizumab achieving remission compared with 2/68 patients (3%) on placebo. Based on the above historical evidence, the assumption was that benralizumab and mepolizumab each have a remission rate of 32%; 140 patients provide approximately 90% power to demonstrate NI with a margin of -25% at the 5% 2-sided significance level (equivalent to a 2.5% one-sided significance level). For the study to be positive, the lower 95% confidence limit for the difference between benralizumab and mepolizumab needs to be higher than the NI margin of -25%.

Randomisation

Randomisation was stratified by region. Approximately 25% of patients were expected to participate in a mechanistic sub-study to explore the PD response and MoA of benralizumab compared to mepolizumab. The aim of the sub-study was the identification of biomarkers of eosinophil recruitment, activation, and survival, investigation of inflammation and immunological mechanisms related to EGPA, and identification of baseline biomarkers predicting response to benralizumab or mepolizumab. The number of enrolled patients with ANCA-positive status or an eosinophil count < 150 cells/μL (< 0.15×10^9/L) at screening was restricted to approximately 10% and 40%, respectively, of the total number of randomized patients.

In order to limit the total number of ANCA-positive patients and the patients with eosinophil count of < 150 cells/μL (< 0.15×10^9/L), after approximately 10% and 40% respectively of the total number of randomized patients was reached, further ANCA-positive and patients with eosinophil count of < 150 cells/μL were not randomized into the study and were considered screen failures

Blinding (masking)

During the first 52 weeks of this study - the DB design - the applicant's staff involved in the study, the patients and the Investigators involved in the treatment or clinical evaluation and patient monitoring were not aware of the treatment allocation. Placebo to benralizumab and placebo to mepolizumab solutions were visually matched with benralizumab and mepolizumab solutions, respectively. All packaging and labelling of the IP were prepared in such way as to ensure blinding for all applicant and investigational site staff. Placebo to mepolizumab (0.9% sodium chloride) was prepared and dispensed by the study site using labels provided by the unblinded site pharmacist.

Statistical methods

The analysis of the primary and secondary efficacy endpoints included all data captured during the 52-week DB period. The primary analysis of exposure and AEs included data captured during both the DB period and OLE period at the time of database lock. A primary estimand was applied to the analysis of the primary endpoint whereby all data up to the end of the DB period were included, regardless of whether a patient remained on blinded IP or not, with a similar strategy used for the secondary endpoints. All hypothesis testing was reported using 2-sided tests and all p-values were nominal. Summary data presentation and the calculation of absolute change from baseline is described in the SAP.

Efficacy endpoints were analysed using the Full Analysis Set (for definitions of analysis sets, see below *Numbers Analysed*). Patients were analysed according to their randomized treatment. The rationale for

using the FAS as primary is that all patient data is used in this rare disease setting and the approach allows comparability with the previous mepolizumab placebo-controlled study in patients with EGPA. The analysis of safety endpoints will be based on the safety analysis set. The analysis of the primary and secondary efficacy endpoints and secondary safety endpoints would include all data captured during the 52-week DB treatment period, defined as the period after administration of randomised IP at Visit 2 (Week 0) and the conclusion of Visit 17 (Week 52), inclusive.

Results

Participant flow

Patient disposition shown in Table 7 was generally balanced between the benralizumab and mepolizumab groups. The proportions of patients who discontinued product administration or the study during the DB period were low and similar between groups.

Table 7. Patient Disposition (Enrolled Analysis Set)

	Number (%) of patients		
	Benralizumab 30 mg	Mepolizumab 300 mg	Total
Patients enrolled [a]	NA	NA	157
Patients randomised	70 (100)	70 (100)	140 (100)
Patients enrolled but not randomised	NA	NA	17
Screen failure	NA	NA	10
Withdrawal by patient	NA	NA	3
Adverse event	NA	NA	1
Other	NA	NA	3
Patients randomised and received treatment [b]	70 (100)	70 (100)	140 (100)
Patients who completed DB IP [b c]	69 (98.6)	67 (95.7)	136 (97.1)
Patients who discontinued IP in DB period [b]	1 (1.4)	3 (4.3)	4 (2.9)
Withdrawal by patient	1 (1.4)	2 (2.9)	3 (2.1)
Adverse event	0 (0.0)	1 (1.4)	1 (0.7)
Patients who completed DB period [b d]	69 (98.6)	67 (95.7)	136 (97.1)
Patients who completed DB IP and DB period	69 (98.6)	67 (95.7)	136 (97.1)
Patients who discontinued DB IP but completed DB period	0 (0.0)	0 (0.0)	0 (0.0)
Patients who withdrew from DB period [b]	1 (1.4)	3 (4.3)	4 (2.9)
Adverse event	0 (0.0)	1 (1.4)	1 (0.7)
Withdrawal by patient	0 (0.0)	1 (1.4)	1 (0.7)
Other	0 (0.0)	1 (1.4)	1 (0.7)
Due to COVID-19 pandemic	1 (1.4)	0 (0.0)	1 (0.7)
Patients who enrolled in OLE period [b]	66 (94.3)	62 (88.6)	128 (91.4)
Patients who discontinued IP in OLE period [b]	6 (8.6)	5 (7.1)	11 (7.9)
Withdrawal by patient	3 (4.3)	0 (0.0)	3 (2.1)
Adverse event	2 (2.9)	2 (2.9)	4 (2.9)
Lack of therapeutic response	1 (1.4)	3 (4.3)	4 (2.9)
Patients who withdrew from OLE period [b]	6 (8.6)	5 (7.1)	11 (7.9)
Adverse event	1 (1.4)	1 (1.4)	2 (1.4)
Death	0 (0.0)	1 (1.4)	1 (0.7)
Lack of efficacy	2 (2.9)	2 (2.9)	4 (2.9)
Withdrawal by patient	2 (2.9)	0 (0.0)	2 (1.4)
Other	1 (1.4)	1 (1.4)	2 (1.4)

[a] Informed consent received.

[b] Percentages were based on number of patients randomised.

[c] Completion of DB IP was based upon the number of patients completing treatment with IP up to and including Week 48 (Visit 16).

[d] Includes patients who discontinued IP but attended all study visits in DB period.

Three patients were enrolled but withdrew consent due to COVID-19, therefore not randomised.

COVID-19 = coronavirus disease 2019; DB = double-blind; IP = investigational product; NA = not applicable; OLE = open-label extension

	Number (%) of patients		
	Benralizumab 30 mg	Mepolizumab 300 mg	Total
Withdrawal by patient	2 (2.9)	0 (0.0)	2 (1.4)
Other	1 (1.4)	1 (1.4)	2 (1.4)

[a] Informed consent received.
[b] Percentages were based on number of patients randomised.
[c] Completion of DB IP was based upon the number of patients completing treatment with IP up to and including Week 48 (Visit 16).
[d] Includes patients who discontinued IP but attended all study visits in DB period.

Three patients were enrolled but withdrew consent due to COVID-19, therefore not randomised.
COVID-19 = coronavirus disease 2019; DB = double-blind; IP = investigational product; NA = not applicable; OLE = open-label extension

Recruitment

This study was conducted at 50 centers in 9 countries with a total of 157 enrolled subjects. The majority of participants were enrolled in France (33 subjects, 23.6%), followed by Canada (19 subjects, 13.6%), Italy, United Kingdom (18 subjects, 12.9%) and Germany (17 subjects, 12.1%). Enrolment from United States (13 subjects, 9.3%), Israel (10 subjects, 7.1%), Japan (8 subjects, 5.7%) and Belgium (4 subjects, 2.9%) was of a slightly smaller scale. The first patient enrolled on 29 October 2019; the last patient last visit in the DB period of the study was on 10 August 2023. The primary clinical data cut-off date was 10 August 2023.

Conduct of the study

There were 4 amendments in the original MANDARA clinical study protocol and all were approved by the applicant before being submitted to a regulatory authority and/or an IRB/IEC. None of the amendments had an impact on the analysis of the primary endpoint or affected the integrity of the trial. Substantial changes in the conduct of the study that were implemented by protocol amendments are summarized in Table 8.

Table 8. Protocol Amendments Related to Changes in Study Conduct

Amendment Number/Date	Key details of Amendment	Main reason(s) for Amendment
Amendments made after the start of patient recruitment		
1 (Version 2.0) 27 March 2020	This was a non-substantial amendment.	The protocol was amended to correct and/or clarify inclusion/exclusion criteria, clarify that nasal secretions will be collected from selected sites.
2 (Version 3.0) 04 August 2020	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigations that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.
	Reduced the frequency of spirometry assessments to 12 week intervals (Visit 2, 6, 9, 13, 16, 17) in the Double-blind treatment period. Spirometry is no longer required at IPD/EOT visit.	To decrease patient and HCP exposure to potential pathogens given COVID-19 pandemic.
	Added a bullet to Exclusion Criterion no 14: "- *Receipt of any other marketed or investigational biologic products within 4 months or 5 half-lives prior to screening, whichever is longer*" Modified Exclusion Criterion no 22: "Other investigational *non-biologic* product: receipt of any investigational *non-biologic product* ~~drug~~ within 30 days or 5 half-lives prior to screening (Visit 1) whichever is longer."	These changes were implemented to align with updated safety recommendations based on accumulated safety data.

Amendment Number/Date	Key details of Amendment	Main reason(s) for Amendment
	Section 8.4.2.1: Modified text, "If a patient becomes pregnant during the course of the study, IP should be ~~discontinued immediately~~ *temporarily withheld* and a conversation between the Investigator and a Study Physician has to take place to determine whether continuation on IP or discontinuation of IP is in the best interest of the patient" Section 7.1 Patients will be discontinued from IP in the following situations: Removed bullet "Pregnancy"	These changes were implemented to follow current sponsor safety recommendations in studies with benralizumab
3 (Version 4.0) 24 February 2021	This was a non-substantial amendment.	The protocol was amended to introduce the possibility of self/at-home administration of benralizumab during the OLE period of the study.
4 (Version 5.0) 11 April 2023	Added a new Schedule of Assessments presenting the assessments to be performed during Year 4 onwards in the OLE period.	To ensure continuity of treatment for patients who would end Year 3 of the OLE period before all patients have been allowed at least one year of treatment with open-label benralizumab.
	Changed one secondary objective and clarified one corresponding secondary endpoint and added corresponding secondary endpoints.	To assess the steroid sparing effect of treatment.
	Added a secondary objective.	To combine current endpoints to assess clinical benefit in a clinically relevant way.
	Added derivation of the new endpoints.	To present how the new endpoints will be derived.

COVID-19 = coronavirus disease 2019; EOT = end of treatment; GCP = Good Clinical Practice; HCP = healthcare provider; IP = investigational product; IPD = investigational product discontinuation; OLE = Open-Label Extension

Changes to planned analysis related to protocol amendments were applied before unblinding of the study data and this is acceptable.

Baseline data

EGPA disease history and baseline characteristics (Table 9) were summarized for each treatment group using descriptive statistics on FAS. Median age of subjects was 55 years. The majority of participants were between 18-65 years old. Gender representation was equally distributed between treatment groups.

Table 9. EGPA Disease History and Baseline Characteristics

EGPA Disease History and Baseline Characteristics (Full Analysis Set)

Characteristics	Statistics or category	Benralizumab 30 mg (N = 70)	Mepolizumab 300 mg (N = 70)	Total (N = 140)
EGPA disease history				
EGPA disease characteristics				
Asthma, n (%)	Yes	70 (100.0)	70 (100.0)	140 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
Eosinophilia, n (%)	Yes	70 (100.0)	70 (100.0)	140 (100.0)
	No	0 (0.0)	0 (0.0)	0 (0.0)
Biopsy Evidence of EOS Vasculitis/Inflammation, n (%) [a]	Yes	20 (28.6)	33 (47.1)	53 (37.9)
	No	50 (71.4)	37 (52.9)	87 (62.1)
Neuropathy, n (%) [b]	Yes	38 (54.3)	45 (64.3)	83 (59.3)
	No	32 (45.7)	25 (35.7)	57 (40.7)
Nonfixed pulmonary infiltrates, n (%)	Yes	49 (70.0)	43 (61.4)	92 (65.7)
	No	21 (30.0)	27 (38.6)	48 (34.3)
Sino-nasal abnormality, n (%)	Yes	63 (90.0)	66 (94.3)	129 (92.1)
	No	7 (10.0)	4 (5.7)	11 (7.9)
Cardiomyopathy (ECG/MRI), n (%) [c]	Yes	17 (24.3)	13 (18.6)	30 (21.4)
	No	53 (75.7)	57 (81.4)	110 (78.6)
Glomerulonephritis, n (%)	Yes	4 (5.7)	2 (2.9)	6 (4.3)
	No	66 (94.3)	68 (97.1)	134 (95.7)
Alveolar haemorrhage, n (%)	Yes	2 (2.9)	2 (2.9)	4 (2.9)
	No	68 (97.1)	68 (97.1)	136 (97.1)
Palpable purpura, n (%)	Yes	7 (10.0)	10 (14.3)	17 (12.1)
	No	63 (90.0)	60 (85.7)	123 (87.9)
Historical ANCA-positive, n (%)	Yes	16 (22.9)	20 (28.6)	36 (25.7)
	No	54 (77.1)	50 (71.4)	104 (74.3)
EGPA disease type				
Relapsing disease, n (%)	Yes	45 (64.3)	48 (68.6)	93 (66.4)
	No	25 (35.7)	22 (31.4)	47 (33.6)

EGPA Disease History and Baseline Characteristics (Full Analysis Set)

Characteristics	Statistics or category	Benralizumab 30 mg (N = 70)	Mepolizumab 300 mg (N = 70)	Total (N = 140)
Refractory disease, n (%)	Yes	42 (60.0)	42 (60.0)	84 (60.0)
	No	28 (40.0)	28 (40.0)	56 (40.0)
Both relapsing and refractory EGPA, n (%)	Yes	18 (25.7)	20 (28.6)	38 (27.1)
	No	52 (74.3)	50 (71.4)	102 (72.9)
Time since diagnosis of EGPA (year)	n	70	70	140
	Mean (SD)	5.39 (5.378)	4.93 (5.919)	5.16 (5.639)
	Median (min, max)	3.02 (0.6, 24.0)	2.18 (0.1, 38.0)	2.84 (0.1, 38.0)
	≤ 4 years n (%)	37 (52.9)	42 (60.0)	79 (56.4)
	> 4 years n (%)	33 (47.1)	28 (40.0)	61 (43.6)
Number of relapses over past 2 years	0	12 (17.1)	13 (18.6)	25 (17.9)
	1	24 (34.3)	20 (28.6)	44 (31.4)
	2	17 (24.3)	17 (24.3)	34 (24.3)
	3-5	12 (17.1)	16 (22.9)	28 (20.0)
	> 5	2 (2.9)	2 (2.9)	4 (2.9)
	Not known	3 (4.3)	2 (2.9)	5 (3.6)
Immunosuppressive therapy since diagnosis, n (%)	Yes	41 (58.6)	42 (60.0)	83 (59.3)
	No	26 (37.1)	27 (38.6)	53 (37.9)
	Not known	2 (2.9)	1 (1.4)	3 (2.1)
	Missing	1 (1.4)	0 (0.0)	1 (0.7)
EGPA baseline characteristics				
Absolute eosinophil count at baseline (cells/uL)	n	70	70	140
	Mean (SD)	306.0 (225.02)	384.9 (563.60)	345.4 (429.39)
	Median (min, max)	240.0 (30, 920)	225.0 (0, 3830)	230.0 (0, 3830)
	< 150 n (%)	20 (28.6)	20 (28.6)	40 (28.6)
	≥ 150 n (%)	50 (71.4)	50 (71.4)	100 (71.4)
ANCA-positive at screening, n (%)	Yes	7 (10.0)	7 (10.0)	14 (10.0)
	No	63 (90.0)	63 (90.0)	126 (90.0)
Prednisolone or prednisone dose (mg/day) [d]	n	70	70	140
	Mean (SD)	11.09 (4.577)	10.95 (5.885)	11.02 (5.253)

EGPA Disease History and Baseline Characteristics (Full Analysis Set)

Characteristics	Statistics or category	Benralizumab 30 mg (N = 70)	Mepolizumab 300 mg (N = 70)	Total (N = 140)
	Median (min, max)	10.00 (5.0, 30.0)	10.00 (7.5, 40.0)	10.00 (5.0, 40.0)
	< 12mg/day	52 (74.3)	56 (80.0)	108 (77.1)
	≥ 12mg/day	18 (25.7)	14 (20.0)	32 (22.9)
Immunosuppressive therapy at baseline, n (%)	Yes	26 (37.1)	24 (34.3)	50 (35.7)
	No	44 (62.9)	46 (65.7)	90 (64.3)
BVAS	n	70	70	140
	Mean (SD)	2.3 (3.49)	1.9 (2.92)	2.1 (3.21)
	Median (min, max)	0.0 (0, 18)	0.0 (0, 15)	0.0 (0, 18)
	> 0 n (%)	34 (48.6)	33 (47.1)	67 (47.9)
	= 0 n (%)	36 (51.4)	37 (52.9)	73 (52.1)
VDI	n	70	70	140
	Mean (SD)	4.0 (1.80)	4.0 (1.78)	4.0 (1.78)
	Median (min, max)	4.0 (1, 9)	4.0 (0, 10)	4.0 (0, 10)
	≥ 5 n (%)	23 (32.9)	21 (30.0)	44 (31.4)
	< 5 n (%)	47 (67.1)	49 (70.0)	96 (68.6)
ACQ-6	n	70	70	140
	Mean (SD)	1.35 (1.168)	1.18 (1.083)	1.26 (1.126)
	Median (min, max)	1.17 (0.0, 4.5)	1.00 (0.0, 5.3)	1.17 (0.0, 5.3)
	< 1.5 n (%)	39 (55.7)	42 (60.0)	81 (57.9)
	≥ 1.5 n (%)	31 (44.3)	28 (40.0)	59 (42.1)
SNOT-22 total score	n	70	70	140
	Mean (SD)	32.7 (21.83)	30.4 (21.32)	31.6 (21.53)
	Median (min, max)	31.0 (0, 103)	25.0 (0, 89)	29.0 (0, 103)
IgE (mg/L)	n	69	68	137
	Mean (SD)	0.36 (0.578)	0.39 (0.521)	0.38 (0.548)
	Median (min, max)	0.18 (0.0, 3.2)	0.19 (0.0, 2.4)	0.18 (0.0, 3.2)

a A biopsy showing histopathological evidence of eosinophilic vasculitis, OR perivascular eosinophilic infiltration, OR eosinophil-rich granulomatous inflammation.

b Mono or poly (motor deficit or nerve conduction abnormality).

c Established by echocardiography or magnetic resonance imaging.

d One patient started tapering on day of Visit 2 making baseline prednisolone or prednisone dose 5 mg/day. Screening dose had been stable at 7.5 mg/day.

Time since diagnosis of EGPA (year) = (Date of randomisation – EGPA first diagnosed date + 1)/365.25.

Percentages were based upon all patients in the Full Analysis Set.

Baseline was defined as the last measurement on or prior to the date of randomisation.

ACQ-6 = Asthma Control Questionnaire (6-item version); ANCA = anti-neutrophil cytoplasmic antibodies; BVAS = Birmingham Vasculitis Activity Score; ECG = electrocardiogram; EGPA = eosinophilic granulomatosis with polyangiitis; EOS = eosinophil; IgE = immunoglobulin E; max = maximum; min = minimum; MRI = magnetic resonance imaging; N = number of patients in treatment group; n = number of patients in analysis; SD = standard deviation; SNOT-22 = Sino-nasal Outcome Test-22; VDI = Vasculitis Damage Index

The majority of EGPA disease characteristics were comparable between the two treatment arms. The proportions of patients who discontinued IP or the study during the DB period were low and similar between groups. Of note, there was a marked difference in the number of patients with *Biopsy Evidence of EOS Vasculitis/Inflammation* at baseline, between the mepolizumab group: 33 (47.1%) compared with the benralizumab group 20 (28.6%). Based on a cross-study comparison with MIRRA, which is of equal size with MANDARA, the number of patients with Biopsy Evidence of EOS Vasculitis/Inflammation at baseline in the mepolizumab group was also higher [25(37%)], compared with the number of patients in the benralizumab group in MANDARA.

Regarding EGPA baseline characteristics, max value for *Absolute eosinophil count at baseline (cells/uL*) for the mepolizumab group is significantly higher compared with the respective value for the benralizumab group, despite patients being equally balanced in the eosinophil count subgroups [< 150 n (%) and ≥ 150 n (%)].Median (min, max): Benralizumab: 240.0 cells/µl (30, 920)] *vs* Mepolizumab: 225.0 cells/µl (0, 3830). Mean (SD): Benralizumab: 306.0 cells/µl (225.02) *vs* Mepolizumab: 384.9 cells/µl (563.60). Similar differences were also noted for *Absolute eosinophil count at screening (cells/uL),* where max value for the mepolizumab group reached 2650 cells/µl *vs* 960 cells/µl for the benralizumab group.

The above observations indicate imbalances in disease burden between the groups at baseline – imbalances that could benefit the benralizumab group. The Applicant was asked by the CHMP to provide an additional analysis of the primary endpoint (remission at both weeks 36 and 48). In this analysis, the logistic regression model should be adjusted for Biopsy Evidence of EOS Vasculitis/Inflammation at baseline and max value för absolute eosinophil count, in addition to the variables included in the primary analysis (treatment arm, baseline dose of prednisone, baseline BVAS, region) (see discussion below).

Numbers analysed

Description of the populations used for analyses

The *Enrolled Analysis Set*: all patients who signed the informed consent form. Patient disposition was analysed using the Enrolled Analysis Set.

The *Full analysis set (FAS):* All patients randomized and receiving at least one (1) dose of IP, irrespective of their protocol adherence and continued participation in the study. Patients were analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study were included up to the date of their study termination. All efficacy analyses and demographics were analyzed using the Full Analysis Set.

The *Per Protocol Analysis Set*: subset of FAS consisting of all patients who were randomised and received treatment excluding any patients with protocol deviations affecting the primary efficacy endpoint

The *Safety Analysis Set*: all patients who received at least one dose of IP. Erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received (a patient who has on one or several occasions received benralizumab is classified as benralizumab).

The *Pharmacokinetic analysis set:* all patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries were based on this analysis set.

The *OLE analysis set*: all patients who enter the OLE part of the study and who received at least 1 dose of IP during the OLE treatment period.

The Enrolled Analysis Set included a total of 140 patients and the Full Analysis Set included a total of 70 patients in each of the two treatment groups (Table 10):

Table 10. Analysis Sets

	Number of patients		
	Benralizumab 30 mg	Mepolizumab 300 mg	Total
Patients randomised [a]	70	70	140
Patients included in safety analysis set [b]	70	70	140
Patients excluded from safety analysis set	0	0	0
Patients included in FAS [c]	70	70	140
Patients excluded from FAS	0	0	0
Patients included in per protocol analysis set [d]	63	64	127
Patients excluded from per protocol analysis set	7	6	13
Patients included in PK analysis set [e]	67	0	67
Patients excluded from PK analysis set	3	70	73
Patients included in OLE analysis set [f]	66	62	128
Patients excluded from OLE analysis set	4	8	12

[a] All patients who signed the ICF and were randomised to IP regardless of whether they receive a dose of IP or exited the study prior to receiving the first dose.
[b] All patients who received at least one dose of IP were included in the safety analysis set.
[c] All patients randomised who received any IP were included in the FAS.
[d] All patients randomised and who received IP, excluding any patients with protocol deviations affecting the primary efficacy endpoint as noted in SAP Section 2.2.1, are included in the per protocol analysis set.
[e] All patients who received IP and from whom PK blood samples were obtained were assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose were included in the PK analysis dataset.
[f] All patients who entered the OLE part of the study and who received at least 1 dose of IP during the OLE treatment period.

FAS = Full Analysis Set; ICF = Informed Consent Form; IP = investigational product; PK = pharmacokinetic(s); SAP = Statistical Analysis Plan; OLE = Open-label extension

Outcomes and estimation

Primary endpoint

Proportion of Patients who Achieved Main Remission at Both Weeks 36 and 48

Benralizumab was NI to mepolizumab as demonstrated by the lower bound of 95% CI falling well above the prespecified clinical NI margin of -25% for the difference in main remission rate only at both Weeks 36 and 48 (Table 11). More than half of patients achieved main remission at both Weeks 36 and 48 in the benralizumab group and in the mepolizumab group.

Table 11. Proportion of Patient who Achieved Main Remission at both Week 36 and 48, Treatment Comparison, Logistic Regression Using Marginal Standardisation Method (Full Analysis Set)

Table 1 **Proportion of Patients who Achieved Main Remission at both Weeks 36 and 48, Treatment Comparison, Logistic Regression Using Marginal Standardisation Method (Full Analysis Set)**

				Comparison between groups		
Remission	Treatment group	Number (%) of patients who achieved remission	Adjusted remission rate (%) [a]	Difference in remission rates (%) [a]	95% CI [b]	P-value [c]
Main remission	Benralizumab 30 mg (N=70)	40 (57.1)	57.7	1.21	-14.11, 16.53	0.8773
	Mepolizumab 300 mg (N=70)	40 (57.1)	56.5			
OCS dose ≤ 4 mg/day	Benralizumab 30 mg (N=70)	42 (60.0)	60.6	2.64	-12.67, 17.95	0.7354
	Mepolizumab 300 mg (N=70)	41 (58.6)	58.0 [d]			
BVAS = 0	Benralizumab 30 mg (N=70)	58 (82.9)	83.0	-1.17	-13.27, 10.94	0.8502
	Mepolizumab 300 mg (N=70)	59 (84.3)	84.2			

[a] The remission rates and the difference (benralizumab - mepolizumab) were estimated using marginal standardisation method in a logistic regression model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region (North America, Rest of World, and Japan). Baseline was defined as the last measurement on or prior to the date of randomisation.

[b] The NI test was assessed using a NI margin of -25%. The lower 95% CI for the absolute difference between benralizumab and mepolizumab remission rates needs to be above the NI margin of -25%.

[c] 2-sided p-value testing differences between treatment groups (equivalent to a 1-sided 0.025 level).

[d] Adjusted remission rate in mepolizumab group changed due to the change in dataset fitted to the model.

Main remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day (in the event a patient had achieved remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission).

BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; N = number of patients in treatment group; NI = non-inferiority; OCS = oral corticosteroids.

Source: Table 14.2.1.1.1

A significantly higher proportion of patients who received benralizumab achieved remission at both Weeks 36 and 48 compared with the historical placebo control from the MIRRA study (Table 12):

Table 12. Proportion of Patient who Achieved Main Remission at both Week 36 and 48, Comparison with Historical Placebo, 2 Sample Test (Full Analysis Set)

		Comparison between groups		
Treatment group [a]	**Number (%) of patients who achieved main remission**	**Difference in remission rates (%)**	**95% CI**	**P-value**
Benralizumab 30 mg (N=70)	40 (57.1)	54.2	41.93, 66.47	< 0.0001
Historical Placebo (N=68)	2 (2.9)	-	-	-
	40 (57.1)	24.8	8.73, 40.85	0.0034

Mepolizumab 300 mg (N=70)				
Historical Mepolizumab 300 mg (N= 68)	22 (32.4)	-	-	-

CI Confidence Interval. N Number of subjects in treatment group. n Number of subjects in analysis. BVAS Birmingham Vasculitis Activity Score. OCS Oral corticosteroids.

Main remission is defined as BVAS=0 and OCS dose <= 4 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
The historical placebo remission rate and historical mepolizumab remission rate are gathered from subjects observed within the phase 3 trial, MIRRA (Wechsler et al 2017).

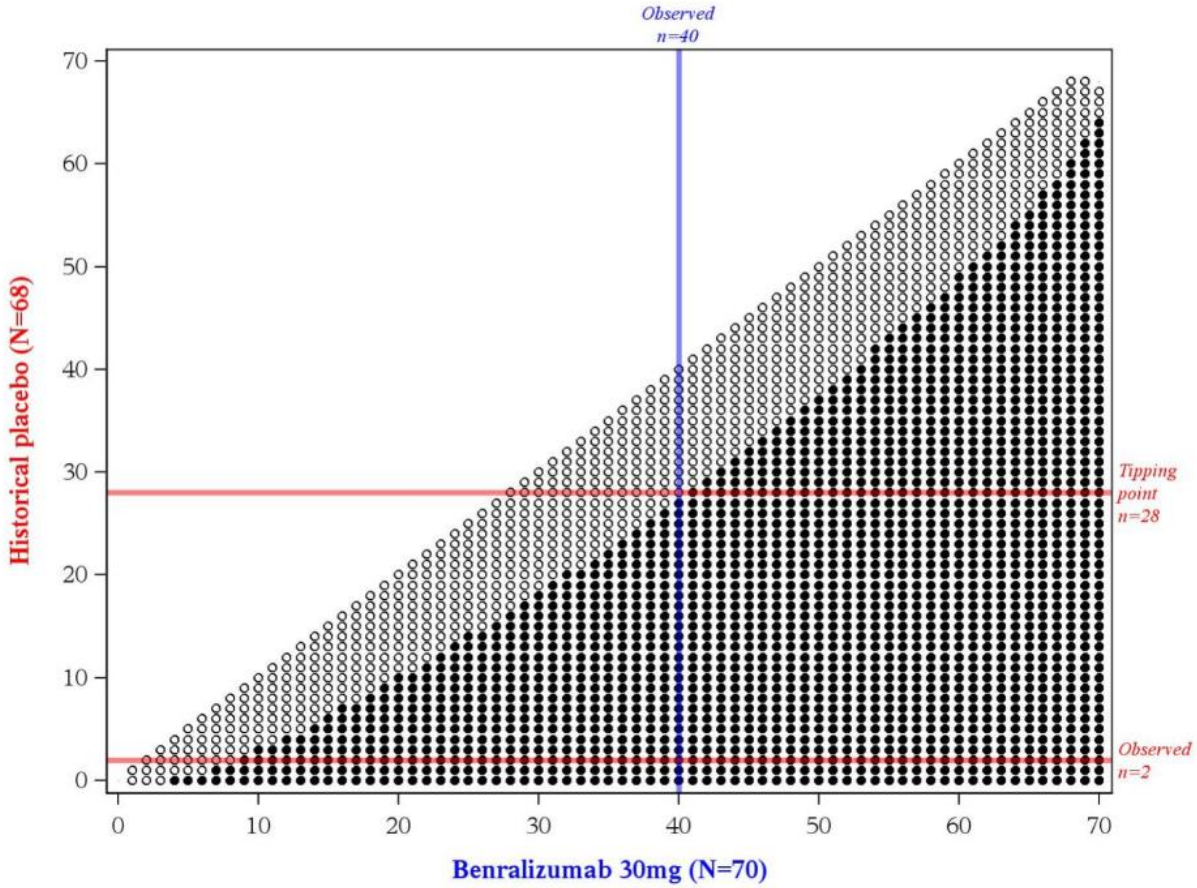
[a] The p-value is evaluated with a 2-sample test for binomial proportions using a one-sided test of Benralizumab having an improved rate over placebo with a 2.5% significance level.

Performance of Mepolizumab Comparator Arm with regards to remission rate in MANDARA was higher compared to that observed in MIRRA study (57.1% *vs* 32.4%, 95% CI [8.73, 40.85]; P = 0.0034)

For the justification of the difference in performance of Mepolizumab Comparator Arm on the proportion of patients who achieved remission at both Weeks 36 and 48 in MANDARA, in comparison with the historical placebo control from MIRRA study, the applicant summarized data from 2 real-world studies. In these studies (N=203, remission definition: BVAS = 0 and OCS ≤ 4 mg/day; N=51 patients remission definition: BVAS = 0 and OCS ≤ 5 mg/day) highly variable remission rates of 31-76% and 37-82% were observed for treatment with 100 mg and 300 mg doses of mepolizumab, respectively. Furthermore, higher treatment effects are generally observed in active comparator trials compared with the placebo-controlled trials.

A tipping point analysis was also conducted to assess the robustness of the indirect comparison to historic placebo (Figure 3). In the analysis, the number of patients meeting the remission endpoint were updated under varying assumptions for the different treatment groups independently. For any given number of patients meeting remission in the benralizumab group, non-responders in the historic placebo arm (66/68 patients) were converted to responder status one at a time. In each scenario evaluated, the superiority of benralizumab over the historic placebo was evaluated at the 2-sided 0.05 level to identify the point at which the result tipped from significant ($p < 0.05$) to non-significant ($p \geq 0.05$).

Figure 3. Sensitivity Analysis: Proportion Of Subjects Who Achieved Main Remission At Both Weeks 36 And 48, Treatment Comparison, Two Sample Test, Tipping Point Analysis (Full Analysis Set)



Main remission at both weeks 36 and 48 is defined as BVAS=0 and OCS dose <= 4 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission). The historical placebo remission rate is gathered from subjects observed within the phase 3 trial. For any given number of subjects meeting remission in the benralizumab group, non-responders in the historical placebo arm (66/68 patients) are converted to responder status one at a time. In each scenario evaluated, the superiority of benralizumab over the historical placebo is evaluated at the 2-sided 5% level to identify the point at which the result tips from significant to non-significant. The dots are presenting the results: filled = p-value <0.05 (significant), open = p-value >=0.05 (non-significant).

With the observed benralizumab remission rate in MANDARA, it would require 26 additional patients in the placebo group to tip the result of the primary endpoint from significance to non-significance, which is more than 10 times the number of patients who achieved remission on placebo in MIRRA.

Similar response rates were observed between benralizumab and mepolizumab groups for the proportion of patients who achieved main remission at both Weeks 36 and 48 when using the supportive remission definition (defined as BVAS = 0 and OCS ≤ 7.5 mg/day), see Table 13.

Table 13. Proportion Of Subjects Who Achieved Remission (Main Remission And Supportive Remission) At Both Week 36 And 48, Treatment Completion, Logistic Regression Using Marginal Standardisation Method (Full Analysis Set)

				Comparison between groups		
Remission	Treatment group	Number (%) of subjects achieved remission	Adjusted remission rate (%) [a]	Difference in remission rates (%) [a]	95% CI [b]	P-value [c]
Supportive remission	Benralizumab 30 mg (N=70)	55 (78.6)	79.0	5.44	(-7.46, 18.34)	0.4085
	Mepolizumab 300 mg (N=70)	52 (74.3)	73.6			
OCS dose <= 7.5 mg/day	Benralizumab 30 mg (N=70)	61 (87.1)	87.0	7.25	(-4.22, 18.72)	0.2153
	Mepolizumab 300 mg (N=70)	56 (80.0)	79.8			

CI Confidence Interval. N Number of subjects in treatment group. BVAS Birmingham Vasculitis Activity Score. OCS Oral corticosteroids.
Main remission is defined as BVAS=0 and OCS dose <= 4 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
Supportive remission is defined as BVAS=0 and OCS dose <= 7.5 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 7.5 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
[a] The remission rates and the difference (Benralizumab - Mepolizumab) are estimated using marginal standardization method in a logistic regression model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region (North America, Rest of World, and Japan). Baseline is defined as the last measurement on or prior to the date of randomisation.
[b] Non-inferiority test is assessed using a NI margin of - 25%. The lower 95% confidence limit for the difference between Benralizumab and Mepolizumab remission rates needs to be above the NI margin of -25%.
[c] This is the p-value for superiority test.

Consistent with the main analysis outcome are the results from sensitivity analyses using the *per-protocol population* [subjects who were randomised and received treatment excluding subjects (n=13) with protocol deviations affecting the primary efficacy endpoint] shown in Table 14:

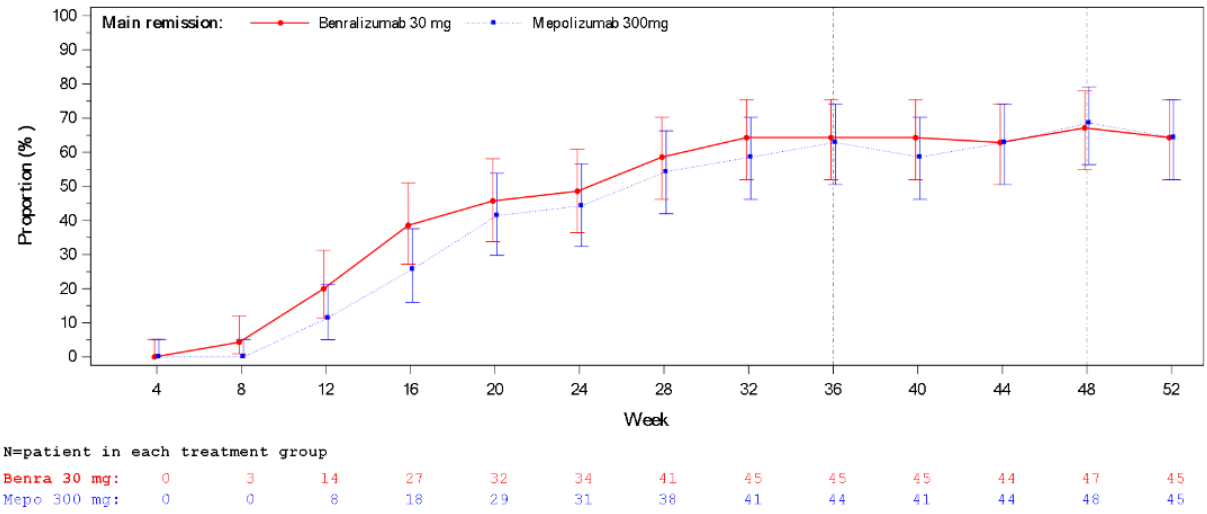
Table 14. Sensitivity Analysis: Proportion Of Subjects Who Achieved Remission At Both Week 36 And 48, Treatment Comparison, Logistic Regression Using Marginal Standardisation Method (Per Protocol Population)

				Comparison between groups		
Remission	Treatment group	Number (%) of subjects achieved main remission	Adjusted remission rate (%) [a]	Difference in remission rates [a]	95% CI [b]	P-value [c]
Main remission	Benralizumab 30 mg (N=63)	36 (57.1)	57.1	-2.40	(-18.25, 13.45)	0.7663
	Mepolizumab 300 mg (N=64)	38 (59.4)	59.5			
OCS dose <= 4 mg/day	Benralizumab 30 mg (N=63)	38 (60.3)	60.3	-0.56	(-16.39, 15.27)	0.9447
	Mepolizumab 300 mg (N=64)	39 (60.9)	60.9			
BVAS = 0	Benralizumab 30 mg (N=63)	54 (85.7)	85.5	-3.75	(-15.03, 7.54)	0.5152
	Mepolizumab 300 mg (N=64)	57 (89.1)	89.3			
Supportive remission	Benralizumab 30 mg (N=63)	49 (77.8)	77.9	1.44	(-11.81, 14.69)	0.8308
	Mepolizumab 300 mg (N=64)	49 (76.6)	76.4			
OCS dose <= 7.5 mg/day	Benralizumab 30 mg (N=63)	54 (85.7)	85.6	4.54	(-7.35, 16.44)	0.4542
	Mepolizumab 300 mg (N=64)	52 (81.3)	81.1			

CI Confidence Interval. N Number of subjects in treatment group. n Number of subjects in analysis. BVAS Birmingham Vasculitis Activity Score. OCS Oral corticosteroids.
Main remission is defined as BVAS=0 and OCS dose <= 4 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
Supportive remission is defined as BVAS=0 and OCS dose <= 7.5 mg/day (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 7.5 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
a] The remission rates and the difference (Benralizumab - Mepolizumab) are estimated using marginal standardization method in a logistic egression model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region (North merica, Western Europe, and Japan). Baseline is defined as the last measurement on or prior to the date of randomization.
b] Non-inferiority test is assessed using a NI margin of -25%. The lower 95% confidence limit for the absolute difference between Benralizumab and Mepolizumab remission rates needs to be above the NI margin of -25%.
c] This is the p-value for superiority test.
Per-protocol population is defined as subjects who were randomised and received treatment excluding any subjects with protocol deviations affecting the primary efficacy endpoint as noted in SAP Section 2.2.1.

Additional analysis of remission response over time demonstrated that in both treatment groups, remission response rates increased similarly over time up to Week 36 and remained consistent for the end of the DB period/Week 52 (Line Plot Figure 4):

Figure 4. Proportion Of Patients Who Achieved Main Remission By Timepoint – Line Plot (Full Analysis Set)



Secondary Endpoints

Superiority of benralizumab compared to mepolizumab was tested using the same logistic regression model at the 2-sided 0.05 level per the statistical analysis plan of the study.

Total Accrued Duration of Remission

Total accrued duration of main remission was similar in the benralizumab group compared with the mepolizumab group (table 15). A total of 61 patients (87.1%) and 55 patients (78.5%) in the benralizumab and mepolizumab groups, respectively, achieved remission at any time during the DB period, 1 of the 3 components included in the clinical benefit endpoint.

Table 15. Total Accrued Duration (Weeks) of Remission, Treatment Comparison, Proportional Odds Model (Full Analysis Set)

		Number (%) of patients					Comparison between groups [a]		
Remission	**Treatment group**	**0 Weeks**	**> 0 to < 12 Weeks**	**12 to < 24 Weeks**	**24 to < 36 Weeks**	**≥ 36 Weeks**	**Odds ratio**	**95% CI**	**P-value**
Main remission	Benralizumab 30 mg (N = 70)	9 (12.9)	13 (18.6)	8 (11.4)	20 (28.6)	20 (28.6)	1.32	0.72, 2.40	0.3653
	Mepolizumab 300 mg (N = 70)	15 (21.4)	10 (14.3)	8 (11.4)	19 (27.1)	18 (25.7)	-	-	-
OCS dose ≤ 4 mg/day	Benralizumab 30 mg (N = 70)	9 (12.9)	11 (15.7)	9 (12.9)	19 (27.1)	22 (31.4)	1.27	0.70, 2.31	0.4371
	Mepolizumab 300 mg (N = 70)	12 (17.1)	12 (17.1)	8 (11.4)	18 (25.7)	20 (28.6)	-	-	-
BVAS = 0	Benralizumab 30 mg (N = 70)	0	0	2 (2.9)	6 (8.6)	62 (88.6)	1.50	0.54, 4.15	0.4312
	Mepolizumab 300 mg (N = 70)	0	2 (2.9)	2 (2.9)	7 (10.0)	59 (84.3)	-	-	-

[a] The odds ratio (benralizumab vs mepolizumab) and its 95% CI were estimated with a proportional odds model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS and region. A > 1 odds ratio means benralizumab is favoured.

Main remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day (in the event a patient had achieved remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission).

BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; N = number of patients in treatment group; OCS = oral corticosteroid

Source: Table 14.2.1.2.1

Results for total accrued duration of remission using the supportive remission definition of BVAS = 0 and OCS ≤ 7.5 mg/day for the benralizumab group compared with the mepolizumab group were consistent with those of the main remission definition.

Total duration of sustained remission is defined as the longest uninterrupted period of weeks where BVAS=0 plus OCS dose of prednisolone/prednisone ≤4 mg/day over the 52-week study treatment period. The results from the supportive analysis of total duration of sustained (uninterrupted) remission during the DB period were comparable between the two treatment groups [95% CI]: 1.34 [0.74, 2.44]) (Table 16).

Table 16. Total Accrued Duration (Weeks) Of Sustained Remission (Main Remission And Supportive Remission) During DB Treatment Period, Proportional Odds Model (Full Analysis Set)

		Number (%) of subjects					Comparison between groups [a]		
Remission	Treatment group	0 weeks	> 0 to < 12 weeks	12 to < 24 weeks	24 to < 36 weeks	> =36 weeks	Odds ratio	95% CI	P-value
Main remission	Benralizumab 30 mg (N=70)	9 (12.9)	15 (21.4)	11 (15.7)	16 (22.9)	19 (27.1)	1.34	(0.74, 2.44)	0.3330
	Mepolizumab 300 mg (N=70)	15 (21.4)	13 (18.6)	8 (11.4)	18 (25.7)	16 (22.9)			
Supportive remission	Benralizumab 30 mg (N=70)	2 (2.9)	5 (7.1)	8 (11.4)	18 (25.7)	37 (52.9)	1.23	(0.64, 2.34)	0.5318
	Mepolizumab 300 mg (N=70)	4 (5.7)	6 (8.6)	10 (14.3)	14 (20.0)	36 (51.4)			

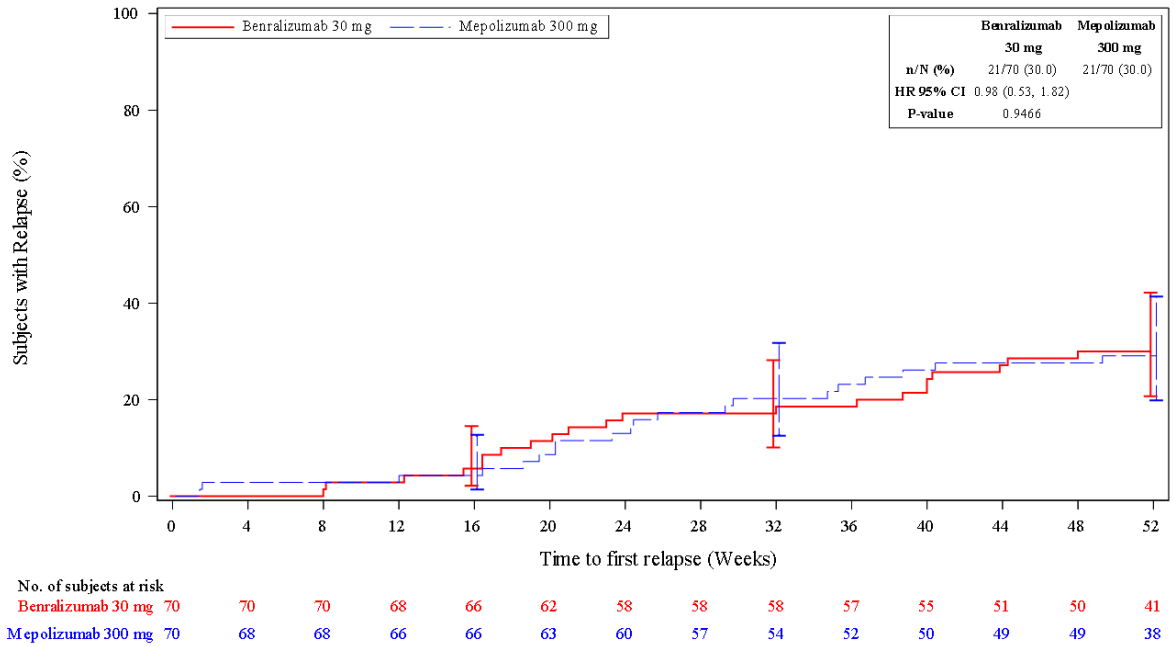
CI Confidence Interval. N Number of subjects in treatment group. n Number of subjects in analysis. BVAS Birmingham Vasculitis Activity Score. OCS Oral corticosteroids.
[a] The odds ratio (Benralizumab vs. Mepolizumab) for 24 or more weeks of accrued duration of remission and its 95% CI are estimated with a proportional odds model. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region.
The total duration of sustained main remission (main remission definition) is defined as the longest uninterrupted period of weeks where BVAS=0 and OCS dose of prednisolone/prednisone <= 4 mg/day over the 52-week treatment period (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
The total duration of sustained supportive remission is defined as the longest uninterrupted period of weeks where BVAS=0 and OCS dose of prednisolone/prednisone <= 7.5mg/day over the 52-week treatment period (in the event a subject has achieved remission and at any subsequent visit has a BVAS=1 which does not require an increase in OCS dose above 7.5 mg/day, or any other significant clinical intervention or investigation, the subject will be considered to be in continued remission).
Baseline is defined as the last measurement on or prior to the date of randomisation.

A sensitivity analysis performed on the patient population that was administered OCS for only treating EGPA demonstrated that the percentage of patients achieving a total accrued duration of remission was similar between the mepolizumab and benralizumab groups.

Time to First Relapse

The time to first relapse was similar in patients in the benralizumab group compared with the mepolizumab group (Table 17 and Figure 5). Major relapse occurred during the DB period in 0 patients in the benralizumab group and 3 patients (4.3%) in the mepolizumab group.

Figure 5. Time to First Relapse – Kaplan Meier Plot (Full Analysis Set)



The time to relapse = start date of relapse - date of randomisation + 1. If a patient did not experience a relapse by Week 52, their time to relapse was right-censored at the last available assessment time. The relapse was defined as worsening or persistence of active disease characterized by: active vasculitis (BVAS > 0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least 1 of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalization related to EGPA worsening.

1 patient had first relapse after Week 52.

The lower bound and upper bound of the 95% CI of the estimated proportion of patients with relapse by Week 16, Week 32 and Week 52 are marked on the lines.

ACQ-6 = Asthma Control Questionnaire (6-item version); BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; EGPA = eosinophilic granulomatosis with polyangiitis; HR = hazard ratio; N = Number of patients in treatment group; OCS = oral corticosteroids

Source: Figure 14.2.1.3

Table 17. Time to First Relapse and Time to First Major Relapse, Cox-proportional hazard model (Full analysis set)

		Benralizumab 30 mg (N=70)	Mepolizumab 300 mg (N=70)
Relapse	Number (%) of subjects with relapse	21 (30.0)	21 (30.0)
	Time to first relapse (weeks) (95% CI) [a]		
	1st quartile	40.43 (23.14, NE)	38.57 (24.14, NE)
	Median	NE (NE, NE)	NE (NE, NE)
	3rd quartile	NE (NE, NE)	NE (NE, NE)
	Percent subject with at least one relapse (95% CI) [a]		
	By Week 16	5.71 (2.18, 14.51)	4.29 (1.40, 12.70)
	By Week 32	17.14 (10.12, 28.21)	20.24 (12.52, 31.77)
	By Week 52	30.00 (20.71, 42.21)	29.10 (19.85, 41.40)
	P-value for unstratified log-rank test	0.9466	
	Hazard ratio (95% CI) [b]	0.98 (0.53, 1.82)	
Major Relapse	Number (%) of subjects with major relapse	0	3 (4.3)
	Time to first relapse (weeks) (95% CI) [a]		
	1st quartile	NE (NE, NE)	NE (53.00, NE)
	Median	NE (NE, NE)	NE (NE, NE)
	3rd quartile	NE (NE, NE)	NE (NE, NE)
	Percent subject with at least one relapse (95% CI) [a]		
	By Week 16	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	By Week 32	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	By Week 52	0.00 (0.00, 0.00)	2.94 (0.74, 11.25)
	P-value for unstratified log-rank test	0.0784	
	Hazard ratio (95% CI) [b]	Not calculable	

CI Confidence interval. N Number of subjects in treatment group. ACQ-6 Asthma Control Questionnaire (6-item version). BVAS Birmingham Vasculitis Activity Score. EGPA Eosinophilic Granulomatosis with Polyangiitis. OCS Oral corticosteroids.
[a] Calculated using the Kaplan-Meier technique.
[b] The hazard ratio (Benralizumab vs. Mepolizumab) and 95% CI are estimated using a Cox regression model with Efron method to control for ties. The covariates in the model include treatment arm, baseline dose of prednisone, baseline BVAS and region. A <1 hazard ratio means Benralizumab is favoured.
The relapse is defined as worsening or persistence of active disease characterized by: active vasculitis (BVAS>0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalization related to EGPA worsening.
The major relapse is a subset of the total relapse events and is defined as any organ or life-threatening EGPA event, BVAS>=6, an asthma relapse requiring hospitalization or sino-nasal relapse requiring hospitalization.
For subjects who have not experienced relapse over the 52-week treatment period, their time to relapse is right-censored at the last available assessment time on or before Week 52.

Annualised Relapse Rate

Relapse was defined as worsening or persistence of active disease characterised by: active vasculitis (BVAS > 0); or active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; or active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting: an increase of OCS therapy; or an increased dose or addition of an immunosuppressive agent or hospitalisation related to EGPA worsening. Major relapse was a subset of the total relapse events and was defined as any organ or life-threatening EGPA event, BVAS ≥ 6, an asthma relapse requiring hospitalisation, or sino-nasal relapse requiring hospitalisation. During the DB period, the number of EGPA relapses reported for patients treated with benralizumab (n=34) was slightly higher compared to the respective number (n=30) reported for patients treated with mepolizumab. The annualised relapse rate was similar in the benralizumab group compared with the mepolizumab group. The rate ratio is 1.03 (95% CI: [0.56, 1.90], p=0.9282). The types of relapses (vasculitis, asthma, and sino-nasal) were similar for both patient treatment groups. Major relapse occurred during the DB period in 0 patients in the benralizumab group and 3 patients (4.3%) in the mepolizumab group.

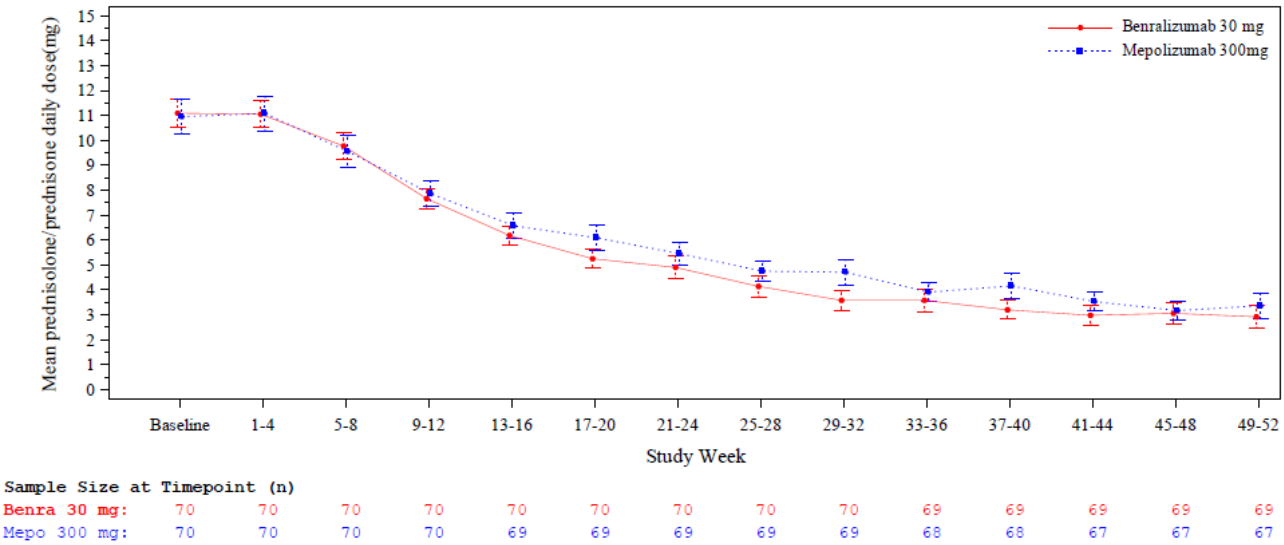
Average Daily Dose of OCS

During Weeks 48 to 52, a higher proportion of patients treated with benralizumab compared with mepolizumab had a 100% reduction in OCS. Reductions of at least 50% in the average daily dose of OCS were observed in numerically higher proportions of patients receiving benralizumab compared with mepolizumab, 1 of the 3 components included in the clinical benefit endpoint.

Interestingly, a similar proportion of patients achieved an average daily OCS dose of ≤ 4 mg/day in the two treatment groups (48 patients [68.6%] in the benralizumab group vs 49 [70%] in the mepolizumab group), and similar proportions of patients achieved OCS dose ≤ 7.5 mg/day (63 patients [90.0%] in the benralizumab group and 62 patients [88.6%] in mepolizumab group).

Reduction in average daily dose of OCS from baseline was possible in a majority of patients in both treatment groups as shown in Table 22; only 3 patients in benralizumab group and 7 patients in mepolizumab group had no reduction in OCS or withdrew from IP before Week 48. A similar reduction in mean average daily OCS dose from baseline was observed in patients treated with benralizumab compared with mepolizumab starting at Weeks 5 to 8 through the DB period (Figure 6).

Figure 6. Mean Average Daily Dose of Prednisolone/Prednisone by Timepoint, Line Plot (Full Analysis Set)



Consistent findings were obtained in a sensitivity analysis on the patient population who achieved remission at weeks 36 and 48 using OCS only for treating oEGPA.

Remission within the First 24 Weeks and Remaining in Remission for the Remainder of the Double-Blind Period

Similar proportions of patients in the benralizumab group compared with the mepolizumab group achieved remission within the first 24 weeks of treatment and remained in remission through Week 52. Results for total accrued duration of remission using the supportive remission definition of BVAS = 0 and OCS ≤ 7.5 mg/day for the benralizumab group compared with the mepolizumab group were consistent with those of the main remission definition.

Clinical benefit

The proportions of patients who achieved any clinical benefit were high and similar in both treatment groups (Table 18). Similar proportions of patients in the benralizumab group compared with the mepolizumab group achieved complete response.

Table 18. Proportion Of Patients Who Achieved Any Clinical Benefit And Patient Who Achieved Complete Response, Logistic Regression Using Marginal Standardisation Method (Full Analysis Set)

				Comparison between groups [a]		
	Treatment group	Number (%) of patients who achieved response	Adjusted response rate (%)	Difference in response rates (%)	95% CI	P-value
Any clinical benefit	Benralizumab 30 mg (N = 70)	66 (94.3)	94.4	4.60	-4.22, 13.41	0.3068
	Mepolizumab 300 mg (N = 70)	63 (90.0)	89.8	-	-	-
Complete response	Benralizumab 30 mg (N = 70)	43 (61.4)	62.5	7.90	-7.32, 23.12	0.3088
	Mepolizumab 300 mg (N = 70)	39 (55.7)	54.6	-	-	-

[a] The response rates, the difference (benralizumab – mepolizumab) and 95% CI were estimated using marginal standardisation method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS, and region.

Any clinical benefit was defined as any of the following:

- Main remission (defined as BVAS = 0 and OCS dose ≤ 4 mg/day) at any time during the double-blind treatment period
- ≥ 50% reduction in average daily OCS dose during Weeks 48 through 52
- EGPA relapse free during the double-blind treatment period.

Complete response was defined as meeting all the criteria above.

BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; EGPA = eosinophilic granulomatosis with polyangiitis. N = number of patients in treatment group; OCS = oral corticosteroid

The results from the analysis for the supportive remission definition were consistent with those based on the main remission definition.

Secondary Endpoints for the assessment of additional measures of efficacy and health status/health-related quality of life

BVAS: Similar decreases from baseline LS mean BVAS were observed in the benralizumab and mepolizumab groups over the 52-week DB period.

VDI: VDI documents features of vasculitis due to persistent damage, without disease activity. Damage is defined as the presence of nonhealing scars. VDI has a range of 0 to 64. A score of 0 indicates no damage. Similar and small increases were observed in LS mean change from baseline VDI in the benralizumab and mepolizumab groups at Week 52 (0.13 *vs* 0.10, respectively). The LS mean difference between treatment groups was 0.03 (95% CI: [-0.10, 0.16], p = 0.6799).

Patient reported outcome endpoints

ACQ-6: Similar improvements in mean ACQ-6 score from baseline to Weeks 48 through 52 were observed in the benralizumab group (-0.57) and the mepolizumab group (-0.61), both of which were clinically meaningful. The LS mean difference between treatment groups was 0.05 (95% CI: [-0.18, 0.27], p = 0.6730). Similar proportions of patients in the benralizumab and mepolizumab groups achieved ACQ-6 response (defined as a decrease in score from baseline of at least 0.5) to Weeks 48 through 52 (41.8% and 48.0%, respectively). The difference in response rates was -6.16% (95% CI: [-18.52, 6.21], p = 0.3290).

SF-36v2: Similar changes from baseline at Week 52 were observed in the benralizumab and mepolizumab groups in LS mean SF-36v2 MCS (1.13 and 2.19, respectively) and LS mean SF-36v2 PCS (0.29 and 2.45, respectively). Similar proportions of patients in the benralizumab and mepolizumab groups achieved SF-36v2 MCS response at Week 52 (37.1% *vs* 28.6%, respectively). The difference in response rates was 6.43% (95% CI: [-7.09, 19.96], p = 0.3513). Similar proportions of patients in the benralizumab and

mepolizumab groups achieved SF-36v2 PCS response at Week 52 (24.3% *vs* 37.1%, respectively). The difference in response rates was -11.77% (95% CI: [-26.21, 2.67], p = 0.1102).

SNOT-22: Similar reductions from baseline SNOT-22 were observed in the benralizumab and mepolizumab groups over the 52-week DB period. Though a minimal clinically important difference in SNOT-22 score has not been established in EGPA, neither group met the thresholds established in previous research in chronic rhinosinusitis.

SSQ: Similar minimal changes from baseline in SSQ scores were observed in the benralizumab and mepolizumab groups over the 52-week DB period.

PGIS and PGIC: Similar changes from baseline PGIS were observed in the benralizumab and mepolizumab groups over the 52-week DB period. A greater proportion of patients provided a response in the milder categories (mild, very mild, and no symptoms) at Week 52 than at baseline in both treatment groups. The most common category at baseline was "moderate" for both groups, while at Week 52 the most common response was "very mild" for both groups. By Week 4, patients in the benralizumab and mepolizumab groups were reporting similar levels of improvement in health status measured by PGIC from baseline (most common response for both groups was "about the same" at Week 4), without discernible pattern of difference.

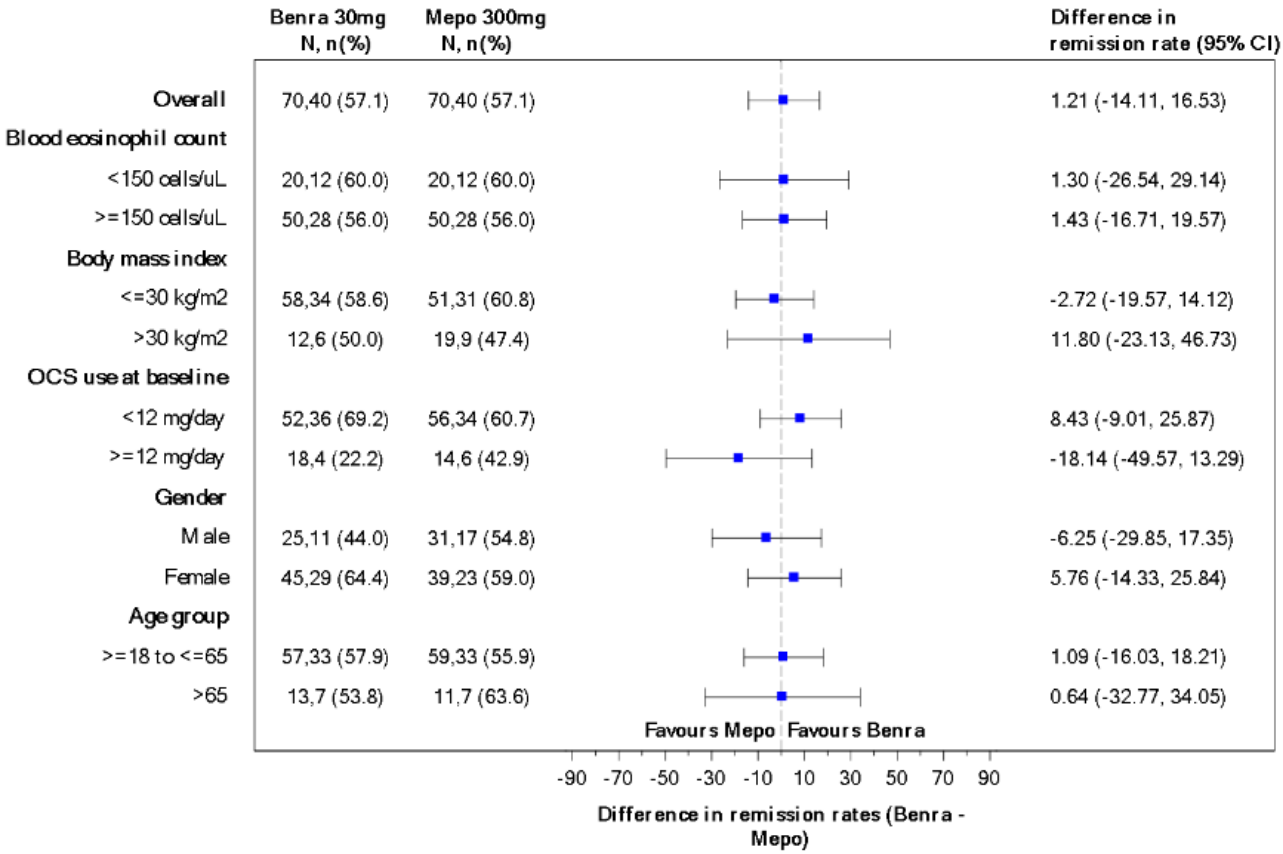
WPAI-GH: Similar changes from baseline were observed in WPAI-GH total score in the benralizumab and mepolizumab groups over the 52-week DB period. Similar improvements in change from baseline mean WPAI-GH activity impairment scores were also observed in the benralizumab and mepolizumab groups at Week 52 (-3.28 and -7.78, respectively).

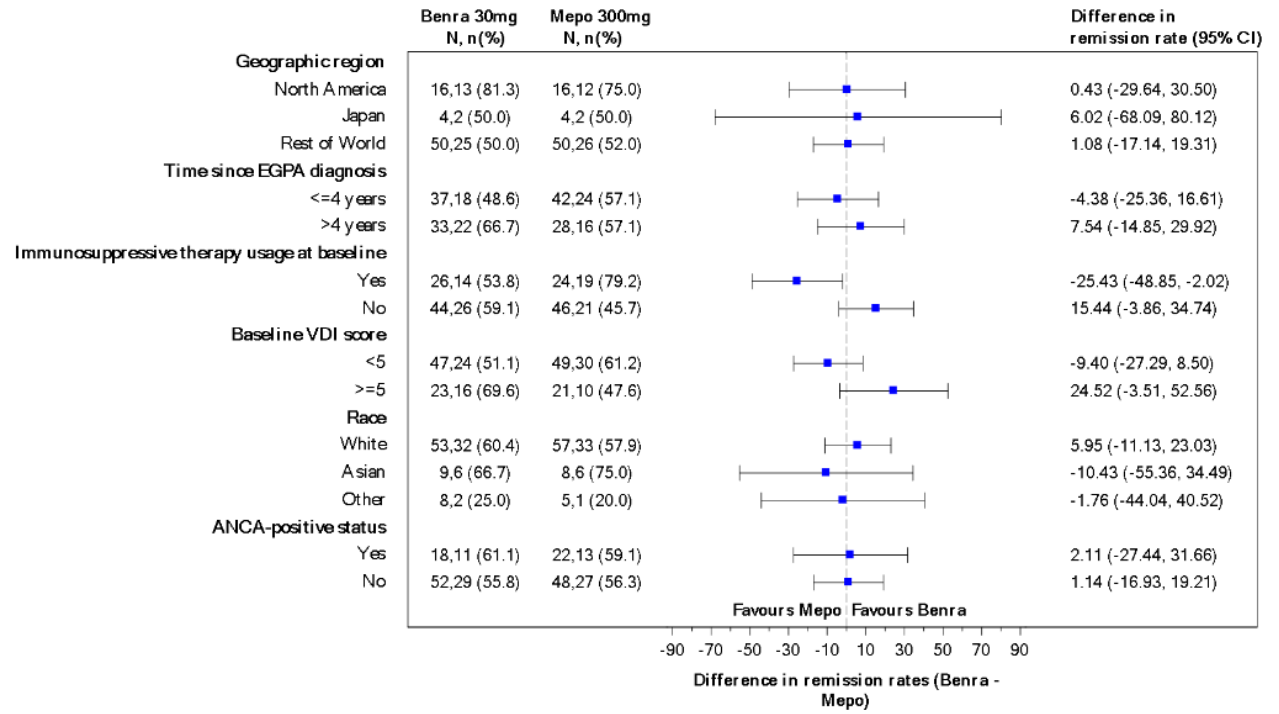
Spirometry: Similar changes from baseline FEV1 and FVC were observed in the benralizumab and mepolizumab groups over the 52-week DB period.

Ancillary analyses

The Forest Plot in Figure 7 shows the analysis of the primary endpoint in prespecified subgroup populations accounting for eleven patient characteristics (blood eosinophil count at baseline, BMI, OCS dose at baseline, gender age group, region, time since EGPA diagnosis, immunosuppressive therapy at baseline, VDI score, race, ANCA –positive status). Two nominal interactions with Pvalue < 0.05 were observed for the subgroups of immunosuppressant use at baseline and for baseline VDI score. In the benralizumab group, the remission rates for immunosuppressant use at baseline subgroups were consistent with the overall remission rate.

Figure 7. : Subgroup Analysis: Proportion of Patients Who Achieved Main Remission at Both Weeks 36 and 48, Treatment Comparison by Subgroups, Logistic Regression Using Marginal Standardisation Method – Forest Plot (Full Analysis Set)





Main remission was defined as BVAS = 0 and OCS dose ≤ 4 mg/day (in the event a patient had achieved remission and at any subsequent visit had a BVAS = 1 which did not require an increase in OCS dose above 4 mg/day, or any other significant clinical intervention or investigation, the patient was considered to be in continued remission).

The remission rates and the difference (benralizumab – mepolizumab) were estimated using marginal standardisation method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of prednisone, baseline BVAS, region, the subgroup, and interaction between treatment arm and the subgroup (treatment arm*subgroup).

The p-value for each interaction term is estimated from logistic regression without using marginal standardization method.

Baseline was defined as the last measurement on or prior to the date of randomisation.

Missing race was included in the category 'Other'.

Positive ANCA status was either baseline positive or historical positive.

ANCA = anti-neutrophil cytoplasmic antibody(ies); Benra = benralizumab; BVAS = Birmingham Vasculitis Activity Score; CI = confidence interval; EGPA = eosinophilic granulomatosis with polyangiitis; Mepo = mepolizumab; N = number of patients in treatment group; OCS = oral corticosteroids; VDI = Vasculitis Damage Index

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of Efficacy for MANDARA trial

Title: A Randomised, Double-blind, Active-controlled 52-week Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab Compared to Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in Patients Receiving Standard of Care Therapy (**MANDARA Study**)		
Study identifier	D3253C00001, MANDARA, EudraCT Number 2019-001832-77	
Design	This Phase III study in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy included a 52-week double-blind (DB) period in which the efficacy and safety of benralizumab was compared with an active comparator, mepolizumab. Eligible patients were randomised 1:1 at baseline to receive benralizumab 30 mg Q4W or mepolizumab 300 mg Q4W. The study also includes an ongoing open label extension (OLE) period that intends to allow each patient at least one additional year of treatment with open-label benralizumab 30 mg Q4W, to assess long-term safety and tolerability of benralizumab in this patient population. At the time of this submission, the primary analysis (including all data collected from patients in the during the DB phase and safety data (exposure and AE/SAE) data from the OLE) is completed.	
	Duration of main phase:	52 weeks DB active-controlled
	Duration of Run-in phase:	1-4 weeks
	Duration of Extension phase:	At least 1-year OLE
Hypothesis	Non-inferiority	
Treatments groups	Benralizumab	1 x 30 mg plus 3 placebo to mepolizumab SC Q4W, 70 randomised
	Mepolizumab	3 × 100 mg plus 1 placebo to benralizumab SC Q4W, 70 randomised

Endpoints and definitions during the double-blind period	Primary endpoint	Remission at both Week 36 and 48	Proportion of patients achieving main remission, defined as BVAS = 0 and OCS dose ≤ 4 mg/day (main remission definition) at both Week 36 and Week 48.
	Secondary endpoints	Total duration of remission during DB period	Total accrued duration of remission for the following categories: 0 wk, > 0 to < 12 wk, 12 to < 24 wk, 24 to < 36 wk, ≥ 36 wk.
	Secondary endpoints	Relapse during DB period	Time from randomisation to first EGPA relapse, where relapse was defined as any of the following: Active vasculitis (BVAS > 0); OR Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; Warranting any of the following: An increased dose of OCS therapy to > 4 mg/day prednisolone total daily dose; OR An increased dose or addition of immunosuppressive therapy; OR Hospitalisation related to EGPA worsening. Annualized relapse rate
	Secondary endpoints	Corticosteroid dose required during Weeks 48 through 52	Based on the average daily prednisolone/prednisone dose during Week 48 through Week 52: • Proportion of patients in each category: 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg, and > 7.5 mg. • Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25% reduction; 25 to < 50% reduction; 50 to < 75% reduction; 75 to < 100% reduction; 100% reduction. • Proportion of patients with ≥ 50% reduction from baseline. • Proportion of patients with 100% reduction from baseline.

	Secondary endpoints	Clinical benefit during DB period	Proportion of patients who had achieved any clinical benefit when meeting any of the criteria below. Proportion of patients who had achieved complete response when meeting all of the criteria below. Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the double-blind treatment period. ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52. EGPA relapse free during the double-blind treatment period.
	Secondary endpoints	Remission during DB period	Proportion of patients who had achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period.
Primary Database lock	05 September 2023		
Results and Analysis: MANDARA			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis is to demonstrate NI of benralizumab versus mepolizumab based on the primary endpoint of main remission at both Weeks 36 and 48. All subjects in the Full Analysis Set who were randomised and received at least one dose of IP were used for primary analysis. Subjects were analysed according to their randomised treatment irrespective of whether or not they prematurely discontinued, according to the ITT principle.		
Descriptive statistics and estimate variability	**Treatment group**	**Benralizumab**	**Mepolizumab**
	Number of subjects	70	70
	Subjects with main remission (Primary endpoint) at both Week 36 and 48 n (%)	40 (57.1)	40 (57.1)
Effect estimate per comparison	Subjects with main remission (Primary endpoint) at both Week 36 and 48 n (%[1])	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	1.21
		95% CI	-14.11, 16.53
		P-value	0.8773

Notes	Patient disposition: All randomised subjects in MANDARA study were dosed, and 97.1% of the randomised subjects completed the 52-week DB period. A total of 4 patients discontinued IP during the DB period, and discontinuation from IP was similar between treatment groups. The primary reason for discontinuation from IP was withdrawal by patient (3 patients [2.1%])		
Analysis description	**Secondary Analysis**		
Descriptive statistics and estimate variability	**Treatment group**	**Benralizumab**	**Mepolizumab**
	Number of subjects	70	70
	Subjects with total accrued duration of remission during DB period n (%) 0 weeks > 0 to < 12 weeks 12 to < 24 weeks 24 to < 36 weeks ≥ 36 weeks	 9 (12.9) 13 (18.6) 8 (11.4) 20 (28.6) 20 (28.6)	 15 (21.4) 10 (14.3) 8 (11.4) 19 (27.1) 18 (25.7)
	Subjects who achieved main remission within the first 24 Weeks and remained in remission for the remainder of the double-blind period n (%[1])	28 (42.1)	27 (36.5)
	Time to first relapse Subject with relapse n (%)	 21 (30.0)	 21 (30.0)
	Annualized relapse rate	0.50	0.49
	Subjects with average daily dose of prednisolone/prednisone during Week 48 through 52 n (%) 0 > 0 to ≤ 4.0 mg > 4.0 to ≤ 7.5 mg > 7.5 mg	 29 (41.4) 19 (27.1) 15 (21.4) 7 (10.0)	 19 (27.1) 30 (42.9) 13 (18.6) 8 (11.4)
	Subjects with ≥ 50% OCS reduction during Weeks 48 and 52 n (%[1])	59 (84.7)	52 (73.9)
	Subjects with 100% OCS reduction during weeks 48 to 52 n (%[1])	29 (41.4)	18 (25.8)
	Subjects with any clinical benefit (main remission) n (%[1])	66 (94.4)	63 (89.8)

	Subjects with complete response (main remission) n (%[1])	43 (62.5)	39 (54.6)
Effect estimate per comparison	Secondary endpoint: Subject with total accrued duration of remission during DB period	Comparison groups	Benralizumab vs. Mepolizumab
		Odds ratio	1.32
		95% CI	0.72, 2.40
		P-value	0.3653
	Secondary endpoint: Subject who achieved main remission within the first 24 Weeks and remained in remission for the remainder of the double-blind period	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	5.54
		95% CI	-9.30, 20.37
		P-value	0.4643
	Secondary endpoint: Time to first relapse	Comparison groups	Benralizumab vs. Mepolizumab
		Hazard ratio	0.98
		95% CI	0.53, 1.82
		P-value	0.9466
	Secondary endpoint: Annualized relapse rate	Comparison groups	Benralizumab vs. Mepolizumab
		Rate ratio	1.03
		95% CI	0.56, 1.90
		P-value	0.9282
	Secondary endpoint: Subjects with average daily dose of prednisolone/prednisone during Week 48 through 52	Comparison groups	Benralizumab vs. Mepolizumab
		Odds ratio	1.38
		95% CI	0.75, 2.54
		P-value	0.3062
	Secondary endpoint: Subjects with ≥ 50% OCS reduction during Weeks 48 and 52	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	10.79
		95% CI	-2.25, 23.83
		P-value	0.1047
	Secondary endpoint: Subjects with 100% OCS reduction during weeks 48 to 52	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	15.69
		95% CI	0.67, 30.71

		P-value	0.0406
	Secondary endpoint: Subjects with any clinical benefit (main remission)	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	4.60
		95% CI	-4.22, 13.41
		P-value	0.3068
	Secondary endpoint: Subjects with complete response (main remission)	Comparison groups	Benralizumab - Mepolizumab
		Difference between group	7.90
		95% CI	-7.32, 23.12
		P-value	0.3088
Notes	See notes under primary endpoint		

[1] The percentages are model adjusted.

2.4.3. Discussion on clinical efficacy

The key benralizumab EGPA clinical trial was Phase III MANDARA study and the product is developed for the new indication for the treatment of EGPA in adult patients with a dose of 30 mg Q4W by SC injection.

Design and conduct of clinical studies

MANDARA was a randomised, double blind, active-controlled non-inferiority study to evaluate the efficacy and safety of Benralizumab compared to Mepolizumab in the treatment of EGPA in patients, receiving Standard of Care. The study included a 52-week DB, active-controlled treatment period in which the efficacy and safety of 30 mg benralizumab administered SC Q4W was compared with 3x100 mg mepolizumab administered SC Q4W and an ongoing OLE period that intends to allow each patient at least one additional year of treatment with open-label benralizumab to assess long-term safety and tolerability of benralizumab in this patient population. IP was administered Q4W from baseline until week 48 in a double-blind fashion. Those patients that completed the double-blind treatment period on IP, would receive open-label benralizumab administered Q4W from week 52 onwards. Tapering of daily oral prednisolone/prednisone dose was allowed from Week 4 onwards to a target of ≤ 4 mg/day. The primary endpoint of the study was the "proportions of patients who achieved remission at both Weeks 36 and 48 using a NI margin of -25%". Additional analysis was conducted using a supportive remission definition of BVAS = 0 and OCS dose ≤ 7.5 mg/day. Overall, the study design and determination of NI margin followed the principles described in the *'Guideline on the Choice of the Non-Inferiority Margin' EMEA/CPMP/EWP/2158/99* and the ICH guideline: *'E10 Choice of Control Group in Clinical Trials'.* The target population of the study was adult female or male patients aged 18 years and above with documented EGPA diagnosis and a history of relapsing or refractory disease and documentation of at least 2 additional features of EGPA.

Despite that the main inclusion criteria were generally acceptable and aligned with the respective criteria of MIRRA study (asthma), the target population of the *"adult female or male patients aged 18 years and above documented EGPA diagnosis and a history of relapsing or refractory disease and documentation of*

at least 2 additional features of EGPA" was not reflected in the originally proposed indication by the applicant: " *Fasenra is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis*". Consequently, on request of the CHMP, a warning that Fasenra has not been studied in patients with active organ threatening or life-threatening manifestations of EGPA was added to section 4.4, as well as the relevant information on posology in these patients to sections 4.2 of the SmPC.

The applicant justified the absence of dose-response studies as a result of the rarity of EGPA. The use of a more frequent dosing regimen (30 mg SC Q4W) was selected for benralizumab in EGPA following discussions with FDA on: 1) the severity of the disease, 2) the extensive database of benralizumab from asthma studies, and 3) the approval of a higher dose of mepolizumab in EGPA compared with its approved dose in asthma (MIRRA). The currently approved dosing regimen of benralizumab in severe asthma is 30 mg administered SC Q4W for the first 3 doses and Q8W thereafter. The applicant's argument that the Q4W frequency is further supported by the long-term pivotal studies in asthma exacerbations and severe asthma, SIROCCO and CALIMA can be supported.

Efficacy data and additional analyses

The primary objective of MANDARA was to assess the durability of response to treatment with benralizumab compared with mepolizumab in patients with relapsing or refractory EGPA who are receiving standard of care therapy, assessed by the proportion of patients in remission at both Weeks 36 and 48. A total of 140 patients were randomized. The primary endpoint *proportion of patients with relapsing or refractory EGPA, achieving remission, defined as BVAS = 0 and OCS dose ≤ 4 mg/day (main remission definition) at both Weeks 36 and 48* was met. This was supported by the results from the analysis of the supportive endpoint, sensitivity analysis on the proportion of patients with relapsing or refractory EGPA. To compensate for the absence of placebo in the current study, the applicant performed an indirect comparison of benralizumab and historic placebo from MIRRA on remission rate, using a 2-sided test with a 0.05 significance level. A significantly higher proportion of patients who received benralizumab achieved remission at both Weeks 36 and 48 compared with the historical placebo control from MIRRA study. According to FDA guidance 'Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry' (FDA 2016), the lower bound of the 95% confidence interval (M1) for difference in remission rates between mepolizumab and placebo in MIRRA study, ie, -18%, provided a conservative basis of the NI margin for an active-controlled study, taking into account the variability of the data in MIRRA. Given the rarity of the disease and the goal of recruiting mepolizumab and benralizumab naïve participants in a reasonable timeframe, AZ proposed a recruitment goal of 140 subjects with EGPA and a -25% NI margin. According to the MAH, the potential difference of 10% in remission rates is not considered to be clinically meaningful by the clinical experts. Considering that the lower bound of the CI for the difference in remission rates was 14.1% (close to 10% and also lower than 18%), there is no concern anymore.

Following the results from the primary analysis for demonstration of benralizumab non-inferiority, compared with mepolizumab, the same logistic regression model was used to test superiority of benralizumab over mepolizumab at the 2-sided 5% significance level (equivalent to a 1-sided test at 2.5% significance level). The results from the analysis of secondary endpoints were overall supportive of the results from primary analysis, albeit with limited statistical significance.
Benralizumab effect was comparable to mepolizumab for the majority of secondary objectives assessed:

- total accrued duration of main remission was similar in the benralizumab group compared with the mepolizumab group, the odds ratio is 1.32 (95% CI: [0.72, 2.40], p=0.3653) (table 19 & 27).
- time to first relapse was similar in patients in the benralizumab group compared with the mepolizumab group with 0 major relapses occurred during the DB period in patients in the benralizumab group and 3 patients (4.3%) in the mepolizumab group

- composite endpoint of any clinical benefit from treatment (defined as any of: Remission at any time during the double-blind treatment period, ≥ 50% reduction in average daily OCS dose during Weeks 48 through 52 & EGPA relapse free during the double-blind treatment period), the proportions of patients were high and similar in both treatment groups (94.3% and 90.0%, respectively). Complete response was also similar between groups (61.4% and 55.7%, respectively).
- annualised relapse rate, was similar in patients treated with benralizumab compared with those treated with mepolizumab (rate ratio [95% CI]: 1.03 [0.56, 1.90]).
- The proportion of patients who achieved an average daily OCS dose of ≤ 4 mg/day was similar in the two treatment groups (48 patients [68.6%] in benralizumab vs 49 [70%] in mepolizumab group), and similar proportions of patients achieved ≤ 7.5 mg/day (63 patients [90.0%] in the benralizumab group and 62 patients [88.6%] in mepolizumab group).
- proportion of patients who achieved remission within the first 24 weeks and remained in remission for the remainder of the DB period, similar results were obtained for benralizumab and mepolizumab groups (40.0% *vs* 38.6%, respectively) (p = 0.4643).
- additional measures of efficacy in asthma (ACQ-6) Sino-nasal (SNOT-22 and SSQ), spirometry results (FEV1 and FVC) and health status/health-related quality of life assessments (SF-36v2, PGIS, PGIC, and WPAI-GH) were similar in the benralizumab and mepolizumab groups at Week 52.

A marked difference was only observed between benralizumab and mepolizumab groups on the OCS use during Week 48 through Week 52 where, 100% reduction in average daily dose of OCS was observed in a statistically significant percentage of patients receiving benralizumab compared with mepolizumab (41.4% *vs* 25.7%, respectively; nominal p = 0.0406). In addition, reductions of at least 50% in the average daily dose of OCS were observed in numerically higher proportions of patients receiving benralizumab compared with mepolizumab (84.3% *vs* 74.3%, respectively; nominal p = 0.1047).

Measurement of disease activity by BVAS was similar in the benralizumab and mepolizumab groups over the 52-week DB period.

VDI records organ damage due to vasculitis, treatment or unrelated, that has occurred at least three months prior to recording and therefore it is a measure of the cumulative burden of disease. The damage index score can only remain stable or deteriorate as time progresses. In the current study, VDI results presented as estimation of the mean change from baseline at weeks 24 and 52 in the benralizumab and mepolizumab group showed minimal increases in LS mean change from baseline in both treatment groups at Week 52. Of note, statistically non-significant differences on VDI have also been reported between mepolizumab and placebo in MIRRA study (mepolizumab had a similar baseline VDI score and was administered under the same dosing scheme as in MANDARA).

In addition, similar values were reported for the majority of the exploratory variables: Cumulative OCS use, Number of EGPA-related hospitalizations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test). It is noted, however, that the results for certain variables (although of exploratory nature) related to EGPA healthcare resource utilization i.e., the number of general care hospitalization days, hospital admissions or emergency department > 24 hours, number of subjects having spirometry assessments & number of subjects with emergency room visits were slightly increased for the benralizumab group compared to the mepolizumab group.

The pivotal study, MANDARA, evaluated the efficacy and safety of benralizumab compared with mepolizumab, as active comparator, in the treatment of patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. The applicant's decision to use

the Q4W dosing regimen for the proposed indication of benralizumab in EGPA is considered sufficiently justified.

The MAH has applied for the following indication: *"Fasenra is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis."*

As outlined in the inclusion criteria of MANDARA, the study participants were required to have a prior diagnosis of refractory or relapsing EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. Hence, the originally targeted indication was not representative of the population studied in MANDARA. The applicant was asked to modify the proposed indication, so it reflects the enrolled patients' disease characteristics. Hence, the indication wording modified and the following is agreed by the CHMP:

"Fasenra is indicated as an add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis (see section 5.1)."

Section 4.1 of the SmPC has been updated accordingly.

The applicant informed EMA on 28 August 2024 of findings from study monitoring which resulted in correction of source data for one of the patients in benralizumab group. Due to this correction, the patient no longer fulfils the criteria for main remission. Minor changes were introduced to data on remission, accrued duration of remission and oral corticosteroid dose. Additional on-site source data verification for primary endpoint data at the site involved, did not identify additional critical issues. Following re-run of the efficacy analyses impacted by this error it is considered that the changes in efficacy results are non-significant and do not affect the overall efficacy conclusions of the study.

2.4.4. Conclusions on the clinical efficacy

The efficacy of benralizumab in EGPA is dependent on its ability to provide clinically meaningful improvements for patients with EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. In this setting, benralizumab was found to be non-inferior to mepolizumab. The analysis of the primary endpoint was further supported by the treatment comparison in pre-specified subgroups of patients (blood eosinophil count at baseline, BMI, OCS dose at baseline, gender age group, region, time since EGPA diagnosis, immunosuppressive therapy at baseline, VDI score, race, ANCA –positive status) who achieved main remission at weeks 36 and 48.

2.5. Clinical safety

The safety profile of benralizumab in patients with EGPA is primarily supported by the data from MANDARA. Additional data from long-term pivotal studies in asthma populations i.e. SIROCCO (D3250C00017), CALIMA (D3250C00018), and BORA (D3250C00021), further support the safety profile of benralizumab, in particular regarding the Q4W dosing regimen.

Patient exposure

The total number of patients enrolled in MANDARA study, was 157 patients. All 140 randomized patients received at least one dose of IP during the DB period as follows: 70 patients received benralizumab and 70 patients received mepolizumab. All randomized patients were included in the Safety Analysis Set. Up to the primary database lock, 128 patients received at least 52 weeks of benralizumab 30 mg Q4W and 128 patients received at least one dose of IP in the OLE period and were included in the OLE Analysis Set.

The mean duration of IP administration was longer during the ongoing OLE period compared with the DB period in both the benralizumab and the mepolizumab/benralizumab groups consistent with the study design. No new safety concerns regarding duration of IP administration were identified.

Adverse events

Overall, no new safety concerns regarding AEs were identified during the MANDARA study. The most common AEs reported during the DB period were COVID-19 (21.4% patients), headache (17.1% patients), and arthralgia (17.1% patients) in the benralizumab group compared with COVID-19 (27.1% patients), headache (15.7% patients), and nasopharyngitis (14.3% patients) in the mepolizumab group. Most AEs were transient in nature and of mild or moderate intensity. No events of helminth infection were reported. A total of 3 malignant neoplasm events including 2 prostate cancer AEs in the mepolizumab group and 1 marginal zone lymphoma AE in the benralizumab group were reported during the DB period. No new notable trends were observed during the OLE period of the study compared with the DB period. The most common AEs during the DB period were defined as those with a PT frequency of > 3% in either treatment group. The below AE summaries (Table 20 (DB) and 21 (OLE)) included all patients on benralizumab at any time as the *total* while on benralizumab 30 mg group, and it is referred to as the *total benralizumab group*.

Table 20. Adverse Events in Any Category – DB Period (Safety Analysis Set)

	Number (%) of patients	
AE category	**Benralizumab 30 mg [a] (N = 70)**	**Mepolizumab 300mg [a] (N = 70)**
Any AE	63 (90.0)	67 (95.7)
Any AE with outcome of death	0	0
Any SAE (including events with outcome of death)	4 (5.7)	9 (12.9)
Any AE leading to discontinuation of IP	0	2 (2.9)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. Percentages are based upon number of patients in each treatment group within the Safety Analysis Set.

An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period).

Adverse events were coded using MedDRA version 26.0.

AE = adverse event; DB = double-blind; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = open-label extension; SAE = serious adverse event

Table 21. Adverse Events in Any Category – OLE Period (OLE Analysis Set)

	Number (%) of patients	
AE category	Benralizumab 30 mg [a] (N = 66)	Mepolizumab switched to Benralizumab [a] (N = 62)
Any AE	54 (81.8)	57 (91.9)
Any AE with outcome of death	0	1 (1.6)
Any SAE (including events with outcome of death)	10 (15.2)	13 (21.0)
Any AE leading to discontinuation of IP	2 (3.0)	1 (1.6)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. The OLE period was defined from the first dose of OLE benralizumab 30 mg to the end of the study.

Percentages were calculated using the number of patients in each treatment group (N) as denominator.

Only events that started during the OLE period were counted.

Adverse events were coded using MedDRA version 26.0.

AE = adverse event; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = open-label extension; SAE = serious adverse event

Adverse Events by System Organ Class and Preferred Term

Small numerical differences were observed between treatment groups for the most common AEs (PT frequency of > 3% in either group), during the DB period without identification of specific trends or pattern. The most frequent (PT frequency > 3%) reported Adverse Events (by PT) are listed in Table 22. The most frequently reported common AE was COVID-19; 15 patients (21.4%) in the benralizumab group and 19 patients (27.1%) in the mepolizumab group were identified with COVID-19 AEs during the DB period. Despite two of the events (one in each treatment group) being serious, both resolved.

Table 22. Most Common AEs – DB Period (PT Frequency >3%) (Safety Analysis Set)

	Benralizumab 30 mg (N = 70) (Exp = 70.2 years) [a]		Mepolizumab 300 mg (N = 70) (Exp = 70.3 years) [a]	
PT	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100 PY) [c]
Any most common (frequency of > 3%) AE	51 (72.9)	72.65	61 (87.1)	86.77
COVID-19	15 (21.4)	21.37	19 (27.1)	27.03
Headache	12 (17.1)	17.09	11 (15.7)	15.65
Arthralgia	12 (17.1)	17.09	8 (11.4)	11.38
Nasopharyngitis	6 (8.6)	8.55	10 (14.3)	14.22
Sinusitis	5 (7.1)	7.12	8 (11.4)	11.38
Fatigue	5 (7.1)	7.12	6 (8.6)	8.53
Bronchitis	5 (7.1)	7.12	5 (7.1)	7.11
Sinusitis bacterial	5 (7.1)	7.12	3 (4.3)	4.27
Upper respiratory tract infection	4 (5.7)	5.70	4 (5.7)	5.69
Influenza like illness	4 (5.7)	5.70	3 (4.3)	4.27
Nausea	1 (1.4)	1.42	6 (8.6)	8.53
Viral upper respiratory tract infection	1 (1.4)	1.42	6 (8.6)	8.53
Asthenia	6 (8.6)	8.55	0	0
Hypertension	1 (1.4)	1.42	5 (7.1)	7.11
Injection site bruising	2 (2.9)	2.85	4 (5.7)	5.69
Injection site pain	3 (4.3)	4.27	3 (4.3)	4.27
Oral candidiasis	2 (2.9)	2.85	4 (5.7)	5.69
Rash	4 (5.7)	5.70	2 (2.9)	2.84
Urinary tract infection	5 (7.1)	7.12	1 (1.4)	1.42
Back pain	2 (2.9)	2.85	3 (4.3)	4.27
Diarrhoea	2 (2.9)	2.85	3 (4.3)	4.27
Myalgia	4 (5.7)	5.70	1 (1.4)	1.42
Skin laceration	1 (1.4)	1.42	4 (5.7)	5.69
Tooth infection	3 (4.3)	4.27	2 (2.9)	2.84
Abdominal pain	0	0	4 (5.7)	5.69

	Benralizumab 30 mg (N = 70) (Exp = 70.2 years) [a]		Mepolizumab 300 mg (N = 70) (Exp = 70.3 years) [a]	
PT	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100 PY) [c]
Adrenal insufficiency	1 (1.4)	1.42	3 (4.3)	4.27
Asthma	1 (1.4)	1.42	3 (4.3)	4.27
Contusion	1 (1.4)	1.42	3 (4.3)	4.27
Muscle spasms	3 (4.3)	4.27	1 (1.4)	1.42
Pain in extremity	0	0	4 (5.7)	5.69
Rhinitis	1 (1.4)	1.42	3 (4.3)	4.27
Vomiting	1 (1.4)	1.42	3 (4.3)	4.27
Constipation	3 (4.3)	4.27	0	0
Herpes zoster	0	0	3 (4.3)	4.27
Osteopenia	0	0	3 (4.3)	4.27

[a] Exp = Total PY across all patients in DB period in the given treatment group.

[b] Number (%) of patients with AEs, sorted on descending frequency for PT according to total frequency. Patients with multiple events in the same PT are counted only once for that PT. Patients with events in more than one PT are counted once in each of those PTs. Percentages are based upon number of patients in each treatment group within the Safety Analysis Set.

[c] The event rate per 100 PY was defined as the number of patients with an AE divided by the total PY multiplied by 100.

An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period).

Most common is defined as a total frequency of > 3% in any treatment group.

Adverse events were coded using MedDRA version 26.0.

AE = adverse event; DB = double blind; Exp = exposure; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = open-label extension; PT = preferred term; PY = patient-years

Relatedness was recorded for each AE by response to a prompt if there was a reasonable possibility the AE was caused by the IP; therefore, relatedness is referred to as *possibly related* or *not possibly related*.

The majority of AEs during the DB period were assessed as not possibly related to IP by the Investigator. No clinically meaningful difference was observed between treatment groups during the DB period in the proportion of patients with AEs *possibly related to IP*. During the DB period, AEs related to benralizumab treatment i.e. headache (7.1%) and fatigue (2.9%) were reported with higher frequency in MANDARA study compared with the Phase III asthma studies.

No significant difference in the proportion of patients with severe AEs during the DB period between the two groups was observed: 5 severe adverse events were reported in the benralizumab group (COVID-19, headache, syncope, neuropathy peripheral, and anosmia) and 6 severe adverse events in the mepolizumab group (prostate cancer [2 events], acute respiratory failure, cholangitis, infusion related reaction, and wound infection). Similarly to the DB period safety observations, no clinically meaningful differences were seen between benralizumab and mepolizumab/benralizumab groups in the OLE period.

Serious adverse event/deaths/other significant events

During the DB period, 4 SAEs were reported in the benralizumab group and 9 SAEs in the mepolizumab group. One of three SAEs reported in the mepolizumab group was assessed as possibly related to IP, and 2 SAEs led to discontinuation of IP. All patients in the benralizumab group and most patients in the mepolizumab group recovered from SAEs reported during the DB period. No hypersensitivity AEs were

serious, and no events of anaphylactic reactions were reported. The proportions of patients with injection site reaction AEs were low and similar in the benralizumab group an in the mepolizumab group.

During the OLE period, 10 and 13 SAEs were reported in the benralizumab group and in the mepolizumab/benralizumab group, respectively. One of the SAEs in the mepolizumab/benralizumab group was assessed by the Investigator as possibly related to IP, 2 SAEs led to discontinuation of IP, and most SAEs had resolved at the time of data cut-off. No death was reported in the DB period in any of the two treatment groups.

One death from pulmonary embolism occurred during the OLE period in the mepolizumab/benralizumab group. This event was assessed as not possibly related to the IP by the Investigator. Based on information from the patient narrative, a patient who was in remission from EGPA developed an AE with outcome of death from pulmonary embolism. It was noted by the CHMP that the event of pulmonary embolism occurred two months after treatment with benralizumab in a patient from the mepolizumab switched to benralizumab group. Taking into consideration that pulmonary embolism was one of the fatal AEs reported in the benralizumab Phase III exacerbation studies, the Investigator assessment of the fatal event in MANDARA as '*not possibly related to the IP*' based on the patient's underlying conditions, was questioned and the MAH was asked to discuss further this fatal event (see discussion below).

Serious Adverse Events (SAEs)

DB Period: There were no clinically meaningful differences in the frequency and event rate of SAEs between the benralizumab and mepolizumab groups during the DB period (Table 23). All but one of the SAEs were assessed as having no causal relationship to the IP; most events resolved.

Table 23. SAE – DB Period (Safety Analysis Set)

	Benralizumab 30 mg (N = 70) (Exp = 70.2 years) [a]		Mepolizumab 300mg (N = 70) (Exp = 70.3 years) [a]	
SOC PT	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100 PY) [c]
Patients with any SAE	4 (5.7)	5.70	9 (12.9)	12.80
Infections and infestations	2 (2.9)	2.85	4 (5.7)	5.69
COVID-19	1 (1.4)	1.42	1 (1.4)	1.42
Appendicitis	0	0	1 (1.4)	1.42
Bronchitis	1 (1.4)	1.42	0	0
Streptococcal urinary tract infection	0	0	1 (1.4)	1.42
Wound infection	0	0	1 (1.4)	1.42
Hepatobiliary disorders	0	0	2 (2.9)	2.84
Cholangitis	0	0	1 (1.4)	1.42
Hepatic infiltration eosinophilic	0	0	1 (1.4)	1.42
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2 (2.9)	2.84
Prostate cancer	0	0	2 (2.9)	2.84
Nervous system disorders	2 (2.9)	2.85	0	0
Neuropathy peripheral	1 (1.4)	1.42	0	0
Syncope	1 (1.4)	1.42	0	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (1.4)	1.42
Acute respiratory failure	0	0	1 (1.4)	1.42

[a] Exp = Total PY across all patients in the DB period in the given treatment group.

[b] Number (%) of patients with SAEs, sorted on descending frequency order for SOC and descending frequency for PT according to total frequency. Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than one PT were counted once in each of those PTs. Percentages were based upon number of patients in each treatment group within the Safety Analysis Set.

[c] The event rate per 100 PY was defined as the number of patients with an SAE divided by the total PY multiplied by 100.

An SAE during the DB period was defined as a SAE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period).

Serious AEs were coded using MedDRA version 26.0.

AE = adverse event; DB = double-blind; Exp = exposure; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = Open-label extension; PT = preferred term; PY = patient-years; SAE = serious adverse event; SOC = system organ class

OLE Period: There were no clinically meaningful differences in the frequency and event rate of SAEs between the benralizumab and mepolizumab/benralizumab groups during the OLE period. With the exception of *Clostridium difficile* infection in the mepolizumab/benralizumab group all SAEs were assessed as having no causal relationship to the IP and most events were resolved.

Other Significant Adverse Events

Injection Site Reactions: Similar proportions of patients were identified with injection site reaction AEs during the DB period between the benralizumab group and the mepolizumab group (Table 24).

Table 24. AEs of Injection Site Reactions – DB Period (Safety Analysis Set)

	Benralizumab 30 mg (N = 70) (Exp = 70.2 years) [a]		Mepolizumab 300 mg (N = 70) (Exp = 70.3 years) [a]	
PT	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100 PY) [c]
Patients with any injection site reaction	11 (15.7)	15.67	12 (17.1)	17.07
Injection site bruising	2 (2.9)	2.85	4 (5.7)	5.69
Injection site pain	3 (4.3)	4.27	3 (4.3)	4.27
Injection site erythema	2 (2.9)	2.85	2 (2.9)	2.84
Injection site haematoma	2 (2.9)	2.85	0	0
Injection site induration	1 (1.4)	1.42	1 (1.4)	1.42
Injection site pruritus	1 (1.4)	1.42	1 (1.4)	1.42
Injection site urticaria	0	0	2 (2.9)	2.84
Injection site hypoaesthesia	1 (1.4)	1.42	0	0
Injection site oedema	0	0	1 (1.4)	1.42
Injection site reaction	0	0	1 (1.4)	1.42

[a] Exp = Total PY across all patients in the DB period in the given treatment group.

[b] Number (%) of patients with AEs, sorted on descending frequency for PT according to total frequency. Patients with multiple events in the same PT were counted only once in that PT. Patients with events in more than one PT/inject site location were counted once in each of those PT/inject site locations. Percentages were based upon number of patients in each treatment group within the Safety Analysis Set.

[c] The event rate per 100 patient-years was defined as the number of patients with an AE divided by the total PY multiplied by 100.

An AE during the DB period was defined as an AE with an onset date on or after day of the first dose of study DB treatment and prior to the first dose of open-label benralizumab (up to end of study for patients who did not roll over to the OLE period).

Adverse events were coded using MedDRA version 26.0.

Adverse events of all injection sites are displayed.

AE = adverse event; DB = double-blind; Exp = exposure; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = open-label extension; PY = patient-years; PT = preferred term

Injection site reaction AEs were reported in low numbers during the DB period and were non-serious with mild or moderate intensity. All injection site reaction AEs were assessed as possibly related to IP. Overall, during the DB period no consistent pattern or trend in the injection site reaction AEs was observed in the benralizumab and mepolizumab groups. However, an increase was observed in the frequency of injection site AEs for benralizumab group in the current study compared with the respective frequency for the same dosing schedule (Q4W) in the Phase III asthma exacerbation studies (15.7% *vs* 3.2%). This increase could possibly be explained by the increase in the number of injections/visit: in MANDARA study each patient in the benralizumab group received 4 injections (1x30mg + 1 placebo/visit, double-dummy design) *vs* 1x30mg injection in the Phase III asthma studies.

A similar increase in frequency was also observed in mepolizumab group in the current study compared with the mepolizumab group in MIRRA (17.1% *vs* 10%): in MANDARA study each patient received 4 injections (3x100mg + 1 placebo/visit, double-dummy design) *vs* 3x100mg injections in MIRRA.

The applicant was asked to discuss this issue (see discussion below).

Other: Helminth infections and malignancy are considered AEs of interest in the context of benralizumab mechanism of action. Malignancy is considered an important potential risk of the eosinophil lowering therapies based on the putative effect of eosinophils in neoplastic diseases, although a definite link has yet to be established. Overall, no helminth infections were reported in the study. Three events of malignant neoplasm were reported in the DB period of which 2 serious events of prostate cancer in the mepolizumab group that led to study discontinuation and 1 nonserious event of marginal zone lymphoma

in the benralizumab group. A total of 2 malignant neoplasm events in the benralizumab group were also reported during the OLE period. None of the malignant neoplasm events, reported in the DB/OLE periods, were assessed as possibly related to the IP.

Laboratory findings

The results from clinical laboratory evaluations for haematology, clinical chemistry and urinalysis variables were analysed as: changes in mean values over time, changes in individual patients over time and individual clinically important abnormalities. Overall, no new safety concerns regarding clinical laboratory evaluations were identified. During the DB period, the proportions of patients with AEs related to laboratory parameters were low across treatment groups, with no AEs leading to discontinuation of the IP.

Discontinuation due to adverse events

The number of subjects experiencing AEs leading to discontinuation of IP are presented in Table 25 for the DB period and Table 26 for DB+OLE periods. During the DB period there were two patients from the mepolizumab group which experienced AEs that led to discontinuation of IP. During the DB and OLE period there were two patients from the benralizumab group, which discontinued IP due to EGPA.

Table 25. AEs Leading to Discontinuation of IP – DB Period (Safety Analysis Set)

	Benralizumab 30 mg (N = 70) (Exp = 70.2 years) [a]		**Mepolizumab 300 mg (N = 70) (Exp = 70.3 years) [a]**	
SOC PT	**Number (%) of patients [b]**	**Event rate (per 100 PY) [c]**	**Number (%) of patients [b]**	**Event rate (per 100 PY) [c]**
Patients with any AE causing discontinuation of IP	0	0	2 (2.9)	2.84
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2 (2.9)	2.84
Prostate cancer	0	0	2 (2.9)	2.84

[a] Exp = Total PY across all patients in the DB period in the given treatment group.

[b] Number (%) of patients with AEs, sorted on descending frequency for SOC and PT according to total frequency. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.

[c] The event rate per 100 patient-years was defined as the number of patients with an AE divided by the total PY multiplied by 100.

Adverse events were coded using MedDRA version 26.0.

AE = adverse event; DB = double-blind; Exp = exposure; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; PT = preferred term; PY = patient-years; SOC = system organ class

Table 26. AEs Leading to Discontinuation of IP – DB and OLE Periods (Safety Analysis Set)

	Benralizumab 30 mg (N = 70) (Exp = 146.0 years) [a d]		Mepolizumab 300 mg (N = 70) (Exp = 148.8 years) [a d]		Total while on Benralizumab 30 mg (N = 132) (Exp = 224.7 years) [a e]	
SOC PT	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100 PY) [c]	Number (%) of patients [b]	Event rate (per 100PY) [c]
Patients with any AE causing discontinuation of IP	2 (2.9)	1.37	3 (4.3)	2.02	3 (2.3)	1.34
Immune system disorders	2 (2.9)	1.37	0	0	2 (1.5)	0.89
Eosinophilic granulomatosis with polyangiitis	2 (2.9)	1.37	0	0	2 (1.5)	0.89
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	2 (2.9)	1.34	0	0
Prostate cancer	0	0	2 (2.9)	1.34	0	0
Infections and infestations	0	0	1 (1.4)	0.67	1 (0.8)	0.45
Clostridium difficile infection	0	0	1 (1.4)	0.67	1 (0.8)	0.45

[a] Exp = Total PY across all patients in the given treatment group.
[b] Number (%) of patients with AEs, sorted on descending frequency for SOC and PT according to total frequency. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[c] The event rate per 100 patient-years was defined as the number of patients with an AE divided by the total PY multiplied by 100.
[d] All events that happened during the entire study were summarised in these treatment groups, even though the Mepolizumab column included time on Mepolizumab and Benralizumab.
[e] Only events that happened after starting Benralizumab were summarised in this treatment group, and the denominator (N) was all patients who received Benralizumab at any time during the study. All events included during the study.

Adverse events were coded using MedDRA version 26.0.

AE = adverse event; DB = double-blind; Exp = exposure; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in treatment group; OLE = open-label extension; PT = preferred term; PY = patient-years; SOC = system organ class

The CHMP noted that during the DB period, there were no patients from the benralizumab group who discontinued IP. During the DB+OLE period, there were 3 patients who discontinued IP, 2 patients in the benralizumab group as a result of EGPA, and one patient in the mepolizumab switched to benralizumab group who developed *Clostridium Difficile* infection. These differences are small, and applicant will continue to monitor the discontinuation rate until the end of OLE period.

Post marketing experience

Benralizumab is approved for the treatment of severe eosinophilic asthma in 80 countries. The summary of safety data from post-marketing sources is regularly presented in periodic safety update reports.

2.5.1. Discussion on clinical safety

The safety profile of benralizumab is updated with the data from MANDARA study, conducted with patients with relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) on corticosteroid therapy with or without stable immunosuppressive therapy. The Safety Analysis Set included all randomized patients (N=140) who were assigned to the two treated groups. The primary analysis of MANDARA study provided all safety data of benralizumab in EGPA from the complete follow-up of the 52-week DB period and exposure and AE data from the OLE period until the primary analysis data cut-off date. The applicant's large safety database already contains data from the long-term pivotal studies SIROCCO, CALIMA and BORA in patients with a history of asthma exacerbations and severe asthma. It is noted that the safety profile of benralizumab is comparable between the two dosing frequencies, Q4W and Q8W applied in the long-term studies on asthma. The safety data from the current study are generally consistent with data from the applicant's long-term pivotal studies considering that the predominant characteristic in the majority of EGPA patients is eosinophilic vasculitis combined with asthma.

Treatment with benralizumab in patients with EGPA was in general well tolerated with no new safety findings. The most common AEs reported during the DB period in the benralizumab group were COVID-19, headache and arthralgia. Differences were observed between the two treatment groups for asthenia (higher

% number of patients in the benralizumab group *vs* no patients in the mepolizumab group), abdominal pain and pain in extremities (higher % number of patients for both PTs in the mepolizumab group), however these events were not multiplicity corrected and no clinical relevance is expected. Most common AEs were transient in nature with mild or moderate intensity and with similar pattern between the benralizumab and mepolizumab treatment groups when analysed according to age, gender, race and geographic region.

The higher frequency of injection site reactions reported for benralizumab group in MANDARA study compared with long-term Phase III studies on asthma and MIRRA study was highlighted to the applicant during the assessment. The applicant's argument on the possible outsized effect of few events in comparisons between studies, when taking into consideration the difference in size of MANDARA and the pivotal Phase III studies in patients with severe asthma was acknowledged by the CHMP. It is also recognised that due to the nature of EGPA, similar numbers for patient recruitment are difficult to achieve.

There were no clinically meaningful differences observed in AE or SAE rates between patients who had treatment-emergent ADAs compared with those who were ADA negative. During the DB period, 5 patients in the benralizumab group who were treatment-emergent ADA positive reported AEs, none of which were serious. There were no anaphylactic reactions reported. Two nonserious hypersensitivity reactions were reported in patients with treatment-emergent ADA positive status in the benralizumab group; both were assessed as mild and not possibly related to the IP by the investigator.

During the DB period the proportion of patients reporting AEs and the event rates in any category were higher compared to the OLE period for both treatment groups. No death was reported in the DB period in any of the two treatment groups. One death from pulmonary embolism occurred during the OLE period in the mepolizumab switched to benralizumab group which was considered 'not possibly related to the IP'. Since fatal pulmonary embolism was also reported in the Phase III exacerbation studies, the CHMP questioned the applicant. A causal relationship of pulmonary embolism with benralizumab administration at present cannot be clearly excluded and therefore the applicant agreed to follow up SAE "Pulmonary embolism" in the PSURs.

Safety data from MANDARA study do not provide evidence for increase in malignancy AEs during the DB and OLE period of the study and no new safety concerns were identified from laboratory evaluations.

Based on the safety profile of benralizumab in asthma indication, it is considered important to further monitor AEs related to malignancies in light of the frequent dosing schedule for benralizumab in the proposed indication. To this direction, the results from the on-going PASS evaluating the potential risk on malignancy are considered mostly relevant.

2.5.2. Conclusions on clinical safety

The primary evidence for safety of benralizumab in EGPA is based on the analysis of MANDARA, which contains all safety data from the complete follow-up of the 52-week DB period and exposure and AE data from the OLE period by the primary analysis data cut-off date. The selected dose of 30 mg Q4W was well tolerated in patients with EGPA with no new safety findings. The analyzed safety data demonstrated a safety profile that was generally consistent with benralizumab's known safety profile in asthma. It is noted that some AEs were assessed as related to benralizumab (i.e. headache, fatigue) and reported with higher frequency for benralizumab in MANDARA compared with the asthma database of the applicant. No additional ADRs were identified. There are no major concerns regarding the safety profile of benralizumab in patients with relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) who are on corticosteroids with or without stable immunosuppressive. The MAH will continue to monitor the safety profile in the PSURs. The SmPC has been updated with the relevant safety information.

Overall, the safety profile is considered similar to that of benralizumab in asthma.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application. The CHMP received the following PRAC Advice on the submitted Risk Management Plan. The PRAC considered that the risk management plan version 6.2 is acceptable.

Safety concerns

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

The summary of safety concerns in the RMP is acceptable.

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones for EMA**	**Due dates for EMA**
Category 1 - Not applicable				
Category 2 – Not applicable				
Category 3 - Required additional pharmacovigilance activities				
D3250R00042 Descriptive Study of the Incidence of Malignancy in Severe Asthma Patients Receiving Benralizumab and Other Therapies, a Post Authorization Safety Study. Ongoing	The primary objective of this study is to assess the incidence of malignancies in severe asthma patients receiving benralizumab compared with those receiving non-benralizumab biologics, and those not receiving biologics. The secondary objective is to describe the clinical characteristics of the new malignancy cases that develop in severe asthma patients and relevant subgroups.	Important potential risk: Malignancy	Start of data collection End of data collection Submit final report of study results (CSR)	Q1 2018 Q4 2023 Q4 2024

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Malignancy	Routine risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse event follow-up for spontaneous reports Additional pharmacovigilance activities: D3250R00042 (Malignancy Post Authorization Safety Study)
Missing information		
Use in pregnancy and lactation	Routine risk minimisation measures: SmPC Section 4.6	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is also updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The EGPA, formerly known as Churg-Strauss syndrome, is a rare, multisystemic, immune mediated inflammatory disease. EGPA is considered a form of antineutrophil cytoplasmic antibody-associated vasculitis, along with granulomatosis with polyangiitis and microscopic polyangiitis. It is histologically defined by eosinophil-rich, necrotising granulomatous inflammation primarily involving the respiratory tract, along with necrotising vasculitis of small- to medium-sized arteries. These diverse processes are

responsible for heterogeneous clinical manifestations and therefore clinical phenotypes can be variable. Vasculitis is often not apparent in the initial phases of the disease. The prevalence of ANCAs in patients with EGPA varies widely (30–47% EGPA patients are ANCA positive) and their clinical significance remains uncertain. Eosinophils play a pathological role across the spectrum of EGPA regardless of ANCA status.

3.1.2. Available therapies and unmet medical need

Systemic corticosteroids, immunosuppressants, and biologics (rituximab and mepolizumab) are currently recommended in treatment guidelines for EGPA, with mepolizumab being the only approved therapy. A key therapeutic goal in treatment of EGPA is to induce and maintain remission while reducing the burden of corticosteroids and immunosuppressants because these therapies are often associated with significant adverse events, including toxicity, and a high relapse rate. Rituximab has limited evidence to support efficacy in EGPA, particularly in controlling airway manifestations and reducing corticosteroid dependency. A high proportion of EGPA patients treated with mepolizumab either do not achieve remission and/or relapse, with limited reduction in corticosteroid dependency. Therefore, a significant unmet medical need remains for patients with EGPA.

3.1.3. Main clinical studies

The benralizumab EGPA clinical development programme consists of the pivotal Phase III MANDARA study. MANDARA was a randomised, double-blind, multicentre, parallel group, active-controlled, NI study that evaluated the efficacy and safety of benralizumab compared with mepolizumab in the treatment of patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy.

3.2. Favourable effects

On the primary endpoint (proportion of patients who achieved main remission at both weeks 36 and 48), benralizumab was non-inferior to mepolizumab as demonstrated by the lower bound of 95% CI falling well-above the prespecified clinical NI margin of -25% for the difference in remission rate (1.21, 95% CI [-14.11,16.53]) at both Week 36 and Week 48. Using an indirect method to compensate for the absence of placebo control in MANDARA, it was demonstrated that a statistically significant higher proportion of patients on benralizumab achieved remission at both Weeks 36 and 48 when compared with the historical placebo control from MIRRA study. The analysis of the primary endpoint was further supported by the results on treatment comparisons for pre-specified subgroups of patients (including age, gender, region, blood eosinophil count at baseline, BMI, time since EGPA diagnosis, OCS dose at baseline, VDI score, immunosuppressive therapy at baseline, race, ANCA –historical or at baseline positive status), who achieved main remission at weeks 36 and 48.

Based on the results from the assessment of benralizumab efficacy compared with mepolizumab on clinically relevant secondary endpoints, a marked difference between benralizumab and mepolizumab groups was observed for the effect on average daily dose of OCS use during Week 48 through Week 52. A 100% reduction in average daily OCS dose was observed in a statistically significant percentage of patients receiving benralizumab compared with mepolizumab. In addition, reductions of at least 50% in the average daily dose of OCS were observed in numerically higher proportions of patients receiving benralizumab compared with mepolizumab.

3.3. Uncertainties and limitations about favourable effects

The target population in the proposed indication was wider compared to the population investigated in MANDARA study and hence, the indication was narrowed. The level of evidence presented by the applicant to justify the decision to use the Q4W dosing regimen of benralizumab in EGPA is limited but can be acceptable. Study limitations were identified in the primary analysis: imbalances in disease burden between the groups at baseline, that could benefit the benralizumab group were observed for biopsy evidence of EOS vasculitis/inflammation and maximum value for absolute eosinophil count. Similar results were obtained for both benralizumab and mepolizumab from the comparative assessment of secondary endpoints. Only numerical differences were reported in favour of benralizumab for the proportion of patients who achieved an average daily prednisolone/prednisone dose of ≤ 4 mg/day. No difference between the two treatment groups was observed for the time to first relapse, the proportion of patients who achieved remission within the first 24 weeks and the annualized relapse rate.

3.4. Unfavourable effects

Treatment with benralizumab in patients with EGPA was in general well tolerated with no new safety findings for benralizumab. The most common AEs reported during the DB period were COVID-19, headache, and arthralgia in the benralizumab group compared with COVID-19, headache, and nasopharyngitis in the mepolizumab group.

There were no clinically meaningful differences observed in AE or SAE rates between patients who had treatment-emergent ADAs compared with those who were ADA negative. During the DB period, 5 patients in the benralizumab group who were treatment-emergent ADA positive reported AEs, none of which were serious. There were no anaphylactic reactions reported. Two nonserious hypersensitivity reactions (rash and vulvovaginal rash) were reported in patients with treatment-emergent ADA positive status in the benralizumab group; both were assessed as mild and not possibly related to the IP. During the DB period the proportion of patients reporting AEs and the event rates in any category were higher compared to the OLE period for both treatment groups.

There were no clinically meaningful differences in the frequency and event rate of SAEs between benralizumab and mepolizumab groups during the DB period. Similarly, there were no clinically meaningful differences in the frequency and event rate of SAEs between the benralizumab and mepolizumab/benralizumab groups during the OLE period.

No death was reported in the DB period in any of the two treatment groups. One death from pulmonary embolism occurred during the OLE period in the mepolizumab/benralizumab group which was considered 'not possibly related to the IP'. Since fatal pulmonary embolism was also reported in the Phase III exacerbation studies, the applicant will monitor these events and report them in the PSUR.

Safety data from MANDARA study do not provide evidence for increase in malignancy AEs during the DB and OLE period of the study.

3.5. Uncertainties and limitations about unfavourable effects

The TEAEs headache, fatigue, asthenia occurred at a higher frequency in the benralizumab group compared to mepolizumab group. Conversely, injection site bruising/pain/erythema/haematoma were more frequent in the benralizumab group. It is also noted that headache and fatigue AEs assessed by the investigator as related to benralizumab treatment i.e. were reported with higher frequency in MANDARA study compared with the asthma studies.

Noted is also the higher frequency of injection site reactions reported in MANDARA study compared with long-term Phase III studies on asthma and MIRRA study, although not numerically significant.

Further evaluation of SAEs occurring in the mepolizumab switched to benralizumab group during the OLE period which were attributed to mepolizumab treatment per investigator's opinion despite occurrence post benralizumab treatment will be conducted.

3.6. Effects Table

Table 27. . Effects Table for FASENRA in EGPA (data cut-off: 10 August 2023)

Effect	Short description	Unit	Treatment Benralizumab (30 mg)	Control mepolizumab (300 mg)	Uncertainties / Strength of evidence	References
Favourable Effects						
Remission at both Week 36 and 48	Proportion of Subjects who achieved main remission at both Week 36 and 48 n (%)	% subjects	40 (57.1)	40 (57.1)	Difference 1.21 95% CI 1-14.11, 16.53 p-value <0.8773	Primary endpoint
	BVAS = 0	% subjects	58 (82.9)	59 (84.3)	Difference -1.17 95% CI -13.27,10.94 p-value <0.8502	
	OCS dose ≤ 4 mg/day	% subjects	42 (60)	41 (58.6)	Difference 2.64 95% CI -12.67, 17.95 p-value <0.7354	
Total duration of remission during DB period	Subjects with total accrued duration of remission during DB period n (%) 0 weeks > 0 to < 12 weeks 12 to < 24 weeks 24 to < 36 weeks ≥ 36 weeks	% subjects	9 (12.9) 13 (18.6) 8 (11.4) 20 (28.6) 20 (28.6)	15 (21.4) 10 (14.3) 8 (11.4) 19 (27.1) 18 (25.7)	OR 1.32 95% CI 0.72, 2.40 p-value <0.3653	Secondary endpoint
Average daily dose of OCS	Average daily dose of Prednisolone /prednisone during Week 48 through 52: 0 mg > 0 to ≤ 4.0 mg > 4.0 to ⩽ 7.5 mg > 7.5 mg	% subjects	29 (41.4) 19 (27.1) 15 (21.4) 7 (10.0)	19 (27.1) 30 (42.9) 13 (18.6) 8 (11.4)	OR 1.38 95% CI 0.75, 2.54 p-value <0.3062	
	Subjects with 100% OCS reduction during weeks 48 to 52 n (%)	% subjects	29 (41.4)	18 (25.7)	Difference 15.69 95% CI -0.67, 30.71 p-value <0.0406	Secondary endpoint
	Subjects with 50% OCS reduction during weeks 48 to 52 n (%)	% subjects	59 (84.3)	52 (74.3)	Difference 10.79 95% CI -2.25, 23.83 p-value <0.1047	Secondary endpoint
Unfavourable Effects						
	Any AE	% subjects	63 (90.0)	67 (95.7)		MANDARA
	Any AE with outcome of death	% subjects	0	0		MANDARA
	Any SAE (incl. events with outcome of death)	% subjects	4 (5.7)	9 (12.9)		MANDARA
	Patients with any related AE	% subjects	20 (28.6)	16 (22.9)		MANDARA
	Any AE leading to discontinuation of IP	% subjects	0	2 (2.9)		MANDARA

Effect	Short description	Unit	Treatment Benralizumab (30 mg)	Control mepolizumab (300 mg)	Uncertainties / Strength of evidence	References
	Covid-19	% subjects	15 (21.4)	19 (27.1)		MANDARA
	Headache	% subjects	12 (17.1)	11 (15.7)		MANDARA
	Arthralgia	% subjects	12 (17.1)	8 (11.4)		MANDARA
	Nasopharyngitis	% subjects	6 (8.6)	10 (14.3)		MANDARA
	Sinusitis	% subjects	5 (7.1)	8 (11.4)		MANDARA
	Fatigue	% subjects	5 (7.1)	6 (8.6)		MANDARA
	Upper respiratory tract infection	% subjects	4 (5.7)	4 (5.7)		MANDARA
	Asthenia	% subjects	6 (8.6)	0		MANDARA

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy and safety of benralizumab compared to mepolizumab in the treatment of EGPA were investigated in MANDARA study. Based on the analysis of the primary endpoint of the study, Non-Inferiority was demonstrated for Benralizumab compared to mepolizumab by the lower bound of 95% CI falling well-above the prespecified clinical NI margin of -25% for the difference in remission rate at both Week 36 and Week 48. This is not considered clinically meaningful. MANDARA was a well conducted study with low IPDs, low study discontinuation rate, and high data quality. Benralizumab showed similar efficacy for the primary endpoint and a consistent trend of efficacy for all secondary endpoints, including OCS reduction endpoints, compared to mepolizumab, which will be a clinically relevant benefit to EGPA patients.

The analysis of the secondary endpoints indicated that benralizumab did not demonstrate superior efficacy in EGPA compared with mepolizumab. A higher treatment effect for benralizumab compared with mepolizumab was achieved for the average daily dose of OCS use during Week 48 through Week 52: 100% reduction in average daily OCS dose was observed in a statistically significant percentage of patients receiving benralizumab (41.4%) compared with patients receiving mepolizumab (25.7%) during Week 48 through Week 52. Reductions of at least 50% in the average daily dose of OCS were observed in numerically higher proportions of patients receiving benralizumab compared with mepolizumab. A numerically similar proportion of patients achieved an average daily OCS dose of ≤4mg/day in the two treatment groups (68.6% in the benralizumab group vs. 70.0% in the mepolizumab group).

Treatment of patients with refractory or relapsing EGPA receiving standard of care therapy, with benralizumab was in general well tolerated with no new safety findings for benralizumab. The AEs assessed by the investigator as related to benralizumab treatment (headache, fatigue) were reported with higher frequency in MANDARA study compared with the asthma studies. Injection site reactions were more frequent in the benralizumab group. There were no clinically meaningful differences in the frequency and event rate of SAEs between benralizumab and mepolizumab groups during the DB period, however a higher proportion of patients reported SAEs and SAE event rates in the OLE period compared to the DB period. No hypersensitivity AEs were serious, and no events of anaphylactic reactions were reported. No fatal events were reported during the DB period of the study. One death from pulmonary embolism occurred during the OLE period in the mepolizumab/benralizumab group.

The pharmacodynamic effect of benralizumab in patients with EGPA was consistent with its effect observed in patients with severe asthma, showing rapid and near complete depletion of blood eosinophils.

3.7.2. Balance of benefits and risks

Regarding efficacy evaluation, uncertainties initially identified regarding the representation of the study population in the proposed indication were resolved by narrowing the indication to reflect the studied population. The frequency of the dosing regimen selected for the treatment is agreed. Some uncertainties remain in relation to the safety evaluation, in aspects related to the frequency of AEs in MANDARA study compared with long-term asthma studies. Considering all the favourable and unfavourable effects evaluated, benralizumab is recommended for treatment of patients with EGPA, as per the agreed indication.

3.8. Conclusions

The overall B/R of Fasenra is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include add-on treatment for adult patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis, based results from study D3253C00001 (Mandara); this was a randomised, double-blind, multicentre, parallel group, active-controlled, non-inferiority study that evaluated the efficacy and safety of benralizumab compared with mepolizumab in treatment of patients with EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.2 of the RMP has been agreed. In addition, the MAH took this opportunity to introduce editorial changes.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the RMP.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.