Statistical Analysis Plan

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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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire (6-item version)
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic antibodies
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BP	Bodily pain (in SF-36v2 questionnaire)
BVAS	Birmingham Vasculitis Activity Score
CRF	Case report form
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CYC	Cyclophosphamide
ECG	Electrocardiogram
eCRF	Electronic case report form
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EOT	End of Treatment
ePRO	Electronic patient-reported outcome
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiration volume in 1 second
FVC	Forced vital capacity
GH	General Health Perceptions (in SF-36v2 questionnaire)
GPA	Granulomatosis with polyangiitis
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICS	Inhaled corticosteroids
IEC	Independent ethics committee
IgE	Immunoglobulin E
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational product
IPD	Investigational product discontinuation

Abbreviation or special term	Explanation
IRB	Institutional review board
MCID	Minimal Clinical Importance Difference
MCS	Psychometrically-based mental health component summary score (in SF-36v2 questionnaire)
MH	Mental health (in SF-36v2 questionnaire)
MoA	Mechanism of action
MPA	Microscopic polyangiitis
NI	Non-inferiority
OCS	Oral corticosteroids
OLE	Open-label extension
PCS	Psychometrically-based physical health component summary score (in SF-36v2 questionnaire)
PD	Pharmacodynamic
PF	Physical functioning (in SF-36v2 questionnaire)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PRO	Patient-reported outcome
Q4W	Every 4 weeks
QRS	QRS complex
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected Fredericia's
RNA	Ribonucleic acid
SABA	Short acting β2 agonist
SAE	Serious adverse event
SAP	Statistical analysis plan
SF	Social functioning (in SF-36v2 questionnaire)
SF-36v2	36-Item Short Form Health Survey (Version 2)
SNOT-22	Sino-Nasal Outcomes Test 22
SoA	Schedule of assessments
ULN	Upper limit of normal
VDI	Vasculitis Damage Index
VT	Vitality
WPAI	Work Productivity and Activity Impairment Questionnaire

AMENDMENT HISTORY

Date	Brief description of change
04JUL2023	1. To accommodate the updates from CSP version 5.0 (Amendment 4), 4 endpoints are added to the secondary objective "To assess the effect of benralizumab on corticosteroid dose required during weeks 48 through 52 compared to mepolizumab." in Section 1.1.2: (1) 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. (2) Proportion of patients with ≥ 50% reduction from baseline. (3) Proportion of patients with 100% reduction from baseline. (4) Proportion of patients with ≤ 4 mg in average daily dose. 2. To accommodate the updates from CSP version 5.0 (Amendment 4), one secondary objective and corresponding endpoints are added in Section 1.1.2: "To assess the clinical benefit of benralizumab compared to mepolizumab". 3. To accommodate the updates from CSP version 5.0 (Amendment 4), whole blood for PAXgene RNA, nasal secretions, and tissue biopsies and sputum (mechanistic sub-study only) is removed from the exploratory biomarker endpoints in the OLE (Section 1.1.5). 4. Section 1.2 originally stated that only data of double-blind period would be included at primary analysis and all OLE data would be presented in an addendum to primary analysis CSR. It is updated to that DB data and OLE safety data will be included at primary analysis, and OLE efficacy data will be presented in an addendum to primary analysis CSR. This is also added to Section 7: changes to original clinical study protocol. 5. Section 2.2.1 Table 1 list of important protocol deviations is aligned to Protocol Deviation Plan v4.0. 6. It is added to Section 3.1.1 that the data of follow-up visit of patients who are prior to CSP version 4.0 will not be included in any analysis nor visit window mapping. 7. Details of visit windowing for 4-weekly collected and not 4-weekly collected data are updated in Section 3.1.1. 8. Week 52 definition is added to Section 3.1.2. 9. It is added to Section 3.3.4 that how the gaps and overlaps of prednisolone/prednisone daily dose will be handled, and how the average daily prednisolone/prednisone dose during weeks 48 to 52 of the study treatment will be derived. 10. The variables of the 4 endpoints are added to Section 3.3.4: (1) Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25%

Date	Brief description of change
	reduction; 25 to < 50% reduction; 50 to <75% reduction; 75 to < 100% reduction; 100% reduction. (2) Proportion of patients with ≥ 50% reduction from baseline. (3) Proportion of patients with 100% reduction from baseline. (4) Proportion of patients with ≤ 4 mg in average daily dose. 11. Clinical benefit is added as a new section (Section 3.3.5). 12. The method to derive remission within 24 weeks and remained in remission for remainder of the double-blind treatment period is clarified in Section 3.3.6. 13. Sustained responder to ACQ-6 is clarified in Section 3.3.10.1. 14. Sustained responder to SF-36v2 is clarified in Section 3.3.10.2. 15. Complete blood eosinophil depletion (defined as blood eosinophil count =0 cells/uL) is updated to near complete eosinophil depletion (defined as blood eosinophil count <=30 cells/uL) in Section 3.3.11. 16. Summary of blood eosinophil depletion for the first 2 months is updated to by post-baseline timepoint through DB period for both near complete depletion (Section 3.3.11) and <150 cells/uL depletion (Section 3.3.12). 17. Change from baseline in blood eosinophil count is added as a new section (Section 3.3.13). 18. The formula to calculate cumulative OCS use is added to Section 3.4.1. 19. The definition of on-study AEs is clarified in Section 3.7.1. 20. IgE is added to laboratory variables in Section 3.7.2. 21. The original text describing ECG test is updated to “The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant” in Section 3.7.3. 22. It is added to Section 4.1 that how OLE data will be analysed for primary analysis. 23. Detailed participant flow of OLE period is added to patient disposition (Section 4.2.1). 24. Details of the conversion of baseline OCS to equivalent prednisone dose and categorization of ICS dose is added to Section 4.2.2. 25. IP administration is specified to DB period in Section 4.2.4. 26. Duration of study is clarified in Section 4.2.6. 27. The comparison of mepolizumab to historic mepolizumab is added in Section 4.2.7.1. 28. On-treatment sensitivity analysis is removed from Section 4.2.7.2.

Date	Brief description of change
	29. The covariates same as analysis for primary endpoint are added to the logistic regression model of subgroup analysis (Section 4.2.7.3). 30. The analyses of proportion of patients with BVAS=0, proportion of patients with OCS dose <=4 mg/day, and proportion of patients with OCS dose <=7.5 mg/day are added to supportive analysis (Section 4.2.7.4). 31. The analyses of the new endpoints of daily OCS dose, and a line plot of average daily OCS dose over time are added to Section 4.2.8.4). 32. The analyses of Proportion of patients with clinical benefit are added as a new section (Section 4.2.8.5). 33. The Kaplan-Meier plot of time to first ACQ-6 sustained response is removed from Section 4.2.8.10.1. 34. The Kaplan-Meier plot of time to first SF-36v2 sustained response is removed from Section 4.2.8.10.2. 35. The model fitting of SSQ data into mixed model with repeated measures is removed from Section 4.2.8.10.4. 36. The summary of change from baseline in PGIS is removed from Section 4.2.8.10.5. 37. Analysis method of cumulative OCS is added as Section 4.2.9.1. 38. Miettinen and Nurminen analysis of Adverse events in any category by subgroup, Miettinen and Nurminen analysis of specific AEs are added in Section 4.2.11.1. 39. The rate of AEs per person year is clarified in Section 4.2.11.1. 40. The analysis method of AST and ALT parameters is updated in Section 4.2.11.2. 41. The analysis method of ECG data is updated in Section 4.2.11.3. 42. High-level analysis to OLE period is updated in Section 5. 43. The handling of partial dates is separated for AE and CM and updated (Section 9.1). 44. Derivation of major relapse is clarified in Section 9.4. 45. Two ADA groups are added to Section 9.5: 1) non-treatment-emergent ADA positive, and 2) ADA positive with titre > median of maximum. 46. The analysis of ADA response and demographics and patient characteristics is removed from Section 9.5. 47. The analysis of ADA response and secondary efficacy endpoints is removed from Section 9.5. 48. The analyses of the potential impact on causality and hypersensitivity of AEs and SAEs are removed from Section 9.5. 49. The order of sections is adjusted throughout Section 3 and 4.

Date	Brief description of change
	50. Minor amendments to wording and grammar have been made throughout for improved clarity.

1 STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR). Additional analyses required for regional submissions will be prespecified in a separate analysis plan and will be submitted to the appropriate authorities.

1.1 Study objectives

1.1.1 Primary objective

The following primary objective will be assessed in the double-blind period of the study.

Primary Objective:	Endpoint/Variable:
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	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.

EGPA: Eosinophilic Granulomatosis with Polyangiitis; BVAS: Birmingham Vasculitis Activity Score. OCS oral corticosteroid.

1.1.2 Secondary objectives

The following secondary objectives will be assessed in the double-blind period of the study.

Secondary Objectives:	Endpoint/Variable:
To assess the efficacy of benralizumab compared with mepolizumab on duration of clinical remission, defined as accrued duration in weeks where a patient achieves remission.	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 will be repeated based on main and supportive remission definitions.
To assess the efficacy of benralizumab compared with mepolizumab on time to first relapse.	Time from randomisation to first EGPA relapse, where relapse is 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: • An increase of OCS therapy (>4mg prednisolone total daily dose or equivalent) **OR** • An increased dose or addition of an immunosuppressive agent **OR** • Hospitalisation related to EGPA worsening.
To assess the effect of benralizumab on corticosteroid dose required during Weeks 48 through 52 compared to mepolizumab.	Based on the average daily prednisolone/prednisone dose during Weeks 48 through 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.
To assess the clinical benefit of benralizumab compared to mepolizumab	Proportion of patients who have achieved any clinical benefit when meeting <u>any of</u> the criteria below. Proportion of patients who have achieved complete response when meeting <u>all of</u> 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. Analysis will be repeated for the supportive remission definition.
To assess the annualised relapse rate in patients receiving benralizumab compared to mepolizumab	Annualised relapse rate
To assess the proportion of patients who achieve remission within the first 24 weeks and remain in remission for the remainder of the double-blind treatment period in patients receiving benralizumab compared to mepolizumab	Proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period. Analysis will be repeated based on main and supportive remission definitions.
To assess additional measures of the efficacy and health status/health-related quality of life in patients receiving benralizumab compared to mepolizumab	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 and blood eosinophil counts will be assessed as change from baseline over the 52-week double-blind treatment period. PGIC will be assessed as response proportions at each weekly assessment between Visits 2 and 4.

ACQ-6 Asthma Control Questionnaire (6-item version); AE adverse events; BVAS Birmingham Vasculitis Activity Score; EGPA Eosinophilic Granulomatosis with Polyangiitis; 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. WPAI Work Productivity and Activity Impairment Questionnaire.

1.1.3 Safety objectives

The following safety objectives will be assessed in the double-blind period of the study.

Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of benralizumab compared to mepolizumab	Safety and tolerability will be evaluated based on AEs, Vital signs, physical exam, Clinical laboratory, and electrocardiogram (ECG). Assessments related to AEs include: • Occurrence/Frequency • Relationship to IP as assessed by the Investigator • Intensity • Seriousness • Death

	• AEs leading to discontinuation of Investigational Product [IP] • Other significant AEs
To assess the pharmacokinetics and immunogenicity of benralizumab	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralizing antibodies

ECG electrocardiogram; IP investigational product; AE adverse events.

1.1.4 Exploratory objectives

The following exploratory objectives will be assessed in the double-blind period of the study.

Exploratory Objective	**Endpoint/Variable:**
To assess the cumulative OCS use in response to treatment with benralizumab compared to mepolizumab	Cumulative OCS use, as measured by AUC for daily OCS dose, over the 52-week double-blind treatment period
To evaluate the effect of benralizumab compared to mepolizumab on health care resource utilization due to EGPA	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)
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers of inflammation [a]	Biomarkers of inflammation, e.g., C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers related to the mechanism of action (MoA), eosinophilic inflammation and EGPA disease pathogenesis, as well as baseline predictors of response to benralizumab or mepolizumab [a]	Exploratory biomarkers in: • serum • whole blood • nasal secretions • tissue biopsies and sputum (Mechanistic sub-study only)
To characterize the patient-reported experience and treatment benefits of benralizumab compared with mepolizumab through patient interviews [a]	Patient interviews to characterize patient-reported experience and treatment benefits (sub-study)

OCS oral corticosteroid.AUC area under the curve; EGPA Eosinophilic Granulomatosis with Polyangiitis; ICU intensive care unit; CRP C-reactive protein; ESR erythrocyte sedimentation rate; MoA mechanism of action.

[a] The following endpoints (except for CRP/ESR and IgE) related to the objective above will be reported outside of the CSR: 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).

1.1.5 Objectives within the open-label extension (OLE) period

The following objectives will be assessed in the open-label extension period of the study.

To evaluate the effect of benralizumab on remission, relapse, and OCS use [a]	Remission, relapse (as defined in 1.1.2 [c]), OCS use
To assess patient reported outcomes in patients receiving benralizumab [b]	Asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT-22 questionnaire), health-related quality of life (SF-36v2) and WPAI
To assess the safety and tolerability of benralizumab [a]	Safety and tolerability will be evaluated in terms of AEs, Vital signs, physical exam, Clinical laboratory, and ECG Assessments related to AEs cover: • Occurrence/Frequency • Relationship to IP as assessed by the Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To assess the pharmacokinetics and immunogenicity of benralizumab[d]	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralizing antibodies
To evaluate the effect of benralizumab on health care resource utilization due to EGPA[b]	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)
To assess biomarkers of inflammation[b]	Biomarkers of inflammation, e.g., C-reactive protein and erythrocyte sedimentation rate
To assess biomarkers related to the MoA of benralizumab, eosinophilic inflammation and EGPA disease pathogenesis[b]	Exploratory biomarkers in serum

ACQ-6 Asthma Control Questionnaire (6-item version); AE adverse events; ECG electrocardiogram; EGPA Eosinophilic Granulomatosis with Polyangiitis; ER Emergency room; ICU Intensive care unit; IP investigational product; MoA mechanism of action; OCS oral corticosteroid. OLE Open-label extension; SF-36v2 Short Form 36-item health survey (version 2, acute recall); SNOT-22 Sino-nasal Outcome Test-22; WPAI Work productivity and Activity Impairment Questionnaire.

[a] Applicable to full duration of OLE

[b] Applicable to 1st year of OLE only

[c] Applicable to 1st year of OLE only. From the 2nd year, the definitions of remission and relapse will be based on the Investigator's overall clinical assessment.

[d] Applicable to OLE Year 1-3.

1.2 Study design

This is a randomised, double blind, active-controlled, parallel group, multicentre 52-week Phase 3 study to compare the efficacy and safety of benralizumab 30 mg versus mepolizumab 300 mg administered by subcutaneous (SC) injection Q4W in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy.

The target population is adult female and male patients with EGPA diagnosis based on the history or presence of asthma and eosinophilia plus documentation of at least two additional typical features of EGPA.

After initial enrolment and confirmation of entry criteria (Visit 1), potentially eligible patients will enter a screening period of up to 4 weeks (minimum of 1 week) and will be required to be on a stable dose of OCS ≥7.5 mg/day prednisolone/prednisone (but not >50 mg/day), for at least 4 weeks prior to baseline (Visit 2). Patients on immunosupressive therapy must be on a stable dose for at least 4 weeks prior to baseline (Visit 2) and should remain on the same dose until the end of the 1st year OLE (dose reductions for safety reasons will be permitted).

Approximately 140 eligible patients will be randomised 1:1 at baseline (Visit 2), to receive benralizumab or mepolizumab Q4W for a 52-week double-blind treatment period. Randomisation will be stratified by region (North America, Japan, Rest of world). A minimum of approximately 25% patients will be included in a mechanistic sub-study to explore the pharmacodynamic (PD) response and MoA of benralizumab compared to mepolizumab. The number of patients with ANCA positive status and an eosinophil count <150 cells/uL (<0.15 x 10^9/L) will be restricted to approximately 10% and 40%, respectively. Approximately 45 patients will participate in a non-interventional interview to collect data on health-related quality of life and the patients experience during the double-blind portion of the study.

The final dose of the double-blind treatment period will be given at Week 48 and the double-blind treatment period will complete at Week 52.

All patients who complete the 52-week double-blind treatment period on investigational product (IP) may be eligible to continue into an OLE period. The OLE period is intended to allow each patient at least 1 year of treatment with open-label benralizumab 30 mg administered SC every fourth week (earlier enrolled patients may therefore be in the OLE for longer than 1 year).

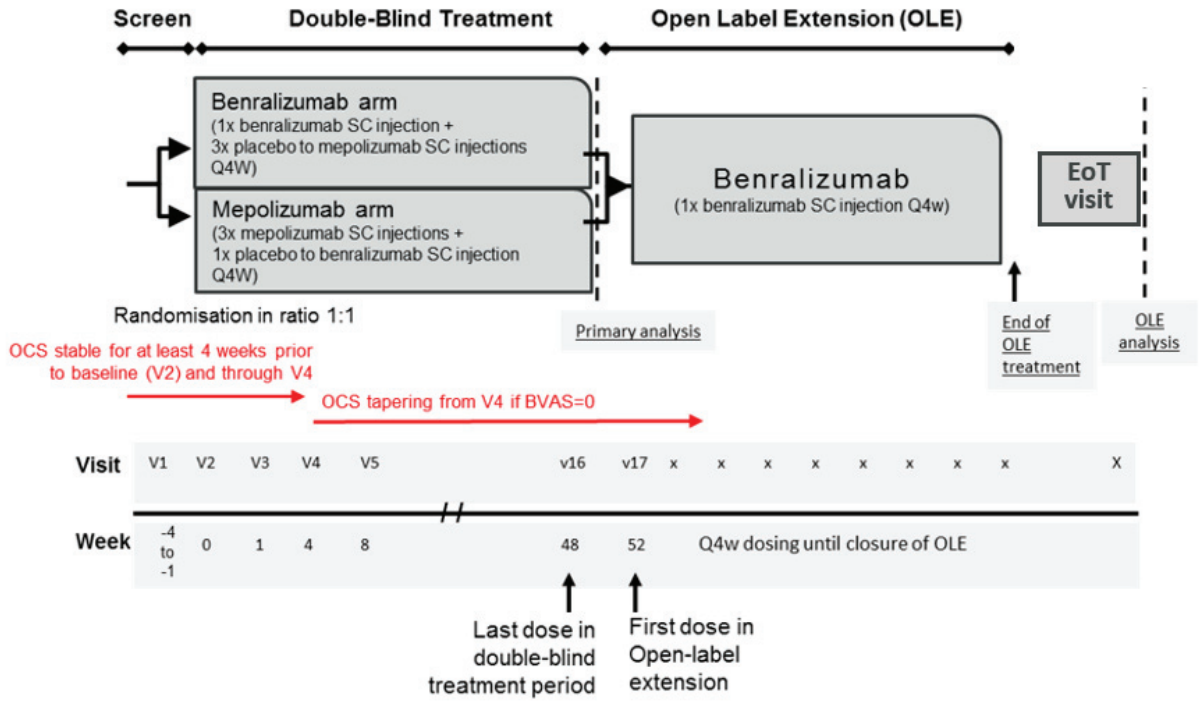
The primary database lock will occur after all randomised patients have been followed up for the 52-week double-blind treatment period. The study will remain blinded until the primary database lock. The primary analysis will include all data captured during the double-blind

period. Safety data from the open-label period available at the time of primary database lock will also be reported. Additional analyses may be performed after the primary database lock to analyse the data that were not available in the primary analysis. The final database lock will occur after the last patient has completed at least one year in the OLE and when the end of the study has been declared. All efficacy data and safety data from the OLE period of the study will be presented in an addendum to the primary analysis clinical study report (CSR).

This study will be conducted at approximately 80 sites in 9 countries.

The general study design is summarised in Figure 1. See CSP Section 1.1, Tables 1 and 2 for a detailed list of visits and assessments.

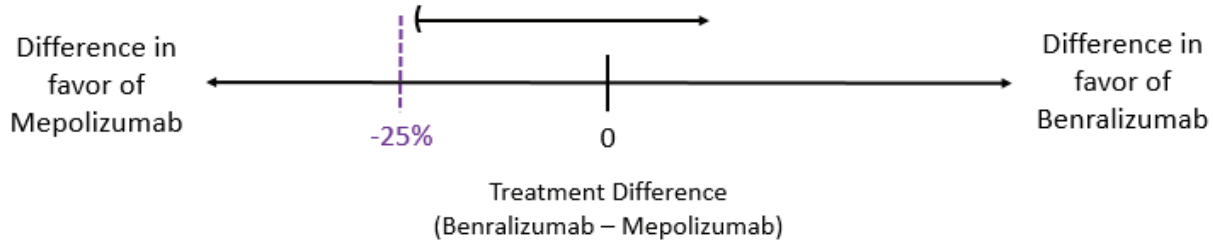
Figure 1 Study design



1.3 Number of subjects

Approximately 140 eligible patients will be randomised in a 1:1 ratio to either the benralizumab 30 mg or mepolizumab 300 mg treatment group, respectively.

The study sample size is based on the assumption that mepolizumab and benralizumab each have a remission rate of 32%; 140 patients will provide ~90% power to demonstrate non-inferiority with a non-inferiority margin of -25% at the 2.5% 1-sided significance level. For the study to be positive, the lower 95% 2-sided confidence limit for the difference between benralizumab and mepolizumab needs to be above the NI margin of -25%.



2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Enrolled analysis set

This analysis set comprises all patients who sign the ICF.

2.1.2 Randomly assigned to study treatment set

All patients who sign the ICF and are randomised to IP regardless of whether they receive a dose of IP or exit prior to receiving the first dose.

2.1.3 Full analysis set

The Full analysis set (FAS) Analysis Set will be used as the primary means of assessing non-inferiority hypotheses. All patients randomised and receiving at least one (1) dose of IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be analysed using the full analysis set.

2.1.4 Per protocol population

The Per Protocol Analysis Set is the subset of the full analysis set consisting of all patients who were randomised and received treatment excluding any patients with protocol deviations affecting the primary efficacy endpoint as noted in Section 2.2.1.

2.1.5 Safety analysis set

The Safety analysis set consists of all patients who have 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.

2.1.6 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 will be based on this analysis set.

2.1.7 Open-label extension analysis set

The OLE analysis set will include all patients who enter the OLE part of the study and who receive at least 1 dose of IP during the OLE treatment period.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still randomised will be analysed according to the analysis sets described in Section 2.1.

2.2.1 Important protocol deviations

Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. IPDs that have a very high likelihood of affecting the interpretation of the primary study results or the safety of participating patients are included in the table below.

Table 1: List of Important Protocol deviations

Deviation Code	Deviation	CSP version & date	Criteria for Per-Protocol Population exclusion?
1 **Inclusion Criteria Deviations**			
1.1	Documented EGPA diagnosis with 2 additional features not met (inclusion #3)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
1.2	History of relapsing OR refractory EGPA not met (inclusion #4)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
1.3	Stable dose of oral prednisolone or prednisone ≥ 7.5 mg/day (but not > 50 mg/day) for at least 4 weeks prior to baseline (Visit 2) not met (inclusion #5)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
1.4	If receiving immunosuppressive therapy stable dose for the 4 weeks prior to baseline (Visit 2) not met (inclusion #6)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
1.5	QTcF < 450 msec or QTcF < 480 msec for patients with bundle branch	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	

	block on ECG evaluation at screening (Visit 1) not met (inclusion#7)		
1.6	Negative pregnancy test for WOCBP at screening (Visit 1) not met (inclusion #8)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	
1.7	Study procedures performed prior to signed informed consent or re-consent	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	
2 Exclusion Criteria Deviations			
2.1	Diagnosed with granulomatosis with polyangiitis or microscopic polyangiitis (exclusion #1)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
2.2	Organ-threatening EGPA within 3 months prior to screening (Visit 1) and through randomization (Visit 2) (exclusion #2)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
2.3	Life-threatening EGPA within 3 months prior to screening (Visit 1) and through randomization (Visit 2) (exclusion #3)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
2.4	Subject meets key safety-related exclusion criteria that could confound interpretation of safety within 3 months prior to screening (Visit 1) (exclusion # 4- 13, 15-21, 23-26)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	
2.5	Subject received prohibited medication as per CSP prior to screening (exclusion #14, 22, 27)	Version 1.0 11Jun2019 - Version 5.0 11Apr2023	Yes
3 **Discontinuation Criteria for study product met but patient not withdrawn from study treatment**			
3.1	An AE/SAE that, in the opinion of Investigator and AstraZeneca, contraindicates further dosing or significantly affect a patient's safety if continue the IP	Version 5.0 11Apr2023	Yes
3.2	Severe non-compliance with the CSP	Version 5.0 11Apr2023	Yes
3.3	IP unblinding of treatment code	Version 5.0 11Apr2023	Yes
3.4	Study-specific criteria for IP discontinuation is met but patient was not discontinued	Version 5.0 11Apr2023	Yes
4 Discontinuation Criteria for overall study withdrawal met but patient not withdrawn from study – N/A			
5 Investigational Product (IP) Deviation			
5.1	Subject received incorrect IP (corporate IPD)	Version 5.0 11Apr2023	Yes
5.2	Subject received incorrect dose of IP	Version 5.0 11Apr2023	Yes

5.3	Use of expired IP	Version 5.0 11Apr2023	
5.4	Use of drug after temperature excursion without Clinical Study Supply Lead approval	Version 5.0 11Apr2023	
6 Excluded Medications taken			
6.1	Subject received concomitant medication defined as prohibited in the CSP	Version 5.0 11Apr2023	Yes
7 **Deviations to study procedure**			
7.1	BVAS scores missing at Week 36 or Week 48	Version 5.0 11Apr2023	Yes
7.2	Multiple BVAS scores missed during the double-blind period or significant inconsistency in scoring as per medical review	Version 5.0 11Apr2023	
7.3	OCS doses missing in RAVE at Week 36 or Week 48	Version 5.0 11Apr2023	Yes
7.4	Delay in reporting Serious Adverse Event (SAE), pregnancy or overdosing	Version 5.0 11Apr2023	
7.5	Other important deviations to study procedure	Version 5.0 11Apr2023	
8 Other Important Protocol Deviations (including missing PI eCRF signature, others to be agreed by Study Team)			
8.1	If receiving imunosuppresive therapy, dose is not stable throughout the double-blind period or until completion of the first 6 months of OLE	Version 5.0 11Apr2023	Yes if double-blind period
8.2	Any deviation considered important that was not predicted or prespecified	Version 5.0 11Apr2023	
8.3	Assessments done and data collected after withdrawal of patient's Informed Consent	Version 5.0 11Apr2023	

3 PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Visit window definitions

The subjects who enrolled prior to Clinical Study Protocol amendment 3, version 4.0 and prematurely discontinue IP had follow-up visit 8 weeks after last dose of IP. The follow-up visit data from these subjects will not be included in any analysis nor visit window mapping.

For endpoints that present visit-based data, the variables will be summarised based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined visit windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable.

Visit windows will be constructed so that every observation collected can be allocated to a visit. No visit windows will be defined for screening visits and randomisation visit.

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, the upper limit will be taken as the midpoint value minus 1 day. The adjusted analysis-defined visit windows for assessments conducted every 4 weeks are summarised in Table 2.

Table 2: Visit windows for assessments conducted every 4 weeks

Adjusted defined window visit	Scheduled study day	Maximum windows
Baseline	1	Study Day ≤ 1
Week 4	29	2 ≤ Study Day ≤ 42
Week 8	57	43 ≤ Study Day ≤ 70
Week 12	85	71 ≤ Study Day ≤ 98
Week 16	113	99 ≤ Study Day ≤ 126
Week 20	141	127 ≤ Study Day ≤ 154
Week 24	169	155 ≤ Study Day ≤ 182
Week 28	197	183 ≤ Study Day ≤ 210
Week 32	225	211 ≤ Study Day ≤ 238
Week 36	253	239 ≤ Study Day ≤ 266
Week 40	281	267 ≤ Study Day ≤ 294
Week 44	309	295 ≤ Study Day ≤ 322
Week 48	337	323 ≤ Study Day ≤ 350
Week 52	365	351 ≤ Study Day ≤ Last assessment day in double-blind period
Week 56	393	Last assessment day in double-blind period + 1 ≤ Study Day ≤ 406

Adjusted defined window visit	Scheduled study day	Maximum windows
Week 60	421	407 ≤ Study Day ≤ 434
Week 64	449	435 ≤ Study Day ≤ 462
Week 68	477	463 ≤ Study Day ≤ 490
Week 72	505	491 ≤ Study Day ≤ 518
Week 76	533	519 ≤ Study Day ≤ 546
Week 80	561	547 ≤ Study Day ≤ 574
Week 84	589	575 ≤ Study Day ≤ 602
Week 88	617	603 ≤ Study Day ≤ 630
Week 92	645	631 ≤ Study Day ≤ 658
Week 96	673	659 ≤ Study Day ≤ 686
Week 100	701	687 ≤ Study Day ≤ 714
Week 104	729	715 ≤ Study Day ≤ 742

The windowing will only be performed for assessments within the appropriate periods e.g., double blind versus open label

The last assessment day in the DB period will usually be the day of the first OLE dose for those entering the OLE except when first OLE dose is delayed more than 35 days after the last dose in DB, in which case it will be the day of the 52 week assessments (e.g. BVAS) or if none done, it will be the day of the last dose in DB + 35 days. For those that do not enter the OLE, it will be the day of the last assessments (e.g. BVAS). If both IPD assessments and 52 week assessments are available then the day of the 52 week assessments will be considered the last assessment day in the DB period.

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as follows:

Date of assessment – Date of randomisation + 1

Study days before randomization will be defined as follows:

Date of assessment – Date of randomisation

By this definition, the day of randomisation will be study day 1 and the day before the day of randomisation will be study day – 1. There is no study day 0. The planned date of Visit 4 (Week 4) will be study day 29 (= 28 + 1), for example.

If multiple readings are recorded within a single visit window, the rules below will be applied.

- If there are 2 or more observations within the same visit window, then the non-missing observation closest to the scheduled visit will be used in the analysis.

- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 observations are collected on the same day, then the non-missing observation with the earlier collection time will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing.

The following endpoints are recorded on a weekly or daily basis, and will be averaged into 4-weekly periods:

- ACQ-6 (weekly)
- Sino-nasal symptoms (weekly)
- Prednisolone/prednisone dose (daily)

Reporting Period	**First Study Day Included**	**Last Study Day Included**
Weeks 1-4	2	29
Weeks 5-8	30	57
Weeks 9-12	58	85
Weeks 13-16	86	113
Weeks 17-20	114	141
Weeks 21-24	142	169
Weeks 25-28	170	197
Weeks 29-32	198	225
Weeks 33-36	226	253
Weeks 37-40	254	281
Weeks 41-44	282	309
Weeks 45-48	310	337
Weeks 49-52	338	Last assessment day in double-blind period

Reporting Period	First Study Day Included	Last Study Day Included
Weeks 53-56	Last assessment day in double-blind period+1	392
Weeks 57-60	393	420
Weeks 61-64	421	448
Weeks 65-68	449	476
Weeks 69-72	477	504
Weeks 73-76	505	532
Weeks 77-80	533	560
Weeks 81-84	561	588
Weeks 85-88	589	616
Weeks 89-92	617	644
Weeks 93-96	645	672
Weeks 97-100	673	700
Weeks 101-104	701	728

For assessments that are not scheduled on a 4-weekly basis, visit windowing rule will be as follows:

Reporting Period	First Study Day Included	Last Study Day Included
VDI, MPO/PR3 (ANCA status)		
Baseline		1
Week 24	2	266
Week 52	267	Last assessment day in double-blind period

Reporting Period	First Study Day Included	Last Study Day Included
Week 76 (VDI only)	Last assessment day in double-blind period+1	616
Week 100 (VDI only)	617	896
Week 156 (VDI only)	897	1274
Week 208 (VDI only)	1275	
Spirometry, ADA/nAb		
Baseline		1
Week 12	2	126
Week 24	127	210
Week 36	211	294
Week48	295	350
Week 52	351	Last assessment day in double-blind period
SNOT-22, WPAI-GH		
Baseline		1
Week 4	2	42
Week 8	43	70
Week 12	71	98
Week 16	99	154
Week 28	155	238
Week 40	239	322

Reporting Period	First Study Day Included	Last Study Day Included
Week 52	323	Last assessment day in double-blind period
Week 64	Last assessment day in double-blind period + 1	490
Week 76	491	574
Week 88	575	658
Week 100	659	742
Week 112	743	826
SF-36v2		
Baseline		1
Week 1	2	18
Week 4	19	42
Week 8	43	70
Week 12	71	98
Week 16	99	154
Week 28	155	238
Week 40	239	322
Week 52	323	Last assessment day in double-blind period
Week 64	Last assessment day in double-blind period + 1	490
Week 76	491	574
Week 88	575	658
Week 100	659	742
Week 112	743	826

Study Day is defined as Date of assessment – Date of randomisation + 1 for efficacy summaries, Date of assessment – Date of first dose+ 1 for safety summaries.

For each analysis parameter, the windowing will be based on the protocol-specified schedule of events as defined in the clinical protocol.

For the patient-report questionnaires/surveys collected by electronic patient reported outcomes (ePRO), data for all ePRO assessments will be collected up to the end of 1 year OLE or study discontinuation date. In the event that data is captured in the ePRO device after the patient has withdrawn consent, all results collected on or after the evening of the date of consent withdrawal will be excluded from analysis.

3.1.2 Baseline and Week 52 definition

In general, the last recorded value on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints. If there is no value on or prior to randomisation date, then the baseline value will not be imputed and will be set to missing.

The last recorded value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints, PK and immunogenicity variables. When time of assessment is not recorded or missing, it is assumed that assessments recorded on the date of first dose of study treatment were performed prior to dosing, except in cases of protocol-specified post-dose assessments. If there is no value prior the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

For categorical baseline EGPA disease characteristics captured directly in the eCRF (e.g. captured as yes or no), if ‘yes’ is indicated in any visit during enrollment (scheduled or unscheduled), ‘yes’ will be used.

Additional analyses for the patients who switch from mepolizumab to benralizumab at Week 52 may be performed where the baseline value is set to the last recorded value on or prior to date of the first OLE benralizumab (i.e. likely the Week 52 measurement) to obtain an assessment of the changes occurring while actually receiving benralizumab.

For the daily or weekly assessment variables including OCS and ACQ-6 which are aggregated to a 4-weekly period, the average calculated during the cycle prior to the last DB assessment (i.e., Weeks 49-52) will be used to calculate the Week 52 score (i.e., Study Day 338 to last DB assessment, see Section 3.1.1.

For the endpoints collected every 4 weeks, the Week 52 value will follow the visit windows defined in Table 2 in Section 3.1.1 any record that’s collected after the first open label dose date will not be considered as Week 52 value. If no Week 52 record is available or the Week 52 record is collected after the first open label dose date, Week 52 value will be set as missing.

3.1.3 Prior/concomitant medications

Background EGPA medication will be classified as an 'EGPA medication at baseline' if it started on or prior to randomisation and was ongoing after randomisation. EGPA concomitant medications will be identified using the approach described below.

A medication will be regarded as prior if it was stopped on or before the date of randomisation (medication stop date ≤ date of randomisation).

A medication will be regarded as 'concomitant' if the start date is after the date of randomisation, or if it started on or prior to the date of randomisation and was ongoing after the date of randomisation.

3.2 Primary efficacy variable

The primary efficacy outcome variable is the proportion of patients who achieve remission at both nominal visits Week 36 and Week 48 of the double-blind period.

Remission is defined as:

- A Birmingham Vasculitis Activity Score (BVAS) = 0 **and**
- OCS dose of prednisolone/prednisone ≤4 mg/day

BVAS is a validated, clinician-completed tool used for the comprehensive multisystem clinical assessment of disease activity in systemic vasculitis. The Investigator will be required to complete the paper BVAS form and transfer data to the eCRF BVAS module at screening, baseline and Q4W until the end of the first year of the OLE, or IPD/EOT visit.

The BVAS form is divided into 9 organ-based systems; a total score on all systems gives an indication of the disease activity of each patient at the time of scoring and reflects the need for therapy.

All corticosteroids administered systemically will be included to calculate daily OCS dose regardless of reason of administration. The corticosteroid conversion factors in Table 7 will be used, regardless of the route of administration, to convert each corticosteroid dose to a prednisone equivalent dose. Prednisone equivalent daily dose will be calculated for each study day during the 52-week double-blind treatment period and used to derive OCS-related endpoints and remission endpoints.

In addition to the main definition of remission described above, a supportive definition will be investigated (BVAS= 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day).

In the event a patient 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 7.5 mg/day as per

supportive definition), or any other significant clinical intervention or investigation, the patient will be considered to be in continued remission (See Section 9.2).

Patients with missing remission data due to withdrawal from the study will be assumed to be not in remission after the date of withdrawal from the study over the remainder of the DB Period.

3.2.1 Approach to handling missing data

The following approach to handling missing data will be planned:

- If a patient withdraws from the study then the patient will be considered to not be in remission from that time-point.
- For patients in remission with subsequent intermittent missing BVAS then they will be assumed to be in remission at that subsequent time-point if there is no evidence of OCS (based on the CRF) use above the remission threshold (e.g. <= 4 mg/day); otherwise they will assumed to be not in remission.
- For patients in remission with subsequent intermittent missing OCS (based on the CRF) then they will be assumed to be in remission at the subsequent time-point if BVAS=0; otherwise they will assumed to be not in remission.
- For patients in remission with subsequent intermittent missing both BVAS and OCS then a patient will be assumed to still be in remission.

3.3 Secondary efficacy variables

3.3.1 Total accrued duration of remission

Total accrued duration of remission (as defined in Section 3.2) will be evaluated during the 52-week treatment period. The accrued duration will be assigned with the following categories: 0 weeks, > 0 to < 12 weeks, 12 to < 24 weeks, 24 to < 36 weeks and ≥ 36 weeks.

Patients who never achieved remission will be classified into the Zero category.

Patients with missing remission data due to withdrawal from the study will be assumed to be not in remission after the date of withdrawal from the study over the remainder of the DB Period.

The analysis will be repeated on the supportive endpoint (i.e. BVAS= 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day) as defined in Section 3.2.

In addition, as a supportive analysis, the total duration of sustained remission will be evaluated over the 52-week treatment period. 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.

3.3.2 Time to relapse

Time from randomisation to first relapse will be evaluated over the 52-week treatment period. Relapse will be 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 Asthma control Questionnaire (6-item version) (ACQ-6) score (compared to the most recent previous score); **OR**
- Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions (compared to the most recent previous assessment);

warranting:

- An increase of OCS therapy (>4mg prednisolone total daily dose or equivalent) **OR**
- An increased dose or addition of an immunosuppressive agent **OR**
- Hospitalisation related to EGPA worsening.

The time to relapse is calculated as: start date of relapse - date of randomisation + 1. Date of relapse will be captured in the CRF. The start date of relapse is defined as the earliest of the warranting events as noted above.

For patients who have not experienced a relapse by end of DB period, their time to relapse will be right-censored at the last available assessment time.

Note, in the event a patient has achieved remission (as defined in Section 3.2) and at a subsequent visit has a BVAS=1 which does not require an increase in corticosteroid dose above 4 mg/day, or any other significant clinical intervention or investigation, this will not be considered a relapse.

The ACQ-6 and sino-nasal symptoms will be assessed by the patient in a handheld ePRO device on a weekly basis using a weekly recall period. Worsening will therefore be captured by comparison with the previous week's evaluation. If a relapse is recorded between study visits it will depend on the BVAS score for the next visit, scheduled or unscheduled.

3.3.3 Time to major relapse

A major relapse (a sub-set of the total relapse events) will be defined as:

- any organ or life-threatening EGPA event; **OR**
- BVAS≥6 (involving at least two organ systems in addition to any general symptoms where present [myalgia, arthralgia/arthritis, fever >38°C or weight loss >2 kg]); **OR**
- an asthma relapse requiring hospitalisation; **OR**

- sino-nasal relapse requiring hospitalisation.

The time to major relapse will be calculated using the approach described in Section 3.3.2. For patients who have not experienced a relapse by end of DB period, their time to major relapse will be right-censored at the last available assessment time.

3.3.4 Average daily prednisolone/prednisone dose during double-blind treatment period

All corticosteroids administered systemically will be included to calculate daily prednisolone/prednisone dose regardless of reason of administration. The corticosteroid conversion factors in Table 7 will be used, regardless of the route of administration, to convert each corticosteroid dose to a prednisone equivalent dose.

Prednisolone/prednisone equivalent daily dose will be derived for each study day for the 52-week double-blind treatment period, and be used to derive OCS-related endpoints (see below) and remission endpoints.

If there are two or more corticosteroid records that overlap on a particular study day, these overlapping records will be summed in order to obtain a total prednisone/ prednisolone equivalent dose for the days in question. If the overlap is only one day and it is an artefact of data entry, only the latter record will be counted for the day in question. If there is gap in the corticosteroid record, it will be assumed that the subject was corticosteroid-free during this period, i.e. a daily dose of zero will be assumed for deriving remission status, average daily prednisone dose etc. If a prednisone/prednisolone daily dose has a missing stop date but is indicated as ‘ongoing’, it will be assumed that the subject remained on this dose until the end of 52-week double-blind treatment period.

For the summary of prednisolone/prednisone average dose during each reporting period, the average prednisolone/prednisone dose will be derived within each 4-weekly period, as described in Section 3.1.1.

The average prednisolone/prednisone daily dose will be calculated for weeks 1-52 (i.e. from 1 day after the day of first dose to the last double-blind assessment day). If these data are unavailable because a subject withdrew from the study prior to week 52, the average prednisone/ prednisolone daily dose will be derived from day 1 until the date of last double-blind assessment.

For the endpoint:

- Average daily prednisolone/prednisone dose during Weeks 48 through 52 of the study treatment

the average prednisolone/prednisone daily dose will be calculated for weeks 49-52 (i.e. from study day 338 to the last assessment day of double-blind period, as described in Section 3.1.1). If these data are unavailable because a subject withdrew from the study prior to week 52, the average prednisone/ prednisolone daily dose will be derived using the 28 days prior to the last double-blind assessment.

The average daily dose will be assigned with the following categories: 0, >0 to ≤4 mg/day, >4 to ≤7.5 mg/day and >7.5 mg/day. The percent reduction of average daily prednisolone/prednisone dose from baseline at weeks 48-52 will also be calculated and with categories: no reduction or withdrawal from investigational product before Week 48, <25% reduction, 25-<50% reduction, 50-<75% reduction, 75-<100% reduction and 100% reduction. The categorisation will be based on the endpoint average daily dose during Weeks 48 through 52, with one exception: the patients who prematurely discontinued IP before Week 48 will be categorised to "no reduction or withdrawal from investigational product before week 48". The proportion of patients with ≥50% reduction, 100% reduction, and ≤4 mg/day during Weeks 48 through 52 will also be calculated.

For this endpoint, the analysis will include all daily prednisolone/prednisone doses recorded in the eCRF, regardless of whether the patient had withdrawn from study treatment during the DB period at the time of receiving the dose. While it is expected that the majority of OCS administered in the study will be for the treatment of EGPA, it is possible that patients may receive systemic corticosteroids for other reasons, such as treatment of AEs. To inform sensitivity analyses, outlined in sections 4.2.7.2, 4.2.8.1, 4.2.8.6, average OCS over time, excluding corticosteroids administered for reasons other than EGPA, will be calculated in a similar manner to that describe above.

3.3.5 Clinical benefit

Clinical benefit (definition 1) is defined as <u>any of</u> the following:

- Remission (defined as BVAS =0 and prednisolone/prednisone dose ≤4 mg/day) at any time during the double-blind treatment period. Patient will be considered not in remission after study withdrawal.
- ≥50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52. Patients who withdraw from study treatment before Week 48 will be considered non-responders for ≥50% OCS reduction. If patients withdraw from study prior to Week 52 but complete DB IP treatment, the last 28 days prior to withdrawal will be used to derive the OCS reduction.
- EGPA relapse free during the double-blind treatment period.

Proportion of patients who have achieved any of above will be calculated. Complete response (definition 1) is defined as meeting all the criteria above. Proportion of patients who have achieved complete response (definition 1) will be calculated.

Clinical benefit (definition 2) is defined as any of the following:

- Remission (defined as BVAS =0 and prednisolone/prednisone dose ≤7.5 mg/day) at any time during the double-blind treatment period. Patient will be considered not in remission after study withdrawal.
- ≥50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52. Patients who withdraw from study treatment before Week 48 will be considered non-responders for ≥50% OCS reduction. If patients withdraw from study prior to Week 52 but complete DB IP treatment, the last 28 days prior to withdrawal will be used to derive the OCS reduction.
- EGPA relapse free during the double-blind treatment period.

Proportion of patients who have achieved any of above will be calculated. Complete response (definition 2) is defined as meeting all the criteria above. Proportion of patients who have achieved complete response (definition 2) will be calculated.

3.3.6 Remission within 24 weeks and remained in remission for remainder of the double-blind treatment period

Remission (as defined in Section 3.2) over the first 24 weeks and remained in remission for the remainder of the double-blind treatment period will be evaluated over the 52-week treatment period. A subject will be considered a responder if they meet the respective criteria for remission during the first 24 weeks of the study (i.e. date of start of remission ≤ study day 168) and the remission status remains unchanged until the end of the double-blind Treatment Period. Subjects for whom the remission status at Visit 17 was unknown (e.g. due to withdrawal from the study) will be non-responders. If a patient completes DB period but not rolling over to OLE, the remission status at the IPD visit after Visit 16 will be used to derive the remission status of the end of the DB treatment period. The proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of 52-week treatment period will be calculated.

Patients with missing remission data due to withdrawal from the study will be assumed to be not in remission after the date of withdrawal from the study over the remainder of the DB Period.

The analysis will be repeated on the supportive endpoint (i.e. BVAS= 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day) as defined in Section 3.2.

3.3.7 Change from baseline in BVAS

Change from baseline in BVAS will be evaluated at each scheduled visit during the 52-week treatment period.

3.3.8 BVAS responder analysis

BVAS responders are defined as patients having a BVAS score of 0 or 1 at week 52. Patients with a missing BVAS score at week 52 (e.g. due to withdrawal from the study) will be considered to be non-responders.

3.3.9 Vasculitis Damage Index

VDI (Exley et al 1998) will be used to document those features of vasculitis which are due to persistent damage, where there is no current disease activity. Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. The VDI is divided into 11 organ systems and records items of damage, due to vasculitis, treatment or unrelated, that have occurred since the onset of vasculitis. Completion of the form provides a numerical score. A copy of the VDI questionnaire will be provided to the site separately.

The Investigator will be required to complete the paper VDI form and transfer data into the eCRF VDI module as specified in Schedule of Assessments in the CSP.

Absolute and change from baseline values will be calculated at each scheduled assessment.

3.3.10 Patient Reported Outcomes

3.3.10.1 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 was developed for self-administration by adults and adolescents by omitting the forced expiration volume in 1 second (FEV1)% predicted question (Juniper et al 1999).

Patients are asked to record their experience with 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and use of short-acting β_2 agonist (SABA) over the previous week using a 7-point scale (0= no impairment; 6=maximum impairment). The ACQ-6 score is calculated by taking the mean of the 6 equally weighted items. The ACQ-6 score range is 0 (well controlled) to 6 (extremely poorly controlled). Individual score change of at least 0.5 is meaningful and is used to support the responder definition (Juniper et al 2005, Juniper et al 2006).

Weekly ACQ-6 ePRO data for asthma symptoms will be aggregated over 4-week periods, and the average weekly score, excluding weeks with missing data, will be calculated for each 4-week period. The average of 4-week ACQ-6 scores will be used for the derivations of ACQ-6 responder and response status.

An ACQ-6 responder will be defined as a patient who had improvement on 4-weekly averaged ACQ-6, i.e., an ACQ-6 responder variable takes value 1 if change from baseline to 4-weekly averaged ACQ-6 during Weeks 48 to 52 is ≤ -0.5 and 0 otherwise. Patients with missing or non-evaluable ACQ-6 score during Weeks 48 to 52 will be considered non-responders.

ACQ-6 response status will be derived based on the classifications below and summarised at each visit until the end of the 52-week DB treatment period:

- ACQ-6 (Post-baseline visit – baseline) ≤ -0.5 —> Improvement
- -0.5 < ACQ-6 (Post-baseline visit – baseline) < 0.5 —> No change
- ACQ-6 (Post-baseline visit – baseline) ≥ 0.5 —> Deterioration

Patients will also be categorized according to their ACQ-6 defined asthma control status at baseline and Week 52 using the following score thresholds (Juniper et al 2006).

- ACQ-6 ≤ 0.75 —> Well controlled
- 0.75 < ACQ-6 < 1.5 —> Partly controlled
- ACQ-6 ≥ 1.5 —> Not well controlled

ACQ-6 sustained responder is defined as a patient who had 4-weekly averaged ACQ-6 meeting responder threshold by week 48 and continue to respond until end of 52-week DB treatment period. For patients who do not roll over to OLE, if there is an IPD visit following Visit 16 visit, the IPD assessment will be used for end of 52-week to decide a sustained responder. The time to first sustained responder (1st time meeting responder threshold by week 48 and continue to respond until end of 52-week DB treatment period) will be assessed and calculated as: start date of responder threshold reached - date of randomisation + 1. For those patients who do not have sustained response during the DB treatment period, the time to first sustained responder will be right censored at the date of their last visit during the DB treatment period, and at the date of last contact for lost-to-follow-up patients.

During the double-blind treatment period, the patient will complete the ACQ-6 on the ePRO device; assessments are made at the site on Visits 1 and 2; every 7 days (+/- 2 days) after Visit 2 until Visit 17; unscheduled visits at the site; and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the OLE period (Visit 18 to Visit 30), the patient will be assessed every 28 days (+/-2 days) after Visit 18 until Visit 30; unscheduled visits at the site; the IPD visit at the site if the patient chooses to discontinue use of ePRO device; and the EOT visit.

3.3.10.2 Short Form 36 version 2 (acute recall) (SF-36v2)

The SF-36v2 is a 36-item, self-report survey of functional health and well-being, with a 1-week recall period (Lincoln 2011, Maruish, 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks patients to rate how their current state of health compared to their state of health 1 week ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). Psychometrically-based physical and mental health component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and mental HRQoL.

The SF-36v2 threshold is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (Lincoln 2011).

Table 3: Threshold values for the SF-36v2 scale and summary measures

	SF-36v2 score									
Threshold	**PCS**	**MCS**	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
Individual change	3.4	4.6	4.3	3.4	6.2	7.2	6.2	6.9	4.5	6.2

BP Bodily Pain; GH General Health Perceptions; MCS Mental Health Summary; MH Mental Health; PCS Physical Component Summary; PF Physical Functioning; RE Role Limitations due to Emotional Problems; RP Role Limitations due to Physical Health; SF Social Functioning; VT Vitality.

SF-36v2 sustained responder is defined as a patient meeting responder threshold by week 48 and continue to respond until end of 52-week DB treatment period. For patients who do not roll over to OLE, if there is an IPD visit following Visit 16 visit, the IPD assessment will be used for end of 52-week to decide a sustained responder. The time to first sustained responder (1st time meeting responder threshold by week 48 (V16) and continue to respond until end of 52-week DB treatment period) will be assessed and calculated for component scores as: start date of threshold reached - date of randomisation + 1. For those patients who do not have sustained response during the DB treatment period, the time to first sustained responder will be right censored at the date of their last visit during the DB treatment period, and at the date of last contact for lost-to-follow-up patients.

During the double-blind treatment period, the patient will complete the SF-36v2 on the ePRO device; assessments are made at the site on Visits 1 and 2; 7 days (+/- 2 days) after Visit 2; every 28 days (+/- 2 days) after Visit 3 until Visit 7; every 84 days (+/- 2 days) after Visit 7 until Visit 17; unscheduled visits at the site and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the OLE period (Visit 18 to Visit 30), the patient will be assessed every 84 days (+/-2 days) after Visit 18 until Visit 30; the IPD visit at the site if the patient chooses to discontinue use of ePRO device; and the EOT visit.

3.3.10.3 Sino-Nasal Outcome Test 22 (SNOT-22)

The SNOT-22 is a condition-specific HRQoL assessment which captures patient-reported physical problems, functional limitations, and emotional consequences of sino-nasal conditions (Piccirillo et al 2002, Hopkins et al 2009). Patient reported symptom severity and symptom impact over the past 2 weeks are captured via a 6-point scale (0- No Problem to 5- Problem as bad as it can be). The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes). A Minimal Clinical Importance Difference (MCID) of 8.90 has been established for individual score change (Hopkins et al 2009).

If the patient does not complete any questions at a visit then they will not have any missing values imputed and their total score for that visit will be missing. If a patient has some missing scores (but no more than 50% missing at that visit) then scores for the missing responses will be imputed as the mean of the non-missing responses for that patient at that visit.

During the double-blind treatment period, the patient will complete the SNOT-22 on the ePRO device; assessments are made at the site on Visits 1 and 2; every 28 days (+/- 2 days) after Visit 2 until Visit 7; every 84 days (+/- 2 days) after Visit 7 until Visit 17; and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the OLE period (Visit 18 to Visit 30), the patient will be assessed every 84 days (+/-2 days) after Visit 18 until Visit 30; the IPD visit at the site if the patient chooses to discontinue use of ePRO device; and the EOT visit.

3.3.10.4 Sino-nasal Symptoms Questionnaire (SSQ)

The SSQ asks patients to report the severity of their symptoms over the previous week: “Considering your sinus and nasal symptoms over the last week, rate each symptom against the following categories: very severe, severe, moderate, mild, none.” Symptoms include runny nose, post-nasal discharge (sensation of liquid in your throat), facial pain/pressure, loss or reduction in sense of taste/smell, and blockage/congestion of nose. Higher scores indicate greater severity (0 = none to 4 = very severe).

During the double-blind treatment period, the patient will complete the SSQ on the ePRO device; assessments are made at the site on Visits 1 and 2; every 7 days (+/- 2 days) after Visit 2 until Visit 17; unscheduled visits at the site; and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the OLE period (Visit 18 to Visit 30), the patient will be assessed every 28 days (+/-2 days) after Visit 18 until Visit 30; unscheduled visits at the site; the IPD visit at the site if the patient chooses to discontinue use of ePRO device; and the EOT visit.

3.3.10.5 Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

The PGIS is a single item designed to capture the patient's perception of overall symptom severity at the time of completion using a 6-point categorical response scale (0 = no symptoms to 5 = very severe symptoms).

The PGIC instrument captures the patient's overall evaluation of response to treatment. The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point scale (1 = 'much better' to 7='much worse'). Patients will also be categorized according to the following improvement categories post-baseline:

- A little better, moderately better, much better → 'A little better'
- Moderately better, much better → 'Moderately better'
- Much better → 'Much better'

During the double-blind treatment period, the patient will complete the PGIS on the ePRO device; assessments are made at the site on Visits 1 and 2; every 7 days (+/- 2 days) after Visit 2 until Visit 17; and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the double-blind treatment period, the patient will complete the PGIC on the ePRO device; assessments are made at the site every 7 days (+/- 2 days) for 28 days after Visit 2.

3.3.10.6 Work Productivity and Activity Impairment - General Health (WPAI-GH)

The WPAI-GH is a self-administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI-GH outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity (Reilly Associates 2012).

The following WPAI-GH endpoints will be derived:

Table 4: Derivation of WPAI-GH endpoints

Percent of work time missed due to health:	[Q2/(Q2+Q4)]*100%
Percent impaired while working due to health:	[Q5/10]*100%

Percent of overall work impairment due to health:	[Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]]*100%
Percent of activity impairment due to health:	[Q6/10]*100%

During the double-blind treatment period, the patient will complete the WPAI-GH on the ePRO device; assessments are made at the site on Visits 1 and 2; every 28 days (+/-2 days) after Visit 2 until Visit 7; every 84 days after Visit 7 until Visit 17; and the IPD visit at the site if the patient chooses to discontinue use of ePRO device.

During the OLE period (V18-V30), the patient will be assessed every 84 days (+/- 2days) until Visit 30; the IPD visit at the site if the patient chooses to discontinue use of ePRO device; and the EOT visit.

3.3.11 Change from baseline in Blood Eosinophil Count

Change from baseline in blood eosinophil count will be calculated by timepoint during DB period for each treatment group.

3.3.12 Blood Eosinophil Count depletion

The proportion of patients with blood eosinophil count ≤ 30 cells/uL will be calculated by post-baseline timepoint during double-blind treatment period for each treatment group.

The time to first depletion of blood eosinophil count ≤ 30 cells/uL is calculated as: time of first depletion – date of randomisation + 1.

For patients who have not experienced depletion of blood eosinophil count ≤ 30 cells/uL by end of DB period, their time to depletion will be right-censored at the last available assessment time on or before end of DB period.

The similar analyses described above will be repeated for patients with blood eosinophil count < 150 cells/uL and patients who achieve at least 90% reduction in blood eosinophil count from baseline, respectively.

3.3.13 Spirometry

Forced expiratory volume (FEV_1) and forced vital capacity (FVC) measurements will be recorded in accordance with the CSP. Reversibility is calculated as follows: Percent reversibility = (post-BD FEV1 – pre-BD FEV1) × 100%/pre-BD FEV1. Changes in FEV_1 and FVC variables between baseline and each subsequent scheduled assessment will be calculated. There will be no imputation for missing values.

3.4 Exploratory outcome variables

3.4.1 Cumulative OCS use

Cumulative OCS use will be measured by AUC for daily OCS dose over the 52-week double blind treatment period. For each recorded OCS dose, if the start date is before Day 1, Day 1 will be used as start date. If the end date is after the end of the double-blind period (see definition in Section 3.1.1), the end of the double-blind period will be used as end date. The AUC calculation for each recorded OCS dose will be derived by multiplying the daily dose (mg/day) by the duration (days). If there is a gap between two consecutive doses, it will be assumed that patient does not receive OCS during the period. The duration of each recorded daily dose is calculated as end date – start date + 1. The cumulative OCS dose is the sum of the AUCs of the recorded doses for each patient. All OCS doses patients took during the DB treatment period will be included in calculation regardless of treatment status. The standardized cumulative OCS dose will be derived as the cumulative OCS dose divided by the duration of DB treatment period multiplied by 365.25 for each patient.

3.4.2 Healthcare resource utilisation

Healthcare related resource utilisation information will be collected by the Investigator or designee at each visit as specified in the CSP and recorded in the appropriate eCRF module.

The number of days/time for the following resources utilised through Week 52 of the DB treatment period will be presented for each patient:

- Number of EGPA related hospitalisations
- 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)

The same measures will be collected in the OLE setting during the 1st year.

3.5 Pharmacokinetic variables

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Pharmacokinetic (PK) analysis will only be done on samples from patients who received benralizumab during the DB and OLE periods.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the

AstraZeneca and site study files, but will not constitute a protocol amendment. The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

For the PK analysis it is important that the date and time of each SC injection and sample collection is recorded for each patient.

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the study sites.

All serum samples, except for samples collected at Week 1 and Week 25, will be collected pre-dose according to the schedule of study procedures (see CSP Table 1, Table 2, Table 3, Table 4 and Table 5).

Serum concentrations that are <LLOQ will be reported as follows:

Individual concentrations below the LLOQ of the bioanalytical assay are non-quantifiable and will be reported as <LLOQ in the listings with the LLOQ defined in the footnotes of the relevant table and listing. Serum concentrations that are <LLOQ will be handled as follows for the provision of descriptive statistics:

- All <LLOQ values will be substituted with the value of zero, and all descriptive statistics will be calculated accordingly.
- If all concentrations are <LLOQ at a time point, no descriptive statistics will be calculated for that time point. The Geometric mean, Arithmetic mean, SD, min, Q1, median, Q3 and max will be reported as <LLOQ and the CV% as not calculated (NC).
- The number of <LLOQ values, n will be reported for each time point along with the total number of collected values (n).

A summary of PK analysis results will be reported in the CSR.

3.6 Immunogenicity variables

Anti-drug antibodies (ADA) variables, such as ADA responses, will be generated and analysed as per the details in Section 9.5.

3.7 Safety outcome variables

The following safety data will be collected: reported AEs (including SAEs), clinical chemistry, haematology, urinalysis, 12-lead electrocardiogram (ECG), physical examination and vital signs.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarised by means of using descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates for AEs and prior/concomitant medications is detailed in Section 9.1. Duration of AEs and prior/concomitant medications will not be calculated using imputed dates and will instead be set to missing.

3.7.1 Adverse events

Adverse events experienced by the patients will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) per the Data Management Plan.

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IP
- Worsening of pre-existing events on or after first dose of IP.

Treatment emergent adverse event data will be categorised according to their onset date into the following study periods:

- AEs in the DB period are defined as those with onset date on or after day of first dose of study DB treatment and the day prior to the first dose of open-label benralizumab inclusive (all AEs onset on or after first dose of IP for patients who do not roll over to OLE or withdraw early from IP). If the onset date of an AE is the same as the date of the first dose of open-label benralizumab, to decide the study period of the AE, the variable “AE onset during or after first OLE dose” on the Adverse Events CRF need to be checked. If “Yes” is not checked for the variable, the AE is an AEs in the DB period.
- AEs in the OLE period are defined as those with onset date on or after the day of the first dose of open-label benralizumab. If the onset date of an AE is the same as the date of the first dose of open-label benralizumab, to decide the study period of the AE, the variable “AE onset during or after first OLE dose” on the Adverse Events CRF need to be checked. If “Yes” is checked for the variable, the AE is an AEs in the OLE period.

AEs occurring during screening are AEs with a date of onset ≥ date of first screening visit and < date of the first dose of IP. AEs occurring during screening will only be listed.

If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered an treatment emergent AE. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an treatment emergent AE.

Adverse events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related. If no information about seriousness is available, the AE will be considered serious.

3.7.2 Laboratory variables

Blood samples for determination of clinical chemistry, CRP, IgE, haematology parameters will be taken at the times detailed in the CSP and will be assessed in a central laboratory. ESR and urinalysis parameters will be assessed in local laboratories. The parameters outlined in Section 8.2.1, Tables 1, 2, and 15 of the CSP will be collected.

In summaries, figures, and listings, lab results and normal ranges will be presented in System International (SI) units. Eosinophils data will be presented in both SI and conventional units (cells/µL) in summaries.

For the purposes of clinical chemistry, hematology, and urinalysis shift tables, baseline will be defined as the last available non-missing assessment prior to first dose of randomised treatment, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the post-treatment period.

Changes in hematology and clinical chemistry variables between baseline and each post-baseline assessment will be calculated. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values. For values recorded with a leading greater than or less than (‘>’, ‘<’) symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each time-point.

For the liver function tests: aspartate Aminotransferase (AST), alanine Aminotransferase (ALT), alkaline phosphatase (ALP), gamma-GT (GGT) and total bilirubin (TBL), the multiple

of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point.

Multiple = Value / ULN

That is, if the ALT value was 72 IU/L (ULN=36) then the multiple would be 2.

Patients who meet any of the following criteria at any point during the study will be flagged:

- AST ≥ 3x ULN
- ALT ≥ 3x ULN
- TBL ≥ 2xULN

3.7.3 Twelve-lead ECGs

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.7.4 Physical examination

Complete and brief physical examinations will be performed at time points specified in Tables 1 and 2 of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described the CSP. Only information on whether the assessment was performed or not is to be recorded. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.7.5 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, and oral temperature) will be assessed in accordance with the visit schedule provided in the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Baseline is defined as the last value prior to the first dose of randomised treatment. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values.

Absolute values will be compared to the reference ranges in Table 5 and classified as low (below range), normal (within range or on limits) or high (above range). All values falling outside the reference ranges will be flagged.

Table 5: Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120

Parameter	Standard Units	Lower Limit	Upper Limit
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38

4 ANALYSIS METHODS

4.1 General principles

The current SAP focuses on the DB study period with a high-level description of the descriptive analysis for the OLE analysis.

The statistical analyses of the DB period, is designed to compare both efficacy and safety of benralizumab to mepolizumab while the OLE period is designed to evaluate the long-term safety and tolerability and persistence of effect of benralizumab in this patient population.

Efficacy endpoints will be analysed using the full analysis set (FAS). Patients will be analysed according to their randomised 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 (Wechsler et al 2017).

The analysis of safety endpoints will be based on the safety analysis set. Analysis sets are defined in Section 2.1. The analysis of the primary and secondary efficacy endpoints will include all data captured during the 52-week DB treatment period. The primary analysis of exposure and adverse events will include both data captured during DB treatment period and OLE period. Additional analyses may be performed after the primary database lock to analyse the data that were not available in the primary analysis.

Further assessments of safety, tolerability, efficacy, pharmacokinetics and immunogenicity will be reported after the final database lock including summaries of data from the OLE period.

A primary estimand will be applied to the primary analysis of the primary endpoint whereby all data up to end of DB treatment period is included, regardless of whether a patient remains on blinded study treatment or not. Details regarding estimands are provided in Table 6.

Table 6: Primary and safety estimands (DB period)

Statistical category	Estimand			Section
	Endpoint (Population)	Intercurrent event strategy	Population level summary (Analysis)	
Primary	Proportion of patients with relapsing or refractory EGPA, achieving remission at both weeks 36 and 48 [Full Analysis Set]	Data in DB period included in analysis regardless of treatment discontinuation or adherence	Difference in proportions (C.I. approach to assess non-inferiority)	4.2.7.1
Safety	Incidence of TEAEs [Safety Analysis Set]	Included regardless of treatment discontinuation	Descriptive summaries	4.2.11.1

A similar strategy for intercurrent events will be used for secondary endpoints.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards and validation procedures.

Summary data will be presented in tabular format by treatment group. Categorical data will be summarised by the number and percentage of patients in each category. Continuous variables for parametric data will be summarised by descriptive statistics including N, mean, SD, median, minimum and maximum. All data will be listed. Data listings will be sorted by treatment and patient number.

In general, all hypothesis testing will be reported using 2-sided tests. All p-values will be nominal and will be displayed in SAS pvalue6.4 format.

The absolute change from baseline is computed as (*visit value – baseline value*). Percent change from baseline is computed as ((*visit value – baseline value*)*/baseline value*) × 100%. If either a visit value or the baseline visit value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing.

4.1.1 Testing strategy to account for multiplicity considerations

If non-inferiority (NI) is demonstrated for the primary endpoint, the same logistic regression model used to evaluate NI will be used to test superiority of benralizumab compared to mepolizumab at the 2-sided 0.05 level (equivalent to 1-sided 0.025 level). In this case, the null hypothesis is that the benralizumab remission rate is equal to the mepolizumab remission rate, and the alternative hypothesis is that the benralizumab remission rate is different from mepolizumab. Superiority for benralizumab compared to mepolizumab will be concluded if the p-value is <0.05 and the treatment effect, difference in remission rates, favors benralizumab.

The above testing strategy requires no multiplicity adjustment as it corresponds to a simple closed test procedure and involves only one primary endpoint and one dose of the test treatment.

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the enrolled analysis set. The total number of patients will be summarised for the following groups: those who enrolled, those who were randomised, and those who enrolled but were not randomised (and reason). The number and percentage of patients within each treatment group will be presented by the following categories: randomised and received treatment with study drug, completed DB IP, discontinued IP in DB period (and reason), completed DB period, completed DB IP and DB period, discontinued DB IP but completed DB period, and withdrew from DB period (and reason), enrolled in OLE period, completed OLE IP, discontinued OLE IP (and reason), completed OLE period, and withdrawn from OL period (and reason). The two categories "completed OLE IP" and "completed OLE period" will only be presented at final analysis.

The number of patients randomised by country and centre will be summarised. A listing of disposition of patients and the reasons for screen failures will be provided.

4.2.2 Demography data and patient characteristics

Demographic data and key baseline characteristics will be summarised for each treatment group using descriptive statistics on FAS. The demographic data and key baseline characteristics will include but not are limited to the following variables:

- Age (continuous and categorised as ≥18-≤65 years old, >65 years old)
- Gender
- Country
- Region (North America, Japan, rest of world)
- Race
- Ethnicity
- Height
- Weight
- Body Mass Index

EGPA disease history and baseline characteristics will be summarised for each treatment group using descriptive statistics on FAS. EGPA disease history and baseline characteristics will include but are not limited to the following variables:

- EGPA disease history characteristics

  - EGPA diagnostic disease characteristics (asthma, eosinophilia, etc.)
  - EGPA disease type (relapsing, refractory, or both relapsing and refractory)
  - Absolute eosinophil count at screening (continuous and categorised to <150 cells/uL, ≥150 cells/uL)
  - ANCA-positive status (ANCA-positive at screening or historical ANCA-positive)
  - Time since diagnosis of EGPA (continuous in year and categorised to ≤4 years, > 4 years)
  - Number of relapses over past 2 years
  - Immunosuppressive therapy since diagnosis (yes or no)

- EGPA baseline characteristics
  - Absolute eosinophil count at baseline (continuous and categorised to <150 cells/uL, ≥150 cells/uL)
  - Prednisolone or prednisone dose (continuous and categorised to <12 mg/day, ≥12 mg/day)
  - Immunosuppressive therapy at baseline (yes or no)
  - BVAS (continuous and categorised to >0 or =0)
  - VDI (continuous and categorised to ≥5 or <5)
  - ACQ-6 (continuous and categorised to <1.5 or ≥1.5)
  - SNOT-22 total score
  - IgE

Lung function at baseline will be summarised for each treatment group using descriptive statistics on FAS. The variables of lung function at baseline include FEV1 and FVC pre and post bronchodilator (BD) (in L and percent of predicted normal value), FEV1/FVC (%) pre and post BD and reversibility (%) which is Percent reversibility = (post-BD FEV1 – pre-BD FEV1) × 100%/pre-BD FEV1.

Cardiovascular risk at screening will also be summarised. The variables of cardiovascular risk at baseline include diabetes mellitus, hypertension, hyperlipidemia, cigarette smoking, history of myocardial infarction, unstable angina, coronary revascularization, symptomatic carotid artery disease, heart failure, stroke.

Past and current medical history will be summarised by System Organ Class (SOC) and Preferred Term (PT) using MedDRA. Past medical history is defined as medical history which was not identified as ongoing at screening. Current medical history is defined as medical history which was identified as ongoing at screening. The number and percentage of patients with past and current medical history will be summarised by treatment group and overall.

Surgical history will be summarised by SOC and PT using MedDRA. The number and percentage of patients with surgical history will be summarised by treatment group and overall.

4.2.3 Prior and concomitant medications

The number and percentage of patients who take background EGPA therapy will be summarised by treatment group and overall.

The number and percentage of patients who take prior medications, those who take permitted concomitant medications and those who take non-permitted concomitant medications during the study, will be presented by treatment group. The concomitant medication will be summarised over the DB treatment period and over the OLE treatment period, respectively. Summary tables of background asthma medications and sino-nasal medications at baseline will also be performed. Concomitant medications will be classified according to the WHODRUG dictionary. The summary tables will present data by generic term within Anatomical Therapeutic Chemical (ATC) code.

The number and percentage of patients taking maintenance asthma medications at baseline will be summarised. Summary statistics will also be provided for OCS doses and ICS doses at baseline; OCS doses will be converted to their Prednisolone equivalent in milligrams as Table 7, and ICS doses will be categorized to high, medium, and low as Table 8.

Table 7: Conversion of Total Corticosteroid to Prednisone Equivalent

Corticosteroid	Approximate equivalence dose (mg)
Prednisone	10
Prednisolone	10
Betamethasone	1.2
Cortisone	50
Dexamethasone	1.5
Hydrocortisone	40
Methylprednisolone	8
Triamcinolone	8

Table 8: Maintenance ICS dose categories by compound

Adults and adolescents Inhaled corticosteroid	Total daily ICS dose (µg)		
	Low	Medium	High
BDP (pMDI*, HFA)	200-500	>500-1000	>1000
BDP (pMDI, extrafine particle, HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80-160	>160-320	>320
Fluticasone furate (DPI)	NA	100	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (pMDI*, HFA)	100-250	>250-500	>500
Mometasone furoate (DPI)	NA	200-400	>400
Mometasone furoate (pMDI*, HFA)	NA	200-400	>400

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant (non-CFC); pMDI: pressurized metered dose inhaler; CFC: chlorofluorocarbons. * standard (non-fine) particle.

4.2.4 Study treatment administration

Duration of IP administration of the double-blind period will be calculated in days as:

last DB dose date of IP - first DB dose date of IP + 1

Duration of IP administration of the double-blind period will be summarised by treatment group for the safety analysis set.

4.2.5 Study treatment compliance

The treatment compliance for an individual patient will be calculated using the sum of administrated injection doses over the DB treatment period divided by the total number of injection doses until Week 52/IPD visit (excluding the first dose of OLE IP).

IP compliance will be calculated as:

(total doses administered/total doses expected) × 100.

IP compliance will be summarised by treatment group for the full analysis set:

The total number of doses expected includes all visits with protocol scheduled IP administration on or before a patient's IP discontinuation or treatment completion date

4.2.6 Duration of study

Duration of the double-blind period will be summarised on the safety analysis and calculated as:

- For subjects who completed DB period and had dosing in OLE: Date of first OLE dosing - Date of randomisation
- For subjects who early withdrew study in DB period: Date of early withdrawal (on the Disposition CRF page) - Date of randomisation + 1
- For subjects who early withdrew study treatment but completed the remainder of DB period: Date of last DB visit - Date of randomisation + 1
- Subject who lost to Follow-Up in DB period: date of the last contact - Date of randomisation + 1

4.2.7 Primary outcome variable

4.2.7.1 Primary analysis

The primary analysis is to demonstrate NI of benralizumab versus mepolizumab based on the primary endpoint of remission evaluated in the Full Analysis Set.

Non-inferiority will be assessed using a non-inferiority margin of – 25%.

The null and alternative hypotheses are outlined below:

$$H_0: p_{b-} p_m \leq -0.25$$

$$H_a: p_{b-} p_m > -0.25$$

where p_b and p_m represent remission rates for benralizumab and mepolizumab, respectively.

For the null hypothesis to be rejected, the lower 2-sided 95% confidence limit for the absolute difference between benralizumab and mepolizumab remission rates needs to be above the NI margin of -25%.

The primary endpoint will be analysed using a logistic regression model. The model will include covariates of treatment arm, baseline prednisone daily dose (continuous), baseline BVAS (continuous) and region. From this model, the absolute difference in remission rates (benralizumab -mepolizumab) will be estimated, with the associated 2-sided 95% CI. Marginal standardisation methods (Bartlett 2018) will be used for the model estimates for all logistic model analyses, unless otherwise specified.

If NI is demonstrated for the primary endpoint, the same logistic regression model used to evaluate NI will be used to test superiority of benralizumab compared to mepolizumab at the 2-sided 0.05 significance level (equivalent to 1-sided 0.025 level). In this case, the null hypothesis is that the benralizumab remission rate equals to the mepolizumab remission rate, and the alternative hypothesis is that the benralizumab remission rate is different from mepolizumab remission rate.

The hypothesis can be stated as:

$$H_0: p_b = p_m$$

$$H_a: p_b \neq p_m$$

An unadjusted rate for benralizumab from this study will be compared to a historic rate of 2/68 (~2.9%) for placebo. Superiority of benralizumab over historical placebo will be evaluated with a two-sample test for binomial proportions using a 2-sided test of benralizumab having an improved rate over placebo with a 5% significance level. This method accounts for the uncertainty assuming the sample size of 68 from the historical placebo estimate and a sample size of 70 for the benralizumab arm in the current trial. A normal approximation will be used for this comparison of benralizumab to historic placebo.

The hypothesis can be stated as:

$$H_0: p_b = p_p$$

$$H_a: p_b \neq p_p$$

where p_b and p_p represent remission rates for benralizumab and historic placebo, respectively.

While the description above corresponds to a 2-sided test, superiority of benralizumab compared to placebo will be concluded if the 2-sided p-value is <0.05, and the difference in remission rates (benralizumab - mepolizumab) favors the benralizumab group.

The comparison of mepolizumab to historic mepolizumab will also be evaluated in the same way. An unadjusted rate for mepolizumab from this study will be compared to a historic rate of 22/68 (~32%) for mepolizumab.

Proportion of patients who achieved remission will be summarised every 4 weeks at patient's nominal 4-weekly visit by treatment group. A line plot will also be provided.

4.2.7.2 Sensitivity analysis for the primary outcome variable

Two sensitivity analyses for the primary endpoint may be conducted:

1. Using per-protocol population where patients are excluded based on important protocol deviations related to efficacy,
2. Using corticosteroid administered treating EGPA to calculate daily OCS dose and derive remission variable.

The logistic regression model with marginal standardisation method described in section 4.2.7.1 will be used for the sensitivity analyses.

4.2.7.3 Subgroup analysis for the primary outcome variable

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses will include, but may not be limited to the following factors: Body Mass Index (≤30 kg/m^2, >30 kg/m^2), blood eosinophil count at baseline (<150 cells/ul, ≥150 cells/ul), OCS use at baseline (<12 mg/day, ≥12 mg/day), gender, age group (≥18 to ≤65 years old, >65 years old), geographic region (North America, Japan, rest of world), time since EGPA diagnosis (≤4, >4 years), immunosuppressive therapy usage at baseline (yes/no), baseline VDI score (<5, ≥5), race (white, Asian, other) and ANCA-positive status (yes (either historical positive or positive at screening)/no).

Consistency of treatment effect across covariates fitted in the primary efficacy endpoint analysis models will be examined by fitting separate models to examine treatment interactions with the subgroups (i.e. logistic regression analyses with the same covariates as in the primary analysis along with treatment, subgroup, and treatment-by-subgroup interaction terms. A confounding covariate will be removed when conducting corresponding subgroup analysis.

For example, baseline prednisone daily dose will be removed for the subgroup analysis of OCS use at baseline (<12 mg/day, ≥12 mg/day); race will be removed for the subgroup analysis of geographic region. Marginal standardisation method will be used as the primary analysis). Results from the models will be shown, also a forest plot will be presented. If the percentage of patients is small within a particular subgroup, then the subgroup categories may be refined prior to unbinding the trial.

4.2.7.4 Supportive analysis for the primary outcome variable

The primary analysis of the primary endpoint will be repeated on the supportive endpoint (i.e. BVAS= 0 plus OCS dose ≤7.5 mg/day) as defined in Section 3.2.

The proportion of patients who achieved BVAS=0 at both Week 36 and Week 48, proportion of patients who achieved OCS dose≤4 mg/day at both Week 36 and Week 48, proportion of patients who achieved OCS ≤7.5 mg/day at both Week 36 and Week 48 will be analysed the same as the primary analysis of the primary endpoint.

4.2.7.5 Tipping point analysis for historic placebo comparison

A tipping point analysis will be conducted to assess the robustness of the indirect comparison to historic placebo. In the analysis, the number of patients meeting the remission endpoint will be 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) will be converted to responder status one at a time. In each scenario evaluated, the superiority of benralizumab over the historic placebo will be evaluated at the 2-sided 5% level to identify the point at which the result tips from significant ($p<0.05$) to non-significant ($p\geq0.05$). Results will be presented graphically with the observed benralizumab and placebo remission numbers highlighted as reference lines.

4.2.8 Secondary efficacy outcome variables

4.2.8.1 Total accrued duration of remission

Total accrued duration of remission (as defined in Section 3.3.1) will be evaluated over the 52-week treatment period. The accrued duration will be assigned with the following categories: 0 weeks, >0 to <12 weeks, 12 to <24 weeks, 24 to <36 weeks and ≥36 weeks.

A proportional odds model will be used to analyse total accrued duration of remission. The model will include treatment arm, baseline prednisone daily dose, baseline BVAS and region. Results from the proportional odds model will be presented in terms of p-value, an adjusted odds ratio with associated 2-sided 95% confidence intervals.

In addition, as a supportive analysis, the total duration of sustained remission will be evaluated over the 52-week treatment period. Total duration of sustained remission will be analysed using a proportional odds model as described above.

The analyses described above will be repeated on the supportive endpoint (i.e. BVAS= 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day) as defined in Section 3.2. The total accrued duration of BVAS =0, and the total accrued duration of OCS dose of prednisolone/prednisone ≤4 mg/day will be analysed the same as above.

A sensitivity analysis will be conducted for total accrued duration of remission using corticosteroid administered treating EGPA to calculate daily OCS dose and derive remission variable. The proportional odds model described above will be used for the sensitivity analysis.

4.2.8.2 Time to relapse

Time from randomisation to first relapse will be evaluated over the 52-week treatment period.

Time to first relapse will be analysed using a Cox-proportional hazards model. Treatment arm, baseline prednisone daily dose, baseline BVAS and region will be included as covariates in the model. Cox-proportional hazards model results will be presented in terms of adjusted hazard ratios with associated 2-sided 95% confidence intervals. The Efron method to control for ties will be used. A p-value from log-rank test, the estimates and 2-sided 95% confidence intervals at Weeks 16, 32 and 52 using Kaplan-Meier approach will be generated.

Time to relapse will be displayed graphically using a Kaplan-Meier plot by treatment with median time to event and associated 2-sided 95% CI if estimable. If not estimable, hazard ratio (benralizumab vs mepolizumab) and associated 2-sided 95% CI, p-value from log-rank test will be presented as legend.

The time to first major relapse will be analysed similarly. In addition, in order to aid interpretation of this endpoint, a summary of BVAS by organ system class will be summarised at each visit.

4.2.8.3 Annualised relapse rate

A negative binomial model will be used to analyse annualised relapse rate. The number of relapses observed for a patient during the 52-week double-blind treatment period will be used as the response variable. The response variable in the model will be the number of relapses experienced by a patient during the DB period. The model will include covariates for treatment arm, baseline prednisone daily dose, baseline BVAS and region. The logarithm of the patient's corresponding follow-up time up to Week 52 will be used as an offset variable in the model to adjust for patients having different follow-up times during which the events occur. Marginal standardisation method will be used for model estimates.

For the production of summary statistics, number of relapses per subject will be categorised into 0, 1, 2, 3, >3. Number of subjects and number of events in each relapse category will also be presented including vasculitis, asthma, sino-nasal, vasculitis/asthma, vasculitis/sino-nasal, asthma/sino-nasal, vasculitis/asthma/sino-nasal, any vasculitis, any asthma, any sino-nasal. The annual relapse rate in each treatment group will be calculated using the time-based approach below:

*Annual Relapse Rate = 365.25*Total Number of relapses / Total duration of* follow-up within the treatment group (days).

Annualised major relapse rate is defined similarly and will be analysed similarly.

4.2.8.4 Average daily dose of OCS required during weeks 48 and 52

The proportion of patients with an average daily prednisolone/prednisone dose during the last 4 weeks of the study treatment period (48 through 52) in each of the following categories:

- Zero
- >0 to <= 4.0 mg
- >4.0 to <= 7.5 mg
- 7.5 mg

A proportional odds model will be used to analyse the average of daily OCS dose during Weeks 48 and 52 for the categories above. Treatment arm, baseline prednisone daily dose, baseline BVAS and region will be included as covariates in the model. The treatment group effect will be presented with p-value, the adjusted odds ratio and its associated 2-sided 95% confidence intervals.

Proportional odds models will also be used to analyse the percentage reduction from baseline in average prednisolone/prednisone dose at Weeks 48-52 for the following categories:

- No reduction or withdrawal from IP before Week 48
- <25% reduction
- ≥25% to <50% reduction
- ≥50% to <75% reduction
- ≥75% to <100% reduction
- 100% reduction

Treatment arm, baseline prednisone daily dose, baseline BVAS and region will be included as covariates in the model. The treatment group effect will be presented with p-value, the adjusted odds ratio and its 2-sided 95% confidence intervals.

The primary analysis for the primary endpoint (as described in Section 4.2.7.1) will be repeated for proportion of subjects with reduction from baseline in average daily dose of prednisolone/prednisone during Week 48 through 52 for the following categories:

- Subjects with >=50% reduction from baseline
- Subjects with =100% reduction from baseline
- Subjects with OCS dose <=4 mg/day

Descriptive statistics will be provided for OCS for observed and absolute and percent change from baseline values 4-weekly over time by treatment group. A line plot showing average daily OCS dose (mean with +/- standard error) over time by treatment group will also be provided.

As a sensitivity analysis, descriptive statistics will be calculated for OCS treating EGPA for observed and absolute and percent change from baseline 4-weekly over time by treatment group.

4.2.8.5 Proportion of patients with clinical benefit

Logistic regression as the primary analysis for the primary endpoint (Section 4.2.7.1) will be used to analyse the variables (any clinical benefit and complete response, both definition 1 and definition 2) in Section 3.3.5.

4.2.8.6 Proportion of patients achieving remission within the first 24 weeks and remaining in remission for the remainder of the double-blind period

Logistic regression will be used to analyse remission within the 24 weeks and remaining in remission for the remainder of the double-blind period. The model will include covariates of treatment arm, baseline prednisone daily dose, baseline BVAS and region. From this model, the absolute difference in remission rates (benralizumab -mepolizumab) will be estimated, with the associated 2-sided 95% CI. Results will be presented in terms of adjusted remission rates and difference in remission rates with associated 2-sided 95% confidence intervals and p-values. Marginal standardisation methods will be used for the model estimates.

The analysis described above will be repeated on the supportive endpoint (i.e. BVAS= 0 plus OCS dose of prednisolone/prednisone ≤7.5 mg/day) as defined in Section 3.2.

4.2.8.7 BVAS

The change from baseline in the BVAS by visit will be analysed using a repeated measures Analysis of Covariance (ANCOVA) analysis with treatment arm, baseline prednisone daily dose, baseline BVAS score, region, visit, and visit by treatment group as covariates.

The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary

analysis will fit a repeated measures ANCOVA model using the data collected up to the last DB assessment date. The treatment effect at Week 52 will be estimated from this repeated measures ANCOVA model. Graphical displays of LS mean (95% CI) change from baseline over time by treatment group will also be presented for BVAS.

Descriptive statistics will be provided for BVAS observed and change from baseline values over time by treatment group.

4.2.8.8 BVAS responder

The proportion of patients who are BVAS responders will be summarised by treatment group.

The proportion of patients who are BVAS responders will be analysed using a logistic regression model. The model will include covariates of treatment arm, baseline prednisone daily dose, baseline BVAS and region. From this model, the absolute difference in BVAS responder rates (benralizumab -mepolizumab) will be estimated, with the associated 2-sided 95% CI. Results will be presented in terms of adjusted response rates and difference in response rates with associated 2-sided 95% confidence intervals and p-values. Marginal standardisation methods will be used for the model estimates.

4.2.8.9 Vasculitis damage index

The Vasculitis Damage Index (VDI) will be used to document those features of vasculitis, which are due to persistent damage, where there is no current disease activity. Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity.

The VDI has a range of 0-64. A score of 0 indicates no damage.

The change from baseline in VDI score by visit will be analysed using a repeated measures ANCOVA analysis as described in Section 4.2.8.7 with additional baseline VDI as covariate.

Descriptive statistics will be provided for VDI for observed and change from baseline values over time by treatment group.

4.2.8.10 PRO endpoints

4.2.8.10.1 Asthma Control Questionnaire (ACQ-6)

The change from baseline in ACQ-6 by 4-weekly time-period will be analysed using a repeated measures ANCOVA analysis with treatment arm, baseline prednisone daily dose, baseline BVAS score, region, baseline ACQ-6, time period, and time period by treatment arm as covariates. Graphical displays of LS mean change from baseline will also be presented.

The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary analysis will fit a repeated measures ANCOVA model using the data collected up to and

including the Week 52/IPD time-point. The estimate of the treatment effect at time period of Week 49-52 will be based on a contrast from this repeated measures ANCOVA model.

An ACQ-6 responder analysis based on average ACQ-6 score during Weeks 48 through 52 will be performed using a logistic regression model adjusted for treatment arm, baseline prednisone daily dose, baseline BVAS score, baseline ACQ-6 and region. From this model, the absolute difference in response rates (benralizumab -mepolizumab) will be estimated, with the associated 2-sided 95% CI. Results will be presented in terms of adjusted response rates and difference in response rates with associated 2-sided 95% confidence intervals and p-values. Marginal standardisation methods will be used for the model estimates.

Time to first sustained responder will be analysed using a Cox-proportional hazards model. Cox-proportional hazards model results will be presented in terms of adjusted hazard ratios with associated 2-sided 95% confidence intervals. Treatment arm, baseline prednisone daily dose, baseline BVAS, baseline ACQ-6 and region will be included as covariates in the model.

Descriptive statistics will be provided for ACQ-6 for observed and change from baseline values over time by treatment group. The proportion of responders will be presented over time by treatment group. The asthma control status based on ACQ-6 score at baseline and average ACQ-6 score during Weeks 48 through 52 will be presented by treatment group.

4.2.8.10.2 Short Form 36 version 2 (acute recall)

The change from baseline in the SF-36v2 scales and component scores by visit will be analysed using a repeated measures ANCOVA analysis as described in section 4.2.8.10.1. Visit will be included as a covariate instead of time period. Baseline SF-36v2 instead of baseline ACQ-6 will be included as one of the covariates. Graphical displays of LS mean change from baseline will also be presented for MCS and PCS.

SF-36v2 responder at Week 52 based on individual change thresholds will be analysed using a logistic regression model as described in section 4.2.8.10.1. Baseline SF-36v2 instead of baseline ACQ-6 will be included as one of the covariates.

Time to first sustained responder will be analysed using a Cox-proportional hazards model as described in section 4.2.8.10.1. Baseline SF-36v2 instead of baseline ACQ-6 will be included as one of the covariates.

Descriptive statistics will be provided for SF-36v2 (scales and component scores) observed and change from baseline values over time by treatment group. The proportion of responders based on individual change thresholds will be presented over time by treatment group.

4.2.8.10.3 Sino-Nasal Outcome Test 22

The change from baseline in the SNOT-22 scale by visit will be analysed using a repeated measures ANCOVA analysis as described in section 4.2.8.10.1. Visit will be included as a covariate instead of time period. Baseline SNOT-22 instead of baseline ACQ-6 will be included as one of the covariates. Graphical displays of LS mean change from baseline will also be presented.

Descriptive statistics will be provided for SNOT-22 for observed and change from baseline values over time by treatment group.

4.2.8.10.4 Sino-nasal Symptoms Questionnaire

SSQ symptom scores will be summarised by treatment group for each 4-week period. Weekly sino-nasal symptoms will be aggregated over 4-week periods, and for each question, the highest (i.e. worse) score will be calculated for each 4-week period.

Responses to each of the below questions (i.e. 4 = very severe; 3 = severe; 2 = moderate; 1 = mild; 0 = none) will be summarised for each 4-week period, using the highest (i.e. worse) score reported during each period.

- Runny nose
- Post-nasal discharge (sensation of liquid in your throat)
- Facial pain/pressure
- Loss or reduction in sense of taste/smell
- Blockage/congestion of nose

Descriptive statistics will be provided for SSQ observed and change from baseline values over time by treatment group.

4.2.8.10.5 Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

Descriptive statistics will be provided for PGIS and PGIC responses over time. PGIC improvement categories will also be presented over time.

4.2.8.10.6 Work Productivity and Activity Impairment (WPAI) Questionnaire

Descriptive statistics will be provided for WPAI-GH over time, including endpoints defined in Section 3.3.10.6.

4.2.8.11 Change from baseline in Blood Eosinophil Count

Change from baseline in blood eosinophil count will be summarised over time by treatment group. Mean, standard deviation, first quartile (Q1), median, third quartile (Q3), min, max will be presented.

The blood eosinophil count will be log10-transformed prior to analysis. The change from baseline in log-transformed blood eosinophil by timepoint will be analysed using a repeated measures ANCOVA analysis with treatment arm, baseline prednisone daily dose, baseline BVAS score, region, baseline blood eosinophil count, timepoint, and timepoint by treatment arm as covariates. Graphical displays of LS mean change from baseline will also be presented.

The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary analysis will fit a repeated measures ANCOVA model using the data collected up to the last DB assessment date. The treatment effect at Week 52 will be estimated from this repeated measures ANCOVA model.

4.2.8.12 Blood Eosinophil Count depletion

The proportion of patients experiencing depletion of blood eosinophil count ≤30 cells/uL will be summarised by post-baseline timepoint during DB treatment period for each treatment group.

The proportion of patients who experience depletion of blood eosinophil count ≤30 cells/uL will be analysed using a logistic regression model at each time-point. The model will include covariates of treatment arm, baseline prednisone daily dose, baseline BVAS, baseline blood eosinophil count and region. From this model, the absolute difference in depletion rates (benralizumab -mepolizumab) will be estimated, with the associated 2-sided 95% CI. Results will be presented in terms of adjusted depletion rates and difference in depletion rates with associated 2-sided 95% confidence intervals and p-values. Marginal standardisation methods will be used for the model estimates.

Time from randomisation to the first depletion of blood eosinophil count ≤30 cells/uL will be evaluated over the DB treatment period and analysed using a Cox-proportional hazards model. Cox-proportional hazards model results will be presented in terms of adjusted hazard ratios with associated 2-sided 95% confidence intervals. Treatment arm, baseline prednisone daily dose, baseline BVAS, baseline blood eosinophil count and region will be included as covariates in the model.

For patients who have not experienced a depletion of blood eosinophil count ≤30 cells/uL during DB treatment period, their time to first depletion will be right-censored at the last available assessment time during the DB treatment period.

The above analyses will be repeated for patients who experience depletion of blood eosinophil count < 150 cells/uL and have had at least 90% reduction from baseline in blood eosinophil count, respectively.

4.2.8.13 Spirometry

Pre-BD FEV1 and pre-BD FVC will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding change from baseline.

The change from baseline of pre-BD FEV1 will be analysed using a repeated measures ANCOVA analysis with treatment arm, baseline prednisone daily dose, baseline BVAS score, region, baseline pre-BD FEV1, timepoint, and timepoint by treatment arm as covariates. Graphical displays of LS mean change from baseline of pre-BD FEV1 will also be presented.

The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary analysis will fit a repeated measures ANCOVA model using the data collected up to the last DB assessment date. The treatment effect at Week 52 will be estimated from this repeated measures ANCOVA model.

The change from baseline of pre-BD FVC will be analysed using the similar method described above.

4.2.9 Exploratory outcome variables

4.2.9.1 Cumulative OCS

Cumulative OCS dose over the 52-week period will be summarised by treatment group.

4.2.9.2 Healthcare resource utilization due to EGPA

The number and annualised rate of patients with EGPA specific resource utilization during the treatment period will be summarised by treatment group.

4.2.9.3 Relationship between baseline eosinophil measures assessed by the central laboratories

In this trial, paired assessments of the eosinophil count (cells/μL) were introduced during the study. All patients will have an assessment available from the primary central laboratory (analysed via Advia 2120i instrument), while a subset of patients will also have assessments available from the alternative central laboratory (analysed via DXH800 instrument). Available results from both laboratories will be included in summary tables and summarised separately. It is expected that these paired assessments will be positively correlated, and the relationship between the paired samples at baseline will be displayed via scatter plots on the logarithmic scale, with Spearman's Rank correlation coefficient added as an annotation for the full analysis set.

4.2.10 Pharmacokinetics and immunogenicity variables

Benralizumab serum concentrations will be summarised over DB period for all patients in the pharmacokinetic analysis set. The number of patients with result, number of patients with

result <LLOQ, geometric mean and associated 95% CI, coefficient variation (%), arithmetic mean, standard deviation, minimum, first quartile (Q1), median, third quartile (Q3), and maximum will be summarised over time.

Immunogenicity variables will be summarised over DB period for all patients in the safety analysis set with at least one available Anti-drug antibody (ADA) result. ADA assessments will be conducted and analysed as per the details in Section 9.5.

4.2.11 Safety outcome variables

4.2.11.1 Adverse events

Adverse events (AEs) will be summarised separately for the DB period and OLE period.

All AEs will be listed for each patient. All summaries will be presented by treatment group and will be exposure-adjusted to account for the variability in OLE period.

The rate of AEs per person-years at risk will be calculated as (number of patients reporting the AE)/(total study period with patients at risk of AE). The total period at risk for each patient will be the duration of the on-study DB and OLE periods. Rates will be expressed in terms of events per 100 patient-years.

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories: AEs, serious adverse events (SAEs), AEs with outcome of death, and AEs leading to discontinuation of investigational product (DAEs).

AEs, AEs with outcome of death, SAEs and DAEs will be summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number, percentage and exposure-adjusted rate of patients reporting at least one occurrence will be presented (i.e., multiple occurrences of an AE for a patient will only be counted once).

A summary of the most common (frequency of >3%) AEs will be presented by PT.

Additionally, a summary of non-serious AEs occurring in >5% of patients in any treatment group will be presented by PT.

AEs and SAEs will be summarised by preferred term and investigator's causality assessment (related vs. not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe).

Other significant adverse events will include but may not be limited to injection site reactions and hypersensitivity events. Adverse events of injection site reactions (high level term of administration and injection site) and hypersensitivity (standardised MedDRA query of

hypersensitivity (SMQ) [narrow]) will be summarised by preferred term. The summary of injection site reactions will be summarised by injection site location and number of IP administrations. The summary of AEs of hypersensitivity will be presented overall and repeated for events causally related to IP as assessed by the investigator.

Plot of frequencies and risk differences (forest plots) between treatment arms will be presented for the most common adverse events, serious adverse events, adverse events causing discontinuation of investigational product and other specific events of interest including malignancy and serious hypersensitivity. Estimates and confidence intervals based on the Miettinen Nurminen (M-N) method will also be presented for the most common adverse events, adverse events causing discontinuation of investigational product and any other specific events of interest included in the structured assessment of benefit risk.

Summaries of overall adverse events by category will be produced in the following subgroups.

- Age group (≥18 to ≤ 65, >65 years old)
- Gender (Male, Female)
- Race (White, Asian, Other)
- Geographic region (North America, rest of world, Japan)

The differences in the proportion of patients (benralizumab – mepolizumab) reporting at least 1 AE, at least 1 AE with outcome of death, at least 1 SAE, and at least 1 AE leading to discontinuation of investigational product by the above subgroup, with associated 2-sided 95% confidence intervals using the Miettinen Nurminen (M-N) method will be constructed. The results for patients reporting any AE will be presented in a forest plot.

4.2.11.2 Safety laboratory data

All protocol-specified continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarised in SI units, with the exception of blood eosinophil counts which will be summarised in both SI and conventional units. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, and high values. The shift tables will present baseline and maximum/minimum on-treatment value, as applicable for each parameter and will include patients with both baseline and post-baseline data. As for AST and ALT parameters, the multiple of central laboratory ULN defined in section 3.7.2 will be calculated for each timepoint.

Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.

4.2.11.3 ECG

The Investigator's assessment of the 12-lead ECG (normal or abnormal) will be listed for all patients, along with detailing whether any abnormalities were clinically significant or not. The number and percentage of patients with normal, abnormal not clinically significant, abnormal clinically significant ECGs will be summarised by treatment group. If there are multiple ECG records at the same date, the most severe assessment will be used for summary.

4.2.11.4 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented for each treatment group by visit. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data.

4.2.12 Impact on analyses due to COVID-19 pandemic

While the study was recruiting at the time of the COVID-19 worldwide pandemic, for ongoing patients, patient dosing and scheduled visits all became difficult to perform according to protocol.

Efforts are ongoing to collect outstanding data via alternative means where possible, when onsite visits cannot be performed. As a result, the following changes have been made to the planned analyses:

- Protocol deviations, including doses or visits missed due to COVID-19 related protocol deviations will be described separately in the CSR. These deviations will be identifiable in the database with a 'COVID' prefix.
- Confirmed or suspected cases of COVID-19 will be listed and included as AEs as appropriate.

5 OLE TREATMENT PERIOD

For patients entering the OLE, summaries from the OLE will be presented for the overall population, and by prior randomised treatment (benralizumab or mepolizumab).

The only OLE data that will be presented at the primary analysis (when the double-blind period has completed) is a top level overview of exposure and AEs, integrated with the double-blind and open-label periods data to give a view of the safety profile over the longest follow-up accrued in the study at that point. The final database lock will occur after the last patient has completed at least one year in the OLE and when the end of the study has been declared. Selected efficacy and safety data may be integrated for those patients randomised to

benralizumab, to describe efficacy and safety data over the entire study follow-up period at the final analysis. All efficacy data and safety data from the OLE period of the study will be presented in an addendum to the primary analysis clinical study report (CSR).

OLE analyses will primarily be presented on the FAS, but a repeat of key analyses may also be produced on the open-label benralizumab analysis set to ensure only patients who switched to receive benralizumab after 52 weeks are included in the denominator for that group and to ensure a meaningful interpretation of the mepolizumab-to-benralizumab patients.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES OF ANALYSIS FROM PROTOCOL

For repeated measures endpoints, including BVAS, VDI, pulmonary function, asthma symptoms, sino-nasal symptoms, HRQoL and blood eosinophils, the CSP indicated that analysis would be conducted using a mixed effect model for repeated measures. However, as the models actually incorporate subject in the repeated statement of PROC MIXED rather as a random effect, these analyses are now referred to as "repeated measures ANCOVA analyses" to more appropriately describe the intended analysis.

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9 ADDITIONAL SPECIFICATIONS

9.1 Partial dates for adverse events and prior/concomitant medications

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify treatment-emergent AEs and to classify prior/concomitant medications:

Adverse Events

- The missing day of onset of an AE will be set to:
    - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
    - The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
    - The date of informed consent, if the onset YYYY-MM is before the YYYYMM of the first treatment.
- The missing day of resolution of an AE will be set to:
    - The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
- If the onset date of an AE is missing both the day and month, the onset date will be set to:
    - January 1 of the year of onset, if the onset year is after the year of the first study treatment
    - The date of the first treatment, if the onset year is the same as the year of the first study treatment
    - The date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an AE is missing both the day and month, the date will be set to:
    - December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

- The missing day of start date of a therapy will be set to the first day of the month of the occurrence.
- The missing day of end date of a therapy will be set to the last day of the month of the occurrence.

- If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.
- If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the earliest of the imputed partial end date and the date of the first study visit.
- If the start date of a therapy is null and the end date is a complete date
  - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
  - otherwise the start date will be set to the end date of the therapy.
- If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the study end date.
  - If the end date of a therapy is null and the start date is a complete date and the start date is prior to the study end date then the end date will be set to the study end date.
  - otherwise, the end date will be set to the start date of the therapy.

9.2 Derivation of Remission

Each study day will be assessed for the remission status of the patient, using the prednisolone/prednisone daily dose and the BVAS score (recorded at each visit in the eCRF, including all scheduled and unscheduled visits). Because the recall period of BVAS is 4 weeks, for the days between 2 consecutive scheduled visits, the later visit BVAS will be used to impute the daily BVAS score (even if two visits are more than 28 days apart). If a patient came for a scheduled visit but BVAS is missing, the next visit BVAS score (if available) will be used for the days between missing BVAS visit and next visit. BVAS will be missing for days between this scheduled visit with missing BVAS and the previous visit. If a patient missed a scheduled visit completely, the next visit BVAS (if available) will be used to impute the BVAS score for 28 days prior to the visit with BVAS. BVAS will be missing for the remaining days between the visit with BVAS and the previous visit.

Initially, patients will be flagged as being in remission for each study day in which the prednisolone/prednisone daily dose is less than or equal to the threshold value (defined as either 4mg or 7.5mg, as appropriate) and the BVAS score is zero. However once a patient has achieved remission, any subsequent study day (within the current period of remission) will be defined as in remission if prednisolone/prednisone daily dose is less than or equal to the threshold value and the relevant BVAS score is ≤ 1.

Table 9 illustrates how a patient is considered to be still in remission if the BVAS score increases to 1 and the prednisolone/prednisone daily dose remains $\leq$ 4mg (i.e. study day 2 and

3). However once a patient has lost their remission status, the patient must once again achieve a prednisolone/prednisone daily dose ≤ 4mg and BVAS=0; therefore study day 10 would not be considered to be in remission.

Table 9: Illustration of derivation of remission

Study Day	Prednisolone/prednisone daily dose	BVAS	Remission (i.e. BVAS=0 and prednisolone/prednisone dose <= 4mg/day)
1	4	0	Y
2	4	1	Y
3	4	1	Y
4	5	3	N
5	5	3	N
6	3	0	Y
7	3	0	Y
8	5	1	N
9	5	1	N
10	4	1	N

9.3 Derivation of Relapse

Relapse is defined as follows:

Worsening or persistence of active disease ***since the last visit*** characterised by:

- Active vasculitis (BVAS >0) or
- Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score (compared to the most recent previous score) or
- Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions (compared to the most recent previous assessment);

warranting:

- An increased dose of OCS therapy (or other systemic corticosteroid therapy) to >4 mg/day prednisolone total daily dose or equivalent, or
- An increased dose or addition of immunosuppressive therapy or
- Hospitalisation related to EGPA worsening.

Table 10 provides a detailed description of the derivation of this endpoint.

Table 10: Derivation of relapse

Criterion	Condition
Active vasculitis (BVAS > 0)	a

Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score (compared to the most recent previous score)	b
Active nasal and/or signs with a corresponding worsening in at least one of the sino-nasal symptom questions (compared to the most recent previous assessment)	c
An increased dose of OCS therapy	d
An increased dose or addition of immunosuppressive therapy	e
Hospitalisation related to EGPA worsening	f
Programming logic: if (a or b or c) and (d or e or f)	

9.4 Derivation of Major Relapse

Major Relapse will be defined programmatically.

A Major relapse is defined as follows:

- Any organ or life-threatening EGPA event; OR
- BVAS ≥6 (involving at least two organ systems in addition to any general symptoms where present [myalgia, arthralgia/arthritis, fever >38ºC or weight loss >2 kg]); OR
- An asthma relapse requiring urgent care visit or hospitalisation; OR
- Sino-nasal relapse requiring hospitalisation.

Table 11 provides a detailed description of the derivation of major relapse.

Table 11: Derivation of major relapse

<table>
<tr><th colspan="2">Criterion</th><th>Condition</th><th></th></tr>
<tr><td colspan="2">Meets general definition of Relapse</td><td>See Table 10: Derivation of relapse</td><td>a</td></tr>
<tr><td colspan="2">Any organ or life-threatening EGPA event</td><td>These will be reviewed by the Clinical team, following manual review of SAEs and other data as required.</td><td>b</td></tr>
<tr><td rowspan="2">BVAS ≥ 6 (involving at least two organ systems in addition to any general symptoms where present [myalgia, arthralgia/arthritis, fever > 38 degrees C or weight loss > 2 kg])</td><td>BVAS total score</td><td>BVAS ≥6</td><td>c</td></tr>
<tr><td>At least two organ systems</td><td>≥2 organ systems:
cutaneous
mucous membranes/eyes
ENT
chest
cardiovascular
abdominal
renal
nervous system</td><td>d</td></tr>
<tr><td></td><td>in addition to any general symptoms where present</td><td>myalgia, arthralgia/arthritis, fever > 38 degrees C or weight loss > 2 kg</td><td>e</td></tr>
<tr><td colspan="3">An asthma relapse requiring hospitalisation</td><td>f</td></tr>
</table>

Sino-nasal relapse requiring hospitalisation	g
Programming logic: if a and (b or (c and d and e) or f or g)	

The time of the relapse or major relapse will be the date entered into the eCRF. If a relapse is recorded between study visits, the definition of major relapse will depend on the BVAS score for the next visit.

9.5 Analysis plan for ADA data

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titre) and ADA data will be collected at scheduled visits shown in the CSP. ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well. In addition, the presence of neutralizing antibodies (nAb) will be tested in all ADA-positive samples using a ligand binding assay. The nAb results will be reported as positive or negative.

In general, patients with a missing baseline ADA assessment will be assumed to be ADA negative at baseline as a conservative approach to ensure that all subjects are included in all analyses. If a positive ADA titre result is reported as ≤50, then the titre will be imputed as 50 for titre summaries. ADA results from samples collected post-dose instead of pre-dose on an IP administration day are considered unreliable and should be excluded from all derivations.

For each subject, the following ADA responses will be evaluated over the entire on-study period through EOT:

- Subjects who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as ADA positive). The proportion of ADA-positive subjects in a population is known as ADA prevalence.
- Subjects who are ADA negative at all assessments, including baseline and post-baseline (also generally referred to as ADA negative).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and at least one post-baseline assessment.
- Treatment-emergent ADA positive (referred to as ADA incidence). A positive post-baseline result and either of the following statements holds:
  - Baseline is ADA negative and at least one post-baseline assessment is ADA positive. This is called treatment-induced ADA positive.
  - Baseline is ADA positive, and the baseline titre is boosted by greater than the variability of the assay (i.e. ≥ 4-fold increase) at ≥1 post-baseline timepoint. This is called treatment-boosted ADA positive.
- Subjects who are ADA positive but not fulling the conditions above for Treatment-emergent ADA positive (also referred to as non-TE ADA positive).

- Subjects who are persistently ADA positive, which is defined as ADA negative at baseline and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.
- Subjects who are transiently ADA positive, defined as ADA negative at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- nAb prevalence; defined as nAb positive at any visit including baseline and/or post-baseline (also referred to as nAb positive)
- nAb incidence; defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit. Patients who are ADA-negative at baseline are included to ensure that all patients who are nAb positive for the first time post-baseline satisfy this definition, given that all patients who are ADA negative at baseline will not have a nAb result reported.
- Subjects who are treatment-emergent ADA positive with maximum post-baseline titre > median of maximum post-baseline titres. The median of maximum post-baseline titres will be calculated based on the maximum post-baseline titre of each ADA positive subject.

The responses above will be summarised as counts and percentages. The maximum ADA titre over the on-study period will also be summarised for patients in each of the ADA positive response categories listed above. The maximum titre will be derived based on all available ADA titres reported for each subject, including any unscheduled assessments.

ADA positive response and titre will be summarised at baseline and at all scheduled post-baseline visits using derived visit windows (refer to Section 3.1.1 for detailed definition of visit windows). In the event a patient has more than one result within a given visit window, the maximum ADA titre will be used in the by-visit summary. In addition, the ADA response will be presented cumulatively. The cumulative ADA response is positive for a specific visit if a positive ADA result is detected at any time point up to and including the specific visit. If all ADA result are negative up to the specific visit, then the cumulative ADA response is negative for that visit. A summary of the number and percentage of patients who are ADA positive at a post-baseline assessment for the first time by visit will also be presented. A line plot of the proportion of subjects who are ADA positive at each visit will be provided.

The proportion of patients with positive nAb response will be summarised by visit.

Key patient information will be listed for patients with positive ADA results, including overall ADA category during the study, nAb status, ADA result, titre, benralizumab serum concentration, and eosinophil level.

All analyses will be conducted on the safety analysis set unless otherwise specified. All ADA results will be listed.

ADA and eosinophil levels

Eosinophil levels will be summarised by visit for the following ADA response categories of patients: ADA negative, treatment-emergent ADA positive, Non-TE ADA positive, ADA persistently positive, ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive. A line plot of eosinophil levels by visit and ADA status will also be presented.

ADA and efficacy

The effects of ADA on the primary endpoint will be evaluated through summary statistics by ADA status (ADA negative, treatment-emergent ADA positive, ADA persistently positive, ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive).

ADA and safety

Adverse events overall summary and hypersensitivity during the study will be summarised by ADA status (ADA negative, treatment-emergent ADA positive, Non-TE ADA positive).

ADA and PK

Benralizumab serum concentrations will be summarised by visit and ADA status (ADA negative, treatment-emergent ADA positive, ADA persistently positive, ADA transiently positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titre, nAb-positive) for patients in the PK analysis set.

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