Statistical Analysis Plan	
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A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 24-week Phase 3 Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients with Hypereosinophilic Syndrome (HES)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AEC	Absolute Eosinophil Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis Of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
APFS	Accessorised prefilled syringe
BMI	Body Mass Index
BP	Bodily Pain
CH	Cox Proportional Hazard
CHMP	Committee For Medicinal Products For Human Use
CPK	Creatine phosphokinase
CSP	Clinical Study Protocol
DAE	Discontinuation Of Investigational Product due to Adverse Event
DB	Double-blind
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End Of Trial
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
GGT	Gamma-glutamyl Transferase
GH	General Health (perceptions)
HES	Hypereosinophilic Syndrome
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent To Treat

LDH	Lactate dehydrogenase
MoA	Mechanism of action
MCS	Mental Component Summary
MH	Mental Health
MI	Multiple Imputation
MMRM	Mixed-effect Model Repeated Measures
NA	North America
OCS	Oral Corticosteroid
OL	Open-label
OLE	Open-label Extension
PCS	Physical Component Summary
PGIC	Patient Global Impression of Changes
PGIS	Patient Global Impression of Severity
PF	Physical Functioning
PH	Physical Health
PK	Pharmacokinetic
PROMIS	Patient-reported Outcomes Measurement Information System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Systemic Corticosteroids
SF	Social Functioning
SF-36	Short Form - 36
SS	Safety Set
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Events
TESAE	Treatment Emergent Serious Adverse Events
ULN	Upper Limit of Normal
US	United States
VT	Vitality
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Version 3.0				
All applicable sections	1 Nov 2024	Primary analysis to be implemented once all randomised patients have completed the 24-week DB period, rather than when the flare target is achieved	Yes	Change made in line with amended CSP to ensure complete DB period follow up is available for all patients at the time of the primary analysis, in line with Health Authority feedback
1.3 Number of patients	1 Nov 2024	Clarification of sample size calculation and drop-out rate assumed	Yes	To ensure sample size assumptions can be understood and the calculation re-produced
2.1 Definition of analysis sets 4.2.7.1 Proportion of patients with HES worsening/flare	1 Nov 2024	Addition of an all-randomised patient's analysis set and a sensitivity analysis of the proportion of patients flaring endpoint with this analysis set	Yes	To enable the additional sensitivity analysis to be performed to explore the impact of including any patients in the analysis who were randomised but not dosed
2.2.1 Important protocol deviations	1 Nov 2024	Clarification of deviations that will be considered important	Yes	To ensure alignment with study specific protocol deviation list, ensuring only deviations that may meaningfully impact reliability and interpretation of study data are included as important
3.3 Secondary efficacy variables	1 Nov 2024	For the proportion of patients with a HES worsening/flare endpoint, and the proportion of patients with a hematologic relapse endpoint, the analysis has been updated so that patients who withdraw from the study without having these events, will be considered as if they had a flare / relapse event	Yes	Patients who withdraw from the study without having had a flare / hematologic relapse will not count as flare-free / hematologic relapse-free, ensuring that missing data are handled in a conservative manner, in line with Health Authority feedback

3.3.7 Proportion of patients who require an increase in corticosteroid dose	1 Nov 2024	Clarification around events that will be considered an increase in corticosteroid dose	Yes	To ensure only medications given to treat a patients HES or for symptoms that may be closely related to their HES are included in this analysis
Table 9 Primary and key secondary estimands	1 Nov 2024	Clarification of intercurrent event handling strategies	Yes	To ensure intercurrent event handling strategies are clear
4.2.6 Primary efficacy variable Other endpoint analysis sections as applicable	1 Nov 2024	Removal of HES flare status at screening covariate from analyses, but adding the potential to explore the impact of any imbalances in this covariate if needed	Yes	Too few patients were randomised under the not actively flaring at screening strata to allow adjustment for this covariate in analyses
4.2.6.2 Sensitivity analyses	1 Nov 2024	Removing sensitivity analyses no longer required	Yes	Withdrawals now considered flare events in proportion flaring endpoint, and a low number of withdrawals have occurred, therefore less need for sensitivity analyses exploring impact of missing data due to withdrawal from the study
4.2.6.3 Subgroups	1 Nov 2024	Updated rules for when subgroup analyses can be performed in the case of low event counts in levels of a subgroup	Yes	To ensure subgroup analyses are performed, when possible, i.e. there is a sufficient number of events enable them
4.2.6.4 Subgroup analyses for China and Japan	1 Nov 2024	Section added to outline analysis requirements within regional subgroup populations	Yes	To support regional submission requirements
4.2.7.4 Improvement in fatigue (PROMIS fatigue short form 7a)	1 Nov 2024	Addition of summary tables of individual question responses and changes from baseline	Yes	To allow evaluation of whether individual items are overly influencing changes in total score, in line with Health Authority feedback
4.2.7.4 and other continuous endpoint analysis sections as applicable	1 Nov 2024	'Mixed model for repeated measures (MMRM)' terminology updated to 'repeated measures ANCOVA'	Yes	This is not a change of the analysis method but a clarification in how it is described

4.2.12 Relationship between eosinophil measures assessed by central laboratories	1 Nov 2024	Removal of exploratory analyses that will no longer be included in the clinical study report	Yes	To allow simplification and prioritisation of analysis methods, exploratory analyses not forming part of the submission have been moved to an exploratory analysis plan
5 Open label extension period	1 Nov 2024	Addition of flare definition within the OLE period ensuring that flares are only considered when background medication was previously stable	Yes	To clarify that during the OLE, failed attempts at tapering background medications are not analysed as flare events
Version 2.0				
1.1 Study Objectives 4.1.1 Testing strategy to account for multiplicity considerations 4.2.7 Secondary efficacy variables	25 Sep 2023	Some secondary endpoints promoted to key secondary	Yes	Adjustment of endpoint prioritization including promotion of endpoints to key secondary endpoints to ensure that clinically meaningful endpoints are multiplicity protected.
1.2 Study Design	25 Sep 2023	Design updated to have primary DBL occur at time of 38th flare.	Yes	This updated primary analysis target is appropriate for an event-driven primary endpoint given that the appropriate power for the primary analysis is achieved when the target number of flare events are available.
1.2 Study Design 1.3 Number of Patients	25 Sep 2023	Number of flares required reduced from 47 to 38	Yes	This revision was made due to the challenges of identifying and recruiting HES patients as well as the availability of mepolizumab as a treatment option. This change in the number of flares still provides robust data to adequately assess the clinical objectives.
2.1 Analysis sets	25 Sep 2023	Randomly assign to study treatment analysis set and Enrolled analysis set removed	Yes	Analysis sets are not needed for outputs.
2.2 Violations and Deviations	25 Sep 2023	Sections about windowing and baseline definitions moved	Yes	Windowing and baseline definitions were originally under this category. They were moved to section 3 where they fit better.

3.1.2 Visit Windows	25 Sep 2023	Windowing rules adjusted	Yes	Windowing rules adjusted and more clearly defined.
3.1.3 Study periods for data summary	25 Sep 2023	Study periods reworked	Yes	Study periods clarified.
3.1.6 Data Cutoff	25 Sep 2023	Section added	Yes	Detail on how the data cut-off will be handled programmatically added.
3.2 Primary efficacy variables	25 Sep 2023	Censoring rules updated	Yes	Censoring rules updated to more accurately report the primary endpoint.
3.3 Secondary efficacy variables	25 Sep 2023	Secondary endpoint sections and definitions updated	Yes	Secondary endpoints were updated with the changes to key secondaries in the CSP. How these endpoints were defined were reworked to make sure they were more readily understood and derivations accurately reported the endpoints.
3.4 Exploratory efficacy variables	25 Sep 2023	HES symptom questionnaire section removed	Yes	The exploratory analysis will not be reported in the CSR.
3.5 Safety outcome variables	25 Sep 2023	Adverse event treatment emergent classifications definitions updated	Yes	Updated to be in line with updated study period definitions
4.1 General principles	25 Sep 2023	Clarification that SAP will mainly focus on DB analysis Data cutoff handling	Yes	Text added to clarify that SAP will focus on DB analysis with some OLE safety analysis How to window patients for the data cutoff added for at week 24 endpoints
4.2 Analysis methods	25 Sep 2023	HES flare status at screening covariate	Yes	With the update to inclusion criteria to allow patients who are not actively flaring, HES flare status at screening was added as a covariate to multiple endpoints
4.2.6 Primary efficacy variable	25 Sep 2023	Sensitivity analysis censoring rules updated	Yes	Censoring rules for the sensitivity analysis were reworked to account for changes in background medication.

		Subgroups added		Subgroups added to prespecify clinically meaningful groups for analysis
4.2.10 Safety outcome variables	25 Sep 2023	Subgroups added Risk difference with M-N confidence intervals analysis added for key safety events. Some safety labs outputs removed HES physical examination, Spirometry, and ECG sections removed	Yes	Subgroups added to prespecify clinically meaningful groups for analysis Added so analysis method for AE summary comparison between arms is pre-defined Following a program-wide recommendation by the AstraZeneca Safety team, these summaries were confirmed to not be required. Collection of these reduced in latest CSP version and reporting of outcomes collected already determined to not be clinically meaningful.
8.1 Partial dates	25 Sep 2023	Rules for partial dates added	Yes	Imputation rules for missing dates for HES disease characteristics added
8.2 Immunogenicity variables	25 Sep 2023	Categories and definitions updated	Yes	ADA and nAB categories and definitions were updated to be in line with more recent standards and definitions.

1 STUDY DETAILS

1.1 Study objectives

The objectives and endpoints for the double-blind (DB) treatment period and the open-label extension (OLE) treatment period of the study are presented in Table 1 and Table 2, respectively.

Table 1 Study objectives - double-blind treatment period

The following objectives/endpoints are for the 24-week DB treatment period of the study:

Primary Objective:	**Estimand Description/Endpoint/Variable:**
To evaluate the effect of benralizumab on the time to first HES worsening/flare	Time to first HES worsening/flare [a] • Population [b]: Full analysis set • Intercurrent event strategy [b]: Included in analysis regardless of treatment discontinuation (treatment policy) • Population-level summary: Hazard ratio
Secondary Objectives	**Endpoint/Variable:**
To evaluate the effect of benralizumab on the proportion of patients who experience HES worsening/flare	Key: Proportion of patients who experience HES worsening/flare during the DB treatment period [a, c]
To evaluate the effect of benralizumab on the number of HES worsenings/flares	Key: Number of HES worsenings/flares (rate/year) during the DB period [c]
To evaluate the effect of benralizumab on the time to first haematological relapse	Key: Time to first haematologic relapse (AEC $\geq$ 1000 cells/µL) [c, d]
To evaluate the effect of benralizumab on patient-reported measure of fatigue	Key: Fatigue severity (Patient-reported Outcomes Measurement Information System [PROMIS] fatigue short form 7a) at Week 24 [c]
To evaluate the effect of benralizumab on the proportion of patients with haematologic relapse	Proportion of patients who have haematologic relapse relapse during the DB treatment period [d]
To evaluate the effect of benralizumab on the number of patients who maintain AEC < 500 cells/µL for 24 weeks	Proportion of patients who have AEC < 500 cells/µL for 24 weeks

Table 1	**Study objectives - double-blind treatment period**
The following objectives/endpoints are for the 24-week DB treatment period of the study:	
To evaluate the effect of benralizumab on corticosteroid use	Proportion of patients who require an increase in corticosteroid dose from baseline at any point in the DB treatment period
To evaluate the effect of benralizumab on health status/HRQoL measures	HRQoL (36-Item Short Form Health Survey Version 2 [SF-36v2]), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC)
To evaluate the pharmacokinetics and immunogenicity of benralizumab in patients with HES	Serum benralizumab concentrations Anti-benralizumab antibodies and nAbs
Safety Objective:	**Endpoint/Variable:**
To evaluate the safety and tolerability of benralizumab in patients with HES	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
Exploratory Objectives:	**Endpoint/Variable:**
To evaluate the effect of benralizumab on health-care resource utilisation due to HES	Number of HES-related hospitalisations; length of hospital stay; Intensive care unit days; number of HES-related emergency room visits; number of HES-related outpatient visits (by type); number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on HES-related hospitalisation	Proportion of HES worsening/flare resulting in hospitalisation

Table 1	**Study objectives - double-blind treatment period**
The following objectives/endpoints are for the 24-week DB treatment period of the study:	
To evaluate the effect of benralizumab on patient-reported measure of HES symptom severity	HES symptom questionnaire
To characterise the patient-reported experience and treatment benefits of benralizumab through patient interviews [e]	Patient qualitative interview to characterise patient-reported experience and treatment benefits (sub-study)
To evaluate the effect of benralizumab on CRP	CRP levels
To evaluate the effect of benralizumab on biomarkers related to the mechanism of action of benralizumab, eosinophilic inflammation, and HES disease pathogenesis, as well as HES clinical subtypes and baseline predictors of response to benralizumab [e]	Exploratory biomarkers in: • Serum • Plasma • Urine • Whole blood (including mechanistic sub-study) • Tissue biopsies
To assess effect of lymphocyte phenotype on responsiveness to benralizumab [e]	Whole blood lymphocyte phenotyping

a HES worsening/flare: see Section 3.2
b The population and intercurrent event strategy also apply to the secondary endpoints.
c Key secondary endpoint (multiplicity protected Section 4.1.1)
d Haematologic relapse post-baseline: AEC ≥1,000 cells/μL; baseline is the randomisation AEC
e Results will be reported outside of the Clinical Study Report. Available select exploratory biomarker data may be included in the primary CSR.

Table 2 Study objectives - open-label extension treatment period

The following objectives/endpoints are for the OLE treatment period of the study:	
Objectives:	**Endpoint/Variable:**
To evaluate the effect of benralizumab on the proportion of patients who experience a HES worsening/flare [a]	Proportion of patients who experience HES worsening/flare [b]
To evaluate the effect of benralizumab on the number of HES worsenings/flares [a]	Annualised rate of HES worsening/flare [b]
To evaluate the effect of benralizumab on patient reported measure of fatigue [c]	Fatigue (PROMIS Fatigue Short Form 7a)
To evaluate the effect of benralizumab on HRQoL [c]	HRQoL (SF-36v2)
To evaluate the safety and tolerability of benralizumab in patients with HES [a]	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory assessments Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To evaluate the PK and immunogenicity of benralizumab in patients with HES [a]	Serum benralizumab concentrations Anti-benralizumab antibodies and nAb
To evaluate the effect of benralizumab on healthcare resource utilisation due to HES [c]	Number of HES-related hospitalisations; Length of hospital stay; ICU days; Number of HES-related ER visits; Number of HES-related outpatient visits (by type); Number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on patient reported measure of HES symptom severity [c]	HES symptom questionnaire
To evaluate the effect of benralizumab on CRP [a]	CRP levels

Table 2 Study objectives - open-label extension treatment period

The following objectives/endpoints are for the OLE treatment period of the study:	
To evaluate the effect of benralizumab on biomarkers related to the MoA of benralizumab, eosinophilic inflammation, and HES disease pathogenesis [c]	Exploratory biomarkers in: • Serum • Plasma • Urine • Tissue biopsies
To better characterise the early onset of eosinophils depletion to support extrapolation to build a relationship between adults, adolescents, and younger patients	PK: Benralizumab concentrations PD: Eosinophil counts

a. Applicable to full duration of OLE
b. HES worsening/flare: see in section 3.2
c. Applicable to 1st year of OLE only
d. Only OLE safety data will be included in the primary analysis Clinical Study Report. Other OLE objectives will be assessed in a later report.

1.2 Study Design

This is a randomised, double-blind, parallel-group, multicentre, placebo-controlled 24-week Phase 3 study to compare the efficacy and safety of benralizumab 30 mg versus placebo administered by subcutaneous injection every 4 weeks in patients with symptomatic HES.

The target patient population is male and female patients 12 years of age and older with active HES (AEC ≥1000 cells/μL at Visit 1) who have been on stable HES therapy for at least 4 weeks prior to Visit 1. Eligible patients must have either signs/symptoms of HES worsening/flare at visit 1, OR a documented history of 2 or more HES worsenings/flares within 12 months prior to visit 1 that require an escalation in therapy. Eligible patients must also be negative for the FIP1L1-PDGFRA fusion tyrosine kinase gene translocation. Potential eligible patients will enter a 3-day screening period and will be required to have AEC ≥ 1000 cells/μL at local laboratory testing to proceed to the second day of the screening period. Patients will be assessed for corticosteroid responsiveness (defined as an AEC < 1000 cells/μL after 2 days of oral corticosteroids [OCS] [prednisone/prednisolone] 1 mg/kg/day given on top of the patient's background therapy for HES) prior to randomisation. Patients who are not corticosteroid responsive or fail any other eligibility criteria will be screen failed.

All patients will remain on stable background HES therapy during screening and throughout 36 weeks of treatment (until Visit 12 [Week 36] of OLE when the therapy can be adjusted). During this time, background HES therapy may only be modified if a patient has HES clinical

worsening/flare or an AE thought to be due to background medication. The Sponsor, sites, and patients will be blinded to the absolute eosinophil, basophil, and monocyte counts, differential blood counts (percentages) for all white blood cells (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) and biopsy cell counts (if applicable) after randomisation/baseline (Week 0/Visit 3), during the entire the DB treatment period, and for the first 4 weeks of the OLE treatment period (until Week 28 [Visit 10] after which no blinding to WBC counts or biopsy cell counts is required). After the primary DBL, AstraZeneca will become unblinded to all patients' blood and biopsy cell counts obtained during DB treatment period.

The final dose of the DB treatment period will be given at Week 20 and the DB treatment period will complete at Week 24.

All patients who complete the 24-week DB treatment period on IP may be eligible to continue into an OLE treatment period on benralizumab (30 mg SC Q4W). The OLE is intended to allow treatment with open-label benralizumab for at least 1 year for adults and at least 2 years for adolescents after completion of the DB treatment period (earlier enrolled patients may therefore be in the OLE for longer than 1 year). AstraZeneca may choose to extend the study depending on the overall development program; AstraZeneca reserves the right of terminating the OLE early (eg, if development of the asset is terminated or marketing authorisation is obtained).

The primary database lock (DBL) will occur when approximately 38 patients have had their first HES worsening/flare during the DB treatment period, and all randomised patients have had the opportunity to be followed up for the 24 week DB treatment period. This means that all randomised patients will either have had their week 24 visit (regardless of whether they remain on IP) or have withdrawn from the study prior to week 24. . The study will remain blinded until the primary DBL. The primary analysis will focus on data from the DB treatment period of the study. All randomised patients will complete the 24-week DB treatment period before considering entering the OLE treatment period. The final DBL will occur after the last patient completes the OLE. Data from the OLE treatment period of the study will be presented in an addendum to the primary analysis CSR and/or a separate OLE treatment period CSR.

1.3 Number of patients

Approximately 120 patients are expected to be randomised at a 1:1 ratio to receive benralizumab or matching placebo; however, randomisation may continue until the target number of events is achieved. The primary analysis will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period. The number of events calculated is based on a log-rank test of survival. Based on

this, 38 first HES worsening/flare events during the DB period are required to detect a statistically significant difference between treatment groups at the 2-sided 5% significance level with 82% power if the true treatment effect is a hazard ratio of 0.389 (equivalent to 30% of patients on benralizumab experiencing an event by the end of the DB period compared to 60% of patients on placebo assuming exponential survival). An anticipated dropout rate of 5% of patients withdrawing from the study without having flared was factored into the calculation of number of patients needed to be randomized in order to observe 38 flares.

2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

The Full Analysis Set (FAS) will include all patients who are randomised and receive at least 1 dose of IP, 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 Intent-To-Treat (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. Demographic, baseline characteristics, prior medication, concomitant medication and study treatment compliance will be presented using FAS.

2.1.2 All randomised patients (ITT) analysis set

The all-randomised patients analysis set will include all patients who are randomised, irrespective of whether they go on to receive doses of IP and 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 Intent-To-Treat (ITT) principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. The all randomised patients analysis set will be used for a sensitivity analysis of the proportion of patients flaring endpoint.

2.1.3 Safety analysis set

The Safety Analysis Set will include all patients who receive at least 1 dose of IP. Erroneously treated patients during the DB period (e.g., those randomised to benralizumab but actually given placebo) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received active IP (benralizumab) is classified as active (benralizumab).

For OLE period, patients will be reported in their randomized treatment groups in DB treatment period. All safety summaries and anti-drug antibodies (ADA) analyses will be based on Safety Analysis Set.

2.1.4 Pharmacokinetic analysis set

The PK analysis set will include all patients who receive at least 1 dose of 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. All PK summaries will be based on this analysis set.

2.1.5 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 benralizumab 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. There is no intention to perform a per protocol analysis in this study.

2.2.1 Important protocol deviations

Important protocol deviations 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.

The final list of important protocol deviations will be documented prior to unblinding the study based on the separate study specific Protocol Deviation list. Deviations under the following categories, which are defined in the protocol deviation list with further detail including which are key inclusion and exclusion criteria, will be reviewed and a determination of their importance will be made in line with the criteria outlined above (potential impact on accuracy and reliability of study data, patients rights, safety or well-being):

- Deviations from informed consent procedures
- Deviations from study conduct / procedures, including:
  - Eligibility criteria not met – deviations from key inclusion or exclusion criteria
  - Study Assessments not performed or incorrectly performed
  - Deviations from study restrictions / withdrawal criteria including use of prohibited / restricted concomitant medication, and changes of background medication in DB period prior to first HES worsening/flare (unless allowed by the protocol)

  - Dose formulation / dose administration deviations
- Deviations related to investigational product handling / storage
- Deviations related to safety reporting and follow-up
- Other potentially important deviations, including:
  - Other severe non-compliance to the study protocol
  - Unblinding of subjects treatment assignment for reasons unrelated to patient safety

Only important protocol deviations will be summarized and listed in the CSR. Potential important protocol deviations, both programmable or observable, will be reviewed quarterly at a minimum and at the time of blinded data reviews.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General principles

3.1.1 The definition of baseline

In general, the last valid value on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints while the last valid value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints.

If there is no value prior to randomisation (or the first dose of IP, depending on the endpoint), then the baseline value will not be imputed and will be set to missing. No safety data known to be collected post first dose will be used in determining the baseline value, unless otherwise specified.

Additional analyses for the patients who switch from placebo to benralizumab at Week 24 (Visit 9) may be performed where the baseline value is set to the last recorded value prior to starting open-label benralizumab to obtain an assessment of the changes occurring while actually receiving benralizumab.

3.1.2 Visit window definitions

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 have been 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 general adjusted analysis-defined visit windows for assessments conducted every 4 weeks are summarised in the Table 3 below.

Table 3 Windows for assessments conducted every 4 weeks		
Analysis-Defined Windows Visit	**Scheduled Study Day**	**Maximum Windows**
Week 0 (Day 1)	1	-3 ≤ Study Days ≤ 1
Week X	X*7+1=a	(a-(a - b)/2)≤ Study Days≤ ((c-a)/2+a)-1 Except for X=4 where window is 2≤ Study Days≤ ((c-a)/2+a)-1

a is the scheduled study day for Week X.
b is the scheduled study day corresponding to the preceding scheduled assessment of Week X.
c is the scheduled study day corresponding to the next scheduled assessment of Week X.
*Knowing that b=a-4*7 days and c= a+4*7 days.*
For efficacy assessments on or after randomization, study day will be defined as follows: (Date of assessment – date of randomisation) +1
For safety assessments on or after randomization, study day will be defined as follows: (Date of assessment – date of first dose) +1
For assessments prior to randomization, study day will be defined as: (Date of assessment – date of randomisation)
By these definitions the day of randomization will be study day 1 and the day before the day of randomization will be study day -1. There is no study day 0.

For assessments conducted not on 4-weekly basis, the window for the visits following baseline will be constructed as shown in Table 4.

Table 4 General windows for non-4-week assessments		
Analysis-Defined Windows Visit	**Scheduled Study Day**	**Maximum Windows**
Week 0 Day 1	1	Study Day≤1
Week X	X*7+1=a	2≤ Study Days≤ ((b-a)/2+a)-1
Week Y	Y*7+1=b	((b-a)/2+a)≤ Study Days≤ ((c-b)/2+b)-1
Week Z	Z*7+1=c	((c-b)/2+b≤ Study Days

For efficacy assessments on or after randomization, study day will be defined as follows: (Date of assessment – Date of randomization + 1)
For safety assessments on or after randomization, study day will be defined as follows:(Date of assessment – Date of first dose+ 1)
If (b-a) or (c-b) is odd number, then use (b-a+1) or (c-b+1), respectively.

For each analysis parameter, the windowing will be based on the protocol-specified schedule of events as defined in Section 1.3 of the CSP. The windowing will only be performed for assessments within the appropriate periods e.g., double blind versus open label extension, where the definition of the DB period is as outlined in section 3.1.3.

If multiple assessments are recorded within a single adjusted visit window, please refer to the rules below.

- 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.

Flare visit data will also be windowed and will be used for analysis if there is no other visit data that can be used for that windowed visit. If both flare visit and a scheduled visit fall under same visit window or have same day under the visit window, irrespective of timing, non-flare visit should be selected for analysis.

For analyses not based on any particular study visit, all data will be listed and/or analysed, including any repeated or unscheduled visits, unless otherwise specified. For safety endpoints, all post-baseline results will be included in the analysis up to and including the IPD/EOT visits. For efficacy endpoints, the post-baseline treatment period will be included up to and including the end of treatment (EOT) visit.

For the patient-report questionnaires/surveys collected by electronic clinical outcomes assessments (eCOA), data for all eCOA assessments will be analysed up to the study completion or study discontinuation date. In the event data is captured in the eCOA 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.

3.1.3 Study periods for data summary

The following study periods will be derived for reporting purposes:

- DB treatment period:
    - Efficacy: this is defined as the period starting from the date of randomization until the earliest of the date of the first dose of open label benralizumab, study day 183, the date of last contact, and data cut-off date inclusive.
    - Safety: this is defined as the period starting from the date of the first dose of IP until the day **before** the first dose of open-label benralizumab inclusive for patients who roll over to the OLE, or up to the day of the scheduled IPD visit for patients who do not roll over to the OLE, or last contact date for patients who exit the study, or data cut-off date .

- OLE treatment period:

Efficacy/Safety: this is defined as the period starting from the date of first administration of open-label benralizumab until the IPD or EOT visit or the data cut-off date for ongoing patients.

3.1.4 Definition of prior/concomitant medications

A medication will be classified as:

- **Prior**: if it was stopped on or before the date of randomisation (medication stop date ≤ date of randomisation).
- **Background HES therapy at baseline:** background HES therapy collected in the eCRF started on or prior to randomization and ongoing after randomization.
- **Concomitant**: if the start date is on or after the date of randomisation, or if it started prior to the date of randomisation and was ongoing after the date of randomisation. If a medication started and stopped on the date of randomization, it will be considered as concomitant.

Note: Medications with start date after the end of the study periods (as defined in Section 3.1.3) will not be considered as concomitant for that period.

3.1.5 Derivation for response variables

Patients will be classified as responders or non-responders based on the specified criteria under each efficacy endpoint where applicable.

3.1.6 Data cut-off

The data cut-off for the primary analysis will occur when approximately 38 patients have had their first HES worsening/flare during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24 week double-blind period. Any data entered after the data cut-off may be programmatically cut from the raw datasets at the primary analysis, to ensure all data included is cleaned appropriately and patients' status at the primary analysis data cut-off is accurately captured in the analyses.

3.2 Primary efficacy variables

The time to first HES worsening/flare is the primary endpoint of the DB treatment period.

An HES worsening/flare is defined as HES clinical manifestations or laboratory abnormalities that result in:

a. an increase/burst of OCS equivalent to ≥10 mg/day of prednisone/prednisolone for at least 2 days, OR

b. an increase or addition of new cytotoxic and/or immunosuppressive therapy increase, OR

c. hospitalisation.

The time to first HES worsening/flare in the DB period is calculated as: start date of HES worsening/flare during the DB period - date of randomisation + 1.

The start date of HES worsening/flare is defined as the first day of increased dose/burst of OCS, first day of any increase or addition of new cytotoxic and/or immunosuppressive therapy, or date of hospital admission, whichever occurs earlier.

The time to first HES worsening/flare for patients who do not experience a flare during the DB treatment period will be censored at the end of the DB period as defined in section 3.1.3. Alternative censoring mechanisms may be explored as sensitivity analyses (see section 4.2.6.2).

3.3 Secondary efficacy variables

3.3.1 Proportion of patients who experience HES worsening/flare during the DB period (Key secondary endpoint)

The definition of a HES worsening/flare is outlined in section 3.2 Primary efficacy variables. For the analysis of this endpoint, patients who withdraw from the double-blind period early (i.e. patients who do not complete the double-blind period) without having flared will be considered as a flare event. The proportion of patients who experience a HES worsening/flare or withdrawal from the study over the DB treatment period is defined as the number of patients who have a first HES worsening/flare or withdraw prior to completing the DB period divided by the number of patients in the analysis set of interest.

3.3.2 Number of HES worsening/flare events (rate/year) during the DB period (Key secondary endpoint)

The definition of a HES worsening/flare is outlined in section 3.2. The number of times a patient has a HES worsening/flare during the DB period will be counted.

To be considered as a separate HES worsening/flare, the start date of a HES worsening/flare must be at least 14 days after the stop date of the preceding HES worsening/flare. A HES worsening/flare that occurs within 14 days after the stop date of the preceding HES worsening/flare will be combined and counted as a single event.

Maximum follow-up time for calculation of the annualised flare rate is approximately 24 weeks, and is defined as the length of follow-up in the double-blind period as defined by the DB period duration in section 3.1.3. If a flare is ongoing at this date, the flare will be counted in the calculation of annual flare rate but the maximum follow-up time will still be truncated at the date described.

For the production of summary statistics, the annual flare rate in each treatment group will be calculated using:

*Annual flare rate = 365.25 * total number of flares / total duration of follow-up within the treatment group (days).*

3.3.3 Time to first haematologic relapse during the DB period (Key secondary endpoint)

A first haematologic relapse is declared when Absolute Eosinophil Count (AEC) from central laboratory assessments post baseline is greater than or equal to 1,000 cells/μL for the first time during the double-blind period. For this endpoint an assessment of ≥1,000 cells/μL from either of the central laboratory's used to assess eosinophil counts (either the Advia instrument from the LabCorp laboratory, or the Beckman instrument from the Q2 laboratory) can be used to indicate a haematologic relapse event. i.e. if the highest result across the 2 laboratory values is ≥1,000 cells/μL a haematologic relapse event will be counted.

The time to first haematologic relapse is calculated as: start date of relapse - date of randomisation + 1.

Patients who do not experience a haematologic relapse during the DB treatment period will be censored as described in section 3.2.

3.3.4 Improvement in fatigue (PROMIS Fatigue Short Form 7a) (Key secondary endpoint)

The PROMIS Fatigue Short Form (SF) 7a (7-day recall) consists of 7 questions designed to assess the severity of the patient's fatigue-related symptoms and the impact of the symptoms on daily activities over the prior 7 days. The responses to each question are based on a 5-point Likert scale ranging from 1 to 5. A standardized T-score is obtained by rescaling the raw total score into a standardized score using the score conversion table (table 5), with a mean of 50 and a standard deviation of 10.

Table 5 PROMIS Fatigue Short Form Score Conversion Table

Fatigue 7a - Adult v1.0 Short Form Conversion Table		
Raw Score	T-score	SE
7	29.4	5.3
8	33.4	4.8
9	36.9	4.3
10	39.6	4.0
11	41.9	3.8
12	43.9	3.5

13	45.8	3.3
14	47.6	3.2
15	49.2	3.1
16	50.8	3.0
17	52.2	3.0
18	53.7	3.0
19	55.1	3.0
20	56.4	2.9
21	57.8	2.9
22	59.2	2.9
23	60.6	2.9
24	62.0	2.9
25	63.4	2.9
26	64.8	2.9
27	66.3	2.9
28	67.8	2.9
29	69.4	2.9
30	71.1	3.0
31	72.9	3.0
32	74.8	3.1
33	77.1	3.3
34	79.8	3.6
35	83.2	4.1

3.3.5 Proportion of patients who have a hematologic relapse during the DB period

The definition of a haematologic relapse is outlined in section 3.3.3. For the analysis of this endpoint, patients who withdraw from the double-blind period early (i.e. patients who do not complete the double-blind period) without having a haematologic relapse, will be considered as a haematologic relapse event. The proportion of patients who experience a haematologic relapse during the DB treatment period will be defined as the number of patients who have a first haematological relapse in the DB period divided by the number of patients in the analysis set.

3.3.6 Proportion of patients who have AEC<500 cells/µL for 24 weeks

Patients who have AEC<500 cells/µL, from all of their available central laboratory eosinophil results (the Advia instrument from the LabCorp laboratory, and the Beckman instrument from the Q2 laboratory), for the 24-week DB treatment period (i.e. from the first post baseline assessment at week 4 onwards) will be considered as maintaining remission throughout the DB

treatment period. All AEC assessments including repeated, scheduled/unscheduled and flare visits during DB treatment period are to be taken into account. Proportion of patients who maintain remission will be defined as the number of patients who maintained AEC<500 cells/μL divided by the number of patients in the analysis set. If a patient has more than 1 visit window with a missing AEC assessment, including patients with missing assessments due to withdrawing from the study, then they will be considered as not achieving maintenance of AEC<500 cells/μL.

3.3.7 Proportion of patients who require an increase in corticosteroid dose from baseline during the DB period

A patient who requires an increase from their baseline corticosteroid dose of any amount at any point during the DB treatment period will be assigned a value of 1 for corticosteroid increase and 0 if no increase has occurred at any point. This would include increasing dose of systemic OCS for patients already on systemic OCS or starting any Systemic Corticosteroids (SCS). Medical review of increased OCS or initiation of SCS will happen prior to unblinding to confirm that the change in medication to be included in this analysis was for the disease under study or for another condition with symptoms that are closely related to the patient's HES. Further details of this review will be documented in a separate background medication review plan, which will be finalised prior to database lock including a record of final classifications for any patients requiring medical judgement to define whether they are included as events in this analysis. Proportion of patients who require an increase in corticosteroid dose from baseline at any point in the DB treatment period will be calculated as the number of patients who required an increase in the DB period divided by the number of patients in the analysis set.

The number of times a patient requires a corticosteroid increase/burst will be counted. To be considered a separate incidence of corticosteroid increase/burst, the start date of the increase/burst must be at least 14 days after the start date of the previous increase/burst.

Systemic corticosteroid dose will be converted to prednisone equivalent dose (corticosteroid dose/(conversion factor/10)) using the conversion factors in table 6.

Cumulative oral corticosteroid dose given over the double-blind period will be calculated using the cumulative prednisone equivalent dose from baseline to 24 weeks. All patients will be included, including those who did not take corticosteroid at baseline and/or during the study (with a cumulative dose of 0 mg).

The oral corticosteroids will be selected from the concomitant medications received during the study (see definition of concomitance in section 3.1.4).

Table 6 Conversion of Total Corticosteroid to Prednisone Equivalent

Systemic Corticosteroid (SCS)	Approximate equivalence dose (mg)
Prednisone	10
Prednisolone	10

Cortisone	50
Hydrocortisone	40
Methylprednisolone	8
Triamcinolone	8
Betamethasone	1.2
Budesonide	2.25
Dexamethasone	1.5
Deflazacort	12

3.3.8 Improvement in HRQoL

The SF-36v2 (acute recall) is a 36-item, self-report survey of functional health and well-being, with a 1-week recall period (QualityMetric 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 (QualityMetric 2011). A patient will be classified as a responder if the change from baseline ≥ threshold, or a non-responder if change from baseline < threshold. If data are missing, then the patient will be classified as a non-responder.

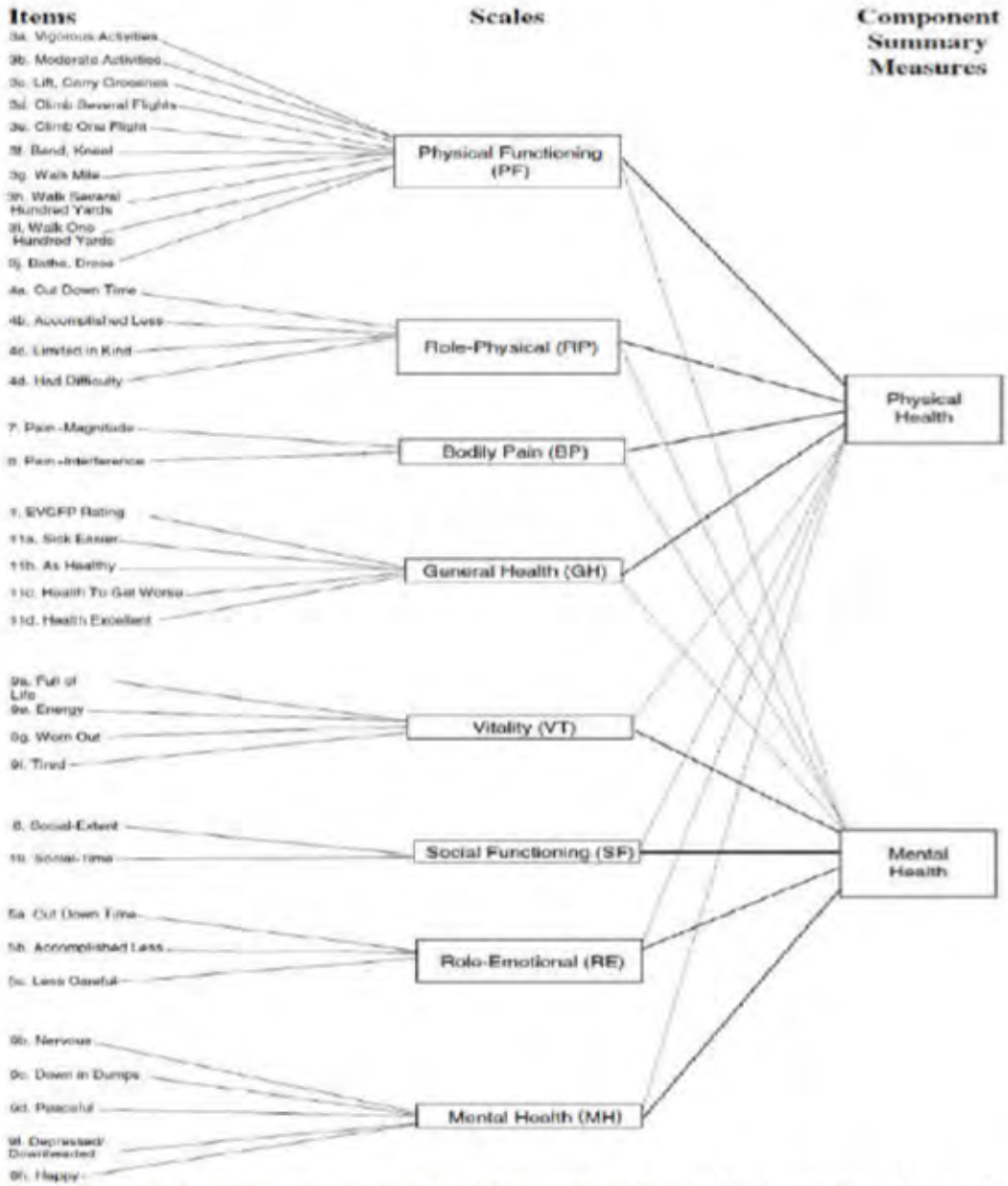
Table 7 Threshold values for the SF-36v2 scale and summary measures

BP Bodily Pain; GH General Health Perceptions; MCS Mental Health Summary; MH Mental Health; PCS Physical Component Summary;

	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

PF Physical Functioning; RE Role Limitations due to Emotional Problems; RP Role Limitations due to Physical Health; SF Social Functioning; VT Vitality.

Figure 1 The 35 questions for the 8-domain scores and physical & mental health component summary scores (PCS and MCS)



Note. All health domain scales contribute to the scoring of both the Physical and Mental Component Summary measures. Scales contributing most to the scoring of the summary measures are indicated by a connecting solid line (—). Scales contributing to the scoring of the summary measures to a lesser degree are indicated by a dotted line (·····).

3.3.9 Improvement in 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 over the past week of the assessment using a 6-point categorical response scale (0='no symptoms' to 5='very severe symptoms').

The PGIC is a single item assessment to evaluate the patient's perception of change in health status. 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 categorised according to the following improvement categories at post-baseline:

a. A little better, moderately better, much better → 'A little better'

b. Moderately better, much better → 'Moderately better'

c. Much better → 'Much better'

3.3.10 Pharmacokinetic variables

Blood samples for pharmacokinetic assessments will be collected from all patients. The baseline sample will be collected prior to first IP administration. Serum concentrations for benralizumab treated patients will be determined using a validated electrochemiluminescent (ECL) immunoassay.

The drug concentration levels will be summarised using descriptive statistics at each visit for patients in the benralizumab treatment group. Results below the lower limit of quantification (BLQ) will be set to LLOQ/2 for analysis and will be listed as <LLOQ

The following cases will be excluded from the PK analyses:

a. Benralizumab patients with all collected plasma concentration levels persistently below the lower limit of quantification (LLOQ=7.72 ng/mL) throughout the DB treatment period.
b. Timepoints from benralizumab patients where the collected plasma concentration is in excess of what is considered to be physiologically possible with dosing: ≥12,000 ng/mL for the benralizumab treatment group (only the timepoints with a result not physiologically possible will be excluded).

3.3.11 Immunogenicity variables

Anti-drug antibodies (ADA) variables, such as ADA responses, will be generated and analysed as per the details in Appendix 8.2.

3.4 Exploratory efficacy variables

3.4.1 Healthcare resource utilisation due to HES

HES related healthcare 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/times the following resources were utilised through Week 24 of the DB treatment period will be presented for each patient

a. Hospitalisations, general care (number of times and days in general care)
b. Hospitalisations, intensive care (number of times and days in intensive care)
c. Emergency room visits
d. Outpatient visits (by type)
e. Type of procedures/tests

3.4.2 HES worsening/flare resulting in hospitalisation

A HES worsening/flare resulting in hospitalisation is defined as HES clinical manifestations or laboratory abnormalities indicative of HES worsening/flare that results in hospitalisation.

3.4.3 Patient reported experience and treatment benefits

Up to 40 adult patients will be invited to participate in a concept elicitation interview to characterise their experience during the DB treatment period of the study. The interview will be non-interventional and will collect data on HRQoL and patients' experiences with the study treatment.

Each participating patient will be interviewed once 7 to 21 days after Visit 8 (or after the IPD visit within the DB treatment period of the study). Interviews will be coded and analysed for themes and patterns.

The results will be presented in a separate report outside of the CSR.

3.4.4 Exploratory biomarkers in serum, plasma, whole blood and urine

Serum, whole blood and urine samples will be analysed centrally in order to evaluate the effect of benralizumab on biomarkers of eosinophilic inflammation and other inflammatory biomarkers. The focus will be on eosinophil recruitment and activation and HES immunological mechanisms. Other biomarkers may be investigated including C-reactive protein.

Absolute levels and changes from baseline (absolute change and % change) will be derived for exploratory biomarkers (including biomarkers of eosinophilic inflammation) at baseline and post baseline visits. Eosinophil related summaries will be produced for each central laboratory

assessments used to assess blood eosinophil levels separately (LabCorp Advia instrument, and Q2 Beckman instrument, see section 4.2.12 for details).

3.4.5 Peripheral blood lymphocyte phenotyping

Whole blood for flow cytometry will be collected at baseline (Visit 1). A descriptive summary will be provided at this visit to determine whether a patient has a specific HES subtype. This data will be presented in a separate report outside of the CSR.

3.4.6 Biopsy

Tissue biopsy samples may be collected at screening, at Visit 6 and at a HES worsening/flare visit at the discretion of the Investigator to aid in the identification and treatment of a HES worsening/flare. Immunohistochemistry analysis of these samples will be reported outside the CSR.

3.5 Safety outcome variables

The following safety data will be collected: reported AEs (including serious adverse events (SAEs) and adverse events leading to discontinuation of IP (DAEs)), clinical laboratory, HES physical examination performed, vital signs, ECG and spirometry.

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 summarized 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 Appendix 8.1. Duration of AEs and prior/concomitant medications will not be calculated using imputed dates and will instead be set to missing.

3.5.1 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:

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

Treatment emergent adverse event (TEAE) data will be categorized according to their onset date into the following study periods:

a. On-study AEs in the DB period are defined as those with onset date on or after day of first dose of study DB treatment up to the day prior to the first dose of open-label benralizumab inclusive for patients who roll over to the OLE, or up to the day of the scheduled IPD/EOT visit for patients who do not roll over to the OLE, or last contact date for patients who exit the study, or data cut-off date if patient has not had the opportunity to reach the OLE.
b. On-study 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.

Pre-treatment (prior) adverse events(AEs occurring during screening) are defined as those with a date of onset $\geq$ 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 on-treatment 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 on-treatment AE.

Adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

3.5.2 Laboratory variables

In summaries, figures, and listings, lab results and normal ranges will be presented in the International System (SI) unit using the primary (LabCorp) central laboratory results. Eosinophil data will be presented in both SI and conventional units (cells/µL) in summaries.

For the purposes of clinical chemistry and hematology shift tables, baseline will be defined as the last available non-missing assessment prior to first dose of randomized treatment.

Changes in haematology 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 central lab reference range and classified as low (below range), normal (within range or on limits) or high (above range). All absolute values falling outside the reference ranges will be flagged. The maximum or minimum value post-

baseline will be calculated over the entire DB treatment period for all patients and during the OLE period for the patients who are included in the OLE period.

For the liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT) and total bilirubin (TBL), the multiple of the central laboratory upper limit of normal (ULN) range will be calculated for each data point. Multiple=Value/ULN, ie, if the ALT value was 72IU/L (ULN 36 IU/L) then the multiple would be 2.

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

- AST ≥3×ULN
- ALT ≥3×ULN
- TBL ≥2×ULN

For patients with documented HES with liver manifestations, AST and ALT will be flagged at ≥5×ULN.

3.5.3 HES physical examination

Physical examination will be performed as defined in the CSP and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems. Any new finding(s) or worsening abnormalities may qualify as AEs.

3.5.4 Vital signs

Pre-dose vital signs (eg pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature) will be obtained in accordance with the schedule provided in the CSP. Changes in vital signs variables between baseline and each subsequent scheduled 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.

Absolute values will be compared to the reference ranges listed in Table 8 and classified as low (below lower limit), normal (within lower limit and upper limit, inclusive) or high (above upper limit). All values falling outside the reference ranges will be flagged.

Table 8 Vital signs reference ranges

Parameter	Standard Unit	Lower Limit	Upper Limit
Diastolic Blood Pressure	mmHg	60	120
Systolic Blood Pressure	mmHg	90	160

Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38

3.5.5 Electrocardiograms

ECG measurements will be recorded in accordance with the CSP.

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.

3.5.6 Spirometry

Forced expiratory volume (FEV_1) and forced vital capacity (FVC) measurements will be recorded for patients with pulmonary involvement in accordance with the CSP, with the baseline visit being defined as the last available non-missing measurement at Visit 1. Changes in FEV_1 and FVC variables between baseline and each subsequent scheduled assessment (V9) will be calculated. There will be no imputation for missing values.

4 ANALYSIS METHODS

4.1 General principles

This SAP focuses on the DB study period which will be the focus of the primary analysis, with a high-level description of the descriptive analysis for the OLE analyses. If required, additional detail regarding descriptive analyses in the OLE will be provided in a separate OLE addendum to this SAP. At the primary analysis, top level exposure and AE data from the OLE period will be summarised, OLE efficacy data will be analysed at a subsequent data cut-off when sufficient follow-up of patients in the OLE is reached.

The analysis of the primary and secondary efficacy, and safety endpoints will include all data captured during the 24-week DB period, as defined in section 3.1.3. Efficacy endpoints will be analysed using the full analysis set (FAS) and patients will be analysed according to their randomised treatment. This includes data regardless of whether IP was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, or change in background medications, unless the patient withdraws consent to study participation, where only data collected until withdrawal of consent will be collected and included in analyses. The statistical analyses will compare benralizumab to placebo. The analysis of safety endpoints will be based on the safety analysis set. Analysis sets are defined in Section 2.1.

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.

The primary efficacy estimand, whereby all data up to Week 24 is included, regardless of whether a patient remains on blinded study treatment or not will apply to the analysis of the primary and key secondary endpoints in the DB period. A similar approach will be used for other secondary endpoints. Details regarding primary and key secondary estimands are provided in Table 9.

Table 9 Primary and key secondary efficacy and main safety estimands (DB period)

Statistical Category	Estimand			Section
	Endpoint (Population)	**Intercurrent Event Strategy**	**Population Level Summary (Analysis)**	
Primary Objective: To evaluate the effect of benralizumab on the time to first HES worsening/flare				
Primary/MCP	Time to first HES worsening/flare (FAS)	Treatment Policy Strategy – include DB period data in analysis regardless of the occurrence of intercurrent event. Intercurrent events include: • Increase in background medication (below flare definition) • Treatment discontinuation • Use of prohibited medication	Hazard ratio (Log-rank test and Cox-proportional hazards Model)	4.2.6.1
Key Secondary Objective: To evaluate the effect of benralizumab on the time to first haematological relapse				
Secondary/MCP	1. Proportion of patients with a HES worsening/flare (FAS) 2. Number of HES worsenings/flares (FAS) 3. Time to first haematologic relapse (FAS) 4. CFB in PROMIS fatigue 7a at week 24 (FAS)	Treatment Policy Strategy – include DB period data in analysis regardless of the occurrence of intercurrent event. Intercurrent events include: • Increase in background medication (below flare definition) • Treatment discontinuation • Use of prohibited medication • Key secondaries (3,4) –	1. Odds ratio and proportion difference (CMH test) 2. Rate ratio (Negative binomial model) 3. Hazard ratio (Log-rank test and Cox-proportional hazards Model) 4. Mean difference in CFB between groups (repeated measures ANCOVA analysis)	4.2.7.1 4.2.7.2 4.2.7.3 4.2.7.4

		Increase in background medication (meeting flare definition)		
Safety Objective: To evaluate the safety and tolerability of benralizumab in patients with HES				
Safety	- Presence of TEAEs through V9 (Safety) - Presence of serious TEAEs through V9 (Safety) - Laboratory and vital signs values through V9 (Safety)	Treatment Policy Strategy – include data in analyses regardless of the occurrence of intercurrent event. Intercurrent events: • Treatment discontinuation	Descriptive summaries	4.2.10.1

MCP = multiple comparisons procedure; DB = double-blind; CFB = Change from baseline; CMH = Cochran-Maentel-Haenszel; LSMD = least squares mean difference; ANCOVA = analysis of covariance

Summary data will be presented in tabular format by treatment. Categorical data will be summarised by the number and percentage of patients in each category. Continuous data will be summarised by descriptive statistics including N, mean, SD, median, quartiles and range. Data listings will be sorted by treatment and patient number.

All hypothesis testing will be reported using 2-sided tests. P-values will be rounded to 4 decimal places. The 95% confidence interval (CI) will be reported for efficacy endpoints as appropriate.

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.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC) and will be developed and validated according to relevant SOPs. Pharmacokinetic analyses will be performed using an appropriate software.

4.1.1 Testing strategy to account for multiplicity considerations

To account for multiplicity for the primary endpoint (time to first HES worsening/flare) and key secondary endpoints, a hierarchical fixed-sequence testing strategy (in the order listed in the objectives) will be used to control the overall Type-I error rate at the 0.05 level.

The primary endpoint will be tested at a 2-sided 0.05 significance level.

1. If the null hypothesis, that there is no difference in time to first HES worsening/flare between treatment groups, can be rejected with a p-value<0.05, and time to HES worsening/flare is longer in the benralizumab arm compared to placebo, hierarchical fixed sequence testing will continue for the key secondary endpoints at the 2-sided 0.05 level in the following order:
    - Proportion of patients who experience a HEs worsening/flare during the DB period
    - Number of HES worsening / flares during the DB period
    - Time to first haematologic relapse during the DB period
    - Change from baseline in PROMIS fatigue short form 7a score at week 24
2. If at any time the null hypothesis cannot be rejected at the 2-sided 0.05 level, or if the treatment difference favours the placebo group compared to the benralizumab arm, further testing for the key secondary endpoints will stop, and no subsequent null hypothesis will be rejected.

The analyses of the OLE period will not be multiplicity protected.

4.2 Analysis methods

4.2.1 Patient disposition

The total number of patients will be summarized for patients who enrolled, who were not randomized (and reason). The number and percentage of patients within each treatment group will be presented by the following categories; randomized, randomized in error, received treatment with IP, did not receive treatment with IP (and reason), completed treatment with IP in DB treatment period, discontinued treatment with IP in DB treatment period (and reason), discontinued treatment with IP but completed DB treatment period (and reason), completed DB treatment period, and withdrawn from DB treatment period (and reason).

The number and percentage of patients within each treatment group will be presented by the following categories: enrolled in OLE treatment period, did not enrol in OLE treatment period (and reason), completed1 year of OLE treatment period, withdrawn from 1-year of OLE treatment period (and reason), entered 2-year of OLE treatment period, completed 2-year of OLE treatment period, withdrawn from 2-year of OLE treatment period (and reason), entered 3-year of OLE treatment period, withdrawn from 3-year and above of OLE treatment period (and reason).

DB treatment period completers are defined as patients who go through Visit 1 until Visit 9 (Week 24).

Patients who receive at least one open label IP administration on or after Visit 9 are considered entered in OLE.

Patients who complete Visit 22 (Week 76) are considered completers for 1 year of OLE treatment period.

Patients who receive at least one IP administration on or after Visit 23 are considered entered in 2-year of OLE treatment period. 2-year of OLE treatments period completers are those who completed Visit 35 (Week 128) in OLE treatment period.

Patients who receive at least one IP administration on or after Visit 36 are considered entered in 3-year of OLE treatment period.

The number of patients randomised by country and centre will be summarised. A listing of disposition of patients will be provided.

4.2.2 Demography data and patient characteristics

Demographic data and key baseline characteristics will be summarised for each treatment group and the total population using descriptive statistics on FAS. Summary data presentation is detailed in section 4.1. The demographic data and key baseline characteristics will include but not limited to the following variables:

a. Age (calculated as date of randomisation – date of birth)

b. Sex
c. Country
d. Region
e. Race
f. Ethnicity
g. Baseline Characteristics – including baseline background medications, baseline eosinophils, HES subtypes, asthma history, organ involvement (primary and non-primary)

4.2.3 Prior and concomitant medications

The number and percentage of patients who take background HES 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. A summary table of background 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.

4.2.4 Study treatment administration

Duration of IP administration within each period will be calculated in days as:

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

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

Total number of IP administrations and total number of active doses received will be summarized by treatment group. Patient counts by number of IP administrations and patient counts by number of active doses received will also be presented.

4.2.5 Study treatment compliance

The study 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 intended to be given until Week 24/IPD visit (excluding the first dose of OLE IP) x 100.

Study treatment (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. If a patient discontinued from IP study but remained on study, doses administered and expected have to be counted in the calculation.

4.2.6 Primary efficacy variable: Time to first HES worsening/flare

4.2.6.1 Primary analyses

The time to the first HES worsening/flare during the DB period will be analysed using a stratified log-rank test to make the inferential comparison between treatment groups, the 2-sided p-value will be displayed. Region will be included as a stratification factor.. A Cox proportional hazards model that includes treatment group and region as covariates will be displayed to evaluate the hazard ratio and its 95% CI. Proportionality hypothesis will be tested as specified in the section 4.2.7.2. The tie-handling recommended approach for the log-rank test is the Breslow method and for the Cox proportional hazards model is the Efron method. If there are low event counts in any individual region causing issues with the analyses as planned, regions will be pooled for the purpose of statistical analyses. If needed, this pooling strategy will be documented in a revision to this SAP.

HES worsening/flare is assessed until the first HES flare/worsening occurs regardless of whether or not the patient discontinues IP or changes background therapy.

Time to the first HES worsening/flare will be displayed graphically using a Kaplan-Meier plot by treatment with their 1st quartile, median and 3rd quartile estimates and 95% CI only if estimable.

A repeat of this KM plot will be produced with symbols to indicate where the randomised adolescent patients fall on the plot, whether they have flare events or are censored.

4.2.6.2 Sensitivity analyses

An unadjusted analysis (an unstratified log-rank test and a Cox proportional hazards model adjusting for treatment group only) will be conducted as a sensitivity analysis for the primary endpoint. If there are convergence issues when the study is unblinded (for example due to a stratum experiencing zero events), an unadjusted analysis will replace the primary analysis outlined above, and region will not be included as a covariate for secondary endpoints. If a reasonable number of patients enter the trial with a history of flares rather than actively flaring at screening, and an imbalance in this covariate is observed, a sensitivity analyses may be performed exploring the impact of also including HES flare status as a covariate in the analysis.

A sensitivity analysis will be performed to assess the impact of patients changing systemic background therapy before HES worsening/flare on the primary analysis. In this sensitivity analysis:

1. Patients who had an increase in systemic background therapy, or an increase in concomitant systemic therapy for another condition considered likely to impact the chance of a patient flaring, and did not flare during the DB period will be censored at the date of medication increase.

2. Patients who had a decrease in systemic background therapy prior to a flare and subsequently flared during the DB period will be censored at the date of medication decrease.
3. All other patients will be handled as in the primary analysis.

For this sensitivity analysis, further details of how the events will be identified will be described in a separate background medication review plan, which will be finalised prior to database lock including a record of final classifications for any patients requiring medical judgement to define whether they are included as events in this analysis.

An additional sensitivity analysis for the time to HES worsening/flare endpoint will be performed where all patients who withdraw from the double-blind period of the study without having flared, will be considered as a flare event at the time of withdrawal.

4.2.6.3 Subgroups

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup summaries and/or analyses and statistical modelling including testing for interaction between treatment and covariates will be performed including the following factors:

a. Age (≤21 vs 22-49 vs 50+)
b. Geographical region (NA vs RoW)
c. Sex
d. HES subtype (lymphocytic variant HES (LHES), myeloid HES (MHES), eosinophilic granulomatosis with polyangiitis (EGPA)/HES overlap, single-organ HES (SO-HES), idiopathic HES (IHES)),
e. Race. (white, Asian, other)
f. Baseline blood eosinophils (split at median)
g. Baseline OCS (0, >0 to ≤10mg/d vs >10mg/d)
h. HES flare status at randomisation (not actively flaring at randomisation vs actively flaring)
i. Primary organ involvement: pulmonary, dermatological, GI, other
j. Time since HES diagnosis (0-<5 years, 5+ years)

These analyses are to be considered as exploratory and will be performed on the full analysis set.

Subgroup factors will be formally analysed if there are at least 8 total subjects and 1 event within each subgroup level. Combined categories if needed will be discussed during the blind review of the data. Other baseline variables may also be assessed if there is a clinical or biological justification, or an imbalance is observed between treatment arms.

For each of the subgroup factors in turn, a separate Cox proportional hazards model will be fitted including treatment and additional terms for the subgroup effect and the treatment x subgroup interaction to estimate the HR and 95% CI for each level of the subgroup. The Cox models will be fitted using the Efron method to control for ties. These HRs and associated 2-sided 95% CIs will be summarized and presented on a forest plot, along with the results from the overall primary analysis.

4.2.6.4 Subgroup analyses for China and Japan

The China, Japan and Asia sub-populations are defined as all patients enrolled in sites in China, Japan and Asia (the total patients from China, Japan and South Korea), respectively.

To support registration in China and Japan, study summaries will be repeated for China, Japan and Asia sub-populations to demonstrate consistency with the overall population. The summaries will include, but are not limited to, the following:

- Patient disposition
- Demographic and baseline characteristics
- Extent of exposure
- Prior and concomitant medications
- Efficacy and safety analyses
- PK concentrations

If there is a limited number of patients in the China sub-population, the results will be listed only. Efficacy analyses in these sub-populations will be descriptive given the sample size is likely too small for inferential analysis.

Exploratory and sensitivity analyses may be replicated for the sub-populations if deemed informative. All analyses based on these sub-populations will be considered exploratory and no adjustment for multiplicity will be made. The testing strategy detailed in section 4.1.1 will not be directly applied to these sub-populations.

Safety summaries will include:

- Overview of adverse events (AEs) by category
- AEs by system organ class (SOC) and preferred term (PT)

- SAEs by SOC and PT

4.2.7 Secondary efficacy variables

Analyses on secondary efficacy variables will be done on the full analysis set.

4.2.7.1 Proportion of patients who experience HES worsening/flare (Key secondary endpoint)

The proportions of patients who experience a HES worsening/flare or withdraw during the DB period will be summarised by treatment group. The proportions of patients who experience HES worsening/flare or withdraw in the benralizumab group will be compared to the proportion in the placebo group using the Cochran–Mantel–Haenszel test stratified by region. The pooled proportion difference, its 95% CI and p-value will be presented. A logistic regression model including covariates for treatment and region will be used to estimate the odds ratio. Results will be presented in terms of the odds ratio and its corresponding 95% confidence interval (CI).

As a sensitivity analysis, the above analysis will be repeated but using the all randomised patients analysis set.

Types of HES flare (resulting in an increase/burst of OCS, an increase or addition of new cytotoxic and/or immunosuppressive therapy, hospitalization or withdrawal) will also be summarized on a patient level (number of patients with a flare of each type) and on a flare level (number of flares of each type).

4.2.7.2 Number of HES worsenings/flares (annualised flare rate) (Key secondary endpoint)

The number of individual flare events a patient has over the DB period will be compared between the benralizumab and placebo groups using a negative binomial model. The response variable in the model will be the number of HES worsening/flare events experienced by each patient over the 24-week DB treatment period. The logarithm of the follow-up time will be used as an offset variable in the model. The model will include covariates of treatment group and region. The flare rate and corresponding 95% confidence interval within each treatment group will be presented. The estimated treatment difference from placebo (i.e., the absolute difference between benralizumab and placebo, and the rate ratio of benralizumab versus placebo), corresponding 95% Cis and 2 sided p-values for the rate ratio will be presented. Marginal standardization methods will be used on the model estimates.

4.2.7.3 Time to first haematologic relapse (Key secondary endpoint)

Analysis described in section 4.2.6.1 will be applied for analysing the time to first haematologic relapse using the same covariates.

4.2.7.4 Improvement in fatigue (PROMIS Fatigue Short Form 7a) (Key secondary endpoint)

The improvement in fatigue will be assessed using the standardized T-score of the PROMIS 7a short form as described in section 3.3.4. The cumulative distribution function of absolute changes from baseline in PROMIS Fatigue Short Form 7a standardized T-score at Week 24 by treatment will be also plotted in a figure. The change in standardized T-score from baseline will be analysed using a repeated measures ANCOVA analysis (referred to as MMRM in the CSP) with treatment group, baseline score, visit, region and treatment *visit interaction as covariates. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz, first-order autoregressive, and compound symmetric, variance components variance-covariance matrices will be tried in that order. The analysis will fit a repeated measures ANCOVA analysis using the data collected up to and including the Week 24 timepoint. The estimate of the treatment effect at Week 24 will be based on a contrast from this model. Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% CI and p-values for all visits. Graphical displays of LS mean change from baseline will be presented for PROMIS Fatigue SF 7a standardized T-score.

Summaries of question responses for the individual questions of the PROMIS 7a short form at baseline and post baseline visits, and a summary of change from baseline in the individual question responses will be provided.

To explore whether within-patient changes in PROMIS fatigue SF 7a standardized T-score observed are meaningful to patients and to estimate a minimal improvement threshold, anchor-based methods pooled across treatment arms will be implemented. These analyses will use change in PGI-S as the primary anchor, additional supportive anchors that may also be considered include using PGI-C and/or change in SF-36 vitality score. For this analysis, PGI-S categories will be combined to use: 1) no symptoms, 2) very mild / mild, 3) moderate, 4) severe / very severe. Spearman correlation coefficients between change in PROMIS fatigue score at week 24 and change in anchor categories at week 24 will be assessed. A higher correlation co-efficient indicates greater confidence in the anchor. Change in PROMIS fatigue standardized score at week 24 will be summarised by change anchor category at week 24 including confidence intervals around mean values. One category improvement on the PGI-S scale will be considered as the primary target to anchor the change in PROMIS score against as patients moving from mild to no symptoms, moderate to mild, or severe to moderate is considered likely meaningful to patients. Empirical cumulative distribution functions (eCDF) and probability density function (ePDF) curves of change in PROMIS fatigue score at week 24 using data that are pooled across both treatment arms but grouped by change in anchor categories will be provided to explore potential separation in PROMIS fatigue scores across categories.

Summaries of proportion of patients considered to be PROMIS fatigue responders at week 24 will be produced by treatment group whereby thresholds for responders will be defined prior to unblinding using the anchor analyses described above.

The responder analyses will be supported with a cumulative distribution function plot of change from baseline in PROMIS fatigue at week 24 by treatment group, to explore the range of PROMIS fatigue scores over which the treatment effect occurs.

4.2.7.5 Proportion of patients who have haematologic relapse

Analysis described in section 4.2.7.1 will be applied for analysing the proportion of patients who have haematologic relapse using the same covariates.

4.2.7.6 Proportion of patients who maintain AEC<500 cells/ml

Proportion of patients who maintain haematologic remission (AEC<500 cells/ml) for 24 weeks will be summarised by treatment and analysed as described for the proportion flaring endpoint in section 4.2.7.1. A patient must maintain haematologic remission at each visit during the 24 weeks of DB period to be counted. If a patient has more than 1 missing scheduled AEC assessment they will be considered as not achieving maintenance of AEC<500 cells/μL.

4.2.7.7 Proportion of patients who require an increase in corticosteroids from baseline

Proportion of patients who require an increase in corticosteroids from baseline at any point in the DB treatment period will be analysed as described for the proportion flaring endpoint in section 4.2.7.1. This will include an increase of OCS dose for patients on OCS at baseline or initiating any systemic corticosteroid.

The number of times a patient required a corticosteroid increase/burst will be summarised by treatment for the 24 weeks.

Total oral corticosteroid use will be analysed using an ANCOVA model including treatment and region as covariate. Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% CI and p-values.

4.2.7.8 Improvement in HRQoL using the SF-36 v2 questionnaire

SF-36 scales (PF; RP; BP; GH; VT; SF; RE; MH) and component summary (PCS, MCS) scores as well as changes from baseline will be summarised by treatment group and visit. The change from baseline of SF-36 scales and component scores will also be analysed using a repeated measures ANCOVA analysis (referred to as MMRM in the CSP) as described in section 4.2.7.4.

Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, 95% CI and p-values for all visits. Graphical displays of LS mean change from baseline will also be presented for MCS and PCS.

The proportion of SF-36v2 responders will be summarized by treatment group and visit. SF-36v2 responders at Week 24 will also be analyzed using logistic regression with treatment group, baseline score, and region as covariates. Missing assessments will be considered as non-responders.

4.2.7.9 Improvement in PGIS and PGIC

The PGIS and PGIC responses will be summarised with descriptive statistics by treatment group and visit.

PGIC improvement categories (a little better, moderately better, much better) as described in section 3.3.9 will also be presented with descriptive statistics by treatment group and visit.

4.2.8 Pharmacokinetics and immunogenicity variables

All pharmacokinetics variables will be summarised for the benralizumab group for all patients in the pharmacokinetic analysis set.

Anti-drug antibody (ADA) assessments will be conducted and analysed as per the details in Appendix 8.2 using the safety analysis set.

4.2.9 Exploratory variables

All exploratory variables will be described at each visit with a change from baseline if possible (i.e. except for peripheral blood lymphocytes endpoint where data are collected only at baseline and proportion of patients variables). The data on HRQoL and patients' experiences with the treatment and the biomarkers related to MoA of benralizumab, eosinophilic inflammation and HES disease will be summarised by visit according to the study periods.

4.2.9.1 Mortality rate

The number and percentage of patients who die from any cause will be presented in the AE with outcome death presentations.

4.2.9.2 Exploratory biomarkers

Absolute levels and changes from baseline (absolute change and % change) in exploratory biomarkers will be summarised at baseline and post baseline visits. Arithmetic means, geometric means and medians will be included in the summary statistics. These will be produced for both central laboratory blood eosinophil results (LabCorp Advia instrument, and Q2 Beckman central laboratory), see section 4.2.12.

Plots of the absolute levels and percentage change from baseline in biomarker variables over time will be produced, plotting the median values with error bars for the inter-quartile range.

4.2.10 Safety outcome variables

The first analysis of safety variables will include only data from the double-blind, placebo controlled first 24 weeks of the study (DB period), and data will be summarised using the safety analysis set with data presented according to actual treatment received.

Select safety summaries will also be repeated on the OLE period based on the open-label benralizumab set to summarise available OLE safety data at the time of the primary analysis. Only data from during the OLE period will be included in these analyses and patients will be grouped according to the treatment they received during the DB period.

All safety summaries will use the on-study period as defined in section 3.1.3.

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

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

- Age group 1 (age<18 vs age ≥18)
- Age group 2 (≤21 vs 22-49 vs 50+)
- Sex (Male vs Female)
- Race (White, Asian, Other)
- Geographic region (North America vs Rest of World)

The differences in the proportion of patients (benralizumab – placebo) 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 IP 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.

4.2.10.1 Adverse events

Adverse events (AEs) will be summarised separately for the DB period and OLE period, as defined in Section 3.5.1. 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 time on study 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 as defined in section 3.5.1. Rates will be expressed in terms of events per 100 patient-years.

An overall summary table will be produced showing the number, percentage, and exposure-adjusted rate 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 (ie, 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 also by preferred term 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). Maximum intensity summaries will be reported cumulatively, i.e. any mild, moderate or severe event, any moderate or severe event, any severe event.

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 injection site reactions) and hypersensitivity (standardized MedDRA query of hypersensitivity [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 for the double-blind period only. The summary of AEs of hypersensitivity will be presented overall and repeated for events causally related to IP as assessed by the investigator.

A summary of benralizumab adverse drug reactions and event rates will be produced for the double blind period. This table will summarise the number and % of patients with particular adverse events of interest, as well as the rates of AEs per person-years at risk (as defined earlier in this section dividing the number of patients with events by the total time on study in the treatment group).

4.2.10.2 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 value, as applicable for each parameter and will include patients with both baseline and post-baseline data.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points, then shift plots of these data may be produced. Data for patients who have treatment-emergent changes outside central laboratory reference ranges will be presented.

For CPK (Creatine phosphokinase), LDH (Lactate dehydrogenase) and Troponin, descriptive statistics and change from baseline at each visit (only Visit 9 for CPK and LDH) will be presented by treatment group.

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

4.2.10.3 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 postbaseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data.

4.2.11 Impact on analyses due to COVID-19 pandemic

Given the uncertainty surrounding the impact of the COVID-19 worldwide pandemic on clinical trials, operational procedures are being implemented in this study to maintain the integrity of collected data. Efforts may be made to collect data via alternative means where possible, when on-site visits cannot be performed.

If there is a sufficient number of protocol deviations or study disruptions as a result of COVID 19, then sensitivity analyses will be conducted to evaluate their impact on the interpretation of results. Protocol deviations, including doses or visits missed due to COVID 19 related protocol deviations will be described separately in the CSR.

COVID-19 disruptions are broadly defined as follows:

- Changes to visit schedules, missed visits, changes to study procedures;
- Discontinuation of IP or changes to the IP supply;
- The introduction of alternative monitoring approaches.
- Confirmed or suspected cases of COVID-19 will be listed and included as AEs as appropriate.

4.2.12 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 LabCorp central laboratory (analyzed via Advia 2120i instrument), while a subset of patients will also have assessments available from the Q2 central laboratory (analyzed via Beckman Coulter DXH800 or LH750 instrument). Available results from both laboratories will be included in summary tables of changes in eosinophil values over time and summarized separately. It is expected that these paired assessments will be positively correlated, and additional exploratory analyses to explore the relationship between the paired samples at baseline will be specified in a separate exploratory analysis plan. These analyses include simple plots and correlation analyses along with modelling the relationship between laboratory results if appropriate.

5 OLE TREATMENT PERIOD

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

Summaries involving HES worsening/flares in the OLE period will use a modified flare definition where existing HES therapy must not have been reduced in the 4 weeks prior to the HEs flare/worsening for it to count as an event in the OLE analyses. This is to ensure that unsuccessful attempts at background medication tapering do not confound informal comparisons of flare rates from the OLE period, where background medications are allowed to be modified, back to the DB period where background medications were to remain stable.

Selected efficacy and safety data may be integrated for those patients randomized to benralizumab, to describe efficacy and safety data over the entire study follow-up period.

6 CHANGES OF ANALYSIS FROM CSP

No applicable change from the CSP.

7 REFERENCES

QualityMetric 2011
Lincoln, RI. QualityMetric, Inc. User's manual for the SF-36v2 Health Survey (3 ed.). 2011.

8 APPENDIX

8.1 Partial dates for adverse events and prior/concomitant medication

Date of AE and medications with missing day or missing day and month will adhere to the following conventions to classify AEs and to classify prior/concomitant medications.

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

Adverse Events:

a. The missing start day will be set to:

   - First day of the month of occurrence, if the start YYYY-MM is after the YYYY-MM of first study treatment
   - The day of the first study treatment, if the start 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 YYYY-MM of the first study treatment.

b. The missing end day 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.

c. If the start date is missing both the day and month, the start date will be set to:

   - January 1 of the year of occurrence, if the start year is after the year of the first study treatment.
   - The date of the first study treatment, if the start 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

d. If the end date 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 that the event occurred.
- 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.

In addition to the imputation algorithms above, for HES disease characteristics,

- If the imputed start date is before the subject's birth date, the start date will be set to the date of birth
- If the imputed end date is after the informed consent date, the end date will be set to the informed consent date.

8.2 Immunogenicity variables

Serum samples for ADA assessments will be conducted utilising 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 antibody (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 patient, the following ADA response variables will be evaluated during the on-treatment period through EOT/IPD visit:

- Subjects who are at any timepoint during the study, including baseline and/or post baseline (also generally referred to as ADA positive). The percentage of ADA positive subjects in a population is known as the 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 (the percentage of treatment-emergent ADA positive subjects in a population is referred to as the ADA incidence). A positive post-baseline result and either of the following statements holds:
  a. Baseline is ADA negative and at least one post-baseline assessment is ADA positive. This is called treatment-induced ADA positive.
  b. 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; defined as ADA negative at baseline and at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement, 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 positive; defined as nAb positive at any visit including baseline and/or postbaseline (The percentage of patients nAb positive in a population is known as nAb prevalence.)
- nAb incidence: defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline timepoint. 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 patients who are ADA negative at baseline would not have an 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 within each treatment group.

The responses above will be summarised as counts and percentages across the DB period by treatment group. The maximum ADA titre over the on-study period will also be summarized 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 summarized at baseline and at all scheduled post-baseline visits by treatment group using derived visit windows. The analysis visit windows are defined in Section 2.2.2. 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 results 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 summarized by visit.

Key patient information will be listed for patients with positive ADA results, including ADA status, nAb status, titer, and benralizumab serum concentration, and blood eosinophil level.

All analyses will be conducted on the safety analysis set by treatment group 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: treatment-emergent ADA positive, ADA negative, Non-TE ADA positive, ADA persistently positive, ADA transiently positive, nAb-positive, TE-ADA positive with maximum post-baseline titre > median of maximum post-baseline titres. A line plot of blood 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 of proportion of patients experiencing a HES worsening/flare by treatment group 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). Due to the expected small number of ADA positive subjects in the placebo group, no formal statistical comparisons of benralizumab versus placebo by ADA status (positive/negative) are planned.

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 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) for patients in the PK analysis set using the following descriptive statistics: n, geometric mean, geometric mean 95% CI, geometric mean coefficient of variation (CV), arithmetic mean, standard deviation, median, minimum and maximum.

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