Statistical Analysis Plan	
Study Code	D325BC00001
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A Multicentre, Randomised, Double-Blind, Parallel-group, Placebo-controlled, 52-Week, Phase III Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients with Non-Cystic Fibrosis Bronchiectasis (MAHALE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA(s)	Anti-drug antibody(ies)
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BD	Bronchodilator
BED	Bronchiectasis exacerbation diary
CDL	Clinical data lock
CFB	Change from baseline
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
DAE	Discontinuation of investigational product due to adverse event
DB	Double-blind
DBP	Diastolic blood pressure
ECG(s)	Electrocardiogram(s)
eCRF	Electronic case report form
EFS	Emotional functioning scale (from QoL-B)
EI	Eosinophilic inflammation
ePRO	Electronic patient-reported outcome
FAS	Full analysis set
FEV_1	Forced expiratory volume in one second
FU	Follow-up
HPS	Health perceptions scale (from QoL-B)
HRQoL	Health-related quality of life
IgE	Immunoglobulin E
IP	Investigational product
IPD	Investigational product discontinuation
ITT	Intent-to-treat
IV	Intravenous

Abbreviation or special term	Explanation
LCQ	Leicester Cough Questionnaire
LLOQ	Lower limit of quantification
LSMEANS	Least squares means
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-effect model for repeated measures
N	Sample size
N/A	Not applicable
NCFB	Non-cystic fibrosis bronchiectasis
OLE	Open-label extension
P aeruginosa	*Pseudomonas aeruginosa*
PD	Pharmacodynamics
PFS	Physical functioning scale (from QoL-B)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetics
PN	Percent normal
PRO	Patient-reported outcome
PT	Preferred term
QoL-B	Quality of Life-Bronchiectasis
Q1	First quartile
Q3	Third quartile
Q4W	Every four weeks
RFS	Role functioning scale (from QoL-B)
RSS	Respiratory symptoms scale (from QoL-B)
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SFS	Social functioning scale (from QoL-B)
SI	System international (units)
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
SOC	System organ class
TBL	Total bilirubin

Abbreviation or special term	Explanation
TBS	Treatment burden scale (from QoL-B)
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
V	Visit
VS	Vitality scale (from QoL-B)
WHO DD	World Health Organisation Drug Dictionary
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health

AMENDMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
SAP version 2.0	17 May 2024
Original SAP (version 1.0)	29 October 2020

Summary of Changes Table

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentation	17May2024	Updated visit window in Section 3.1.2	Yes, Version 3.0	To reflect the modification to the study duration and add clarity on the derivation of visit window of different endpoints
Derivation of primary or secondary endpoints	17May2024	The calculation and analyses for primary and secondary outcome variables were updated to during the DB treatment period (Section 3.2, 3.3, Section 4.1 Table 7)	Yes, Version 3.0	To reflect the modification to the study duration
Other	17May2024	Blood eosinophils CCI proteins and sputum eosinophils CCI proteins were removed from Section 3.7.3 – 3.7.5.	Yes, Version 3.0	To exclude the analyses of blood and sputum eosinophils CCI proteins
Other	17May2024	In Section 4.1 General principles, the analyses of DB period and OLE period will be included in a single SAP. No additional SAP or CSR would be created just for OLE period.	Yes, Version 3.0	To align with that there will be only one database lock after the last patient completes the OLE.

Multiple Testing Procedure	17May2024	The original Section 4.1.1 Testing strategy for multiplicity considerations was removed. Multiple testing procedure is also removed from the table of estimands (Section 4.1 Table 7).	Yes, Version 3.0	Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.
Other	17May2024	Extra summaries (e.g. patients who completed Week 28, patients who enrolled to the OLE period, etc.) were added to Section 4.2.1 Patient disposition.	Yes, Version 3.0	To reflect the modification to the study duration and that analyses of OLE period will be included.
Other	17May2024	Duration of DB IP administration and duration of OLE IP administration were clarified.	Yes, Version 3.0	To reflect the modification to the study duration and that analyses of OLE period will be included.
Statistical analysis method for the primary or secondary endpoints	17May2024	The following changes of covariates in the statistical models of analysing primary and secondary outcome variables (Section 4.2.6, 4.2.7): • Baseline blood eosinophil category (< 300 and ≥ 300 blood eos count) added as a covariate. • Pseudomonas aeruginosa sputum culture status (yes, no), current chronic macrolide use (yes, no), and region were removed as covariates.	Yes, Version 3.0	Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.
Statistical analysis method for the primary or secondary endpoints	17May2024	Text related to analyses of primary and secondary outcome variables in patients with different ranges of baseline blood eosinophil counts was removed (Section 4.2.6, 4.2.7).	Yes, Version 3.0	Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.

Statistical analysis method for the primary or secondary endpoints	17May2024	Sensitivity analysis of primary outcome variable was removed (Section 4.2.6.1). The original Section 8.3 Accounting for missing data was also removed.	Yes, Version 3.0	Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.
Statistical analysis method for the primary or secondary endpoints	17May2024	Gender, region, BMI, screening blood eosinophil counts, baseline value of eosinophil CCI proteins, baseline IgE values, IgE categories, and BSI were removed from the subgroup analyses to the primary outcome variable (Section 4.2.6.2).	Yes, Version 3.0	Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.
Other	17May2024	The original interim analysis was updated to "no interim analysis is planned" (Section 5).	Yes, Version 3.0	Interim analysis is not applicable.
Other	17May2024	Two ADA responses were added to the analyses of immunogenicity variables (Section 8.2): nAb-positive, both ADA persistently positive and nAb positive. Analysis of ADA response and demographics/patient characteristics was also added.	N/A	To complete immunogenicity analyses.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other
N/A=Not applicable.

1 STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR) according to clinical study protocol (CSP) version 3.0. It updates the version 1.0 in order to account to numerous changes introduced to the study conception and into the CSP version 3.0. Additional analyses and analyses for exploratory endpoints might be prespecified in a separate analysis plan, and not reported in CSR.

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 Objectives and Variables for the Double-Blind Treatment Period

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on bronchiectasis exacerbations	Annualised exacerbation rate estimated for the DB treatment period **Estimand** *Population* [a]*:* FAS *Intercurrent event strategy* [a]*:* Included in analysis regardless of treatment discontinuation (treatment policy) *Population-level summary:* Rate ratio for interventions (negative binomial model)
Secondary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on time to onset of bronchiectasis exacerbations	Time to first bronchiectasis exacerbation
Secondary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on respiratory symptoms	Change from baseline in QoL-B-RSS over the DB treatment period
Secondary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on pulmonary function	Change from baseline in pre-dose FEV_1 over the DB treatment period
Secondary	Efficacy	To evaluate the effect of benralizumab 30mg Q4W on cough-related quality of life	Change from baseline in LCQ over the DB treatment period
Secondary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on bronchiectasis health-related quality of life	Change from baseline in QoL-B scales (excluding QoL-B-RSS secondary endpoint) over the DB treatment period

Table 1 Objectives and Variables for the Double-Blind Treatment Period

Objective			Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on respiratory health status/health-related quality of life	Change from baseline in SGRQ over the DB treatment period
Secondary	Safety	To evaluate the safety and tolerability of benralizumab 30 mg Q4W	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, physical examinations, and ECGs. Assessments related to AEs cover: • Occurrence/Frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
Exploratory	PK	To evaluate the PK of benralizumab	Serum benralizumab concentration
Exploratory	Immuno-genicity	To evaluate the immunogenicity of benralizumab	Anti-benralizumab antibodies
Exploratory	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on patient impression of overall health status	PGIS and PGIC
Exploratory	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on work productivity loss and activity impairment	WPAI-GH
Exploratory	Efficacy	To evaluate the effect of benralizumab 30 mg Q4W on blood and sputum eosinophils, blood and sputum biomarkers of inflammation, and the sputum microbiome, and to evaluate baseline biomarkers as predictors of response to benralizumab	Baseline levels and change from baseline in blood and sputum eosinophils Baseline levels and change from baseline in blood and sputum biomarkers of inflammation (eg, inflammatory proteins, transcriptomics) Sputum microbiome analysis [redacted]

Table 1 Objectives and Variables for the Double-Blind Treatment Period

Objective			Variable
Priority	**Type**	**Description**	**Description**
Exploratory	Efficacy	To characterise the effect of benralizumab 30 mg Q4W on mucus plugging, air trapping, and airway structure and function using CT scanning	Change from baseline in: • Mucus score • Air trapping expressed as: ° Percentage of the lung with expiratory density < -856 HU ° Expiratory-to-inspiratory ratio (E/I) of mean lung density ° Air trapping/small airway obstruction derived from Disease Probability Mapping • Airway wall and lumen dimensions (wall area%, wall area, wall thickness, lumen area) • Lung density and volumes across lobes • Airway tapering and number of affected branches • Ratio of the diameters of bronchial lumen and adjacent artery (broncho-arterial ratio) • Biomechanical properties such as airway distensibility • Total pulmonary vessel volume and vessel volume for blood vessels with a cross-sectional area < 5 mm^2 (TPVV/BV5)

[a] The population and intercurrent strategy also apply to the secondary endpoints.

AEs = adverse events; CT = computed tomography; DB = double blind; ECG = electrocardiogram; FEV_1 = forced expiratory volume in one second; HU = Hounsfield units; IP = investigational product; LCQ = Leicester Cough Questionnaire; FAS = full analysis set; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; Q4W = every 4 weeks; QoL-B = Quality of Life-Bronchiectasis; QoL-B-RSS = Quality of Life-Bronchiectasis-Respiratory Symptoms Scale; CCI [redacted] SGRQ = St. George's Respiratory Questionnaire, WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health

Table 2 Objectives and Variables During the Open-Label Extension

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To characterise the safety and tolerability of benralizumab 30 mg Q4W [a]	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, physical examinations, and ECGs. Assessments related to AEs cover: • Occurrence/Frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
Exploratory	PK	To characterise the PK of benralizumab [a]	Serum benralizumab concentration
Exploratory	Immuno-genicity	To characterise the immunogenicity of benralizumab [a]	Anti-benralizumab antibodies
Exploratory	PD	To characterise the effect of benralizumab 30 mg Q4W on blood eosinophils	Blood eosinophils

[a] Applicable to the OLE period.
AEs = adverse events; ECG = electrocardiogram; IP, investigational product; PD = pharmacodynamics; PK = pharmacokinetics; Q4W= every 4 weeks

1.2 Study design

This is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, Phase III study designed to test the hypothesis that benralizumab will reduce exacerbation rates compared with placebo on top of standard-of-care therapy in adult patients with non-cystic fibrosis bronchiectasis with eosinophilic inflammation (NCFB+EI). The study was conducted at approximately 84 sites in 16 countries.

To be eligible, patients were required to have a primary diagnosis of NCFB confirmed by CT and a documented history of ≥ 2 exacerbations within the past year. Patients were excluded if they have pulmonary disease other than bronchiectasis as explained in the CSP, Sections 5.1 and 5.2.

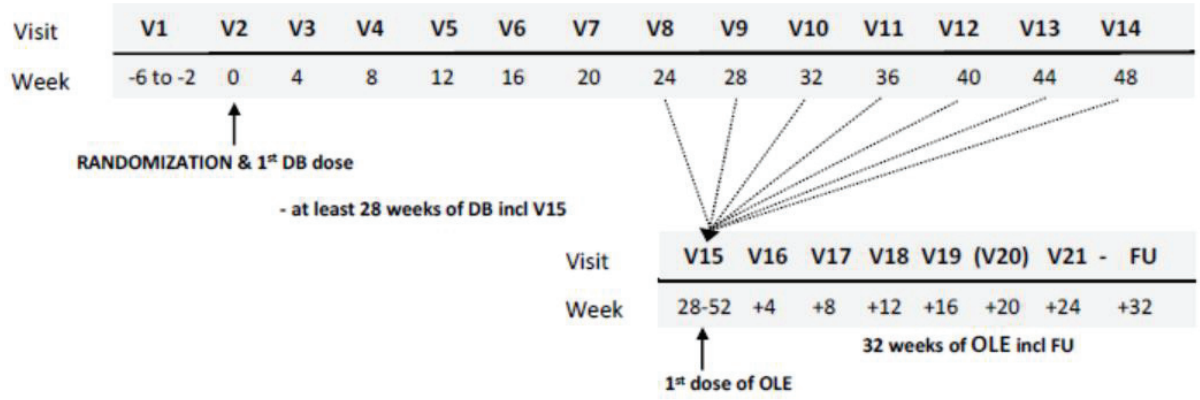
Potentially eligible patients entered a screening period of approximately 2 to 6 weeks. After the screening period, it was planned to randomise 420 eligible patients in a 1:1 ratio to receive either benralizumab 30 mg administered by subcutaneous (SC) injection Q4W or a matching placebo. Patients were stratified at randomisation by screening blood eosinophil count (≥ CCI /µL and < CCI /µL strata), country, and baseline chronic macrolide use (yes/no). Due to the decision to stop recruitment early, as described in the CSP version 3.0, a final number of 100 patients were randomised to receive benralizumab or placebo (ratio of 20:80 in the ≥ CCI /µL:< CCI /µL blood eosinophil strata). The revised DB treatment period will be at least 28 weeks and up to 52 weeks (depending on the timing of patient randomisation and when the revised CSP [version 3.0] became effective).

All patients who complete the DB treatment period on IP may be eligible to continue into an OLE period. The revised OLE period will consist of a treatment period of approximately 24 weeks followed by a follow-up (FU) visit 8 weeks after the last dose of IP (for a total of approximately 32 weeks). Patients in the OLE period will receive open-label benralizumab 30 mg Q4W starting at Visit 15 for collection of long-term safety data.

The clinical database lock (CDL) will occur after the last patient completes the OLE period. The analysis of efficacy endpoints will include all data captured during the DB treatment period (intention-to-treat approach) from patients in the FAS. Given that only 100 patients were randomised in the trial (20 with ≥ CCI /µL blood eosinophil count), this study is not sufficiently powered for the primary efficacy analysis, which was originally based on the patients in the ≥ CCI /µL blood eosinophil stratum. One important change in the analysis strategy is that all the statistical evaluations for endpoints describing disease progression, efficacy, and safety of benralizumab will be based on the FAS population, as opposed to the patients in the ≥ CCI /µL blood eosinophil stratum. Safety data from the OLE period of the study will also be presented in the CSR. Data collected for bronchiectasis exacerbations during DB and OLE periods will be analysed. Other efficacy data collected in OLE before the implementation of the revised CSP (version 3.0) will be listed only.

The general study design is summarised in Figure 1. See CSP Section 1.3, Tables 2-4 for a detailed list of visits and assessments.

Figure 1 Study Design



The IP discontinuation visit is 4 weeks after last dose of IP. In case of early discontinuation from IP, a follow-up visit is required 8 weeks after the last dose of IP.
The duration of the DB period for each patient will be 28 to 52 weeks. Patients should not be transitioned to the new OLE SoA (CSP version 3.0) until they complete Visit 8 of the DB period. All eligible patients who choose to continue into the OLE will receive benralizumab alone on top of standard of care starting at Visit 15 (end-of-DB period/start of the OLE). For patients ineligible or unwilling to participate in the OLE, Visit 15 is then to be completed as the last DB treatment period visit, followed by a FU visit 8 weeks after the last of dose of IP.
If a patient is already in the OLE and has completed Visit 21 of the previous SoA (CSP version 2.0) at the time this revised CSP (version 3.0) becomes effective, the patient will go directly to the FU visit in the new OLE SoA (CSP version 3.0 Table 2). This FU visit should occur 8 weeks after the last dose of IP.
CSP = clinical study report; DB = double-blind; FU = follow-up; IP = investigational product; IPD = investigational product discontinuation; OLE = open-label extension; SoA = schedule of assessments; V = visit; W = week

1.2.1 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study. A patient is considered to have completed the study when he/she has completed his/her last scheduled visit/telephone contact.

This study comprises 2 distinct periods: a DB treatment period, with duration of 28 to 52 weeks (depending on the timing of patient randomisation and when CSP version 3.0 becomes effective), during which patients will be randomised to receive either benralizumab or placebo, and an OLE period, during which all eligible patients who choose to continue into the OLE will receive open-label benralizumab 30 mg Q4W starting at Visit 15 for collection of long-term safety data. The revised OLE period will consist of a treatment period of approximately 24 weeks followed by a FU visit 8 weeks after the last dose of IP (for a total of approximately 32 weeks[1]).

[1] Note that any patient who has already attended or is past Visit 22 of the previous OLE schedule (CSP version 2.0) before the revised protocol (version 3.0) becomes effective will have an OLE period of more than 32 weeks.

1.3 Number of patients

In the original protocol, approximately 420 eligible patients were to be randomised in a 1:1 ratio to receive either benralizumab 30 mg administered by SC injection Q4W or a matching placebo. Patient stratification at randomisation included blood eosinophil count (≥ CCI /µL and < CCI /µL eosinophil strata). Originally, the study was powered for the primary efficacy analysis including only the patients in the ≥ CCI /µL blood eosinophil stratum. However, due to the decision to stop recruitment early and small sample size in ≥ CCI /µL blood eosinophil stratum, the primary efficacy analysis will now be evaluated based on all randomised patients, and the study has no plan to be powered to assess the hypothesis test for the primary efficacy endpoint.

At the time of stopping recruitment, 100 eligible patients had been randomised to receive either benralizumab 30 mg administered by SC injection Q4W or a matching placebo. Patients were stratified at randomisation by screening blood eosinophil count (≥ CCI /µL and < CCI /µL eosinophil strata), country, and current chronic macrolide use (yes/no). Out of 100 patients who had been randomised in the study, 20 patients are in the ≥ CCI /µL blood eosinophil stratum and 80 patients are in the < CCI /µL blood eosinophil stratum.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Five analysis sets are defined below: All-patients analysis set, full analysis set (FAS), safety analysis set, pharmacokinetics (PK) analysis set, and open-label extension (OLE) analysis set. Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation), then the patient will be excluded from all analysis sets defined below.

2.1.1 All-patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

This analysis set comprises all patients randomised and who have received at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study. Patients will be assigned 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 or assent to participate in the study will be included up to the date of their study termination.

All efficacy analyses will be performed using the FAS with an ITT approach. For consistency, demographic and baseline characteristics will be presented using the FAS.

2.1.3 Safety analysis set

The safety analysis set comprises all patients who have received at least 1 dose of IP. Erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received active IP (benralizumab) is classified as active (benralizumab).

All safety summaries and anti-drug antibodies (ADA) analyses will be based on this analysis set.

2.1.4 Pharmacokinetic analysis set

This analysis set comprises all patients who have received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (e.g., disallowed medications) and who had at least 1 quantifiable serum PK observation after the first dose of IP.

All PK summaries will be based on this analysis set.

2.1.5 OLE analysis set

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

All OLE summaries will be based on this analysis set.

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 data and will include but may not be limited to the following categories:

- Eligibility criteria not met (patients incorrectly randomised)
- Deviations from key inclusion criteria
- Deviations from key exclusion criteria
- Deviations from informed consent procedures
- Discontinuation criteria for IP met but patient not withdrawn from study treatment
- Deviations from IP management and administration
- Received prohibited/restricted concomitant medication
- Other important protocol deviations

Only important protocol deviations will be summarised 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. Additional details, including key inclusion and exclusion criteria, are to be provided in the Protocol Deviation Plan.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Study periods for data summary

The following study periods will be derived for reporting purposes:

- DB treatment period: this is defined as the period starting from V2 (Week 0) to the end of DB period (V9 (Week 28) up to V15), depending on the timing of patient randomisation and when CSP version 3.0 became effective.
- OLE treatment period: this is defined as the period starting at V15 (first administration of open label benralizumab) until the end of the follow-up visit.

3.1.2 Visit window definitions

For the exacerbation-related analyses, no windows will be applied. 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 the screening visit.

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits,

then the upper limit will be taken as the midpoint value minus 1 day. For example, windows for 4-weekly scheduled visits are specified in Table 3 and Table 4.

Table 3 summarises the visit windows corresponding to the clinical visits (mostly 4-weekly) of the assessments scheduled in the protocol of the DB period (such as ePRO assessments, vital signs, haematology white blood cells with differential, and urinalysis (dipstick)). For the 4-weekly scheduled assessments of the OLE period, visit windows are specified in Table 4.

Table 3 Visit window of assessments collected 4-weekly

Time point	Target study day	Visit Window
Baseline (Week 0)	1	See Section 3.1.3 for baseline definitions
DB Week 4	29	2 - 42
DB Week 8	57	43 - 70
DB Week 12	85	71 - 98
DB Week 16	113	99 - 126
DB Week 20	141	127 - 154
DB Week 24	169	155 - 182
DB Week 28	197	183 – 210 or last DB assessment day if patient receive first OLE dosing following DB Week 24
DB Week 32	225	211 – 238 or last DB assessment day if patient receive first OLE dosing following DB Week 28
DB Week 36	253	239 – 266 or last DB assessment day if patient receive first OLE dosing following DB Week 32
DB Week 40	281	267 – 294 or last DB assessment day if patient receive first OLE dosing following DB Week 36
DB Week 44	309	295 – 322 or last DB assessment day if patient receive first OLE dosing following DB Week 40
DB Week 48	337	323 – 350 or last DB assessment day if patient receive first OLE dosing following DB Week 44
DB Week 52	365	351 - last DB assessment day

Table 4 Visit windows for assessments in the OLE period

Time point	Target study day	Visit Window
OLE Week 4	varies	First OLE dosing day +1 – V16 visit date
OLE Week 8	varies	V16 visit date +1 – V17 visit date
OLE Week 12	varies	V17 visit date +1 – V18 visit date
OLE Week 16	varies	V18 visit date +1 – V19 visit date

OLE Week 20	varies	V19 visit date +1 – V20 visit date
OLE Week 24	varies	V20 visit date +1 – V21 visit date
OLE Week 32	varies	V21 visit date +1 – FU visit date

Study day is defined as follows: (Date of assessment – date of randomisation) +1

Note that any patient who has already attended or is past Visit 22 of the previous OLE schedule (CSP version 2.0) before protocol version 3.0 becomes effective will have and OLE period of more than 32 weeks. For each analysis parameter, the windowing will be based on the protocol-specified schedule of events as defined in the clinical protocol (version 3.0).

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

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

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

For pre-BD FEV_1 (L) and post-BD FEV_1 (L), the non-missing value with acceptable quality (acceptable or borderline quality grade) which is closest to the scheduled visit will be included in the analysis.

For the electronic patient-reported outcomes (ePRO) assessments, all available data will be analysed up to the end of the study. If data are captured in the ePRO device after the patient has withdrawn consent, all results collected on or after the evening of the date of consent withdrawal will be excluded from analysis.

3.1.3 Baseline definition

In general, the last recorded value on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints while the last recorded value prior to first dose of study treatment will serve as the baseline measurement for safety endpoints. When time of assessment is not recorded or missing, it is assumed that assessments recorded on the date of first dose of study treatment were performed prior to dosing, except in cases of protocol-specified post-dose assessments.

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

For categorical baseline NCFB disease characteristics captured directly in the electronic case report form (eCRF) (e.g. captured as yes or no), if 'yes' is indicated in any visit during enrolment (scheduled or unscheduled), 'yes' will be used.

For pre-BD FEV_1 (L), the last non-missing value with acceptable quality (acceptable or borderline quality grade) on or prior to the date of randomisation will be used as baseline. The first dose of study treatment is scheduled to be administered on the date of randomisation (V2), however if the first dose of study treatment is delayed until after the date of randomisation, the last recorded value with acceptable quality prior to first dose of study treatment will be used as baseline measurement for spirometry parameters.

For QoL-B, LCQ, SGRQ, PGIS and WPAI-GH, baseline is defined as the last non-missing value on or prior to randomisation.

For summaries of laboratory results by visit and in the calculation of change from baseline, baseline is defined as the last non-missing assessment prior to first dose of study treatment. For ECG, the last non-missing measurement at V2 will be used as baseline.

3.1.4 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).
- **Concomitant in DB period:** if it started after the date of randomisation and on or prior to the end of DB period, or if it started on or prior to the date of randomisation and was ongoing after the date of randomisation.
- Concomitant in OLE period: if it started after the first dose of open label benralizumab 30 mg and on or prior to the end of the study.

Medications with start date on or after the end of the study periods (as defined in Section 3.1.1) will not be considered as concomitant for that period.

3.2 Primary outcome variable

3.2.1 The annualised bronchiectasis exacerbation rate

The annualised bronchiectasis exacerbation rate over the DB treatment period will be used as the primary efficacy variable.

An exacerbation is defined as:

- A deterioration in 3 or more key symptoms for at least 48 hours **AND** a treating physician determines that a change in bronchiectasis treatment is required.

- Key symptoms are:
  - o Cough
  - o Sputum volume and/or consistency
  - o Sputum purulence
  - o Breathlessness and/or exercise intolerance
  - o Fatigue and/or malaise
  - o Haemoptysis
- A change in treatment is defined as an initiation of antibiotic medication in addition to the background prophylactic antibiotic (if used by the patient).

AND/OR

- Hospitalisation due to bronchiectasis

AND/OR

- Death due to bronchiectasis

The investigator must document the justification for defining the event as an exacerbation and record it in the eCRF.

An exacerbation will be considered **moderate** if it meets symptom criteria (defined above) and a clinician determines that a change in bronchiectasis treatment is required and does not result in hospitalisation or death. An exacerbation will be considered **severe** if it results in hospitalisation or death. Hospitalisation due to bronchiectasis is defined as in-patient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system.

The start of an exacerbation is defined as the start date of antibiotic treatment or hospital admission due to bronchiectasis, whichever occurs earlier, or death due to bronchiectasis. The end date is defined as the last day of antibiotic treatment or hospital discharge, whichever occurs later, or death due to bronchiectasis.

To ensure that the same event is not counted twice, exacerbations with stop and start dates equal to or less than 14 days apart will be considered the same event when the events are analysed. If the severity of the exacerbation events being combined is different, the greater severity will be used for the combined event.

Total follow-up time for calculation of the annualised bronchiectasis exacerbation rate is up to 52 weeks (depending on the timing of patient randomisation and when the CSP amendment [CSP version 3.0] became effective) and is defined as ‘the time from randomisation to the date of the last DB assessment’. For a patient who discontinues the study or is lost to follow-up during the DB period, the follow-up time will be defined as the time from randomisation to

the time point after which an exacerbation could not be assessed during the DB period. Exacerbations for patients who enter OLE period that start after the last DB assessment date will be counted as OLE exacerbations and will not be included in the analysis of primary endpoint (see Section 4.2.6.1), but analysed separately for the OLE period. If an exacerbation is ongoing at the last DB assessment date, the exacerbation will be counted in the calculation of annualised exacerbation rate, however the total follow-up time will be truncated at the last DB assessment date, as will the duration of the exacerbation in summary tables of the primary endpoint.

In the statistical analysis, the number of exacerbations experienced by a patient during the DB treatment period will be used as the response variable.

For the production of summary statistics by treatment group, the annual exacerbation rate per patient is calculated, and standardised per the length of the DB period according to the formula described below.

Annual Exacerbation Rate (crude) = Number of Exacerbations*365.25 / Total follow-up time within the DB period (days) within the treatment group.

3.3 Secondary outcome variables

3.3.1 Time to first bronchiectasis exacerbation

Time to the first bronchiectasis exacerbation is a secondary efficacy endpoint. Time from randomisation to the first bronchiectasis exacerbation up to the end of DB period will be used as the secondary outcome variable, and is calculated as follows:

Start date of first bronchiectasis exacerbation − Date of randomisation + 1.

An exacerbation event will be defined in the same way as outlined in Section 3.2.1. Patients who have not experienced a bronchiectasis exacerbation will be right censored at their last assessment date on or before the end of their DB treatment period.

3.3.2 Pre-dose/pre-BD FEV_1 (L) at the study site

Pre-dose/pre-BD FEV_1 (L) measured at the study site is a secondary efficacy endpoint.

The change from baseline for each of the post-randomisation visits (post Week 0, V2) up to and including the last visit of the DB treatment period will be calculated. Details regarding the definition of baseline for pre-dose/pre-BD FEV_1 (L) is provided in Section 3.1.3.

3.3.3 Patient-reported outcome assessments

3.3.3.1 Quality of Life – Bronchiectasis (QoL-B)

Change from baseline in the QoL-B Respiratory Symptoms Scale (QoL-B-RSS) during the DB period is another secondary efficacy endpoint.

QoL-B-RSS (consisting of 9 items) evaluates symptoms including chest congestion, cough, shortness of breath, wheeze, and chest pain. QoL-B-RSS is one of the 8 scales of the QoL-B which is a 37-item questionnaire developed to measure symptoms, functioning, and health-related quality of life in patients with non-cystic fibrosis bronchiectasis (Quittner et al 2015). Each item captures patient-reported symptoms and functioning over the past week on a 4-point Likert response scale.

The rest of QoL-B scales, considered as secondary efficacy endpoints, are as following: Physical Functioning Scale (QoL-B-PFS; 5 items), Role Functioning Scale (QoL-B-RFS; 5 items), Emotional Functioning Scale (QoL-B-EFS; 4 items), Social Functioning Scale (QoL-B-SFS; 4 items), Vitality Scale (QoL-B-VS; 3 items), Health Perceptions Scale (QoL-B-HPS; 4 items), and Treatment Burden Scale (QoL-B-TBS; 3 items). Change from baseline will be calculated during the DB treatment period for these scales.

All 8 QoL-B scales, including QoL-B-RSS, are standardised from 0 to 100, with higher scores indicative of better health-related quality of life. No total score is calculated. Missing responses will not be imputed. The score for a scale will be considered missing if more than half the responses in a scale are missing. The scale score is: [(mean of non-missing item responses -1)/3]*100. Specific details on the scoring algorithms are provided in a separate manual.

3.3.3.2 Leicester Cough Questionnaire (LCQ)

The LCQ is a 19-item questionnaire that assesses cough-related quality of life (Birring et al 2003, Murray et al 2009). Each item measures symptoms or the impact of symptoms over the past 2 weeks on a 7-point Likert response scale. The LCQ has three domains: physical (8 items), psychological (7 items) and social (4 items). Each domain is calculated as the mean of the items (range 1 to 7). A total score is calculated by adding the domain scores together (range 3 to 21). Higher scores indicate better quality of life.

The three LCQ domains (physical, psychological, and social) will be derived along with a total score. Missing responses will not be imputed. The score for a domain will be considered missing if more than half the responses in a domain are missing. Similarly, the total score will be considered missing if two or more domains are missing. Change from baseline will be calculated at each visit.

3.3.3.3 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into two parts: Part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; Part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

The symptoms domain score will be set to missing if there are >2 missing items; activity domain score will be set to missing if there are >4 missing items; impacts domain score will be set to missing if there are >6 missing items; and total score will be set to missing if one of the 3 domain scores is missing.

Potential health status treatment benefits of benralizumab will be evaluated by change from baseline to the end of the DB period in SGRQ total score.

3.4 Safety outcome variables

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

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

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

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

3.4.1 Adverse events

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

The following events are considered treatment emergent:

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

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

- AEs in the DB period are defined as those with onset date on or after day of first dose of study DB treatment and the day prior to the first dose of open-label benralizumab inclusive (up to and including day of V15/IPD/FU visit for patients who do not roll over to OLE).
- 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 AEs (AEs occurring during screening) are defined as AEs with a date of onset ≥ date of first screening visit and < date of the first dose of IP. AEs occurring during screening will only be listed.

If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on-study AE for that period, DB or OLE. 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-study AE for that period, DB or OLE.

3.4.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times detailed in the CSP and will be assessed in a central laboratory. The parameters outlined in Section 8.3.4, Table 10 of the CSP version 3.0 will be collected.

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

For laboratory variables, baseline will be defined as the last available non-missing assessment prior to first dose of randomised treatment. There will be no imputation for missing values.

For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged. The maximum or minimum value post-baseline will be calculated over the DB period by treatment group. Also, they will be calculated over the total period when patients are on benralizumab treatment. That is, OLE period for the patients who are in the placebo switched to benralizumab treatment group, or overall (including both DB and OLE periods) for the patients who are in the benralizumab treatment group.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator, will be reported as an AE.

3.4.3 Vital signs

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

Baseline is defined as the last value prior to the first dose of randomised treatment. There will be no imputation for missing values. Absolute values will be compared to the reference ranges in Table 5 and classified as low (below range), normal (within range or on limits) or high (above range). All values falling outside the reference ranges will be flagged. The maximum and minimum value post-baseline will be calculated in the same way as Section 3.4.2.

Table 5 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38

3.4.4 Physical examination

Complete and brief physical examinations will be performed at time points specified in Tables 1 and 2 of the CSP version 3.0. What is included in the assessment will be dependent on

whether the examination is complete or brief, as described in Section 8.3.1 of the CSP version 3.0. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

Each component of complete physical examination will be recorded as normal or abnormal.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.4.5 Electrocardiograms (ECGs)

Triplicate 12 lead-ECGs are to be performed at screening V1 to assess eligibility for this study, and then as clinically indicated during the treatment period in accordance with the protocol using an ECG machine that automatically calculates the heart rate and measures PR, QRS complex, QT, and QTc intervals.

Baseline visit is defined as the last available non-missing measurement prior to first dose of randomised treatment (V2).

Each of the three 12-lead ECGs at each timepoint will be taken in supine position, after the participant has been resting for at least 5 minutes. The assessment should be performed before interventions with the participant (e.g., endoscopy, blood draw).

An independent reader at the ECG vendor will provide overall interpretation as normal or abnormal. The investigator will assess the clinical significance of any potential ECG findings. A reassessment ECG may support evaluation of clinical significance, when uncertain. Further details are provided in a separate ECG User Manual.

3.5 Pharmacokinetics variables

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

Blood samples (processed to serum) for pharmacokinetic assessments will be collected from all patients at baseline prior to first benralizumab administration at Week 0 (V2) Day 1 and at post-baseline visits before benralizumab administrations during the treatment period in accordance with the visit schedule provided in Tables 1 and 2 of the CSP version 3.0. A summary of PK analysis results will be reported in the CSR. For early discontinuations, PK samples collected after last dose + 28 days will not be included in the summary statistics.

The following cases will be excluded from the PK analyses:

- Benralizumab patients with all collected serum concentration levels persistently below the lower limit of quantification (LLOQ=3.86 ng/mL) throughout the DB treatment period where all the samples were taken within the last 84 days of previous dose.
- Benralizumab patients with any collected serum concentration in excess of what is considered to be physiologically possible with dosing: ≥12,000 ng/mL for the benralizumab treatment group.

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

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

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

3.6 Immunogenicity variables

ADA variables, such as ADA and neutralizing antibodies (nAb) responses, will be generated and analysed as per the details in Appendix 9.2.

3.7 Exploratory outcome variables

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

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

The PGIC is a single item designed to capture the patient's perception of change in bronchiectasis symptoms since first dose of IP using a 7-point scale (1- much better to 7 - much worse).

3.7.2 Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH)

The WPAI-GH version 2.0 is a self-administered tool comprised of 6 questions (Q1-Q6) which address absenteeism, presenteeism (reduced effectiveness while working), overall work

productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity (Reilly Associates et al 2012).

The following WPAI-GH endpoints will be derived:

Table 6 Derivation of WPAI-GH endpoints

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

3.7.3 Blood eosinophils

Absolute blood eosinophil counts will be assessed by a central laboratory as a part of safety haematology testing according to the visit schedule defined in Tables 1 and 2 of the CSP version 3.0.

An important marker of the biological activity of benralizumab is the reduction in eosinophils in the peripheral blood. Absolute blood eosinophil counts along with their absolute changes from baseline, and percent changes from baseline for each post-baseline visit will be calculated using conventional units (namely, cells/µL). Baseline is defined as the last non-missing value prior to the first dose of study treatment.

3.7.4 Sputum eosinophils

Differential sputum eosinophil counts will be measured in induced/spontaneous, processed sputum samples, according to the visit schedule defined in Tables 1 and 2 of the CSP version 3.0.

Differential sputum eosinophil counts along with their absolute changes from baseline, and percent changes from baseline for each post-baseline visit will be calculated using conventional units (namely, % (of total cell count)). Baseline is defined as the last non-missing value prior to the first dose of study treatment.

3.7.5 Human biological sample biomarkers

Besides blood eosinophils and differential sputum eosinophils, other blood and sputum biomarkers of inflammation (e.g., inflammatory proteins, transcriptomics) and sputum microbiome analysis [redacted] as specified in Section

8.6.1 and 8.6.2 of the CSP, will be collected as per the schedule in Tables 1 and 2 of the CSP version 3.0.

The results of any investigation will be reported separately from the CSR.

4 ANALYSIS METHODS

4.1 General principles

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

The analyses of the primary efficacy endpoint, secondary efficacy endpoints, safety endpoints and exploratory endpoints will include all data captured during the DB treatment period and OLE period if available, defined in Section 3.1.1.

Unless otherwise specified, all efficacy endpoints will be analysed using the full analysis set (FAS). Patients will be analysed according to their randomised treatment.

A treatment policy estimand will be applied to the primary analysis of the primary endpoint (along with the analysis of secondary endpoints) whereby all data during DB treatment period is included, regardless of whether a patient remains on blinded study treatment or not. A similar approach will be used for other secondary efficacy endpoints. Details regarding primary and secondary estimands are provided in Table 7.

The analysis of safety endpoints will be based on the safety analysis set. Analysis sets are defined in Section 2.1.

Table 7 Primary and secondary efficacy and main safety estimands

Statistical Category	Estimand[1]			Section
	Endpoint (Population[2])	**Intercurrent Event Strategy[1]**	**Population Level Summary[1] (Analysis)**	
Primary Objective: To evaluate the effect of benralizumab 30 mg on bronchiectasis exacerbations				
Primary	• Annualised bronchiectasis exacerbations rate during the DB period (FAS)	Included in analysis regardless of treatment discontinuation (treatment policy)	Rate ratio for interventions (NB model)	4.2.6.14.2.6.1
Secondary Objective: To evaluate the effect of benralizumab 30 mg on onset of bronchiectasis exacerbations				
Secondary	• Time to first bronchiectasis exacerbation during the DB period (FAS)	Included in analysis regardless of treatment discontinuation (treatment policy)	Hazard ratio (Cox proportional)	4.2.7.1
Secondary Objective: To evaluate the effect of benralizumab 30 mg on respiratory symptoms				
Secondary	• CFB in QoL-B-RSS at each post-baseline visit (FAS)	Included in analysis regardless of treatment discontinuation (treatment policy)	Continuous descriptive	4.2.7.3.1
Secondary Objective: To evaluate the effect of benralizumab 30 mg on pulmonary function				
Secondary	• CFB in FEV_1 at each post-baseline visit (FAS)	Included in analysis regardless of treatment discontinuation (treatment policy)	Continuous descriptive	4.2.7.2
Safety Objective: To evaluate the safety and tolerability of benralizumab 30 mg in patients with NCFB				
Safety	• Presence of TEAE/serious TEAEs (Safety)	Included regardless of treatment discontinuation	Categorical descriptive	4.2.8.1

NB = Negative binomial; CFB = Change from baseline; TEAE = Treatment emergent adverse event. DB = Double-blind.
[1] All estimand attributes are explicitly identified for primary and secondary estimands only.
[2] FAS = full analysis set.

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

All hypothesis testing will be reported using 2-sided tests, and associated nominal P-values, 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 standard operating procedure (SOPs).

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the all-patients analysis set. The number and percentage of patients within each treatment group will be presented for the DB and OLE periods separately by the following categories:

Randomised, received treatment with IP, did not receive treatment with IP (and reason), completed treatment with IP, discontinued treatment with IP (and reason), discontinued treatment with IP but completed study follow-up, withdrawn from treatment period (and reason), completed treatment period.

The number of patients randomised by country and centre will also be summarised by treatment group in the full analysis set.

4.2.2 Demography data and patient characteristics

Demography (age, gender, country, region, race, and ethnicity) and baseline characteristics will be summarised by treatment group and for ‘total’ in the FAS, using frequency and percentages (for categorical variables) and descriptive statistics of n, mean, SD, minimum, first quartile (Q1), median, third quartile (Q3), and maximum (for continuous variables).

Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For patients in countries where date of birth is not recorded, the age as recorded in the electronic case report form (eCRF) will be used.

Various baseline characteristics will also be summarised, including NCFB background therapy, medical and surgical histories. Medical and surgical histories will be summarised by MedDRA preferred term (PT) within MedDRA system organ class (SOC). Medical history will be summarised separately for past and current conditions.

The following will also be summarised for patients in the FAS by treatment group.

- Patient characteristics (weight, height, BMI, baseline eosinophil count, screening eosinophil count, chronic macrolide use (yes/no), *P aeruginosa* sputum culture status (yes/no), …etc.)
- Baseline pre-bronchodilator lung function data (pre-and post-BD FEV_1 (L), FEV_1 (% PN))
- Nicotine use and consumption (separately by smoked and non-smoked nicotine products)

4.2.3 Prior and concomitant medications

The number and percentage of patients who take prior medications, those who take permitted concomitant medications and those who take non-permitted concomitant medications during the study, will be presented by treatment group. The concomitant medication will be summarised over the DB treatment period and OLE treatment period separately. 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 DB IP administration will be calculated in days as:

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

and will be summarised by treatment group for the safety analysis set during DB treatment period.

Duration of OLE IP administration will be calculated in days as:

Last dose date of OLE IP-first dose date of OLE IP+1

and will be summarised for the OLE analysis set during OLE treatment period.

4.2.5 Study treatment compliance

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

The treatment compliance for the whole study will be calculated using the sum of administrated injection doses over the whole study divided by the total number of injection doses until the last OLE visit.

IP compliance will be calculated as: (*total doses administered / total doses expected)* $\times$ *100.*

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

The total number of doses expected includes all visits with protocol scheduled IP administration on or before a patient's IP discontinuation or treatment completion date. After CSP version 3.0 became effective, the actual visits patients had between V9 and V15 will be the expected visits and included in the calculation of the number of doses expected, since CSP version 3.0 does not require patients to complete all these visits.

4.2.6 Primary outcome variable

4.2.6.1 Primary analysis

The primary efficacy variable is the annualised bronchiectasis exacerbations rate over the DB treatment period. The primary analysis is to compare the annualised bronchiectasis exacerbations rate of benralizumab with placebo in the full analysis set.

The null hypothesis is that the exacerbation rate on benralizumab is equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on benralizumab is not equal to the exacerbation rate on placebo, i.e.,

H_0: *Rate ratio (benralizumab vs Placebo)* $= 1$
H_a: *Rate ratio (benralizumab vs Placebo)* $\neq 1$

The annualised bronchiectasis exacerbations rate in the benralizumab group will be compared to the annualised bronchiectasis exacerbations rate in the placebo group using a negative binomial model. The response variable in the model will be the number of bronchiectasis exacerbations experienced by a patient over the DB treatment period. The model will include covariates of treatment group, baseline blood eosinophil category ($\geq$ CCI /µL and $<$ CCI /µL blood eosinophil count), and number of exacerbations from previous year. The logarithm of the patient's corresponding total follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

The annualised bronchiectasis exacerbation rate and the corresponding 95% CI within each treatment group will be presented. The estimated treatment difference from placebo (i.e., the difference between benralizumab and placebo, and the rate ratio of benralizumab versus placebo), corresponding 95% CI, and 2-sided p-values for the rate ratio will be presented. Marginal standardisation methods will be used on the model estimates to present model-adjusted rates by treatment group, for the negative binomial analysis.

The total number of exacerbations, total follow-up time, and crude annualised rate of bronchiectasis exacerbations will also be summarised for OLE period.

Bronchiectasis exacerbation summary statistics will be presented by treatment group for DB period and OLE period, respectively.

4.2.6.2 Subgroup analysis for the primary outcome variable

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

- Age (<65, ≥65 years)
- Prior exacerbation (2, ≥3)
- Baseline blood eosinophil counts (< CCI /uL, ≥ CCI /uL)
- *P aeruginosa* sputum culture status (yes/no)

For each of the subgroup factors, a separate negative binomial regression model will be fitted using the same model terms as used for the primary analysis (described in Section 4.2.6.1), with additional terms for the subgroup main effect (when not already included in the model) and the treatment by subgroup interaction. A confounding covariate will be removed when conducting corresponding subgroup analysis. That is, for the subgroup analysis of prior exacerbation (2, ≥3), number of exacerbations from previous year will be removed from the covariates of the negative binomial regression model. Also, baseline blood eosinophil count category will be removed from the covariates in the subgroup analysis of this variable. The p-value for the interaction term will be presented.

Similar outputs will be presented for each subgroup category as for the primary analysis. Results will also be shown in a forest plot.

If any clinically meaningful differences are identified in the subgroup analyses for the primary endpoint, additional subgroup analyses may be conducted for other secondary endpoints.

It is important to note that the study has not been designed or powered to assess efficacy within any of these pre-defined subgroups, and as such these analyses are considered as exploratory.

4.2.7 Secondary efficacy outcome variables

4.2.7.1 Time to first bronchiectasis exacerbation (Secondary endpoint)

Time to first exacerbation in DB period will be analysed as secondary endpoint to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox-proportional hazards model will be fitted to the data with covariates of treatment group, number of exacerbations in previous year and baseline blood eosinophil category (≥ CCI /µL and < CCI /µL blood eosinophil count). Results will be presented in terms of an adjusted hazard ratio, 95% CI and a p-value. Time to first bronchiectasis exacerbation in DB period will also be displayed graphically using a Kaplan-Meier plot.

4.2.7.2 Change from baseline in pre-dose/pre-BD FEV_1 (L) (Secondary endpoint)

The change from baseline in pre-dose/pre-BD FEV_1 (L) during DB period in the full analysis set is a secondary endpoint.

Summary statistics will be provided for pre-dose/pre-BD FEV_1 (L) for observed and change from baseline over time during the DB period by treatment.

4.2.7.3 Patient reported outcome assessments

4.2.7.3.1 Change from baseline in QoL-B-RSS (Secondary endpoint)

The change from baseline in QoL-B-RSS during the DB period in the full analysis set is another secondary endpoint.

Descriptive statistics will be provided for QoL-B-RSS for observed and change from baseline values over time during the DB period by treatment group.

4.2.7.3.2 Change from baseline in LCQ scores

Descriptive statistics will be provided for LCQ (total and domain scores) for observed and change from baseline values over time during the DB period by treatment group.

4.2.7.3.3 Change from baseline in SGRQ scores

Descriptive statistics will be provided for SGRQ (total and domain scores) for observed and change from baseline values over time during the DB period by treatment group.

4.2.7.3.4 Change from baseline in QoL-B scales (excluding QoL-B-RSS)

Descriptive statistics will be provided for QoL-B-PFS, QoL-B-RFS, QoL-B-EFS, QoL-B-SFS, QoL-B-VS, QoL-B-HPS, and QoL-B-TBS for observed and change from baseline values over time during the DB period by treatment group.

4.2.8 Safety outcome variables

4.2.8.1 Adverse events

Adverse events (AEs) as defined in Section 3.4.1 will be summarised for the DB period by treatment group. AEs that occur when patients are on benralizumab treatment, no matter DB or OLE period, will also be summarised.

All AEs will be listed for each patient. All summaries will be presented by treatment group. AEs by system organ class (SOC) and preferred term (PT) and serious AEs (SAEs) by SOC and PT 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 on-study period with patients at risk of AE)*. The total period at risk for each patient will be the duration of the follow-up time. Rates will be expressed in terms of events per 100 patient-years.

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

AEs and SAEs will be summarised by SOC and PT assigned to the event by MedDRA. For each PT, the number, percentage, and exposure-adjusted rate of patients reporting at least one occurrence will be presented (i.e., multiple occurrences of an AE for a patient will only be counted once). Key subject information of SAEs will be presented.

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 causing discontinuation of the study treatment will also be summarised by SOC and PT. Key subject information of AEs causing discontinuation of IP will be presented.

Key subject information of AEs with an outcome of death will be presented.

AEs will be summarised by PT and investigator's causality assessment (related vs. not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the

same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe).

Other significant adverse events will include but may not be limited to injection site reactions. Adverse events of injection site reactions (high level term of injection site reactions) will be summarised by PT. The summary of injection site reactions will be summarised by injection site location and number of IP administrations.

4.2.8.2 Safety laboratory data

All parameters will be summarised in SI units, except for 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 clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, and high values. The shift table will present baseline and post-baseline maximum/minimum value during DB treatment period by treatment group, as applicable for each parameter and will include patients with both baseline and post-baseline data. Baseline and post-baseline maximum/minimum value during the period when patients are on benralizumab treatment, no matter DB or OLE period, will also be summarised.

Urinalysis data will be listed.

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

4.2.8.3 Vital signs

Baseline to maximum post-baseline and baseline to minimum post-baseline of vital signs data during DB treatment period value shift table will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data. Baseline to post-baseline maximum/minimum value during the period when patients are on benralizumab treatment, no matter DB or OLE period, will also be summarised in the table.

4.2.8.4 ECGs

ECG data will be listed.

4.2.9 Pharmacokinetics analyses

Benralizumab serum concentrations will be summarised using descriptive statistics by treatment over the DB study period for all patients in the PK analysis set and data presented according to actual treatment received.

Besides the descriptive PK summary described above, the rest of PK analyses will be performed at or under the guidance of AstraZeneca Research and Development and it will be presented separately.

4.2.10 Immunogenicity analyses

ADA assessments, such as ADA and neutralizing antibodies (nAb) responses, will be conducted and analysed as per the details in Appendix 9.2.

4.2.11 Exploratory outcome variables

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

All PGIS and PGIC responses will be listed.

4.2.11.2 Work Productivity and Activity Impairment (WPAI)

WPAI data will be listed.

4.2.11.3 Other exploratory analyses

Absolute blood eosinophil counts, along with their absolute changes from baseline, and percent changes from baseline will be summarised by treatment group and visit using conventional units (cells/μL). Average Blood eosinophils count over time by timepoint during DB period will be plotted. The test results and change from baseline of sputum differential eosinophil counts will be listed.

4.2.11.4 Human biological sample biomarkers

Biomarker exploratory analyses may be described in a separate analysis plan.

5 OLE TREATMENT PERIOD

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

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

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

6 INTERIM ANALYSES

No interim analysis is planned in this study.

7 CHANGES OF ANALYSIS FROM PROTOCOL

Due to the significant changes in the study conduct, several analyses originally planned and described in the study protocol version 3.0, will not be performed. The protocol analyses to be excluded are:

- "The proportion of patients with ≥ one bronchiectasis exacerbation during the DB treatment period will be a supportive variable to the primary outcome variable", which was described in the CSP Section 9.4.2.1.

- Change from baseline in QoL-B-RSS, FEV1, LCQ, QoL-B scales (excluding QoL-B-RSS), and SGRQ will be analysed from a mixed-effect model for repeated measures, as described in the CSP Section 9.4.2.3.

- "Descriptive statistics will be provided for PGIS and PGIC responses over the DB treatment period", and change from baseline in blood eosinophils will be analysed from a mixed-effect model for repeated measures, as described in the CSP Section 9.4.2.4.

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9 APPENDIX

9.1 Partial dates for adverse events and prior/concomitant medication

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

- 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
- 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
- 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 start year is before the year of the first study treatment
- If the end date is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence
  - Date of death if the patient died in the same year
  - Last study treatment date if the year of occurrence is the same as the last study treatment date
- If the start date is null, the date will be set to:
  - The date of first study treatment
  - January 1 of the same year as the end date, if the end date suggests that the start date could be prior to the date of first study treatment

- If the end date is null and not recorded as ongoing, the date will be set to:
  - The date of the first study treatment, if the start date is prior to the date of first study treatment
  - The date of last visit, if the start date is on or after the date of first study treatment

Prior/concomitant medications

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

9.2 Immunogenicity variables

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titre) and ADA data will be collected at scheduled visits shown in Table 1-2 of the CSP v3.0. ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well. In addition, the presence of neutralizing antibodies (nAb) will be tested in all ADA-positive samples using a ligand binding assay. The nAb results will be reported as positive or negative.

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

For each subject, the following ADA responses will be evaluated over the DB period:

- Subjects who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as ADA positive). The proportion of ADA-positive subjects in a population is known as ADA prevalence.
- Subjects who are ADA negative at all assessments, including baseline and post-baseline (also generally referred to as ADA negative).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and at least one post-baseline assessment.
- Treatment-emergent ADA positive (referred to as ADA incidence). A positive post-baseline result and either of the following statements holds:
  - Baseline is ADA negative and at least one post-baseline assessment is ADA positive. This is called treatment-induced ADA positive.
  - Baseline is ADA positive, and the baseline titre is boosted by greater than the variability of the assay (i.e. ≥ 4-fold increase) at ≥1 post-baseline timepoint. This is called treatment-boosted ADA positive.
- Subjects who are ADA positive but not fulling the conditions above for Treatment-emergent ADA positive (also referred to as non-TE ADA positive).
- Subjects who are persistently ADA positive, which is defined as ADA negative at baseline and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.
- Subjects who are transiently ADA positive, defined as ADA negative at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- nAb prevalence; defined as nAb positive at any visit including baseline and/or post-baseline (also referred to as nAb positive)

- nAb incidence; defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit. Patients who are ADA-negative at baseline are included to ensure that all patients who are nAb positive for the first time post-baseline satisfy this definition, given that all patients who are ADA negative at baseline will not have a nAb result reported.
- Subjects who are treatment-emergent ADA positive with maximum post-baseline titre > median of maximum post-baseline titres. The median of maximum post-baseline titres will be calculated based on the maximum post-baseline titre of each ADA positive subject.

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

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

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