Clinical Study Protocol	
Study Intervention	Benralizumab
Study Code	D325BC00001
Version	3.0
Date	10 January 2023
EudraCT Number	2020-004068-24

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)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Local Sponsor in Japan: AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifier Number(s): EudraCT number 2020-004068-24

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioeth cs and in compliance with prevailing laws and regulations.

Protocol Number: 3.0

Amendment Number: 2

Study Intervention: Benralizumab

Study Phase: III

Short Title: Efficacy and Safety of Benralizumab in Patients with Non-cystic Fibrosis Bronchiectasis

Study Physician Name and Contact Information will be provided separately.

PPD

Scotland, UK

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2 – CSP version 3.0	10 January 2023
Amendment 1 – CSP version 2.0	17 December 2020
Original CSP (version 1.0)	16 November 2020

CSP Version 3 (10 January 2023)

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment

The initial protocol plan was to randomise approximately 420 eligible patients to investigational product with a stratification 2:1 for ≥CCI/µL and <CCI/µL blood eosinophil count, respectively. However, the coronavirus disease 2019 pandemic's impact on population characteristics that are part of the trial's inclusion criteria has resulted in recruitment challenges. These challenges, combined with other external uncertainties, have led to the sponsor's decision to stop further recruitment into the study. This decision was not due to safety or efficacy concerns for benralizumab in the non-cystic fibrosis bronchiectasis (NCFB) population. Therefore, all randomised patients are allowed to continue the treatment. The collected data will be analysed and shared with the scientific community to enhance understanding of NCFB.

Due to the sponsor's decision to stop recruitment early, this clinical study protocol has been modified such that the duration of the double-blind period for each patient is 28 to 52 weeks, after which eligible patients will enter an open-label extension of approximately 32 weeks (approximately 24 weeks of benralizumab administration followed by an 8-week follow-up visit) that will focus on safety assessments. The protocol, including the study duration, sample size, primary study population, evaluated parameters, the timing of endpoint analyses, statistical analyses to be performed, and frequency and timing of activities in the schedule of assessments have been updated to reflect the significant changes in the overall study design and conduct.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
Substantial modifications		
All applicable sections	• Text "over the 52-week treatment period" was changed to "over the DB treatment period."	• Text updated to reflect the changes on study duration.
Naming conventions	• Subheading and definitions for DB and OLE periods were added.	• Text added to define and describe the revised DB and OLE periods after modifications to the study's duration and conduct.
1.1 Synopsis	• Changes were added to the following sections: Objectives and Endpoints, Overall Design, Number of Patients, Study Arms and Duration, Data Monitoring Committee, and Statistical Methods.	• Content updated to reflect the changes on study duration (DB and OLE periods) and conduct and to ensure consistency with the main body of the CSP.
1.2 Schema	• Revisions to Figure 1 and new footnotes added to describe changes to the DB and OLE periods: ° DB period: 28 to 52 weeks ° OLE period: treatment period is approximately 24 weeks followed by a FU visit 8 weeks after the last dose of IP (total of approximately 32 weeks [a]). ° Strategy to transition patients to the new OLE SoA in this amendment (CSP version 3.0) was briefly described.	• Content updated to reflect the changes on study duration and conduct and to ensure consistency with the main body of the CSP.
1.3.1 Strategy to Transition Patients to the New Schedule of Activities	• New section added explaining the strategy to transition patients to the new OLE SoA in this amendment (CSP version 3.0). This strategy takes into account patients who have not reached V8 of the DB period, are between V9 and V14 of the DB period, are between V15 and V20 of the previous OLE SoA, or have completed or are past V21 according to the previous OLE SoA (CSP version 2.0).	• Strategy added because depending on the timing of patient randomisation and when this amendment (CSP version 3.0) becomes effective, patients will have various duration of the DB treatment period, and some patients may already be in the OLE.
1.3 SoA (Table 1 - Schedule of Activities for the Double-blind Period)	• Footnote (a) added to indicate that all patients will complete the DB treatment period up to at least V8, then they will be transferred to the new OLE SoA (CSP version 3.0). The note also indicates that the strategy to transition patients to the new SoA is found in Section 1.3.1. • Various footnotes (g, j, k) were revised to note any revisions to the assessments.	• Footnote (a) was added to clarify the change in study duration for the DB period and how patients will be transition from the previous SoA (CSP version 2.0) to the new one (CSP version 3.0). • Changes in remaining footnotes were made to reflect the changes on study duration and assessments due to early closure of recruitment.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
1.3 SoA (Table 2 - Schedule of Activities for the Open-label Extension	• Table 2 has been replaced by a simplified and shortened version of the OLE (24-week treatment period up to V21, with a FU visit 8 weeks after the last IP dose, ie, Week 32 [a]). • The intended efficacy assessment during the first year of OLE have been omitted. • Footnotes in previous OLE table (CSP version 2.0) were updated as needed.	• All revisions made to clarify protocol: The OLE has been shortened and changes made to streamlined OLE as this period changed from 1 year to approximately 32 weeks [a] (with no further extensions).
1.3 SoA (previous Table 4 - Schedule of Activities for the Open-label Extension (Year 2 and Year 3) (CSP version 2.0)	• Previous Table 4 in CSP version 2.0 was removed. • The possibility for a second and third year of OLE were removed.	• Removed Year 2 and Year 3 of OLE in this amendment (CSP version 3.0) because OLE was changed to approximately 32 weeks [a]; the possibility for a second and third year of OLE is no longer applicable.
1.3 SoA (current Table 3 - Schedule of Assessments for ePRO Endpoints (Double-blind Treatment Period)	• ePRO assessments were omitted for the OLE. • "Open-label Extension Year 1" was removed from the table title.	• All revisions made because no ePRO assessments will be performed during the OLE.
2.3.2 Benefit Assessment	• Text edited from "eligible patients will have access to benralizumab for at least one year in the OLE" to "during the OLE."	• Text revised due to changes in the duration of the OLE period.
3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (Table 5 "Objectives and Variables for the Double-blind Treatment Period")	• The following secondary objectives (and associated endpoints evaluating the effect of benralizumab 30 mg Q4W) were removed: ◦ Effect on severe bronchiectasis exacerbations ◦ Effect on the frequency of antibiotic use for bronchiectasis exacerbations ◦ Effect on NCFB-related healthcare resource utilisation	• These 3 readouts are unlikely to give any additional information given the low number of NCFB+EI randomised patients and short duration of the trial.
3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (Table 5 "Objectives and Variables for the Double-blind Treatment Period")	• The following exploratory objective (and associated endpoints) was removed: Evaluate the effect of benralizumab 30 mg Q4W on bronchiectasis exacerbations of different phenotypes (eg, eosinophilic, neutrophilic, viral, bacterial, paucigranulocytic), classified based on sputum cell counts as well as sputum and blood biomarkers. • The endpoint "Baseline levels and change from baseline in blood and sputum eos CCI proteins CCI " was removed.	• This objective will no longer be feasible given the reduced number of evaluable exacerbations. • Revision made to simplify the language, since eos CCI protein analyses are covered within the scope of the endpoint description for "Baseline levels and change from baseline in blood and sputum biomarkers of inflammation."

Summary of Changes Table

Section # and name	Description of change	Brief rationale
4.1 Overall Design	• The duration of the DB and OLE periods and description of each period were revised. • Number of patients randomised was updated to 100 patients. • Current ratio of patients in the ≥[redacted]/µL and <[redacted]/µL blood eos strata was added. • Number of sites and countries was updated. • Primary objective and description of study and analyses were revised as needed. • Definition of database lock was updated.	• Data updated as of the date of stopping recruitment. • Revisions made to reflect the changes on study duration (DB and OLE periods), assessments, and analyses to be performed.
4.2.1 Rationale for Selection of Patient Population	• Text added to indicate that "Due to the decision to stop recruitment early, the study achieved a total of 100 randomised patients with a ≥[redacted]/µL:<[redacted]/µ blood eosinophil strata size ratio of 1:4." • Text was added to indicated that "Because of the low number of patients randomised in this study, the primary efficacy analysis will be conducted for patients in the FAS."	• Data updated as of the date of stopping recruitment. • Change made because the main analysis based on patients in the ≥[redacted]/µL blood eos stratum will not be feasible due to the low number of patients in this stratum.
4.2.4 Rationale for Selection of Study Duration	• Text added to indicate that due to the early termination of recruitment, the duration of the DB treatment period will fluctuate between 28 and 52 weeks.	• Text was updated to reflect the changes on study duration (DB period).
5.2.1 Criteria to be Confirmed Prior to Commencing OLE at Visit 15	• Requirement for serum pregnancy and HIV-1 or HIV-2 testing at V14 was removed. • The text "Patients who enter the OLE must not have been randomised in error" was removed. • Text was revised to indicate that patients who complete Visit 15 on IP should consult with their investigator before entering the OLE.	• Revisions made because these tests are no longer a requirement. • Revisions made because this is no longer a requirement. • Text added for further clarification.
6.1.2 Duration and Frequency of Treatment with Investigational Products	• DB treatment period duration was updated to "28 to 52 weeks." • OLE period was updated to "a treatment period of 24 weeks followed by a FU visit 8 weeks after the last dose of IP (for a total of approximately 32 weeks [a])." • Footnote added to indicate 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 and OLE period of more than 32 weeks. • The statement indicating that the sponsor may choose to extend the study beyond one year was removed.	• Text updated to reflect the changes on study duration.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
6.2.1 Preparation and Handling of Investigational Product	• Text added to clarify that all doses of IP during the DB and OLE periods (except for the dose at V20 potentially) will be administered by an HCP at the site during the visits. • Text added to clarify that a remote IP administration can optionally be done at V20 during the OLE. • Text added to indicate that "IP is to be administered within the visit windows as scheduled in the SoA." • The serum pregnancy test at V14 was deleted. Instead, the urine pregnancy test will be performed intermittently according to SoA (Table 2).	• Revisions were made according to current study requirements.
6.2.3 Optional At-home or Remote-location Investigational Product Administration	• Added "remote" to the sentence "If the IP is administered at the patient's home/remotely, the patient should administer the IP the same day as the study visit, after the remote visit assessments." • Text following text was revised: ° Old text: To reduce patient burden and to allow flexibility during the OLE treatment period, patients will have the option for at-home or remote-location patient/caregiver administration of IP using the APFS. ° New text: During the OLE period, patients will have the option for one at-home or remote-location visit (Visit 20) with patient/caregiver administration of IP using the APFS.	• Revisions made to clarify study procedures during the optional remote visit.
6.2.3.1 Optional Remote Visits for Patients Doing At-home or Remote-Location Investigational Product Administration	• Remote visits changed from "some visits" to "Visit 20." • Text added to indicate that V20 can be done as a remote visit for patients "who received appropriate training to do at home/remote-location IP administration." • Dispensation of urine dipsticks for pregnancy testing at the optional remote visits during OLE Year 1 was removed. • Mandatory onsite visits during Year 2 and Year 3 extension of the OLE were removed.	• Other optional visits have been removed. • Revisions made to clarify study procedures during the optional remote visit. • Dispensation of urine dipsticks for pregnancy testing at the optional remote visits does no longer apply. • There will be no further extension of the OLE.
6.3.4 Open-label Extension Period – Benralizumab Administration Only	• Week 52 was removed for the sentence "Open-label IP administration will begin at Visit 15."	• Edited because V15 in the new SoA could occur anywhere from 4 weeks after V8 (ie. Week 28) to Week 52.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
7.1.1 Reasons for Discontinuation of Investigational Product	• Revision added" "Upon the approval of this amendment (CSP version 3.0), patients who prematurely discontinue IP will be withdrawn from the study after mandatory visits are performed (Section 7.1.2)."	• Clarification of revised study procedures upon premature discontinuation of IP. Changes made to streamline CSP and reduce burden on patients and sites after decision to stop further recruitment into the study.
7.1.2.1 Early Discontinuation of Study Treatment (Investigational Product Discontinuation During the DB Period)	• Revisions made to indicate that patients who prematurely discontinued IP will be withdrawn from the study.	• Changes made to streamline CSP and reduce burden on patients and sites after decision to stop further recruitment into the study.
7.1.2.2 Discontinuation of Treatment on Notification of Closure of Study	• Content added to clarify procedures once this amendment (CSP version 3.0) becomes effective.	• Changes made to streamline CSP and reduce burden on patients and sites after decision to stop further recruitment into the study.
8.1 Administrative and General Procedures	• Text added to define changes in duration of the DB period. • Text added to indicate the section in which the strategy to transition each patient from the previous amendment (CSP version 2.0) to this amendment (CSP version 3.0) can be found. • Statement added to indicate that blood volume collected per patient will depend on the duration of the patient in the study and may be different for each patient but will not exceed the maximum amounts specified in the CSP.	• Changes made to clarify description of DB period and strategy to transfer patients to the new SoA/study design in CSP version 3.0. • Text added to clarify that the blood volume collected per patient will vary because patients will be transitioned into the new OLE (CSP version 3.0) at different times.
8.2.6 Computed Tomography Scans and SoA Table 2	• Follow-up CT scan performed (when applicable) in both <CCI/µl and ≥CCI/µl eos populations.	• To obtain longitudinal CT data on disease progression and variability in NCFB across eos levels. This is of scientific value and will inform the design of future studies in bronchiectasis.
8.3.4.1 Pregnancy Test	• Dispensation of pregnancy test for remote visits was removed. • Serum beta human chorionic gonadotropin testing at V14 was removed. • V20 (as specified in the SoA [Table 2]) can optionally be done as a remote visit for patients who are doing at home/remote-location IP administration. WOCBP should be asked if they are pregnant during the telephone visit.	• Revisions were made according to current requirements.
8.3.4.2 Serology	• Testing for hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 at V14 was removed.	• Revisions were made according to current requirements.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
8.6.1.1 Sputum Collection	• Text changed from "At Visits 2, 8, and 15, any unscheduled visits, and any IPD visit (Section 1.3), an induced sputum will be collected …" to "Upon the approval of this amendment (CSP version 3.0), an induced sputum sample will be collected at Visits 2 and, 8, any unscheduled visits, and any IPD visit (Section 1.3)." • Text added: No induced sputum samples will be collected during the OLE period.	• Revisions were made according to current requirements.
9.1 Statistical Hypotheses	• Population to be analysed was updated from the PFAS (patients in the ≥[redacted]/µL blood eos stratum of the FAS) to the FAS.	• Change was made to reflect the current patient population due to shortened study duration.
9.4 Statistical Analyses	• "Primary analysis" was changed to "efficacy analysis."	• To reflect the current strategy that only one final database lock is planned for analysis.
9.4.1 General Considerations	• End of DB period changed from Week 52 to V15. • Text was changed from "FAS including all patients through the end of the DB period (Week 52)" to "FAS population, including all patients through the end of the DB period (Visit 15)." • Text revised to indicate that efficacy analysis will be based on the FAS. • Definition of the database lock was updated.	• Edits made because depending on the timing of patient randomisation and when this amendment (CSP version 3.0) becomes effective, patients will have various duration of DB treatment periods from 28 weeks up to 52 weeks. • Changes made to reflect the current patient population and shortened study duration.
9.4.2.2 Primary Endpoint	• Primary population changed from "patients in the ≥[redacted]/µL blood eos stratum" to "the FAS." • Baseline blood eos category (<[redacted] and ≥[redacted] blood eos count) added as a covariate for the primary endpoint analysis. • *Pseudomonas aeruginosa* sputum culture status (yes, no), current chronic macrolide use (yes, no), and region were removed as covariates • The exacerbation rate will be calculated and analysed over the patient's DB treatment period. • Text related to analysis of the exacerbation rate in patients with different ranges of baseline blood eos counts was removed. • Sensitivity analysis was removed. • Gender, region, and BSI were removed from subgroup analysis.	• Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
9.4.2.3 Secondary Endpoint(s)	• All secondary efficacy endpoints will now be summarised for patients in the FAS instead of separately by blood eos stratum. • Data collection for the primary analysis was changed from "up to and including the Week 52 time point" to "up to and including the last visit in the DB treatment period." • Sentence removed: The estimate of the treatment effect at Week 52 will be based on a contrast from this MMRM model. • Analysis of secondary efficacy endpoints in patients with different baseline blood eos counts was removed. • Baseline blood eos category (<CCI and ≥CCI blood eos count) added as a covariate for the secondary endpoint analysis of (a) time to first bronchiectasis exacerbation and (b) change from baseline in QoL-B-RSS and FEV_1. • *P. aeruginosa* sputum culture status (yes, no), current chronic macrolide use (yes, no), and region were removed as covariates for the secondary endpoint analysis of (a) time to first bronchiectasis exacerbation and (b) change from baseline in QoL-B-RSS and FEV_1. • The primary analysis will fit a MMRM model using the data collected "up to and including the last visit in DB treatment period." • Analyses of the (a) proportion of patients with ≥ 1 bronchiectasis exacerbation during the 52-week treatment period, (b) annualised rate of severe bronchiectasis exacerbations and hospitalisations due to bronchiectasis exacerbations, (c) frequency of antibiotic use due to bronchiectasis exacerbations, and (d) frequency and annual rate of healthcare resource utilisations will not-be performed.	• Changes made to reflect the current patient population and study duration and avoid potential model non-convergence issue given the limited sample size.
9.4.5 Methods for Multiplicity Control (in CSP v 2.0)	• Section 9.4.5 in CSP version 2.0 was removed.	• Changes made because this section is no longer applicable.
Appendix A 6 Data Quality Assurance	• Text revised: Records and documents retention changed from "15 years" to "25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal Schedule."	• Changes were made to comply with AstraZeneca new CSP template guidelines.
Appendix C 1 Chain of Custody	• Text added: All appropriately consented samples will be retained for maximum 15 years from last subject last visit.	• To clarify appropriate retention of consented human biological samples per the AstraZeneca CSP template guidelines.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
Non-substantial modifications		
All applicable sections	• "Primary database lock" was changed to "database lock." • Timing of database lock was updated to "after the last patient completes the OLE."	• Due to the changes on study duration, a single database lock will now occur after the last patient completes the OLE.
All applicable sections	• Minor updates to footnotes as needed.	• Revisions made to correct typos, add new definitions, and correct format as needed.
All applicable headings	• Minor updates were made to several heading and subheading titles	• Revision was made to comply with AstraZeneca CSP template guidelines.
Cover page	• EUDRACT number added below version date	• Revision was made to comply with AstraZeneca CSP template guidelines
1.3 SoA (Table 1 - Schedule of Activities for the Double-blind Period)	• New footnote (o) added to clarify that sputum cultures will be performed for all patients including patients in China and collected at V2, V8, and V15 and IPD visit in the DB period. The footnote also indicates that sputum culture will be analysed at the central laboratory and provides procedures to be followed if the sample cannot be delivered to the central laboratory within 48 hours of collection.	• Text added to clarify sample collection and processing procedures in the DB period.
2.3.1 Risk Assessment	• The protocol text has been simplified. Instead, the radiology manual is referenced for additional details regarding radiation exposure.	• It is not possible to accurately determine the previously stated effective dose in mSv on an individual basis, but it is still relevant on a population level. This is described in detail in the radiology manual. Target radiation exposure levels for the study have not changed.
2.3.3 Overall Benefit: Risk Conclusion	• Slight revision of text revision from "Taking into account the measures taken to minimise risk to patients participating in this study …" to "For patients participating in the study …"	• Minor revision in language added due to changes in the duration of the OLE period. There are no changes to the risk/benefit conclusion.
3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (Table 5 "Objectives and Variables for the Double-blind Treatment Period")	• Primary efficacy endpoint was revised from "Annualised exacerbation rate at Week 52" to "Annualised exacerbation rate estimated for the DB treatment period."	• Endpoint was updated to reflect the changes on study duration.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (Table 5 "Objectives and Variables for the Double-blind Treatment Period")	• Text "Response proportions in PGIS and PGIC" was changed to "PGIS and PGIC."	• Slight revisions to these 2 exploratory endpoints to simplify the language.
3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS (Table 6 "Objectives and Variables During the Open-Label Extension")	• Most secondary and exploratory objectives of the OLE were removed, except for characterisation of PK and immunogenicity (exploratory objectives). • The effect of benralizumab 30 mg Q4W on blood biomarkers of inflammation and biomarkers of bronchiectasis pathogenesis will not be evaluated. • Objective "To characterise the effect of benralizumab 30 mg Q4W on blood eos" was changed from efficacy to PD objective.	• Changes made because the OLE will now last approximately 32 weeks [a] (including the FU visit), and it will focus on safety assessments. • Blood eos will be the only PD biomarker assessed in the OLE. • Minor edit was made for consistency across benralizumab protocols.
4.1 Overall Design	• The statement, "The sponsor may reserve the right of terminating the OLE early (eg, if development in this indication is terminated or marketing authorisation is obtained)" was removed.	• This text is covered in Section 7.1.2.2. "Discontinuation of Treatment on Notification of Closure of Study"
4.4 End of Study Definition	• New template text added: definition of the end of the study per the European Union and the FDA.	• Revision was made to comply with AstraZeneca new CSP template guidelines.
5.3.1 Meals and Dietary Restrictions	• New subheading and text added: "Meal restrictions recommended prior to spirometry measurements are found in Section 8.2.5.2."	• Text added to clarify the CSP section where meal restrictions prior to spirometry can be found.
5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/ Administration of Study Intervention	• Heading added per CSP template. No content was added because the section is not applicable for this study.	• Revision was made to comply with AstraZeneca CSP template guidelines
6.2.5 Shipping and Storage	• Text added to clarify that PI or designee is responsible for confirming that appropriate conditions (eg, temperature) are maintained during transit for all IP received at the site and throughout the entire study. • Text added to clarify reporting procedures in the event of a temperature excursion detected at any time during the study.	• Revisions were made to comply with AstraZeneca CSP template guidelines.
6.3.2 Methods for Ensuring Blinding	• Definition of database lock was added.	• Clarification: There will be one database lock in the study once this amendment (CSP version 3.0) is approved.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
6.3.2.1 Maintaining the Blind to the Patient's Blood Eosinophil Counts 6.3.2.2 Maintaining the Blind to the Patient's Induced Sputum Cell Count Analysis – Double-blind Period	• Week 60 was removed. V17 will now correspond to 8 weeks passed the first dose of OLE.	• Content updated to reflect the changes on study duration and to ensure consistency across the CSP sections.
6.8 Treatment of Overdose	• A new section was added. • Text moved from Section 8.4.11 "Reporting of Overdose" to this section.	• Revisions were made to comply with AstraZeneca CSP template guidelines. No new text was added.
7.1.2 Procedures for Early Discontinuation of Investigational Product and at End of Study	• The following sentence was removed: "The EOT visit is only used following the last dose of IP when AstraZeneca declares the end of the study (Section 4.4)."	• This text is no longer applicable.
7.1.2.2 Discontinuation of Treatment on Notification of Closure of Study	• The examples in the statement "The sponsor may reserve the right of terminating the OLE early" were removed.	• As the examples cannot cover all possible reasons for early OLE termination, only the general statement was kept.
8.2.6 Computed Tomography Scans and SoA Table 2	• The following text was deleted: ° The follow-up CT scan will only be performed if the baseline CT scan was evaluable by the central imaging vendor. When CT scans are used for quantitative assessments, the follow-up scans should always be performed on the same scanner and using the same scan parameters as the baseline scan • And replaced with: ° For subjects with an evaluable baseline CT scan (as determined by the imaging vendor), a follow-up CT scan will be performed if possible. The follow-up scan needs to be performed according to the instructions from the imaging vendor.	• Text revised to further clarify the conditions for performing a follow-up CT scan
8.4 AEs, SAEs, and Other Safety Reporting	• Text about how an AE should be reported was updated. • AEs and SAEs variables to be collected was moved from Section "Follow-up of AEs and SAEs" to Section 8.4"AEs, SAEs, and Other Safety Reporting." • Section 8.4 heading was changed from "Adverse Events and Serious Adverse Events" to "AEs, SAEs, and Other Safety Reporting." • "AE description" was added to variables to be collected for SAEs.	• All changes were made to comply with current AstraZeneca template requirements.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
8.4.9 Medication Error, Drug Abuse, and Drug Misuse	• Section 8.3.9 "Medication Error" in CSP version 2.0 was updated to include drug abuse and drug misuse in addition to medication error. • Title was changed from "Medication Error" to "Medication Error, Drug Abuse, and Drug Misuse."	• Changes were made to comply with current AstraZeneca template requirements.
8.4.9.1 Timelines 8.4.9.2 Medication Error 8.4.9.3 Drug Abuse 8.4.9.4 Drug Misuse	• Previous text in Section 8.3.9 "Medication Error" in CSP version 2.0 was added in Section 8.4.9.1. • New template text added in Sections 8.4.9.2, 8.4.9.3, and 8.4.9.3.	• Changes were made to comply with current AstraZeneca template requirements.
8.4.11 Reporting of Overdose	• Section 8.4 "Overdose" in CSP version 2.0 was moved to a new location (Section 8.4.11) within the CSP version 3.0, and the title was changed to "Reporting of Overdose." Some of the language updated but reporting period remains the same. • Definition and treatment of an overdose were moved to new Section 6.8 "Treatment of Overdose."	• Changes were made to comply with current AstraZeneca template requirements.
8.5 Human Biological Samples	• Sputum culture will be analysed at the central laboratory; however, if due to the site's location the sample cannot be delivered to the central laboratory within 48 hours of collection, sputum culture needs to be analysed at the certified local laboratory following the same methodology as the central laboratory.	• Change was made to allow sputum culture at some countries where it needs to be analysed locally.
8.6.1 Collection of Mandatory Samples for Biomarker Analysis	• The following text was added: Results from the exploratory biomarker analyses may be reported separately from the CSR.	• Text was added for clarification.
8.6.1.1 Sputum Collection	• Minor change in text: • "Processed sputum samples **will** be used …" to "Processed sputum samples **may** be used …" • "The spontaneous, unprocessed sputum samples **will** be used for …" to "The spontaneous, unprocessed sputum samples **may** be used for …"	• Text changed from "will" to "may" in several places to reflect the possibility that some of the planned biomarker analyses may not be performed due to the reduced number of patients and the shorter duration of the study.
8.6.2 Transcriptomics and Microbiome Analyses	• Minor change in text: • "Transcriptomic analysis **will** be performed …" to "Transcriptomic analysis **may** be performed …" • "Microbiome analyses **will** be conducted using …" to "Microbiome analyses **may** be conducted using …"	• Text changed from "will" to "may" in several places to reflect the possibility that some of the planned biomarker analyses may not be performed due to the reduced number of patients and the shorter duration of the study.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
8.10 Study Participant Feedback Questionnaire – Not Applicable	• Heading added per CSP template. No content was added because the section is not applicable.	• Change was made to comply with AstraZeneca CSP template guidelines.
9.2 Sample Size Determination	• Added reason explaining why the study is no longer sufficiently powered to assess the hypothesis test for the primary efficacy endpoint as described in CSP version 2.0. • Number of randomised patients and number of patients in the ≥[redacted]/µL and <[redacted]/µL blood eos strata were added. • Planned patient stratification at randomisation was added.	• Change was made to reflect the current patient population and study duration.
9.4.2.1 Calculation or Derivation of Variables for Efficacy Analyses	• Follow-up time for exacerbations for a patient was changed from "the 52-week DB period" to "up to 52 weeks." • Exacerbation follow-up was changed "from randomisation to the date of Visit 15" to "from randomisation to the date of the last DB treatment period visit." • Annualised exacerbation rate per patient to be standardised "per length of the DB period" and not "per the 52-week DB period". • Sections "Annualised Rate of Severe Bronchiectasis Exacerbations" and "Annualised Rate of Hospitalisations due to Bronchiectasis Exacerbations" were removed.	• Changes made to reflect the current patient population and study duration.
9.4.2.4 Exploratory Endpoints	• Descriptive statistics will be provided for PGIS and PGIC responses over the DB treatment period. • WPAI-GH over time will be listed (descriptive statistics will not be provided). • Change from baseline in blood eos will be analysed using a MMRM model with treatment group, baseline blood eosinophil, visit and treatment*visit interaction as covariates in the model.	• Changes were made to reflect the current analysis plan.
9.4.3 Safety Analyses	• Laboratory data summaries via shift tables were removed. • Summary statistics of observed and change from baseline values in vital sign and ECG values were removed. Vital sign and ECG data will be listed. • Summaries of clinically notable vital sign abnormalities will not be presented.	• Changes were made to reflect the current patient population and study duration.
9.5 Interim Analyses	• Text added to indicate that no interim analysis is planned.	• Interim analysis is not applicable.

Summary of Changes Table

Section # and name	Description of change	Brief rationale
9.6 Analyses of Data from the Open-Label Extension	• Efficacy endpoints was removed from analysis and eos count endpoint was added.	• Efficacy endpoints are not applicable for the study due to early closure of recruitment.
9.7 Data Monitoring Committee	• Text added to indicate that a DMC was not established.	• The DMC is not applicable for the study due to early closure of recruitment.
Appendix A 1 Regulatory and Ethical Considerations Appendix A 3 Informed Consent Process Appendix A 4 Data Protection Appendix A 5 Dissemination of Clinical Study Data Appendix A 6 Data Quality Assurance Appendix B 4 Medication Error, Drug Abuse, and Drug Misuse Appendix C 3 International Airline Transportation Association 6.2 Guidance Document	• New template text was added. • For changes related to records and documents retention (Appendix A 6), see substantial changes. • For text related to retention of consented human biological samples (Appendix C 1), see substantial changes.	• Changes were made to comply with AstraZeneca new CSP template guidelines.

[a] Note that any patient who has attended or is past Visit 22 per the previous OLE SoA (CSP version 2.0) when this amendment (CSP version 3.0) becomes effective will have an OLE period more than 32 weeks. These patients will go directly to the FU visit (8 weeks after the last dose of IP) according to the OLE SoA in this amendment (CSP version 3.0).

Formatting improvements, such as updates to abbreviations, minor changes to footnotes, punctuation corrections, and minor editorial changes are not included in this summary.

AE(s) = adverse events(s); BSI = Bronchiectasis Severity Index; CSP = clinical study report; DB = double-blind; CSR = clinical study report; CT = Computed tomography; DMC = Data Monitoring Committee; ECG = electrocardiogram; CCI[CG] CCI [redacted][CG] eos = eosinophil(s); EOT = end of treatment; ePRO = electronic patient-reported outcome; FAS = full analysis set; FDA = Food and Drug Administration; FEV_1 = forced expiratory volume in one second; FU visit = follow-up visit; HCP = Healthcare professional; HIV = human immunodeficiency virus; IP = investigational product; IPD = investigational product discontinuation; MMRM = mixed-effect model for repeated measures; NS = non-substantial; NCFB = non-cystic fibrosis bronchiectasis; NCFB+EI = non-cystic fibrosis bronchiectasis with eosinophilic inflammation; OLE = open-label extension; PFAS = primary full analysis set (patients in the ≥ CCI /µL blood eosinophil stratum in the FAS); PD = pharmacodynamics; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PI = Principal investigator; PK = pharmacokinetics; Q4W = every 4 weeks; SAE(s) = serious adverse events; QoL-B-RSS = Quality of Life-Bronchiectasis-Respiratory Symptoms Scale; S = substantial; SoA = Schedule of Activities; V = visit; WOCBP = woman/women of childbearing potential; WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA(s)	Anti-drug antibody(ies)
AE(s)	Adverse event(s)
APFS	Accessorised prefilled syringe
ATS/ERS	American Thoracic Society/European Respiratory Society
BED	Bronchiectasis exacerbation diary
BSI	Bronchiectasis Severity Index
CFR	Code of Federal Regulations
COPD	Chronic obstructive lung disease
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTIS	Clinical Trial Information System
DB	Double-blind
DNA	Deoxyribonucleic acid
ECG(s)	Electrocardiogram(s)
eCRF	Electronic case report form
ePRO	Electronic patient-reported outcome
EU	European Union
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FU visit	Follow-up visit
FVC	Forced vital capacity
GCP	Good Clinical Practice
HCP	Healthcare professional
HIV	Human immunodeficiency virus
IATA	International airline transportation associations
ICF	Informed consent form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IMP(s)	Investigational medicinal product(s)
IP	Investigational product

Abbreviation or special term	Explanation
IPD	Investigational product discontinuation
IRB(s)/IEC(s)	Institutional review board(s)/independent ethics committee(s)
IxRS	Interactive voice/web response system
LCQ	Leicester Cough Questionnaire
mMRC	Modified Medical Research Council
MMRM	Mixed-effect model for repeated measures
NCFB	Non-cystic fibrosis bronchiectasis
NCFB+EI	Non-cystic fibrosis bronchiectasis with eosinophilic inflammation
NIMP(s)	Non-investigational medicinal product(s)
NTM	Nontuberculous mycobacteria
OLE	Open-label extension
P. aeruginosa	*Pseudomonas aeruginosa*
PD	Pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL-B	Quality of Life-Bronchiectasis
QoL-B-RSS	Quality of Life-Bronchiectasis-Respiratory Symptoms Scale
RTSM	Randomisation and Trial Supply Management
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
WOCBP	Woman/women of childbearing potential
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health

NAMING CONVENTIONS

Throughout this clinical study protocol, the double-blind (DB) and open-label extension (OLE) treatment periods are defined as follows:

DB treatment period: The revised DB period consists of a treatment period of 28 to 52 weeks (depending on the timing of patient randomisation and when this amendment [protocol version 3.0] becomes effective). Note that patients who have already attended or are past Visit 9 of the schedule of assessments for the DB period when this amendment (protocol version 3.0) becomes effective will have a DB treatment period over 28 weeks.

During the DB treatment period, the patients will receive benralizumab 30 mg or matched placebo every 4 weeks starting at Visit 2. For patients ineligible or unwilling to participate in the OLE, Visit 15 is to be completed as the last DB treatment period visit, followed by a follow-up (FU) visit 8 weeks after the last of dose of investigational product (IP).

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

During the OLE period, the patients will receive open-label benralizumab 30 mg every 4 weeks starting at Visit 15. Only patients who complete the DB treatment period on IP may be eligible to continue into the OLE period upon consultation with their investigator.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

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)

Brief Title

Efficacy and Safety of Benralizumab in Patients with Non-cystic Fibrosis Bronchiectasis

Regulatory Agency Identifier Number(s):

EudraCT number 2020-004068-24

Rationale

There is an unmet medical need for treatments for non-cystic fibrosis bronchiectasis (NCFB). Emerging evidence suggests that there is a subpopulation of patients with non-cystic fibrosis bronchiectasis with eosinophilic inflammation (NCFB+EI) who may benefit from treatment with benralizumab, which would target a key underlying driver of inflammation and may reduce bronchiectasis exacerbations. The aim of this study is to test whether benralizumab provides benefit in these patients compared with standard-of-care treatment.

Objectives and Endpoints

Primary and secondary objectives and variables for the DB period are shown below.

Table S1 Primary and Key Secondary Objectives and Variables

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

Table S1 Primary and Key Secondary Objectives and Variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
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	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

[a] The population and intercurrent strategy also apply to the secondary endpoints.
AEs = adverse events; DB = double-blind; ECGs = electrocardiograms; FAS = full analysis set; FEV_1 = forced expiratory volume in one second; IP = investigational product; Q4W = every 4 weeks; QoL-B-RSS = Quality of Life-Bronchiectasis-Respiratory Symptoms Scale

For other secondary and exploratory objectives and endpoints, see Section 3 of this CSP.

Overall Design

This is a multicentre, randomised, double-blind (DB), parallel-group, placebo-controlled, Phase III study originally 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 NCFB+EI. The study is being conducted at approximately 84 sites in 16 countries.

To be eligible, patients were required to have a diagnosis of NCFB confirmed by computed tomography and a documented history of ≥ 2 exacerbations within the past year. Patients were excluded if they have pulmonary disease other than bronchiectasis (eg, asthma, chronic obstructive pulmonary disease, cystic fibrosis).

Potentially eligible patients entered a screening period of approximately 2 to 6 weeks. After the screening period, the plan was to randomise 420 eligible patients in a 1:1 ratio to receive either benralizumab 30 mg administered by subcutaneous (SC) injection every 4 weeks

(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). Due to the decision to stop recruitment early, 100 patients have been randomised to receive benralizumab or placebo (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 this revised clinical study protocol version 3.0 [CSP version 3.0] becomes effective).

All patients who complete the DB treatment period on investigational product (IP) may be eligible to continue into an open-label extension (OLE) period. The revised OLE period consists 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). Patients in the OLE period will receive open-label benralizumab 30 mg Q4W starting at Visit 15 for collection of long-term safety data.

Given the overall study changes, the OLE period has been shortened, the intended efficacy assessment during the first year of OLE omitted, and the possibility for a second and third year of OLE removed. For patients who complete the DB treatment period on IP but are 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.

The database lock will occur after the last patient completes the OLE. The primary objective is to evaluate the effect of benralizumab 30 mg Q4W on bronchiectasis exacerbations compared to placebo. The analysis of efficacy endpoints will include all data captured during the DB treatment period (intention-to-treat approach) from patients in the full analysis set (FAS). Given that only 100 patients were randomised in the trial (20 with ≥ CCI /µL eosinophil count), this study is not sufficiently powered for the primary efficacy analysis, which was originally based on 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. Safety data from the OLE period of the study will also be presented in the clinical study report. Any efficacy data collected in the OLE before the implementation of this revised CSP (version 3.0) will be listed only.

Disclosure Statement

This is a parallel-group treatment study with 2 groups that are blinded to patients and investigators.

Number of Patients

The original protocol plan was to randomise approximately 420 eligible patients to IP with a stratification ratio of 2:1 for the ≥ CCI /µL:< CCI /µL blood eosinophil strata. Due to the

decision to stop recruitment early, enrolment into the MAHALE trial was terminated in August 2022; 139 patients were enrolled and 100 randomised to IP (20 are in the ≥ CCI /µL blood eosinophil stratum and 80 in the < CCI /µL blood eosinophil stratum).

Study Arms and Duration

The IP is benralizumab or matching placebo administered SC using the supplied accessorised prefilled syringe. The IP will be administered onsite during study visits by the investigator/qualified designee or, optionally, by the patient or caregiver at the patient's home during the optional remote visit (Visit 20) after all other assessments have been completed.

The DB treatment period will be 28 to 52 weeks (depending on the timing of patient randomisation and when this revised CSP [version 3.0] becomes effective). Patients will receive IP Q4W, and those who complete the DB treatment period on IP may be eligible to continue into the OLE period. 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]). Patients in the OLE period will receive open-label benralizumab 30 mg Q4W starting at Visit 15 for collection of long-term safety data.

In some situations, IP administration may need to be rescheduled or a dose skipped. Conditions requiring IP administration rescheduling and procedures for postponing or skipping a dose of IP are described in Section 6.2.4. Reasons and procedures for discontinuation of IP are described in Sections 7.1.1 and 7.1.2.

Data Monitoring Committee

No independent Data Monitoring Committee was established for this study.

Statistical Methods

The study will remain blinded until the database lock, which will occur once the last patient completes the OLE.

The analysis of efficacy endpoints will include all data captured during the DB treatment period (intention-to-treat approach).

The primary analysis is to compare the annualised bronchiectasis exacerbation rate of the benralizumab group with placebo. A negative binomial model will be used with the number of bronchiectasis exacerbations over the DB treatment period as the response variable. The model will include covariates of treatment group, number of exacerbations in the previous

[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 and OLE period of more than 32 weeks.

year, and baseline blood eosinophil category (≥ 300/μL and < 300/μL eosinophil count). The logarithm of the patient's corresponding at-risk time will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

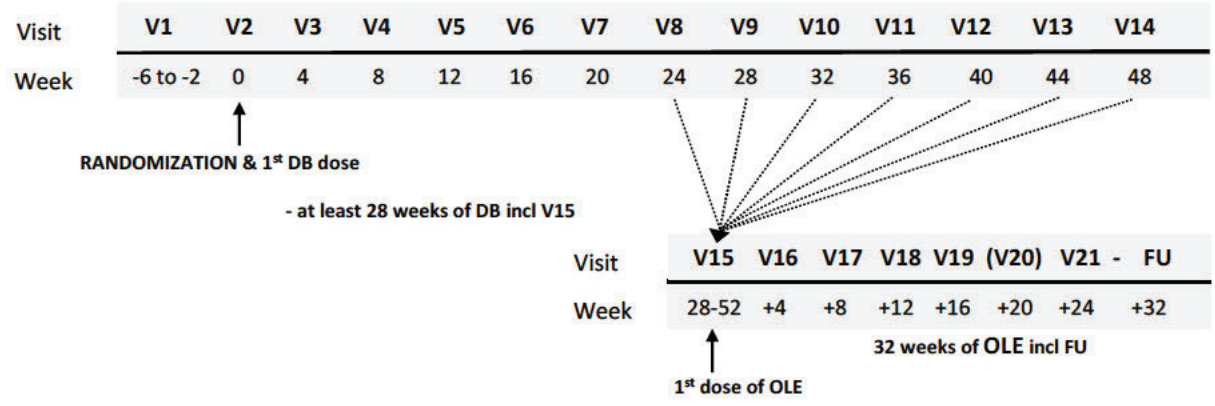
The secondary variable time to first bronchiectasis exacerbation will be analysed using a Cox-proportional hazards model with treatment group, number of exacerbations in previous year, and baseline blood eosinophil category (≥ 300/μL and < 300/μL eosinophil count), as covariates in the model. The secondary endpoints Quality of Life-Bronchiectasis-Respiratory Symptoms Scale (QoL-B-RSS) and forced expiratory volume in one second (FEV_1) will be assessed as change from baseline over the DB treatment period using a mixed-effect model for repeated measures analysis with treatment arm, baseline value for each endpoint of interest, baseline blood eosinophil category (≥ 300/μL and < 300/μL eosinophil count), visit, and interaction between treatment and visit as covariates in the model.

Originally, the study was powered for the primary efficacy analysis of patients in the ≥ 300/μL blood eosinophil stratum. However, due to the decision to stop recruitment early and the small sample size in the ≥ 300/μL blood eosinophil stratum, the primary efficacy analysis will be conducted for all randomised patients, and the study has no plan to be powered to assess the hypothesis test for the primary efficacy endpoint.

1.2 Schema

Figure 1 shows the design of the study and the sequence of treatment periods.

Figure 1 Study Design



The IPD visit is 4 weeks after the last dose of IP. In case of early discontinuation from IP, a FU visit is required 8 weeks after 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 (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

1.3 Schedule of Activities

This study comprises 2 distinct periods: a DB treatment period, during which patients are randomised to receive either benralizumab or placebo, and an OLE period during which all eligible patients who choose to continue will receive benralizumab alone on top of standard of care.

The study will remain blinded until the database lock, which will occur after the last patient completes the OLE.

The SoA for the DB treatment period is provided in Table 1. Patients may have the opportunity to participate in an OLE following completion of the DB period on IP (Section 4.1). The SoA for the OLE period is provided in Table 2, and the SoA for ePRO endpoints for the DB treatment period is provided in Table 3.

1.3.1 Strategy to Transition Patients to the New Schedule of Activities

To allow for continuous dosing of the patients entering the OLE at the time this revised CSP (version 3.0) becomes effective, the following strategy should be followed:

- Patients who have not reached Visit 8: Once patients have completed Visit 8 according to the original SoA (Table 1), they will go directly to Visit 15 in the new SoA (4 weeks after Visit 8) for the last DB period assessments and the start of the OLE (Table 2). The first OLE dosing (Day 1 of the OLE) should coincide with Visit 15 in the new OLE SoA.
- Patients who are between Visit 9 and Visit 14 according to the original SoA (Table 1): Patients will go directly to Visit 15 in the new OLE SoA (Table 2) upon their next visit for last DB period assessments and start of the OLE. First OLE dosing (Day 1 of the OLE) should coincide with Visit 15 in the new SoA.
- Patients who are between Visit 15 and Visit 20 of the OLE according to the previous SoA (CSP version 2.0): Patients will continue at the corresponding upcoming visit number in the new OLE SoA (Table 2) until Visit 21 (24 weeks of OLE treatment). A FU visit will then be conducted 8 weeks after the last IP dose for final safety assessments.
- If a patient is already in the OLE and has completed or is past Visit 21 according to the previous OLE SoA (CSP version 2.0) at the time this revised CSP becomes effective, the patient will go directly to the FU visit in the new OLE SoA (8 weeks after the last dose of IP) (Table 2).

Table 1 Schedule of Activities for the Double-blind Period

Study procedures	Screening	Double-blind treatment period																
Visit	V1	V2 (rand)	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15 [a]	Unsc. V [b]	IPD V [c]	FU V [d]
Week	-2 to -6	0	4	8	12	16	20	24	28	32	36	40	44	48	52			
Visit window			± 7 days															
General procedures																		
Informed consent	X																	
Optional genetic informed consent	X [e]																	
Demography/general medical and surgical history	X																	
Respiratory disease history/treatment	X																	
Smoking status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																	
Weight	X							X							X		X	
Inclusion/exclusion criteria	X	X																
Confirm eligibility to enter OLE															X			
Efficacy assessments																		
Bronchiectasis exacerbation assessment [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bronchiectasis Severity Index		X													X [g]			
mMRC dyspnoea scale		X													X [g]			
Dispense ePRO device and provide instructions	X																	
Review ePRO assessments/compliance [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Return ePRO device																	X [i]	

Table 1 Schedule of Activities for the Double-blind Period

Study procedures	Screening	Double-blind treatment period																
Visit	**V1**	**V2 (rand)**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15** [a]	**Unsc. V** [b]	**IPD V** [c]	**FU V** [d]
Week	**-2 to -6**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit window			± 7 days															
Healthcare resource utilisation		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Pre-bronchodilator spirometry (FEV_1)	X	X	X	X		X		X		X		X		X	X		X	X
Post-bronchodilator spirometry (FEV_1)		X						X							X		X	
Safety assessments																		
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X							X							X		X	
Brief physical examination		X	X	X	X	X	X		X	X	X	X	X	X		X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Supplemental oxygen status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (triplicate recordings)	X							X							X		X	
Laboratory and imaging assessments																		
CT	X														X [j]			
Haematology, white blood cells with differential [k,]	X [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunoglobulin E	X																	
Clinical chemistry	X	X	X	X				X				X			X		X	
Spontaneous, unprocessed sputum [m]			X	X	X	X	X		X	X	X	X	X	X				

Table 1 Schedule of Activities for the Double-blind Period

Study procedures	Screening	Double-blind treatment period																
Visit	V1	V2 (rand)	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15 [a]	Unsc. V [b]	IPD V [c]	FU V [d]
Week	-2 to -6	0	4	8	12	16	20	24	28	32	36	40	44	48	52			
Visit window			± 7 days															
Induced, processed sputum [m, n]		X						X							X	X	X	
Sputum culture [o]		X						X							X		X	
Urinalysis (central lab)	X														X			
Urinalysis (dipstick)		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
PK		X		X	X			X			X			X	X	X	X	X
Anti-drug antibodies		X			X			X			X			X	X	X	X	X
Blood biomarkers (serum and plasma) [m]		X			X			X			X				X	X		
PAXGene RNA [m]		X													X	X		
Genomics Initiative optional, exploratory genetic sample [m]		X [e]																
Hepatitis/HIV serology	X													X				
Serum pregnancy test (WOCBP)	X													X				
Urine pregnancy test (dipstick) (WOCBP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follicle-stimulating hormone test [p]	X																	
IP administration																		
Administer IP		X	X	X	X	X	X	X	X	X	X	X	X	X				
Administer open-label benralizumab onsite (first dose of OLE)															X			
Telephone contact for patients who discontinue IP prematurely and are unwilling/unable to continue with clinic visits																		

Table 1 Schedule of Activities for the Double-blind Period

Study procedures	Screening	Double-blind treatment period																
Visit	V1	V2 (rand)	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15 [a]	Unsc. V [b]	IPD V [c]	FU V [d]
Week	-2 to -6	0	4	8	12	16	20	24	28	32	36	40	44	48	52			
Visit window			± 7 days															
Telephone contact			Telephone contact every 4 weeks from the date of last clinic visit until the end of the double-blind treatment period															

[a] Once the DB period has been completed (Visit 8 minimum), the remaining visits in the DB period (shaded columns) should be skipped, and the patient should attend Visit 15 in Table 2 directly. Patients who are transferred to the OLE SoA for Visit 15 will conduct assessments according to Table 2. Visit 15 is to be completed as the last DB treatment visit and the first OLE dosing. The visit and all assessments at Visit 15 should be performed before administration of open-label benralizumab. The strategy to transition patients from the previous SoA (CSP version 2.0) to the new SoA (CSP version 3.0) is provided in Section 1.3.1.

[b] Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits at the discretion of the investigator. Procedures listed in the table are those that are mandatory if the unscheduled visit is to assess a potential bronchiectasis exacerbation. If an unscheduled visit occurs to administer IP that has been postponed, the only mandatory procedures are the physical exam, vital signs, AEs/SAEs, concomitant medications, and urine pregnancy test (dipstick; WOCBP), provided that other visit assessments have already been completed.

[c] In case of early discontinuation from IP, procedures of the IPD visit are to be performed 4 weeks (± 7 days) after last dose of IP (replaces next regular scheduled visit assessments) (Section 7.1.2.1).

[d] In case of early discontinuation from IP, a FU visit is required 8 weeks (± 7 days) after last dose of IP (Section 7.1.2.1).

[e] It is preferred that genetic informed consent is signed at Visit 1 and that the genetic sample is collected at Visit 2, but genetic informed consent may be signed at any visit, and the genetic sample may be collected at any visit after the genetic informed consent is signed.

[f] Study site evaluations for a bronchiectasis exacerbation (Section 8.2.1) may occur as a part of an ordinary site visit or as an unscheduled visit, if deemed necessary by the Investigator.

[g] mMRC dyspnoea scale (Section 8.2.3) will only be assessed/calculated at Week 52 for patients who entered the OLE according to Table 1.

[h] See Table 3 for details on ePRO assessments.

[i] This is only applicable to patients who are unwilling to continue completing ePRO assessments after the IPD visit but who remain in the study. Upon the approval of CSP version 3.0, patients who prematurely discontinue IP will be withdrawn from the study after mandatory visits are performed, and the ePRO device should be returned at the final onsite visit (Section 7.1.2.1).

[j] CT will only be performed if the baseline CT scan was evaluable by the central imaging vendor (Section 8.2.6).

[k] Eosinophil, basophil, and monocyte counts will be redacted from all central laboratory reports from Visit 2 until V17 in order to prevent discernment of blinded treatment assignment (Section 6.3.2.1).

[l] All patients should have 2 tests for blood eosinophils during screening (Section 6.3.1). The tests should be at least one week apart.

[m] For patients in China, serum/plasma samples for biomarkers, the Genomics Initiative exploratory genetic sample; PAXGene RNA; spontaneous, unprocessed sputum samples; and induced, processed sputum samples will not be collected.

[n] If sputum processing is not possible, an unprocessed sample should be collected and stored. Sites that do not have the appropriate equipment or facilities for sputum processing should only collect unprocessed sputum. See Section 8.6.1.1 for details.

[o] Sputum culture will be performed for all patients including patients in China, and collected at Visits 2, 8, and 15 and the IPD visit in the DB period (Section 8.5). Sputum culture will be analysed at the central laboratory; however, if due to the site's location the sample cannot be delivered to the central laboratory within 48 hours since collection, sputum culture needs to be analysed at the certified local laboratory following the same methodology as the central laboratory.

[p] Follicle-stimulating hormone test done only for female patients to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for ≥ 12 months.

AEs = adverse events; CSP = clinical study protocol; CT = computed tomography; DB = double blind; ePRO = electronic patient-reported outcome; FEV_1 = forced expiratory volume in one second; FU = follow-up; HIV = human immunodeficiency virus; IP = investigational product; IPD = investigational product discontinuation; mMRC = modified Medical Research Council; OLE = open-label extension; PK = pharmacokinetics; rand = randomisation; RNA = ribonucleic acid; SAEs = serious adverse events; SoA = schedule of assessments; Unsc = unscheduled; V = visit; WOCBP = women of childbearing potential

Table 2 Schedule of Activities for the Open-label Extension

Study procedures	**Open-label treatment period**									
Visit	**V15** [a]	**V16**	**V17**	**V18**	**V19**	**V20** [b]	**V21** [c]	**FU V** [d]	**Unsc. V** [e]	**IPD V** [f]
Week of OLE	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**		
Visit window	**± 7 days**									
General procedures										
Weight	X							X		
Smoking status	X									
Confirm eligibility to enter OLE	X									
Efficacy assessments										
Bronchiectasis exacerbation assessment [g]	X									
Review ePRO assessments/compliance [h]	X									
Return ePRO device [i]	X									
Pre-bronchodilator spirometry (FEV_1)	X									
Safety assessments										
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X									X
Brief physical examination				X				X		
Vital signs	X			X				X		
Supplemental oxygen status	X									
AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Laboratory and imaging assessments										
CT [j]	X									
Haematology, white blood cells with differential	X						X	X		X

Table 2 Schedule of Activities for the Open-label Extension

Study procedures	Open-label treatment period									
Visit	**V15** [a]	**V16**	**V17**	**V18**	**V19**	**V20** [b]	**V21** [c]	**FU V** [d]	**Unsc. V** [e]	**IPD V** [f]
Week of OLE	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**32**		
Visit window	**± 7 days**									
Clinical chemistry	X							X		X
Sputum culture [k]	X									
Urinalysis (dipstick)	X									
PK	X							X		X
Anti-drug antibodies	X							X		X
Blood biomarkers (serum and plasma) [l]	X									
Urine pregnancy test (dipstick) (WOCBP)	X			X				X		
IP administration										
Administer open-label benralizumab [m]	X	X	X	X	X	X	X			

[a] After Visit 8 of the DB period, the next visit will be Visit 15 (the last DB period visit and first OLE dosing). Patients who are between Visit 8 and Visit 14 upon approval of the CSP version 3.0 amendment, will go directly to Visit 15 of the OLE SoA upon their next visit. All assessments at Visit 15 to be performed before administration of open-label benralizumab.

[b] For patients who are trained to self-administer IP, this visit can optionally be conducted remotely by telephone contact.

[c] 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.

[d] A FU visit is required 8 weeks (± 7 days) after last dose of IP (FU visit). In addition, this is the last visit and end of study.

[e] Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits at the discretion of the investigator. Procedures listed in the table are those that are mandatory if the unscheduled visit is to assess a potential bronchiectasis exacerbation. If an unscheduled visit occurs to administer IP that has been postponed, the only mandatory procedures are the physical exam, AEs/SAEs, concomitant medications, provided that other visit assessments have already been completed.

[f] In case of early discontinuation from IP, procedures of the IPD visit are to be performed 4 weeks (± 7 days) after last dose of IP (replaces next regular scheduled visit assessments). An additional FU visit will be needed 8 weeks after the last dose according to FU visit assessments.

[g] Study site evaluations for a bronchiectasis exacerbation may occur as a part of an ordinary site visit or as an unscheduled visit, if deemed necessary by the investigator.

[h] See Table 3 for details on ePRO assessments.

[i] ePRO device should be returned at Visit 15 or at the nearest visit in the OLE period upon approval of the CSP version 3.0.

[j] CT will only be performed if the baseline CT scan was evaluable by the central imaging vendor (Section 8.2.6).

[k] Sputum culture will be analysed at the central laboratory; however, if due to the site's location the sample cannot be delivered to the central laboratory within 48 hours since collection, sputum culture needs to be analysed at the certified local laboratory following the same methodology as the central laboratory. Sputum culture will be performed for all patients including patients in China.

[l] Serum/plasma samples for biomarkers will not be collected for patients in China.

[m] Only for patients entering the OLE.

AE(s) = adverse event(s); CSP = clinical study protocol; CT = computed tomography; DB = double blind; ePRO = electronic patient-reported outcome; FEV_1 = forced expiratory volume in one second; FU = follow-up; IP = investigational product; IPD = investigational product discontinuation; OLE = open-label extension; PK = pharmacokinetics; SAEs = serious adverse events; Unsc = unscheduled; V = visit; WOCBP = women of childbearing potential

Table 3 Schedule of Assessments for ePRO Endpoints (Double-blind Treatment Period)

ePRO assessment	Double-blind treatment period (V1-V15) [a]		CSP section with details on assessment
	Visit	Place/frequency of assessment	
Bronchiectasis Exacerbation Diary	V1-V15	Daily at home in the evening	Section 8.2.4.1
	Unsc. visit	At site	
	IPD visit	At site [b]	
Quality of Life-Bronchiectasis	V1	At site	Section 8.2.4.2
	V2	At site	
	After V2	Every 14 days (± 2 days) until V15	
	Unsc. visit	At site	
	IPD visit	At site [b]	
Leicester Cough Questionnaire	V1	At site	Section 8.2.4.3
	V2	At site	
	After V2	Every 14 days (± 2 days) until V15	
	Unsc. visit	At site	
	IPD visit	At site [b]	
St. George's Respiratory Questionnaire	V2	At site	Section 8.2.4.4
	After V2	Every 28 days (± 2 days) until V4	
	After V4	Every 56 days (± 2 days) until V14	
	After V14	Every 28 days (± 2 days) until V15	
	IPD visit	At site [b]	
Patient Global Impression of Severity	After V1	Every 7 days (± 2 days) until V3	Section 8.2.4.5
	After V3	Every 14 days (± 2 days) until V15	
	IPD visit	At site [b]	
Patient Global Impression of Change	After V2	Every 7 days (± 2 days) until V3	Section 8.2.4.5

Table 3 Schedule of Assessments for ePRO Endpoints (Double-blind Treatment Period)

ePRO assessment	Double-blind treatment period (V1-V15) [a]		CSP section with details on assessment
	Visit	Place/frequency of assessment	
	After V3	Every 14 days (± 2 days) until V15	
	IPD visit	At site [b]	
Work Productivity and Activity Impairment Questionnaire: General Health	V2	At site	Section 8.2.4.6
	After V2	Every 56 days (± 2 days) until V4	
	After V4	Every 168 days (± 2 days) until V10	
	After V10	Every 140 days (± 2 days) until V15	
	IPD visit	At site [b]	

[a] After Visit 2, all assessments may be completed at home. If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.

[b] Assessment to be completed at IPD visit only if patient discontinues use of ePRO after IPD visit. Upon the approval of CSP version 3.0, patients who prematurely discontinue IP will be withdrawn from the study after mandatory visits are performed, and the ePRO device should be returned at the final onsite visit (Section 7.1.2.1).

CSP = clinical study protocol; ePRO = electronic patient-reported outcome; IPD = investigational product discontinuation; Unsc. = unscheduled; V = visit

2 INTRODUCTION

Benralizumab is a humanised, afucosylated, monoclonal antibody that binds specifically to the human interleukin-5 receptor alpha subunit on the target cell and directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity that is being developed for the treatment of adult patients with NCFB who have eosinophilic inflammation (hereafter referred to as NCFB+EI).

2.1 Study Rationale

There is an unmet medical need for treatments for NCFB. Emerging evidence suggests that there is a subpopulation of patients with NCFB+EI who may benefit from treatment with benralizumab, which would target a key underlying driver of inflammation and may reduce bronchiectasis exacerbations. The aim of this study is to test whether benralizumab provides benefit in these patients compared with standard-of-care treatment.

2.2 Background

Bronchiectasis is a suppurative lung disease with heterogeneous features and characterised by permanent airway dilatation, chronic productive cough, and recurrent exacerbations (Boyton and Altmann 2012, McShane and Tino 2019). Exacerbations refer to an unpredictable worsening of symptoms that can take days or weeks to resolve (Brill et al 2015). Bronchiectasis can lead to impaired lung function and ultimately respiratory failure and death (Chalmers et al 2018a).

Bronchiectasis is generally thought to result from a vicious cycle in which a robust inflammatory response to pulmonary infection or injury in predisposed individuals contributes to structural airway damage. The structural abnormalities allow for mucus stasis, which favours continued chronic infection or colonisation, thus leading to a persisting cycle (McShane et al 2013). There are numerous causes of bronchiectasis including cystic fibrosis. The target population for this study is NCFB, a type of bronchiectasis that frequently has unknown causes (Lonni et al 2015). Epidemiological data are unavailable for most regions (Chalmers 2018); in adults with health insurance in the US, the prevalence of NCFB between 2009 and 2013 was estimated to be 139 to 213 cases per 100000 persons, depending on whether narrow or broad case-finding criteria were used (Weycker et al 2017).

Emerging evidence suggests NCFB may have multiple subtypes of airway inflammation based on the predominance of specific inflammatory cells (eg, eosinophils or neutrophils) in the blood or sputum (Dente et al 2015, Keir et al 2019, Rademacher et al 2020, Shoemark et al 2019, Tsikrika et al 2017). While inflammation in bronchiectasis has usually been regarded as neutrophilic, eosinophils may play a role in a subset of patients with the disease (Rademacher et al 2020). Targeting these specific inflammatory pathways may ameliorate the clinical manifestations and exacerbations of bronchiectasis. Inconsistent effects observed in clinical

studies of potential NCFB treatments also support the existence of subsets of patients with specific treatable traits. Approximately 20% of NCFB patients have elevated eosinophils and may benefit from eosinophil-depleting treatments (Dente et al 2015, Rademacher et al 2020, Tsikrika et al 2017). In a case series of 21 patients with NCFB+EI (blood eosinophils ≥ 300/μL), treatment with benralizumab or mepolizumab (another humanised monoclonal antibody that reduces blood and tissue eosinophils) reduced blood eosinophils, improved FEV_1, reduced dyspnoea, reduced exacerbations, and improved quality of life over 6 months of treatment compared with patients' individual baseline values (Rademacher et al 2020).

The aim of NCFB management is to treat the underlying disorder, manage comorbidities and reduce symptoms, reduce exacerbations, and preserve lung function (Chalmers et al 2018a, Murray and Hill 2009). There are currently no approved treatments for NCFB, and most treatments used in clinical practice treat only the downstream effects of the disease (Chalmers and Chotirmall 2018, Polverino et al 2017). There is therefore an unmet medical need for treatments for NCFB.

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and safety profile of benralizumab may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Risk minimisation measures will be maintained during this study in conjunction with AstraZeneca's routine pharmacovigilance activities. Potential risks of clinical significance in this study and specific mitigation strategies for these risks are listed in Table 4.

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Benralizumab		
Anti-drug antibodies	Development of ADA to benralizumab has been documented, and all monoclonal antibodies can cause hypersensitivity reactions (eg, anaphylaxis or immune complex disease). Potential risks of developing ADA include decreased drug efficacy and hypersensitivity reactions. To date,	Patients with allergy or reaction to any component of the IP formulation will be excluded from the study. Risk minimisation for anaphylaxis includes observation of the patient at the study site following IP administration for the appearance of any acute drug reactions in line with clinical practice. For patients who select to do the
Hypersensitivity including anaphylaxis or anaphylactic reactions		

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
	no confirmed cases of immune complex disease have been observed and no appearance of a relationship between ADA and treatment-emergent AEs has been established.	optional at-home/remote-location IP administration during the OLE, the first dose of IP during the OLE should be given onsite. In the instructions for remote/at-home administration of IP, the patient will be instructed on what symptoms to watch for and to seek medical care in the event of such symptoms. When IP is administered at the patient's home/remotely, it is strongly recommended that the patient is contacted by the investigator or qualified designee after the dose is administered in line with clinical practice (see Section 6.2.3 for details).
Serious infections (ie, infections that are life-threatening, requiring IV antibiotics or hospitalisation)	A relationship between eosinophil depletion and serious infection has not been established. Serious infections have been reported for benralizumab; however, review of these events in benralizumab clinical programme has not indicated any new safety issues/concerns.	Patients with active infections will not be randomised. The screening period may be extended to allow for resolution and recovery. Specific infections will be excluded (see exclusion criteria 1, 3, and 4). Patients with radiologic findings suggestive of acute infection will be excluded (see exclusion criterion 6). Patients with known immunodeficiency or who are taking immunosuppressive medication will be excluded (see exclusion criteria 9 and 15).
Helminth infections	Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites.	Patients with untreated helminth parasitic infection will be excluded from the study (see exclusion criterion 4).
Malignancies	Although eosinophil infiltration of tumours is common, the cause and consequences (ie, protumorigenic versus antitumorigenic) of this recruitment and accumulation are unclear. Therefore, there is a theoretical risk that prolonged eosinophil depletion may negatively impact the natural history of certain malignant tumours.	Patients with active or recent malignancy will be excluded from the study (see exclusion criterion 8). Radiologic findings of solitary pulmonary nodules require appropriate follow-up and demonstration of stability for the patient to be included in the study (see exclusion criterion 6)

Table 4 Risk Assessment

Potential risk of clinical significance	Summary of data/Rationale for risk	Mitigation strategy
Study procedures		
CT scans	The use of CT involves ionising radiation that increases the risk of radiogenic tumours in patients	Participants will be informed of the risk associated with CT before entering the study. In keeping with ALARA concept (as low as reasonably achievable) the trial uses optimised qCT scan protocols, using the lowest possible radiation dose to each participant in order to provide acceptable image quality of the quantitative measurements performed in the study. For more detailed information related to qCT radiation dose, imaging risks and best imaging practices, please refer to the study Radiology Manual.
Sputum induction	Sputum induction is associated with a predictable risk of bronchoconstriction.	At most visits, only spontaneously produced sputum will be collected. Sputum will only be induced during bronchiectasis exacerbations and a limited number of planned visits. Sputum induction will be undertaken in carefully monitored conditions with rigorous safeguards to identify and treat bronchoconstriction (Fahy et al 2001).

ADA= anti-drug antibodies; AE= adverse event; CT= computed tomography; IP= investigational product; IV= intravenous; OLE= open-label extension; qCT = quantitative computed tomography

2.3.2 Benefit Assessment

Non-cystic fibrosis bronchiectasis + EI is a rare subtype of bronchiectasis with an unmet medical need and no approved treatments. Based on existing clinical data and benralizumab's eosinophil-depleting mechanism of action (Sections 2 and 2.2), benralizumab treatment is expected to result in a clinically meaningful reduction of exacerbations in patients with NCFB+EI. Patients in the study will have a 50% chance of receiving active treatment with benralizumab. In addition, eligible patients will have access to benralizumab during the OLE.

Patients will have the opportunity of advancing the science and developing therapies in an area of high unmet need. Patients will also be monitored and have monthly clinic visits with the investigator. During certain visits, various safety parameters (eg, physical examination, ECG, vital signs, and laboratory assessments) will be conducted to assess the ongoing health of patients.

2.3.3 Overall Benefit: Risk Conclusion

For patients participating in the study, the potential risks identified in association with benralizumab are justified by the anticipated benefits that may be provided by benralizumab to patients with NCFB+EI.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives and variables for the DB treatment period are listed in Table 5.

Objectives and variables for the OLE are listed in Table 6; A summary of data from the OLE will be presented in the CSR.

Table 5 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 30 mg 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 key secondary endpoint) over the DB treatment period

Table 5 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	Immunogenicity	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	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] CCI [redacted]

Table 5 Objectives and Variables for the Double-blind Treatment Period

Objective			Variable
Priority	**Type**	**Description**	**Description**
		as predictors of response to benralizumab	
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 will also apply to the secondary endpoints.

AEs = adverse events; CT = computed tomography; DB = double blind; ECGs = electrocardiograms; 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] CCI SGRQ = St. George's Respiratory Questionnaire; WPAI-GH = Work Productivity and Activity Impairment Questionnaire: General Health

Table 6 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	Immunogenicity	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; ECGs= electrocardiograms; IP= investigational product; PD = pharmacodynamics; PK = pharmacokinetics; Q4W = every 4 weeks

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, randomised, DB, parallel-group, placebo-controlled Phase III study originally 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 NCFB+EI. The study will be 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 (see Sections 5.1 and 5.2 for detailed inclusion and exclusion criteria).

Potentially eligible patients entered a screening period of approximately 2 to 6 weeks. After the screening period, the plan was to randomise 420 eligible patients in a 1:1 ratio 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). Due to the decision to stop recruitment early, 100 patients have been 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 this revised CSP [version 3.0] becomes 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 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.

Given the overall study changes, the OLE period has been shortened, the intended efficacy assessment during the first year of OLE omitted, and the possibility for a second and third year of OLE removed. For patients who complete the DB treatment period on IP but are 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.

The database lock will occur after the last patient completes the OLE. The primary objective is to evaluate the effect of benralizumab 30 mg Q4W on bronchiectasis exacerbations compared to placebo. 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. Safety data from the OLE period of the study will also be presented in the CSR. Any efficacy data collected in OLE before the implementation of this revised CSP (version 3.0), will be listed only.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby

compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the AstraZeneca study physician.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a third-party vendor.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP administration: Performed by a site qualified HCP, HCP provided by a third-party vendor, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Selection of Patient Population

Several potential treatments for NCFB have shown inconsistent effects when tested in randomised clinical studies, including antibiotic studies with similar designs. Combined with emerging evidence on subtypes of airway inflammation in NCFB, this suggests that the population of patients with NCFB is heterogeneous and that identifying subsets of patients with specific treatable traits such as eosinophilic inflammation may allow for more successful treatment.

Approximately 20% of NCFB patients have elevated eosinophils and may benefit from eosinophil-depleting treatments (Dente et al 2015, Rademacher et al 2020, Tsikrika et al 2017), which would target a potential driver of exacerbations. The study will include 2 strata based on screening blood eosinophil counts: a ≥ CCI /µL eosinophil stratum and a < CCI /µL eosinophil stratum, with a plan to randomise in a ratio of approximately 2:1. CCI

CCI [redacted] Patients with NCFB without elevated blood eosinophils (< CCI /µL) are included in this study to better understand the role of eosinophils in NCFB. Due to the decision to stop recruitment early, and the small sample size in the ≥ CCI /µL blood eosinophil stratum (a total of 100 randomised patients with a ≥ CCI /µL :< CCI /µ blood eosinophil strata size ratio of 1:4), the primary efficacy analysis will be conducted for all randomised patients.

4.2.2 Rationale for Selection of Primary Endpoint

Annualised bronchiectasis exacerbation rate was selected as the primary variable because exacerbations are the most clinically important and robust endpoint in studies of bronchiectasis patients (Chalmers and Chotirmall 2018, Crichton et al 2019). Exacerbations are key events in the natural history of NCFB and can result in significant morbidity and reduced quality of life. In a study of over 2500 patients across 10 centres in Europe, the strongest predictor of future exacerbations was a prior history of exacerbations, with more exacerbations associated with greater risk of future events (Chalmers et al 2018b). Patients with frequent prior exacerbations had worse quality of life, were more likely to be hospitalised, and had increased mortality within 5 years of follow-up.

4.2.3 Rationale for Selection of Comparator

The comparator in this study is placebo. Both benralizumab and placebo will be given on top of standard-of-care treatment, and therefore, the placebo group's treatment will correspond to current standard of care for NCFB patients. The use of placebo will allow for a double-blinded treatment period and an unbiased assessment of the effect of benralizumab.

4.2.4 Rationale for Selection of Study Duration

Originally, a 52-week DB treatment period was selected as a clinically relevant time-frame based on prior studies of antibiotic treatment in NCFB patients and other treatments in respiratory diseases such as asthma and COPD (Bleecker et al 2016, Criner et al 2019a, Criner et al 2019b, FitzGerald et al 2016, Goldman et al 2017). This study duration is sufficiently long to capture the manifestation and resolution of a meaningful number of exacerbation events and takes into consideration the naturally occurring seasonal fluctuations of exacerbations (Crichton et al 2019). A United States FDA workshop on cystic fibrosis and NCFB noted that an exacerbation endpoint is clinically important and that a study duration < 6 months would be insufficient to demonstrate efficacy in this population (FDA 2018). However, due to the early termination of recruitment, the duration of the DB treatment period will fluctuate between 28 and 52 weeks.

4.2.5 Patient Input into Design

Patient feedback on the study design was obtained from a panel of 10 patients with NCFB. Patients were interviewed over 3 days in June 2020. During the discussion, the patients shared which aspects of an NCFB study that they found appealing or concerning and asked questions on study procedures. The patients gave input on aspects of the study design such as the use of CT scans, the use of injectable medications and potential for self-administration, onsite versus remote study visits, the use of questionnaires, and the options for collecting sputum.

As a result of the discussion, optional self-administration of IP, the possibility of using historical CT scans for the eligibility evaluation, and reduced frequency of some assessments were incorporated in the CSP.

4.3 Justification for Dose

The dosing regimen in this study is benralizumab 30 mg by SC injection Q4W. This dosing regimen was used in the Phase III registration studies, SIROCCO (Bleecker et al 2016) and CALIMA (FitzGerald et al 2016), in patients with severe asthma. Results from these studies showed a near-complete depletion of blood eosinophils in patients receiving benralizumab 30 mg at a Q4W regimen, and there was an acceptable safety profile. These studies were the basis for the approval of benralizumab for the treatment of severe asthma.

NCFB has many similarities to COPD, another chronic lung disease that results in lung parenchymal damage, cough, sputum production and recurrent exacerbations. In 2 Phase III studies of benralizumab in COPD (GALATHEA/TERRANOVA), the 30 mg Q8W dose regimen was not effective but the 100 mg Q8W dose appeared to have a consistent effect on exacerbation reduction, particularly severe exacerbations (Criner et al 2019b). Therefore, a more frequent administration of benralizumab 30 mg than Q8W is considered appropriate for NCFB.

4.4 End of Study Definition

For the purpose of clinical trial transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol-related activity.

Food and Drug Administration requirements define 2 completion dates:

Primary Completion Date – the date that the final patient is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different

completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final patient is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last patient's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

In this protocol, 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.

As patients may be offered the opportunity to participate in an OLE period after completing the DB treatment period of the study on IP, the end of study is planned to be when the last randomised patient completes the OLE.

After the end of the study, patients should be given standard-of-care therapy, at the discretion of their treating physician, per local practice.

See Appendix A 5 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1 Must be at least 18 years of age inclusive at the time of signing the ICF.

Type of Patient and Disease Characteristics

2 Must have NCFB diagnosed by a physician and confirmed by CT (measured at screening; if a new CT is not possible, a CT performed within 12 months of the screening visit is acceptable). CT must demonstrate > 1 segment affected within a single lobe. On CT, small bronchiectasis features only visible in a single pulmonary segment and judged to be unrelated to clinical features will not be considered as meeting this criterion.

3 Documented history of 2 or more bronchiectasis exacerbations within a year of the screening visit.
NOTE: Examples of documentation include but not limited to: hospital records, medical

records, prescription records, copies or transcriptions certified as being accurate copies (eg, X-rays, records kept at the pharmacy).

4 At least 70% compliance on the daily BED ePRO assessment during the entire screening period.

5 Greater than 50% compliance on the daily BED ePRO assessment in the 14-day period prior to the randomisation visit.

6 If receiving prophylactic systemic or inhaled antibiotics to prevent bronchiectasis exacerbations, the dose/regimen must be stable for at least 3 months prior to the screening visit and remain stable throughout the DB period of the study. If prophylactic macrolides have been recently discontinued, patients must have been off treatment for at least 3 months prior to randomisation. In all other cases of prophylactic antibiotic use, ≥ 4 weeks washout period should be in place after the last dose of antibiotic and prior to randomisation.

7 Patients must be on airway clearance therapy, physiotherapy, or mucus clearance therapy. Examples including active cycle of breathing techniques, postural drainage, positive expiratory pressure (eg, Acapella™), and other clearance devices. The dose and regimen of these therapies and any drugs used to aid expectoration (eg, hypertonic saline, isotonic saline, carbocysteine, N-acetylcysteine) should be stable for at least 3 months prior to the screening visit and remain stable throughout the DB period of the study.

8 If receiving inhaled corticosteroid or bronchodilator (long-acting β-agonists and/or long-acting muscarinic antagonist) therapy, the dose and regimen should be stable with no alteration to dose or formulation for at least 3 months prior to the screening visit, and this should remain stable throughout the DB period of the study.

Sex

9 Male or female.

Reproduction

10 Negative pregnancy test (serum) for WOCBP at the screening visit

11 WOCBP must:

(a) Have a negative urine pregnancy test prior to randomisation, and

(b) Must agree to use a highly effective method of birth control from enrolment, throughout the study duration, and for 12 weeks after the last dose of IP. Highly effective birth control methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral, intravaginal, or transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation – oral, injectable, or implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Sexual abstinence, ie, refraining from heterosexual intercourse (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.)
- Vasectomised sexual partner, provided that the partner is the sole sexual partner of the WOCBP and that the vasectomised partner has received medical assessment of the surgical success

Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for ≥ 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

(a) Women < 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with follicle-stimulating hormone levels in the postmenopausal range. Until follicle-stimulating hormone is documented to be within menopausal range, the patient will be considered as a WOCBP.

(b) Women ≥ 50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

(c) If the criteria are not met, the patient should be regarded as having childbearing potential.

Informed Consent and Other

12 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

13 Provision of signed and dated Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

14 Capable of complying with all study procedures and of completing the study.

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Pulmonary disease other than bronchiectasis (eg, COPD, asthma, active lung infection including tuberculosis or NTM, pulmonary fibrosis, cystic fibrosis, primary ciliary dyskinesia, pulmonary hypertension, lung cancer, a1 anti-trypsin deficiency). Patients with a history of NTM disease may be enrolled if they have completed treatment prior to the screening visit, if at least 3 months have elapsed since the last day of antibiotic treatment for NTM at the screening visit, and if they have had a negative sputum culture prior to the screening visit.

2 Another diagnosed or suspected pulmonary or systemic disease associated with elevated peripheral eosinophil counts (eg, eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis).

3 Respiratory infection or bronchiectasis exacerbation during the screening period. In the event of a respiratory infection or bronchiectasis exacerbation during the screening period, the screening period may be extended once only after the last dose of antibiotics is given to ensure the patient has recovered from the infection or exacerbation.

4 A helminth parasitic infection diagnosed within 24 weeks of the screening visit that has not been treated with or has failed to respond to standard-of-care therapy.

5 Any other clinical condition (ie, including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment) that is not stable in the opinion of the investigator and could:

   (a) Affect the safety of the patient during the study.

   (b) Influence the findings of the study or their interpretation.

   (c) Impede the patient's ability to complete the entire duration of the study.

6 Radiological findings suggestive of a clinically important respiratory disease other than bronchiectasis, suggestive of acute infection, or of solitary pulmonary nodules without appropriate follow-up and demonstration of stability as per standard of care. Pulmonary nodules > 6 mm in size should have at least 2 years of follow-up with no change on CT imaging.

7 Current active liver disease:

   (a) Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen [HBsAg] or hepatitis C antibody) or other stable chronic liver disease is acceptable if patient otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis.

   (b) Patients with alanine aminotransferase or aspartate aminotransferase level ≥ 3 times the upper limit of normal confirmed by repeated testing during screening period should not be randomised. Transient increase of aspartate aminotransferase/alanine

aminotransferase level that resolves by the time of randomisation is acceptable if, in the investigator's opinion, the patient does not have an active liver disease and meets other eligibility criteria.

8 Current malignancy, or history of malignancy, except for:
   (a) Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided the patient is in remission and curative therapy was completed at least 12 months prior to Visit 1.
   (b) Patients who have had other malignancies are eligible provided that the participant is in remission and curative therapy was completed at least 5 years prior to Visit 1.

9 History of known immunodeficiency disorder including a positive test for human immunodeficiency virus, HIV-1 or HIV-2.

10 Current smokers with a tobacco history of ≥ 10 pack-years or ex-smoker with a tobacco history of ≥ 10 pack-years. Current smoking is not in itself an exclusion criterion, provided that the patient has smoked for less than 10 pack-years.

11 History of alcohol or drug abuse within the past year, which may compromise the study data interpretation as judged by investigator or AstraZeneca study physician.

12 Patients receiving long-term oxygen treatment.

13 Patients participating in, or scheduled for, an intensive (active) pulmonary rehabilitation programme. Patients who are in the maintenance phase of a rehabilitation programme are eligible.

14 Use of non-invasive positive-pressure ventilation for conditions other than obstructive sleep apnoea.

15 Use of immunosuppressive medication (including but not limited to methotrexate, cyclosporine, azathioprine, systemic corticosteroids, or any experimental anti-inflammatory therapy) within 3 months of the screening visit or expected need for chronic use (≥ 4 weeks) during study.

16 Receipt of any marketed or investigational biologic products (monoclonal or polyclonal antibody) within one year of the screening visit.

17 Receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to randomisation.

18 Receipt of Ig and blood products within 30 days of the date of the screening visit.

19 Receipt of live attenuated vaccines within 30 days of the date of randomisation.

Other Exclusions

20 Concurrent enrolment in another clinical drug interventional trial.

21 History of anaphylaxis to any biologic therapy or vaccine.

22 Known history of allergy or reaction to any component of the IP formulation.

23 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

24 Judgement by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

25 Previous randomisation in the present study.

26 Currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

5.2.1 Criteria to be Confirmed Prior to Commencing OLE at Visit 15

Patients who complete Visit 15 on IP may continue into the OLE upon consultation with their investigator.

5.3 Lifestyle Considerations

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent to 12 weeks after last dose of the IP.

Women of childbearing potential must use highly effective contraceptive methods throughout the study and 12 weeks after last dose of the IP (see also inclusion criterion 11 in Section 5.1).

Patients should not use electronic cigarettes during the study period.

5.3.1 Meals and Dietary Restrictions

Meal restrictions recommended prior to spirometry measurements are found in Section 8.2.5.2.

5.3.2 Activity

Restrictions on strenuous exertion and dietary considerations are required prior to spirometry measurements, as described in Section 8.2.5.2.

5.4 Screen Failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE. These patients should have the reason for study withdrawal recorded in the eCRF as ‘screen failure’ (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

The screening period may be extended in some situations (eg, an exacerbation during screening) following discussion between the investigator and the AstraZeneca physician/delegate. If the patient ultimately does not meet all inclusion criteria or meets any of the exclusion criteria, the patient should be screen failed using an IxRS.

Patients who do not meet criteria for participation in this study (screen failure) may be rescreened after careful consideration by the investigator and in agreement with the AstraZeneca study physician (eg, if a patient needs a long-term follow-up to rule out an exclusory condition or reason for screen failure was transient). Rescreening is allowed only once for a patient. In case of rescreening, all medical events that have occurred since the first enrolment will be recorded as part of medical history, and all the screening procedures will be repeated. Some procedures may not require retesting, and any exceptions to retesting will be discussed with the AstraZeneca study physician/delegate. The CT scan must not be repeated to limit risk of further radiation exposure. Rescreened patients should sign a new ICF and be assigned the same patient number as for the initial screening. Rescreening will be documented so that its effect on study results, if any, can be assessed.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/ Administration of Study Intervention – Not Applicable

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study patient according to the CSP.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The IPs are described in Table 7.

Table 7 Investigational Products

Treatment	Active	Control
Intervention name	Benralizumab	Placebo
Type	Combination product	Combination product
Dosage form	Solution for injection in APFS, [redacted] mL fill volume	Solution for injection in APFS, [redacted] mL fill volume
Dosage formulation	[redacted] mg/mL solution, [redacted] mM L-histidine/L-histidine hydrochloride monohydrate, [redacted] M trehalose dihydrate, and	Matching placebo solution, [redacted] mM L-histidine/L-histidine hydrochloride monohydrate, [redacted] M trehalose dihydrate, and

Table 7 Investigational Products

Treatment	Active	Control
	CCI % w/v polysorbate CCI at pH CCI, for injection	CCI % w/v polysorbate CCI at pH CCI, for injection
Dosing instructions	Benralizumab active solution will be administered to patients by healthcare professionals, patients, or their caregivers SC using an APFS	Placebo solution will be administered to patients by healthcare professionals, patients, or their caregivers SC using an APFS
Dosage levels	30 mg every 4 weeks	Matching placebo every 4 weeks
Route of administration	SC injection	SC injection
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca
Packaging and labelling	Study intervention will be provided in APFS. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Label text will be translated into local language as required.	Study intervention will be provided in APFS. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. Label text will be translated into local language as required.

APFS = accessorised prefilled syringe; GMP = Good Manufacturing Practice; IMP = investigational medical product; NIMP = non-investigational medical product; SC = subcutaneous(ly); w/v = weight/volume

6.1.2 Duration and Frequency of Treatment with Investigational Products

The DB treatment period will be 28 to 52 weeks (depending on the timing of patient randomisation and when this amendment [CSP version 3.0] becomes effective). During the DB treatment period, patients will receive IP (benralizumab or matching placebo) approximately Q4W. The IP will be administered onsite. The acceptable visit windows specified in the schedule in the SoA (Section 1.3), and reasons and procedures for rescheduling IP administration are detailed in Section 6.2.4.

Patients who complete the DB treatment period on IP may be eligible to continue into the OLE period. The 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[2]). Patients in the OLE period will receive open-label benralizumab 30 mg Q4W starting at Visit 15.

The sponsor reserves the right of terminating the OLE early.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation and Handling of Investigational Product

All doses of IP during the DB and OLE periods (except for the dose at Visit 20 potentially) will be administered by an HCP at the site during the visits. During the OLE period, at home/remote administration of benralizumab by the patient or caregiver is optional at Visit 20, provided that the investigator has assessed and trained the patient and/or caregiver for at-home/remote-location administration (Section 6.2.3). Investigational product will be administered within the visit windows as specified in the SoA (Section 1.3).

Only patients randomised in the study may receive IP and only authorised site staff may supply or administer IP, except when self-administration or administration by the patient's caregiver is an option (Section 6.2.3).

Prior to each IP administration:

- The investigator/qualified designee will assess the injection site as per the standards of medical care.
- For WOCBP, a serum pregnancy test will be performed at screening (Visit 1). A urine pregnancy test will be performed intermittently according to the SoA (Table 2).

6.2.2 Administration of Investigational Product at the Study Site

The IP will be administered by the investigator/qualified designee using the supplied APFS into the upper arm, thighs, or the abdomen (Figure 2). It is recommended that the site of injection is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, or hardened.

After IP administration at the study site, the patient should be observed in case of any acute drug reactions in line with clinical practice (Section 8.4.10). If the patient reports an injection site reaction or other AEs, the investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

[2] 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 and OLE period of more than 32 weeks.

Further details on IP administration are described in the pharmacy manual provided to study sites; IP administration must be carried out in line with the instructions and clinical practice.

Figure 2 Injection Sites

6.2.3 Optional At-home or Remote-Location Investigational Product Administration

During the OLE period, patients will have the option for one at-home or remote-location visit (Visit 20) with patient/caregiver administration of IP using the APFS. The investigator will first assess the patient and/or his/her caregiver to ensure they are appropriate for administration of IP and will provide appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided.

If the IP is administered at the patient's home/remotely, the patient should administer the IP the same day as the study visit, after the remote visit assessments. It is strongly encouraged that the patient is contacted by the investigator or qualified designee after the dose is administered in line with clinical practice. If the patient reports an injection site reaction or other AEs, the investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

Refer to the "Study Instructions for At-home or Remote Location Administration of Benralizumab by the Patient and/or His/Her Caregiver" for step-by-step guidance including investigator assessment/training of patient and/or caregiver, drug accountability, and reconciliation requirements.

The option of at-home or remote-location administration of IP will only be available in countries where this is allowed by local regulations.

6.2.3.1 Optional Remote Visits for Patients Doing At-home or Remote-Location Investigational Product Administration

During the OLE, Visit 20 (as specified in the SoA in Section 1.3) can optionally be done as a remote visit by telephone contact for patients who received appropriate training to do at-home/remote-location IP administration.

For these patients, IP kits for the optional remote visit will be dispensed at the prior, mandatory onsite visit during the OLE. Women of childbearing potential should be asked if they are pregnant during the telephone visit.

6.2.4 Conditions Requiring Investigational Product Administration Rescheduling

If any of the following occur, the investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The patient has an intercurrent illness that, in the opinion of the investigator, may compromise the safety of the patient in the study.
- The patient, in the opinion of the investigator, is experiencing a bronchiectasis exacerbation or acute upper or lower respiratory tract infection requiring medical treatment. Investigational product should not be administered until it is confirmed by the investigator that the exacerbation/infection has resolved, provided that there are no safety concerns as judged by the investigator.
- The patient is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to the IP administration.

If IP cannot be administered at a scheduled treatment visit (eg, due to conditions listed above), it can be postponed as necessary and administered as soon as possible.

When IP dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for IP administration) are still performed within the visit window. Rescheduled IP dose can be administered at home by the patient or caregiver or at an unscheduled visit at the study site. A physical exam and assessment of vital signs, AEs/SAEs, and concomitant medications are the minimum procedures to be performed at this visit. For WOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative. It may also include remaining visit procedures (not performed at the scheduled visit) and additional assessments as deemed necessary by the investigator.

If the visit procedures cannot be conducted within the window (eg, the patient is unable to come to the study site), then the entire visit will be rescheduled along with IP dose.

If a dose is significantly delayed, it is recommended to keep at least a 2-week interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the

postponed dose will be skipped, and the next dose of IP given at the regularly scheduled visit. The visit schedule will always be calculated from the randomisation date.

6.2.5 Shipping and Storage

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. Further details are provided in the separate pharmacy manual.

All shipments of IP include a data logger, which will allow the investigator or designee to confirm that appropriate temperature conditions have been maintained during transit for all IP received. Any discrepancies must be reported and resolved before use of the IP.

In the following cases, the site staff should not use affected IP and should immediately contact the AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- Damaged syringe/cartridge

Damaged or temperature excursed IP should be documented using the IxRS (refer to the IxRS manual for further details).

All IP (ie, benralizumab and placebo) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container. The IP must be kept under conditions specified on the label (between 2°C to 8°C [36°F to 46°F], protected from light), with access limited to the investigator and authorised site staff. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all IP received at the site and throughout the entire study until authorisation is provided for onsite destruction or removal of the IP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IP for clinical use can only occur once the event has been reviewed, and approval is provided by AstraZeneca (or designated party).

6.2.6 Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

An AstraZeneca site monitor will account for all IP received at the site, including unused study treatments, and will confirm destruction of unused study treatments.

Any unused kits will be destroyed locally when allowed according to local regulations (for further details, refer to the pharmacy manual). Documentation of IP delivery and destruction should be maintained according to applicable AstraZeneca and institution procedures. Devices sent to a patient's home must be returned to a site for traceability.

Further guidance and information for the final disposition of unused study treatment are described in the pharmacy manual provided to the sites. In the case of a malfunctioning benralizumab/matching placebo APFS/device, the site should contact the study monitor to initiate a product complaint process according to applicable guidelines.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Patient Enrolment and Randomisation - Double-blind Period

All patients will be centrally assigned to randomised study treatment using IxRS. Before the study is initiated, the directions for the IxRS will be provided to each site.

The investigator(s) will:

At screening (Visit 1)

1 Obtain signed informed consent from the potential patient before any study-specific procedures are performed.
2 Assign the patient a unique enrolment number (which begins with an 'E') via the IxRS.

At baseline (Visit 2)

1 Determine patient eligibility for randomisation at baseline
2 Confirm stratification factors:
   (a) Eosinophil count < CCI or ≥ CCI cells/µL

   All patients will have 2 tests for blood eosinophil values during screening. The tests should be at least one week apart. Testing eosinophils a third time is permitted only in case of technical issues and following a discussion between the investigator and the AstraZeneca physician/delegate. Rescreening a patient due to their eosinophil values alone is not permitted.

   Patients will be assigned to the ≥ CCI /µL blood eosinophil stratum if one test shows eosinophils ≥ CCI /µL and one test shows eosinophils ≥ 150/µL. All other patients will be assigned to the < CCI cells/µL blood eosinophil stratum.

   (b) Country

   (c) Current chronic macrolide use

3 Randomise eligible patients via the IxRS. The IxRS will assign the patient with a unique randomisation code.

Patients will be allocated to treatment groups in a 1:1 ratio.

Randomisation codes will be assigned strictly sequentially in each stratum as patients become eligible for randomisation. The randomisation code will be assigned from a randomisation list prepared by a computerised system provided by CCI on behalf of AstraZeneca (AZRand).

If a patient withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

6.3.2 Methods for Ensuring Blinding

This study includes a DB treatment period. The IP (benralizumab and matching placebo) are not visually distinct from each other. All packaging and labelling of the IP will be done in such a way as to ensure blinding for all sponsor and investigational site staff and the patients. Since benralizumab and placebo are not visually distinct, IP will be handled by an appropriately qualified member of the study team (eg, pharmacist, investigator, or qualified designee) at the site.

A site monitor will perform IP accountability. If the treatment allocation for a patient becomes known to the investigator or other study staff involved in the management of study patients or needs to be known to treat an individual patient for an AE, the sponsor must be notified promptly by the investigator and, if possible, before unblinding.

The following personnel will have access to the randomisation list during the study, prior to database lock:

- Those carrying out the packaging and labelling of IP
- Those generating the randomisation list
- Personnel at the IxRS company
- The sponsor supply chain department
- Bioanalytical laboratory performing the PK sample analysis

The randomisation scheme will be kept in a secure location and no other member of the extended study team at AstraZeneca, or any Contract Research Organisation handling data, will have access to it until database lock.

The study will remain blinded until the database lock, which will occur once the last patient completes the OLE.

6.3.2.1 Maintaining the Blind to the Patient's Blood Eosinophil Counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower eosinophil and basophil counts than patients on placebo. Procedures to mitigate discernment of treatment assignment on this basis are as follows:

- Haematology will be run by the central laboratory. Post-randomisation (starting from Visit 2), eosinophil and basophil counts will be redacted from the full haematology reports sent back to the investigative sites. Because complete knowledge of the remaining cell types could permit deduction of the 'eosinophil + basophil' compartment, monocyte counts will also be redacted from the reports.
- If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if haemoglobin is desired, the investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases.
- During the DB period of the study and until Visit 17, site staff who are directly involved in the patient's management should not receive any eosinophil, basophil, and monocyte results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management to receive and redact any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the patient's management and prior to filing the laboratory report as a source document. Similarly, eosinophil, basophil, and monocyte results must be redacted from all communications with the sponsor.

6.3.2.2 Maintaining the Blind to the Patient's Induced Sputum Cell Count Analysis – Double-blind Period

The induced sputum analysis will be run by the central laboratory. Sputum cell count results will not be provided to the study sites. Sputum cell count results must be redacted from all communications with the sponsor during the DB period of the study and until 8 weeks after the first dose of OLE (Visit 17).

6.3.3 Methods for Unblinding During the Double-blind Period

The IxRS will provide the IP kit identification number(s) to be allocated to the patient at each dispensing visit to the blinded site pharmacists/delegate.

Details on how to unblind a patient's treatment allocation will be described in the IxRS user manual provided to each study site. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator should document and report the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data (ie, the database lock) until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.3.4 Open-label Extension Period – Benralizumab Administration Only

Patients will keep the same E-code in the OLE as assigned in the DB period of the study. Open-label IP administration will begin at Visit 15. The IxRS will continue to allocate IP kit number for each dosing visit of the OLE.

6.4 Study Intervention Compliance

The administration of all study treatments (both in the DB and OLE period of the study) should be recorded in the appropriate section of the eCRF. The study treatment provided for this study will be used only as directed in this CSP.

Investigational product will be administered at the study site or at the patient's home on the day of the treatment visit, at approximately the same time of day as administered at baseline (Visit 2), and within visit windows as specified in the SoA (Section 1.3). Any change from the dosing schedule (dose interruptions or dose discontinuations) should be recorded in the eCRF. Dose reductions are prohibited. It is recommended that the AstraZeneca study physician, or designee, be contacted in case of any questions.

Investigational product dosing should only occur within the allowed visit windows specified in the SoA (Section 1.3). Conditions requiring rescheduling of IP administration are described in Section 6.2.4.

If more than 2 doses of IP are missed during the DB treatment period, it is strongly recommended that a conversation between the investigator and the AstraZeneca study physician takes place to review the patient's adherence to treatment and decide on the patient's further disposition.

The date and time of all IP administrations, as well as any delayed or missed doses, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant Therapy

6.5.1 Background Medications and Therapies

Patients are required to be on background mucus clearance therapy as per inclusion criterion 7 (Section 5.1) during this study. The dose/regimen should remain stable for the duration of the DB period of the study.

Patients who are being treated with prophylactic antibiotics (systemic or inhaled) to prevent exacerbations of bronchiectasis (see inclusion criterion 6 in Section 5.1) at enrolment should remain on the same dose/regimen without alteration for the duration of the DB period of the study. Patients who have been taking prophylactic macrolides for ≥ 3 months at screening must have had a hearing assessment within 3 months prior to enrolment or during the screening period. These patients must be interviewed for potential hearing issues/tinnitus at enrolment; any reported issues should be recorded as part of medical history.

Patients who are being treated with inhaled corticosteroids or bronchodilators (eg, long-acting β-agonists, long-acting muscarinic antagonists) for bronchiectasis at enrolment as per inclusion criterion 8 (Section 5.1) should remain on the same dose/regimen without alteration for the duration of the DB period of the study. Minor changes of formulation of a patient's background inhaled medication, eg, a change of individual components (eg, fluticasone propionate to budesonide at equivalent dose) or a switch between devices (eg, budesonide/formoterol to fluticasone propionate/salmeterol) is allowed as long as the patient remains on equivalent therapy as when he/she was enrolled.

Changes to the patient's background therapy are discouraged during the study, unless judged medically necessary by the investigator. The justification and rationale for treatment changes should be documented in the source notes.

6.5.2 Restricted and Prohibited Medications

Restricted and prohibited medications during the study are listed in Table 8.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Table 8 Restricted and Prohibited Medications

Medication/Class of drug	Restricted/ Prohibited	Details
Inactive/killed vaccinations (eg, inactive influenza)	Restricted	Not allowed within the 7 days prior to or 7 days after any IP administration.
Allergen immunotherapy	Restricted	It is recommended that the patient does not receive allergen immunotherapy on the same day as IP administration.
Antibiotics	Restricted	Allowed to treat NCFB exacerbations and/or AEs.

Table 8 Restricted and Prohibited Medications

Medication/Class of drug	Restricted/ Prohibited	Details
		Initiation of prophylactic chronic use (> 3 months) for the prevention of NCFB exacerbations during the study is disallowed, unless the patient is already taking prophylactic antibiotic prior to screening and has been on stable dose and regimen for ≥ 3 months prior to screening (see inclusion criterion 6, Section 5.1). If prophylactic macrolides had been discontinued prior to screening, the patient should have been off treatment for at least 3 months prior to randomisation. For all other prophylactic antibiotic which may be recently discontinued prior to screening, ≥ 4 weeks washout period should be in place after the last dose of antibiotic and prior to randomisation.
Any immunosuppressive treatment including but not limited to: systemic corticosteroids, methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxylchloroquine, azathioprine, cyclophosphamide	Restricted	Allowed for treatment of an AE where there is no alternative treatment available for the duration of < 4 weeks. If longer treatment is required, this should be discussed with the AstraZeneca study physician to decide on the patient's disposition. If a patient requires immunosuppressive treatment during the screening period but otherwise meets all eligibility criteria, the patient may be randomised provided randomisation occurs at least 4 weeks after the last dose of the immunosuppressant.
Any marketed or investigational biologic (monoclonal or polyclonal antibody)	Prohibited	Not allowed within one year prior to the screening visit, during the study period, and 4 months or 5 half-lives (whichever is longer) after the last dose of IP (benralizumab/placebo).
Non-biologic IP	Prohibited	Not allowed within 30 days or 5 half-lives (whichever is longer) prior to randomisation and during the study period.
Live attenuated vaccines	Prohibited	Not allowed within 30 days prior to randomisation; during the study period, and for 12 weeks after the last dose of the IP.
Blood products or immunoglobulin therapy	Prohibited	Not allowed within 30 days prior to the screening visit and during the study period.
Inhaled marijuana	Prohibited	Use of inhaled marijuana is prohibited during the study period.

AE(s) = adverse event(s); IP = investigational product, NCFB = non-cystic fibrosis bronchiectasis

6.6 Dose Modification

Dose modifications will not be allowed during the study.

6.7 Intervention After the End of the Study

After the end of the study, the patient should be given standard-of-care therapy at the discretion of their treating physician and per local practice.

6.8 Treatment of Overdose

For this study, any single dose of benralizumab ≥ 200 mg will be considered an overdose. There is no specific treatment in the event of overdose of IP, and possible symptoms of an overdose are not established. If overdose occurs, the patient should be treated supportively with appropriate monitoring, as necessary.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the study clinical lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.4.11 for details of AE/SAE reporting related to overdose.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A 8.

7.1 Discontinuation of Study Intervention

7.1.1 Reasons for Discontinuation of Investigational Product

Before a decision to discontinue IP in any patient is made and regardless of the reason for discontinuation, the AstraZeneca study physician should be consulted. Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study. Upon the approval of this amendment (CSP version 3.0), patients who prematurely discontinue IP will be withdrawn from the study after mandatory visits are performed (Section 7.1.2).

IP may be discontinued for the following reasons:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE that, in the opinion of the investigator, contraindicates further dosing
- Severe noncompliance with the CSP
- Risk to patient as judged by the investigator or AstraZeneca

- Pregnancy
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the IP requiring administration of epinephrine
  - Development of helminth parasitic infestations requiring hospitalisation
  - A respiratory-related event requiring prolonged mechanical ventilation

If more than 2 doses of IP are missed during the DB treatment period, it is strongly recommended that a conversation between the investigator and the AstraZeneca study physician takes place to review the patient's adherence to treatment and decide on further patient disposition.

See the SoAs (Section 1.3) and Section 7.1.2 (IPD visit) for data to be collected at the time of IP discontinuation and FU visit and for any further evaluations that need to be completed.

7.1.2 Procedures for Early Discontinuation of Investigational Product and at End of Study

A patient who decides to discontinue IP should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Patients permanently discontinuing IP administration should be given locally available standard-of-care therapy, at the discretion of the investigator.

Discontinuation of IP will be registered in IxRS system.

See the SoA (Section 1.3) for data to be collected at the time of IP discontinuation and FU visit and for any further evaluations that need to be completed.

The IPD visit is used in all other cases when a patient discontinues IP.

7.1.2.1 Early Discontinuation of Study Treatment

All patients who prematurely discontinue IP (during either the DB period or OLE period) should return to the study site for an IPD visit within 4 weeks (± 7 days) after the last dose of IP and a FU visit 8 weeks (± 7 days) after the last dose of IP for procedures described in Section 1.3. The IPD visit replaces the next scheduled visit after IP discontinuation. Reasons for patients not electing to go into the OLE will be collected.

Investigational Product Discontinuation During the DB period

Upon the approval of this CSP (version 3.0), patients who prematurely discontinue IP will be withdrawn from the study after mandatory visits (as described above) are performed. The ePRO device should be returned at the last onsite visit.

Investigational Product Discontinuation During the OLE period

Patients who prematurely discontinue IP during the OLE period of the study will attend an IPD visit at 4 weeks (± 7 days) after last dose of IP and a FU visit at 8 weeks (± 7 days) after the last dose of IP, after which the patient exits the study.

7.1.2.2 Discontinuation of Treatment on Notification of Closure of Study

Once a patient has completed Visit 21 of the OLE period (Table 2), the patient will go directly to the FU visit (8 weeks after the last dose of IP)*, after which the patient exits the study.

The sponsor reserves the right of terminating the OLE early.

The following visits should be performed (Section 1.3; timing dependent on when notification of study closure occurs) for all ongoing patients within 3 months of notification from AstraZeneca of closure of the study (Section 4.4):

- FU visit: within 8 weeks (± 7 days) after last dose of IP

*Note: For patients who are already in the OLE and have completed Visit 21 of the previous OLE SoA (CSP version 2.0) at the time this amendment (CSP version 3.0) becomes effective, see Section 1.3.1.

7.1.3 Procedures for Handling Incorrectly Enrolled or Randomised Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive IP. There can be no exceptions to this rule. Patients who are enrolled but who do not meet all eligibility criteria must not be randomised and must be withdrawn (screen failed) from the study.

When a patient does not meet all the eligibility criteria but is randomised in error or incorrectly started on IP, the investigator should inform the AstraZeneca study physician immediately to discuss potential safety concerns and the best interests of the patient and decide whether IP should be continued or discontinued.

If the agreed decision is to discontinue IP, patients should be encouraged to complete IPD and FU visits, ie, follow-up for 8 weeks after last IP dose (if received) (Section 7.1.2).

The decision to discontinue/continue IP must be appropriately documented, including rationale, particularly if the agreed decision is to continue IP treatment.

7.2 Patient Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.

A patient who considers withdrawing from the study must be informed by the investigator about follow-up options (eg, telephone contact, obtaining information on the patient via a relative or treating physician, obtaining information on the patient from medical records).

At the time of withdrawal from the study, if possible, an IPD visit should be conducted. The SoA (Section 1.3) shows the data to be collected at the time of study withdrawal and follow-up and other evaluations that need to be completed. The IPD visit should take place as soon as the patient notifies the investigator/delegate of intent to withdraw consent, without the need to wait until 4 weeks after the last dose of IP. The patient will return all study supplied equipment including the ePRO device and any IP kits at the withdrawal visit. No FU visit is expected for a patient who has withdrawn from the study prematurely. If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulations. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The investigator will follow up patients as medically indicated.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to

follow-up with unknown vital status at end of study and censored at latest follow-up contact.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Administrative and General Procedures

Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Urgent safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue IP.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Blood volume collected during the study will depend on the duration of the patient in the study and may be different for each patient. However, the maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. In China, the maximum amount of blood collected from each patient over the duration of the study will not exceed 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Depending on the timing of patient randomisation and when this amendment (CSP version 3.0) becomes effective, the DB treatment period will last 28 to 52 weeks. Therefore, the strategy to transition each patient from the previous amendment (CSP version 2.0) to this amendment (CSP version 3.0) will depend on the patient's upcoming visit at the time the new SoA (Section 1.3) becomes effective. The strategy to transition patients who have not reached Visit 8, are between Visits 9 and 14, are between Visits 15 and 20, or have completed or are past Visit 21 of the previous OLE SoA (CSP version 2.0) is provided in Section 1.3.1.

8.2 Efficacy Assessments

8.2.1 Bronchiectasis Exacerbation

8.2.1.1 Exacerbation Definition

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:
  - Cough
  - Sputum volume and/or consistency
  - Sputum purulence
  - Breathlessness and/or exercise intolerance
  - Fatigue and/or malaise
  - 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

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 start and stop 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.

An exacerbation is not a reason to discontinue IP or withdraw from the study, unless, in the investigator's judgement, continued IP administration or study participation represents a contraindication and/or safety risk to the patient. Patients should continue to receive IP after an exacerbation.

Study site evaluations for potential NCFB exacerbations may occur as a part of an ordinary site visit, or as an unscheduled visit, if deemed necessary by the investigator. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites

(eg, by the primary care HCP or at an emergency department/hospital) and details entered into the eCRF exacerbation module in a timely fashion. Changes in concomitant medication due to an exacerbation must be recorded in the appropriate module of the eCRF.

8.2.1.2 Exacerbation Events Identified via Bronchiectasis Exacerbation Diary Alerts

The BED is a daily ePRO questionnaire used during the DB period to capture key bronchiectasis symptoms associated with an exacerbation (Section 8.2.4.1). An alert system based on patient BED responses will be in place to notify both the patient and the study site of a potential symptom deterioration that warrants a contact between the patient and the site for further evaluation. The investigator should follow up with the patient as soon as possible to decide on the need for further evaluations and/or treatment.

8.2.1.3 Exacerbation Events not Identified via Bronchiectasis Exacerbation Diary Alerts

If an exacerbation event is not associated with a BED symptom worsening alert (eg, technical issue, patient self-reports symptom worsening/exacerbation event, the exacerbation is identified during a visit or phone contact, exacerbation is evaluated and treated at non-study site, or an acute/severe symptom deterioration that is not captured in the BED system), the investigator should interview the patient and evaluate potential worsening and duration of the following symptoms:

- Cough
- Sputum volume and/or consistency
- Sputum purulence
- Breathlessness and/or exercise intolerance
- Fatigue and/or malaise
- Haemoptysis
- Other symptoms and/or findings of NCFB

The investigator should record all pertinent findings and symptoms associated with the exacerbation event and their duration in source documents and in the eCRF exacerbation module.

A vast majority of NCFB exacerbations are associated with worsening of the symptoms described above. Clinical presentations may, however, vary among patients. If it is not possible to capture the symptoms as described above (eg, patient intubated upon arrival to the emergency department), the investigator must document the justification for defining the event as an exacerbation and record it in the eCRF.

Patients will be encouraged to contact the study site and/or their primary care physician in case of NCFB symptoms worsening even if a BED alert is not triggered. The patients will be asked to inform the investigator of any NCFB-related events treated outside of the study site.

8.2.2 Bronchiectasis Severity Index

The BSI is an assessment of bronchiectasis severity based on a combination of clinical, radiological, and microbiological features. A higher score indicates greater risk of morbidity and mortality. The BSI will be assessed in accordance with the SoA (Section 1.3):

The BSI (Chalmers et al 2014) incorporates 9 variables:

1 Age: less than 50 years (0 points); 50-69 years (2 points), 70-79 years (4 points), 80 years or more (6 points)
2 BMI: < 18.5 (2 points), ≥ 18.5 (0 points)
3 Pre-bronchodilator FEV_1 % predicted: more than 80% (0 points), 50-80% (1 point), 30-49% (2 points), less than 30% (3 points)
4 Hospital admission in previous year: no (0 points), yes (5 points)
5 Exacerbations in previous year: 0-2 (0 points), 3 or more (2 points)
6 mMRC dyspnoea score: 0-2 (0 points), 3 (2 points), 4 (3 points)
7 *P. aeruginosa* colonisation: no (0 point), yes (3 points)
8 Colonisation with other microorganisms: no (0 point), yes (1 point)
9 Radiological severity (more than 3 lobes involved or cystic bronchiectasis): no (0 points), yes (1 point)

An overall score is derived as a sum of the scores for each variable and it may range from 0 to 26 points. According to the overall score value, the patients with bronchiectasis are classified into 3 BSI classes: patients with low BSI score (overall score 0 to 4 points), patients with intermediate BSI score (overall score 5 to 8 points), and patients with high BSI score (overall score 9 or more points).

8.2.3 mMRC Dyspnoea Scale

The mMRC Dyspnoea Scale is a simple grading system to assess a patient's level of dyspnoea, ie, shortness of breath (Table 9). It is a 5-point scale that considers certain activities, such as walking or climbing stairs, which provoke breathlessness (Fletcher et al 1959). The patient selects a grade on the mMRC scale that most closely matches his/her severity of dyspnoea.

Table 9 mMRC Dyspnoea Scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house, or I am breathless when dressing.

8.2.4 Patient-reported Outcomes

The following PRO assessments will be completed by patients on a handheld ePRO device in accordance with the SoA (Section 1.3):

- BED
- QoL-B
- LCQ
- SGRQ
- PGIS
- PGIC
- WPAI-GH

Appropriately trained site staff and investigators will dispense the ePRO device to each patient at Visit 1 and ensure that patients are properly trained on the ePRO device and the importance of completing assessments as scheduled. The ePRO device is the only acceptable source; data from paper questionnaires are not acceptable.

Minimising missing data is a key aspect of study success. Compliance with ePRO assessment completion must be checked at each study visit at a minimum and should be checked more frequently to identify problems early. Sites should also be aware of the additional guidelines for ePRO administration as provided in a separate manual.

8.2.4.1 Bronchiectasis Exacerbation Diary

The BED is a daily ePRO questionnaire used to capture key bronchiectasis symptoms associated with an exacerbation (Appendix G). It will be completed daily during the DB treatment period. If the patient-reported symptoms meet a specific threshold (ie, deterioration in 3 or more symptoms for at least 48 hours, as specified in Section 8.2.1), the ePRO device will generate a symptom deterioration alert to the patient and the site. This alert should trigger a contact between the patient and the site. The investigator should follow up with the patient as soon as possible to decide on the need for further evaluations and/or treatment.

Each evening, the patient will complete 5 to 8 questions on the severity of bronchiectasis symptoms over the past 24 hours. Questions pertaining to the severity of symptoms compared with their usual state will have multiple response options (eg, "How breathless have you been in the last 24 hours? Less breathless than usual, usual level of breathlessness, more breathless than usual") whereas questions related to the presence or absence of a symptom will have a dichotomous response (eg, "Have you had mucus (phlegm) in the last 24 hours? No or Yes").

8.2.4.2 Quality of Life-Bronchiectasis

The QoL-B is a 37-item questionnaire developed to measure symptoms, functioning, and health-related quality of life in patients with NCFB (Quittner et al 2014, Quittner et al 2015). Each item captures patient-reported symptoms and functioning over the past week on a 4-point Likert response scale.

The QoL-B has 8 scales: Respiratory Symptoms Scale (QoL-B-RSS; 9 items), Physical Functioning (QoL-B-PFS; 5 items), Role Functioning (QoL-B-RFS; 5 items), Emotional Functioning (QoL-B-EFS; 4 items), Social Functioning (QoL-B-SFS; 4 items), Vitality (QoL-B-VS; 3 items), Health Perceptions (QoL-B-HPS; 4 items), and Treatment Burden (QoL-B-TBS; 3 items). For each scale, scores are standardised from 0 to 100, with higher scores indicative of better health-related quality of life. No total score is calculated.

The key secondary endpoint QoL-B-RSS evaluates respiratory symptoms including chest congestion, cough, shortness of breath, wheeze, and chest pain. The remaining 7 scales will be analysed separately as secondary endpoints.

8.2.4.3 Leicester Cough Questionnaire

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 3 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.

8.2.4.4 St. George's Respiratory Questionnaire

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 2 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 component 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 component 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 2009).

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

The PGIS is a single item designed to capture the patient'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).

8.2.4.6 Work Productivity and Activity Impairment Questionnaire: General Health

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

8.2.5 Spirometry

8.2.5.1 General Requirements

Lung function (FEV_1) at the study site will be measured by spirometry using equipment provided by a central vendor. The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly certified.

Spirometry will be performed by the investigator or authorised delegate according to ATS/ERS guidelines (Graham et al 2019).

Spirometry calibration and data quality checks will be detailed in a separate spirometry procedures manual.

Patients should be instructed not to use their long-acting bronchodilator medication within 12 hours (24 hours for once-daily medications) of scheduled site visit spirometry as this will affect the pre-/post-bronchodilator FEV_1 value; they may be taken subsequently, at the site. For the same reason, patients should not use their short-acting bronchodilator medication within 6 hours of a scheduled site visit spirometry. The patient's usual bronchodilator medications may be administered following completion of the lung function procedures. Further details on spirometry are provided in the spirometry manual.

It is recommended that all post-randomisation spirometry assessments are performed within ± 1.5 hours of the time of day that the randomisation spirometry was performed, if possible.

Spirometry will also be performed as part of the sputum induction procedure (Section 8.6.1.1), as described in the separate sputum laboratory manual.

8.2.5.2 Spirometry Technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements or eating a large meal for at least 2 hours prior to spirometry measurements at the site. Forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. The patient should use mouthpieces of the same dimension and shape from enrolment throughout the study.

The forced expiratory manoeuvre (FEV_1) should start with a maximal inspiration and then be followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3, but no more than 8) will be performed for each site spirometry session. Spirometry grading will conform to ATS/ERS acceptability and reproducibility criteria as detailed in the spirometry manual. The highest FEV_1 and FVC will be based on the best efforts meeting the acceptability criteria. The highest recorded FEV_1 and FVC do not need to be from the same effort and can be derived from separate efforts. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value (Quanjer et al 2012) will be recorded. Further details on spirometry are provided in the spirometry manual.

8.2.5.3 Post-bronchodilator Spirometry

Maximal bronchodilation will be induced using 4 inhalations of albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) with or without a spacer device within 30 ± 15 minutes of the final pre-bronchodilator spirometry measurement. Post-bronchodilator spirometry will be performed 20 to 30 minutes later. If a patient cannot tolerate 4 puffs of β-agonist, a lower number of inhalations may be considered based on the investigator's clinical judgement.

8.2.6 Computed Tomography Scans

Prior to randomisation to confirm eligibility, a screening CT should be performed and assessed locally by a radiologist or other qualified specialist according to local regulations. The CT scan will also be used for a detailed characterisation of the disease at baseline and to assess the effect of benralizumab treatment on CT parameters.

A radiology manual and a standardised (CT scanner-specific) CT scan protocol will be provided and should be followed for all CT scanning performed in the study. Additional mandatory training will be provided by the imaging vendor. The standardised protocol will ensure that the image quality will be sufficient for quantitative assessments, while minimising patients' radiation exposure. CT scans must never be repeated due to the radiation exposure.

If a screening CT is not possible (eg, due to local radiation exposure regulations), a CT performed within 12 months of the screening visit is acceptable to confirm eligibility and for a central read of basic disease characteristics and visual mucus scoring.

Any abnormal clinical findings based on the CT should be recorded on the specific imaging eCRF page.

All available CT images (historical and screening) will also be submitted to the central imaging vendor for the following assessments:

- Visual assessment of bronchiectasis, emphysema, airway thickening, etc
- Visual scoring of mucus plugging
- Quantitative assessment (eligible CT scans only) of:
  - Air trapping
  - Airway wall and lumen dimensions
  - Pulmonary vessel volumes
  - Other quantitative airway properties

For subjects with an evaluable baseline CT scan (as determined by the imaging vendor), a follow-up CT scan will be performed if possible. The follow-up scan needs to be performed according to the instructions from the imaging vendor.

All CT images submitted to the imaging vendor must first be de-identified at the site to remove any patient identifiers from the Digital Imaging and Communications in Medicine (DICOM) image files. No clinical interpretation of the CT scans will be performed by the central imaging vendor.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

Physical examinations will be performed at the time points specified in the SoA (Section 1.3). The investigators should pay special attention to clinical signs related to previous serious illnesses as new or worsening abnormalities may qualify as AEs (Section 8.4.4).

8.3.1.1 Complete Physical Examination

A complete physical examination will be performed and 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.

8.3.1.2 Brief Physical Examination

The brief physical examination will include an assessment of the general appearance, abdomen, and cardiovascular and respiratory system. For the brief physical examination, only information on whether the assessment was performed or not is to be recorded.

8.3.2 Vital Signs

Pre-dose vital signs are to be obtained in accordance with the SoA (Section 1.3). Vital signs are to be taken prior to IP administration, and if possible, before blood draw.

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed:

- Body temperature will be measured in Celsius before IP administration in accordance with local standards.
- Blood pressure and pulse measurements will be assessed while sitting and will be assessed using a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Respiration rate will be obtained after patient has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

8.3.3 Electrocardiograms

Triplicate 12-lead ECGs are to be performed at screening (Visit 1) to assess eligibility for this study, and then as indicated in the SoA (Section 1.3) during the treatment period using an ECG machine that automatically calculates the heart rate and measures PR, QRS complex, QT, and QTc intervals.

Each of the three 12-lead ECGs at each time point will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry, blood draw).

An independent reader at the central 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.

The investigator must ensure that any clinically significant abnormal findings on ECG are appropriately evaluated and assessed to determine whether the findings represent an exclusion criterion.

8.3.4 Clinical Safety Laboratory Assessments

See Table 10 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3). Fasting before blood draw is recommended but not mandatory.

For information on methods of collection, assessment, labelling, storage, and shipment of samples, refer to the separate laboratory manual.

The investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.4.4.

Table 10 Laboratory Safety Variables

Haematology/Haemostasis	**Clinical Chemistry**
Haemoglobin	Alkaline phosphatase
Leukocyte count	Aspartate aminotransferase
Mean corpuscular volume	Alanine aminotransferase
Red blood cell	Bilirubin, total
Platelet count	Blood urea nitrogen
White blood cell count with differentials [a]	Calcium, total
	Chloride
Urinalysis	CO_2
U-Protein/Albumin	Creatinine

Table 10 Laboratory Safety Variables

U-Glucose	Gamma-GT (gamma-glutamyl transpeptidase)
U-Pregnancy test for women of childbearing potential	Glucose
Microscopic: white blood cells and red blood cells (screening [Visit 1] only)	Phosphorus
	Potassium
	Sodium
	Uric acid

[a] Eosinophils, basophils, and monocytes counts will be redacted from central laboratory reports after Visit 2.

The clinical chemistry and haematology analysis will be performed at a central laboratory. Urinalysis will be performed at a central laboratory only at Visit 1 and at Visit 15; other analyses will be performed locally using a dipstick provided by the central laboratory.

Additional (repeated or unscheduled) safety samples may be collected if clinically indicated at the discretion of the investigator, for safety reasons, or when there are technical issues with the samples. Such samples would be analysed at the central laboratory. If needed (eg, if clinically indicated and urgent to assess an AE), assessments can be made using local laboratories; however, eosinophil, basophil, and monocyte values should be redacted (Section 6.3.2.1).

8.3.4.1 Pregnancy Test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in the SoA (Section 1.3):

- Serum beta human chorionic gonadotropin: To be performed for all female patients at Visit 1 (the screening visit), except those women who are NOT of childbearing potential as defined in inclusion criterion 11. These tests are to be sent to and analysed at the central laboratory.
- Follicle-stimulating hormone: To be performed at Visit 1 (the screening visit) only for female patients to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for > 12 months. These tests are to be sent to and analysed at the central laboratory.
- Urine human chorionic gonadotropin: To be performed at the study site for all females at each treatment visit **before IP** administration using a dipstick except for those females who are NOT of childbearing potential as defined in inclusion criterion 11. This kit is to be provided by the central lab and analysed locally at the sites. A positive urine test result must be confirmed with serum beta human chorionic gonadotropin analysed at the central laboratory. During the OLE, Visit 20 (as specified in Table 2 of the SoA) can optionally be done as a remote visit by telephone contact for patients who are doing at home/remote-location IP administration. WOCBP should be asked if they are pregnant during the telephone visit.

8.3.4.2 Serology

Testing for hepatitis B surface antigen and hepatitis C antibody is to be performed only at screening at the central laboratory. In case of a positive result of hepatitis B surface antigen or hepatitis C virus antibody, additional testing (eg, hepatitis C RNA PCR test) may be performed to confirm eligibility.

Testing for HIV-1 and HIV-2 antibodies (along with p24 antigen) is to be performed only at screening at the central laboratory.

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

8.3.4.3 Serum Immunoglobulin E

The levels of total Ig E will be evaluated by a central laboratory. This test will be performed at Visit 1 according to the SoA (Section 1.3).

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

8.3.4.4 Weight, Height, and Body Mass Index

Weight and height will be measured in accordance with the SoA (Section 1.3).

The patient's weight will be recorded in kilograms. Height will be recorded in centimetres. Weight and height measurements will be performed in light clothing and with shoes off.

Body mass index will be automatically calculated in the eCRF.

8.4 AEs, SAEs, and Other Safety Reporting

The investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Patients (or, when appropriate, a caregiver, surrogate, or the patient's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition to AE variables listed above, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of serious AE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the time the patient receives the first dose of IP (randomisation) throughout the treatment period and including the follow-up period.

SAEs will be collected from the time the patient signs the informed consent, throughout the treatment period, and including the follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a patient treated, the investigator shall, without undue delay, report the SAE to the sponsor.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The investigator should assess causal relationship between IP and each AE, and answer 'Yes' or 'No' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. For SAEs that could be associated with any study procedure, the causal relationship is implied as 'Yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria,
- are the reason for discontinuation of treatment with the IP, or
- are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.5 Adverse Events Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of NCFB. Any event unequivocally due to the disease under study (bronchiectasis) and/or its progression (increase in the symptoms of the disease, eg, cough, mucus production, and/or increase in the severity of the disease) should be considered as disease under study and not an AE, unless it meets the definition of an SAE (Appendix B).

Bronchiectasis symptom worsening that meets the protocol definition for a bronchiectasis exacerbation (Section 8.2.1.1) will be captured on a specific eCRF module.

Bronchiectasis exacerbation should not be reported as an AE unless it meets the definition of an SAE. In such case, bronchiectasis exacerbation should be reported in the eCRF both as an exacerbation and as an SAE.

8.4.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic data capture system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by fax. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the Investigator's Brochure and product labelling for benralizumab.

8.4.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug

8.4.8.1 Maternal Exposure

Women of childbearing potential must use highly effective birth control methods to be included in this study. Should a pregnancy still occur, IP should be discontinued immediately, and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (Section 8.4.2) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper pregnancy outcome form is used to report the outcome of the pregnancy.

8.4.8.2 Paternal Exposure

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 12 weeks (≥ 5 half-lives) after the last administration of IP should, if possible, be followed up and documented.

Information on the pregnancy of a male patient's partner must be obtained directly from the patient's partner; the male patient should not be asked to provide this information. Prior to obtaining information related to the pregnancy and outcome of the pregnancy, the investigator must obtain the patient's partner consent. A consent form specific to this situation must be used.

8.4.9 Medication Error, Drug Abuse, and Drug Misuse

8.4.9.1 Timelines

If a medication error, drug abuse, **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) or **5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (Section 8.4.1) and **within 30 days** for all other medication errors.

8.4.9.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the patient or has the potential to cause harm to the patient.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.9.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.10 Management of IP-related Toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, and medical equipment to treat acute anaphylactic reactions should be available at the study site, and study personnel should be trained to recognise and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix E.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least one of the following: a) respiratory compromise; b) or reduced blood pressure or symptoms of end-organ dysfunction; or
2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms, and/or persistent gastrointestinal symptoms; or
3 Reduced blood pressure after exposure.

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix E 2.

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration and should be observed after IP administration for the appearance of any acute drug reactions in line with clinical practice.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator.

8.4.11 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose of an AstraZeneca IP occurs during the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, **but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.7) and **within 30 days** for all other overdoses.

8.4.12 Device Constituent Deficiencies

In a combination drug-device IP (eg, APFS), the device constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

A serious adverse device effect is defined as any device constituent deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency. A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.

8.4.12.1 Serious Adverse Device Effect Reporting

There are additional reporting obligations for device constituent deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to device constituents being used in clinical studies.

Any device constituent deficiency that is associated with an SAE must be reported to the sponsor **within 24 hours** after the investigator determines that the event meets the definition of a device constituent deficiency.

The sponsor will review all device constituent deficiencies and determine and document in writing whether they could have led to an SAE. These device constituent deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For storage, reuse, and destruction of human biological samples, see Appendix C.

Pharmacokinetic samples may be disposed of or anonymised by pooling.

Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay, and additional assay development work. The results from future analysis will not be reported in the CSR.

For patients in China, serum/plasma samples for biomarkers, the Genomics Initiative exploratory genetic sample; PAXGene RNA; spontaneous, unprocessed sputum samples; and induced, processed sputum samples will not be collected.

Sputum culture will be performed for all patients, including patients in China. Samples will be collected at Visits 2, 8, and 15 and the IPD visit during the DB period. Sputum culture will be analysed at the central laboratory; however, if due to the site's location, the sample cannot be delivered to the central laboratory within 48 hours of collection, the sputum culture needs to be analysed at the certified local laboratory following the same methodology as the central laboratory.

8.5.1 Pharmacokinetics

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

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

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

All PK samples will be collected according to the SoA (Section 1.3).

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

Details of the analytical method used will be described in a bioanalytical report. Full details of the analytical method used will be described in a separate bioanalytical validation report.

8.5.1.1 Determination of Drug Concentration

Samples for determination of benralizumab concentration in serum will be assayed for all patients receiving benralizumab by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

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

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate bioanalytical report.

The bioanalytical laboratory will have access to the randomisation list (Section 6.3.2).

8.5.1.2 Storage and Destruction of Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the bioanalytical report finalisation or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless consented for future analyses.

Pharmacokinetic samples may be disposed of or anonymised by pooling.

8.5.2 Immunogenicity Assessments

Serum samples for determination of ADA will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterisation of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

8.5.3 Pharmacodynamics

Blood eosinophil levels will be assessed as part of the haematology safety testing (Section 8.3.4). Biomarkers thought to play a role in eosinophilic inflammation and/or NCFB pathogenesis may also be assessed as part of exploratory research (Section 8.6.1).

The samples will be collected as described for PK in Section 8.5.1. For storage, re-use, and destruction of PD samples, see Appendix C.

8.6 Human Biological Samples for Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

The following samples for exploratory biomarker research are required and will be collected from all patients in this study (with the exception of patients in China) as specified in the SoA (Section 1.3):

- Blood (serum, plasma, whole blood PAXgene RNA tube)
- Sputum

These samples will be collected pre-dose according to the SoA (Section 1.3) to evaluate the effect of benralizumab on biomarkers of eosinophil recruitment, activation, and survival [redacted], inflammation, microbiome, and mechanisms related to NCFB pathogenesis, as well as to identify baseline biomarkers predicting response to benralizumab.

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

Results from the exploratory biomarker analyses may be reported separately from the CSR.

8.6.1.1 Sputum Collection

Either a spontaneous or an induced sputum sample will be collected. Upon the approval of this amendment (CSP version 3.0), an induced sputum sample will be collected at Visits 2 and 8, any unscheduled visits, and any IPD visit (Section 1.3). Samples will be collected and processed according to the separate laboratory manual. At other visits according to the SoA (Section 1.3), a spontaneous sputum sample will be collected and frozen without processing; sputum induction is not required at these visits. Sites that do not have the appropriate equipment or facilities for sputum processing should only collect unprocessed sputum. No induced sputum samples will be collected during the OLE period.

Sputum will be collected and processed using a modification of a previously published method (McCormick et al 2007, Pizzichini et al 1998). The sputum will be collected and processed locally at the clinical sites according to the process detailed in separate laboratory manuals provided to the sites. The analyses of these samples will be performed at a central laboratory; this will be indicated in the separate laboratory manuals.

Samples will be checked for quality and analysed at a central facility designated by AstraZeneca. Quality control results from the baseline samples may be reported to sites if necessary. Data generated from sputum collected post-randomisation will not be reported back to the sites; these data will be transferred from the analysing laboratories at the end of the study.

Processed sputum samples may be used to analyse differential cell counts, soluble protein biomarkers [CCI], respiratory pathogen detection, transcriptomics, and the microbiome. The spontaneous, unprocessed sputum samples may be used for respiratory pathogen detection, transcriptomics, and microbiome analyses.

8.6.2 Transcriptomics and Microbiome Analyses

Transcriptomics is the study of the transcriptome, the complete set of RNA transcripts that are produced by the genome using high-throughput methods. These include, but are not limited to RNA microarrays, RNA-Seq and quantitative reverse-transcriptase polymerase chain reaction technologies. Transcriptomic analysis may be performed on RNA samples isolated from whole blood (PAXgene RNA) and sputum samples according to the schedule in the SoA (Section 1.3).

Microbiome analyses may be conducted using RNA and DNA isolated from sputum for the measurement of bacteria, viruses, and other potentially pathogenic organisms including moulds and fungi.

Transcriptomics and microbiome analyses will not be performed for patients in China.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the separate genetic ICF.

A blood sample for DNA isolation will be collected at one time point only from patients who have consented to participate in the genetic analysis component of the study. These samples will not be collected from patients in China. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

Samples can be collected at any time after the genetic consent form is signed. The blood sample should be collected at randomisation (Visit 2); however, it may be taken at any visit until the last study visit.

See Appendix D for information regarding genetic research. Details on processes for collection, shipment, and destruction of these samples can be found in Appendix D or in the laboratory manual.

8.8 Healthcare Resource Utilisation

NCFB-related healthcare resource utilisation data associated with medical encounters will be collected in the appropriate eCRF by the investigator and study-site personnel for all patients throughout the study according to the schedule in the SoA (Section 1.3). CSP-mandated procedures, tests, and encounters are excluded.

At randomisation (Visit 2), NCFB-related healthcare resource utilisation information will be collected with a one-year recall period. All the subsequent visits will collect NCFB-related healthcare resource utilisation information with a recall period of 'since last scheduled visit'.

8.9 Other Assessments and Procedures

8.9.1 Patient Testing Due to Public Health Crisis

If patient testing is performed due to a public health crisis, the results may be documented for this study.

8.10 Study Participant Feedback Questionnaire – Not Applicable

This study will NOT include an option for patients to complete a Study Participant Feedback Questionnaire.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is the annualised rate of bronchiectasis exacerbations over the DB treatment period. The primary endpoint will be assessed in the population comprised in the FAS. A treatment policy estimand will be applied to the primary analysis of the primary endpoint whereby all data is included, regardless of whether a patient remains on blinded IP or not.

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, ie:

H0: Rate ratio (benralizumab vs Placebo) = 1

H1: Rate ratio (benralizumab vs Placebo) ≠ 1

Hypothesis testing will be performed at the 2-sided 5% significance level. If the p-value is less than 0.05 and the treatment effect favours benralizumab, reject H0 and accept H1.

9.2 Sample Size Determination

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 of 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 be conducted for 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 have 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 have 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.

9.3 Populations for Analyses

Populations for analysis are defined in Table 11.

Table 11 Populations for Analysis

Population/Analysis set	Description
All-patients analysis set	All patients screened for the study will be included for reporting of disposition and screening failures
Full analysis set	All patients randomised who have received at least one 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 principle. Patients who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	All patients who have received at least one dose of IP. Erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received.

Table 11 Populations for Analysis

Population/Analysis set	Description
	A patient who has on one or several occasions received active IP is classified as active. All safety summaries and ADA data will be based on this analysis set.
Pharmacokinetic analysis set	All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (eg, 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.
OLE analysis set	The OLE analysis set will include all patients who enter the OLE part of the study and who receive at least 1 dose of IP during the OLE treatment period.

ADA = anti-drug antibodies; IP = investigational product; PK = pharmacokinetics; OLE = open-label extension

9.4 Statistical Analyses

All personnel involved with the analysis of the study will remain blinded until the database lock and CSP deviations identified for the efficacy analysis.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be finalised before database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Analyses for the OLE are described in Section 9.6. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

Efficacy analyses will be performed using the FAS. All analyses described below will be based on the FAS population, including all patients through the end of the DB period (Visit 15), unless otherwise stated. The study will remain blinded until the database lock, which will occur after the last patient completes the OLE. The primary analysis of efficacy endpoints will include all data captured during the DB treatment period (intention-to-treat approach).

A treatment policy estimand will be applied to the primary analysis of the primary endpoint (along with the main analysis of secondary endpoints) whereby all data (in the DB treatment period) is included, regardless of whether a patient remains on blinded IP or not.

Demography and baseline characteristics will be summarised by treatment group for the FAS.

9.4.2 Efficacy

9.4.2.1 Calculation or Derivation of Variables for Efficacy Analyses

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. Details of baseline definitions will be specified in the SAP.

Exacerbation Rate

The annualised bronchiectasis exacerbation rate will be used as the primary efficacy variable. A bronchiectasis exacerbation is defined in Section 8.2.1. If the stop date of an exacerbation and the start date of the subsequent exacerbation are ≤ 14 days apart, the exacerbations will be considered to be a single event to ensure that the same event is not counted twice. In case the severity of the exacerbation events being combined is different, the highest severity will be used for the combined event. This rule will be used to calculate the number of exacerbations experienced by a patient during the DB treatment period. In the primary analysis, the number of exacerbations observed for a patient during the DB treatment period will be used as the response variable.

For the primary efficacy analysis, the maximum follow-up time for exacerbations for a patient is up to 52 weeks (depending on the timing of patient randomisation and when this amendment [CSP version 3.0] becomes effective) and is defined as 'the time from randomisation to the date of the last DB treatment period visit'. For a patient lost to follow-up, this will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed.

In the statistical analysis, the number of bronchiectasis exacerbations experienced by a patient during the DB treatment period will be used as the response variable. The logarithm of the patient's corresponding at-risk 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 time at risk will account for the duration of exacerbations by subtracting the duration of each exacerbation (plus 14 days for each exacerbation) from the follow-up time.

For summary statistics, the annualised exacerbation rate per patient during DB treatment period is calculated and standardised by the length of the DB period according to the following formula:

Annualised Exacerbation Rate = Number of Exacerbations*365.25 / Total time at risk within the DB period (days)

Time to First Bronchiectasis Exacerbation

The time to first bronchiectasis exacerbation (defined in Section 8.2.1) is calculated as:

Start date of first bronchiectasis exacerbation during the DB treatment period - date of randomisation + 1

Patients who have not experienced a bronchiectasis exacerbation during the DB treatment period will be right censored at their last DB treatment period assessment date.

Proportion of Patients with ≥ 1 Bronchiectasis Exacerbation During the DB Treatment Period

The proportion of patients with ≥ one bronchiectasis exacerbation during the DB treatment period will be a supportive variable to the primary outcome variable.

Change From Baseline in QoL-B-RSS

Change from baseline for QoL-B-RSS will be calculated at each visit over the DB treatment period for this scale.

Change From Baseline in Pre-dose FEV_1

The change from baseline for pre-dose FEV_1 will be calculated at each visit over the DB treatment period.

Change From Baseline in LCQ

Three LCQ domains (physical, psychological, and social) will be derived along with a total score. Change from baseline will be calculated at each visit over the DB treatment period for these domains and total score.

Change From Baseline in QoL-B Scales (Excluding QoL-B-RSS Secondary Endpoint)

Seven remaining QoL-B scales (physical functioning, role functioning, emotional functioning, social functioning, vitality, health perceptions, and treatment burden) will be derived. Change from baseline will be calculated at each visit over the DB treatment period for these scales.

Change From Baseline in SGRQ

Three SGRQ components (symptoms, activity, and impacts) will be derived along with a total score. Change from baseline will be calculated at each visit over the DB treatment period for these component and total scores.

9.4.2.2 Primary Endpoint

The primary efficacy endpoint is the annualised bronchiectasis exacerbation rate over the DB treatment period. The primary analysis is to compare the annual bronchiectasis exacerbation rate of the benralizumab group with placebo using the FAS.

Exacerbation rate in the benralizumab group will be compared to exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of bronchiectasis exacerbations over the DB treatment period. The model will include covariates of treatment group, baseline blood eosinophil category (≥ CCI /µL and < CCI /µL blood eosinophil count), and number of exacerbations in previous year. The logarithm of the patient's corresponding at-risk 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 time at risk will account for the duration of exacerbations by subtracting the duration of exacerbations from the follow-up time.

The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval, and 2-sided p-value for the rate ratio will be presented.

Subgroup Analysis

Details of all subgroup analyses and statistical modelling including possible testing of interaction between treatment group and covariates will be described in the SAP. Subgroups will include, but will not necessarily be limited, to the following:

- Age
- Prior exacerbations
- Eosinophil count
- Macrolides
- *P. aeruginosa* sputum culture status

9.4.2.3 Secondary Endpoint(s)

All secondary efficacy endpoints will be summarised for patients in the FAS.

Time to first bronchiectasis exacerbation will be analysed using a Cox-proportional hazards model. Treatment group, number of exacerbations in prior year, and baseline blood eosinophil category (≥ CCI /µL and < CCI /µL blood eosinophil count) will be included as covariates in the model. Results will be presented in terms of the adjusted hazard ratio with a 95% confidence interval and a 2-sided p-value.

QoL-B-RSS and FEV_1 will be assessed as change from baseline over the DB treatment period. The change from baseline in QoL-B-RSS and FEV_1 will be analysed using a MMRM analysis with treatment group, baseline value for each endpoint of interest, baseline blood eosinophil category (≥ CCI /µL and < CCI /µL blood eosinophil count), visit and treatment*visit interaction as covariates in the model. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary analysis will fit a MMRM model using the data collected up to and including the last visit in DB treatment period.

Change from baseline in LCQ, QoL-B scales (excluding QoL-B-RSS key secondary endpoint), and SGRQ will be analysed using a similar repeated measures analysis model as the model for change from baseline in QoL-B-RSS and FEV_1.

9.4.2.4 Exploratory Endpoints

Descriptive statistics will be provided for PGIS and PGIC responses over the DB treatment period. WPAI-GH over time will be listed.

Change from baseline in blood eosinophils will be analysed using a MMRM model with treatment group, baseline blood eosinophil, visit and treatment*visit interaction as covariates in the model.

9.4.3 Safety Analyses

All safety analyses will be performed using the safety analysis set.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities that will have been released for execution at AstraZeneca/designee.

Safety data will be presented using descriptive statistics unless otherwise specified. AEs will be presented for each treatment group by system organ class and preferred term covering number and percentage of patients reporting at least one event and number of events where appropriate.

An overview of AEs will be presented for each treatment group: the number and percentage of patients with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP. Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, intensity, seriousness, death, and events leading to discontinuation of IP. An additional table will present number and percentage of patients with most common AEs (frequency of > 3%). In accordance with the requirements of the United States FDA, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

The following events are considered treatment emergent:

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

Laboratory data will be summarised by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges).

Vital sign and ECG data will be listed.

9.4.4 Other Analyses

Pharmacokinetic, PD, biomarker, and other exploratory analyses will be described in the SAP, which will be finalised before the database lock.

9.5 Interim Analyses – Not Applicable

No interim analysis is planned in this study.

9.6 Analyses of Data from the Open-Label Extension

For the OLE, descriptive statistics will be presented for safety, ADA, PK, and eosinophil count endpoints. A summary of data from the OLE will be presented in the CSR.

9.7 Data Monitoring Committee- Not Applicable

An independent Data Monitoring Committee was not established for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the CSP and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The CSP, revised CSP, ICF, investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any revised CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organisation, but the accountability remains with AstraZeneca.

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and subinvestigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory human biological samples. The investigator or authorised designee will explain to each patient the objectives of the analysis to be done on the samples and any potential future use. Patients will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

If a patient's partner becomes pregnant during or within 12 weeks after the last dose of IP, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

A 4 Data Protection

Patients will be assigned a unique identifier by AstraZeneca. Any patient records or datasets that are transferred to AstraZeneca will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 5 Dissemination of Clinical Study Data

Any results, both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global end-of-trial date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 6 Data Quality Assurance

All patient data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the monitoring plan.

AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.

AstraZeneca assumes accountability for actions delegated to other individuals (eg, contract research organisations).

Study monitors will perform ongoing source data verification as per the monitoring plan to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 7 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the monitoring guidelines.

A 8 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or investigator may include but are not limited to:

- Failure of the investigator to comply with the CSP, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRB/IECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

Patients from terminated sites may have the opportunity to be transferred to another site to continue the study.

A 9 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.

AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca IMP or AstraZeneca NIMP that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IxRS/RTSM errors)
- Wrong drug administered to patient (excluding IxRS/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IxRS/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard-of-care medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the drug abuse report form. This form should be used both if the drug abuse happened in a study patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study patient or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the data entry site using the drug misuse report form. This form should be used both if the drug misuse happened in a study patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each study site keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from the last subject last visit.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures patient's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that patient, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Air Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A infectious substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B infectious substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

This appendix is not applicable to patients in China.

D 1 Use/Analysis of DNA

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications.

This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in healthcare and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

This optional genetic research may consist of the analysis of the structure of the patient's DNA, ie, the entire genome.

The results of genetic analyses may be reported in a separate study summary.

AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the clinical study protocol and: provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for Genetic Research

The blood sample for this genetic research will be obtained from the patients at Visit 2. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the samples either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for

the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The investigator is responsible for ensuring that consent is given freely, and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient Data Protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data from the optional genomics initiative will be reported separately from the CSR for the main study.

Appendix E Anaphylaxis: Definition, Signs, Symptoms and Management

E 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organisation has categorised anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex-mediated]) and non-immunologic (Johansson et al 2004). The clinical criteria for defining anaphylaxis for this study are listed in Section E 2 of this Appendix. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section E 3 of this Appendix. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions should be available at study sites, and study personnel should be trained to recognise and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected as soon as possible after the event, at 90 ± 30 minutes after the event, and at discharge; analysis for serum tryptase will be performed at a local laboratory. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator.

E 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**
   (a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalised hives, itch-flush, swollen lips-tongue-uvula).
   (b) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia).

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

(d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3) Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours). For adults, this corresponds to a systolic blood pressure of less than 90 mm Hg or a greater than 30% decrease from that patient's baseline.

Immune Complex Disease

Immune complex disease or hypersensitivity type III is evoked by the deposition of antigen-antibody or antigen antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis are common.

E 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal oedema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhoea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhoea, abdominal cramps, and bloating
- Light headedness
- Headache
- Uterine cramps

- Generalised warmth

E 4 Management of Acute Anaphylaxis

E 4.1 Immediate Intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.
2 Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock, and unconsciousness.

E 4.2 Possibly Appropriate, Subsequent Measures Depending on Response to Epinephrine

1 Place patient in recumbent position and elevate lower extremities
2 Establish and maintain airway
3 Administer oxygen
4 Establish venous access
5 Normal saline intravenously for fluid replacement

E 4.3 Specific Measures to Consider After Epinephrine Injections, Where Appropriate

1 Consider epinephrine infusion
2 Consider H1 and H2 antihistamines
3 Consider nebulised β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine
4 Consider systemic corticosteroids
5 Consider vasopressor (eg, dopamine)
6 Consider glucagon for patient taking β-blocker
7 Consider atropine for symptomatic bradycardia
8 Consider transportation to an emergency department or an intensive care facility
9 For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary

Adapted from Kemp et al 2008.

Appendix F Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AstraZeneca Study Physician.

F 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the AstraZeneca study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in the SoA (Section 1.3), the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a patient in addition to that detailed in Section 5.4**.** The procedures detailed in Section 1.3 and 5.4 must be undertaken to confirm eligibility using the same randomisation number for the patient.

F 3 Home or Remote Visit to Replace Onsite Visit (Where Applicable)

A qualified HCP from the study site or third-party vendor service may visit the patient's home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

F 4 Telemedicine Visit to Replace Onsite Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, onsite visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, and bronchiectasis exacerbation assessments to be reported and documented and ePRO assessments to be reviewed.

F 5 At-home or Remote-Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures patient safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimise interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

F 5.1 At-home or Remote-Location IP Administration by a Qualified HCP or Third-party Vendor Service

A qualified HCP from the study site or third-party vendor service may administer the IP at the patient's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

F 5.2 At-home or Remote-Location IP Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location IP administration, the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be

provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

F 6 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or third-party vendor service in the source documents, or by the patients themselves.

Appendix G Bronchiectasis Exacerbation Diary Questionnaire

This questionnaire is meant to gather information about the symptoms that you experience related to your bronchiectasis.	
Question	**Response options**
1. How much have you coughed in the last 24 hours?	Less cough than usual Usual level of cough More cough than usual
One of the symptoms that we will ask about is mucus (phlegm). When we talk about mucus (phlegm), we mean the substance that may build up in your throat or lungs that you may have to cough up or swallow.	
2. Have you had mucus (phlegm) in the last 24 hours?	No *[skip to Question 3]* Yes
2a. How much mucus (phlegm) did you have in the last 24 hours?	Less than usual mucus (phlegm) Usual amount of mucus (phlegm) More mucus (phlegm) than usual
2b. How thick was your mucus (phlegm) in the last 24 hours?	Mucus (phlegm) was thinner than usual Mucus (phlegm) was the usual thickness Mucus (phlegm) was thicker than usual I have not noticed the thickness of my mucus (phlegm)
2c. Has the color of your mucus (phlegm) changed in the last 24 hours?	No, mucus (phlegm) was the usual color Yes, mucus (phlegm) was a different color than usual I have not noticed the color of my mucus (phlegm)
3. Have you coughed up blood in the last 24 hours?	No Yes, I have coughed up blood I have not noticed if I have coughed up blood
4. How breathless have you been in the last 24 hours?	Less breathless than usual Usual level of breathlessness More breathless than usual
5. How fatigued have you been in the last 24 hours?	Less fatigued than usual Usual level of fatigue More fatigued than usual

Appendix H Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 2: (17 December 2020)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of patients nor the scientific value of the study.

Overall Rationale for the Modification

This CSP has been amended to modify the Schedule of Activities such that Year 1 to 3 of the open-label extension correspond to 52 weeks each and to change the frequency and timing of some activities.

Table H12 Table of Non-substantial Modifications (CSP version 2.0)

Section # and name	Description of change	Brief rationale
Section 1.3 SoA	Collection of spontaneous, unprocessed sputum removed from Visit 1.	Not needed as a baseline sample of sputum (induced, processed) is collected at Visit 2.
Section 1.3 SoA	In footnote k of Table 2 and footnote g of Table 3, "…until the second visit of the OLE (Week 60, Visit 17)…" revised to "…until Visit 17…"	For consistency.
Section 1.3 SoA	One visit was removed from each of OLE Years 1 to 3, such that each year is 52 weeks long. As a result, some assessments were shifted, and changes were made to which visits could optionally be performed remotely.	For OLE Years 1 to 3 to correspond to 52 weeks each.
Section 1.3 SoA	A pre-bronchodilator spirometry assessment and an ECG during OLE Year 1 were moved from Visit 25 to Visit 23.	For the frequency of these assessments to be more even over time.
Section 1.3 SoA	Pharmacokinetic, anti-drug antibody, and blood biomarker assessments moved from Week 100 to Week 104.	To have these assessments occur on the final visit of OLE Year 1 (Visit 28, Week 104).
Section 1.3 SoA	Frequency of SGRQ assessments revised.	To align the visits at which SGRQ assessments and pre-bronchodilator spirometry assessments are made.

Table H12 Table of Non-substantial Modifications (CSP version 2.0)

Section # and name	Description of change	Brief rationale
Section 8.1.4.4, SGRQ Section 9.4.2.1, Calculation or Derivation of Variables for Efficacy Analyses	Change in terminology to use "component" rather than "domain" when describing symptom, activity, and impact in the SGRQ tool.	At the request of the developer of the SGRQ tool.
Various sections	Typographical errors corrected.	For clarity and correctness.

OLE = open-label extension; SGRQ = St. George's Respiratory Questionnaire; SoA = Schedule of Activities

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Document ID:	Doc ID-004339191	
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