Clinical Study Protocol

Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00045
Version	4.0 (final version)
EudraCT	2017-001040-35
Date	01 May 2020

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI)

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VERSION HISTORY

Version 4.0, amendment 3, 01 May 2020

Changes to the protocol are summarized below:

Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document (minor edits that do not substantively impact the meaning of the text are not listed individually). In addition, references to the GINA 2018 guidance have been replaced by references to the updated GINA 2020 guideline where applicable. Investigator assessment of GINA step assignment has been removed throughout. Main outcome variable for the Open label ANDHI IP Substudy has been reworded to clarify that changes in GINA step refers to reductions as follows: "Number of adapted[a] GINA step category changes from Visit 15 to the EOS Visit 27 (Day 560/Week 80)." An additional main outcome variable has been added: "Number of reductions in asthma controller medications from Visit 15 to EOS Visit 27 (Day 560/Week 80)"; and the main outcome measures have been updated accordingly.

Supportive measures have been added to provide further information on the type and extent of background medication that has been reduced. The main analysis set have been clarified and 2 additional analyses set have been defined: patients with OCS use at V15 and also patients who directly transitioned from the ANDHI study to the ANDHI in Practice (ANDHI IP) Substudy. Minor edits made to improve consistency and clarity that do not substantively affect the content have been made throughout which are not individually listed below.

Major changes:

Protocol synopsis and in body where applicable: main outcome variables for the Open label ANDHI IP Substudy has been reworded as previously indicated and the following updates to the main outcome measures have been added:

- New main variable was added: Number of reductions in asthma controller medications from Visit 15 to the end of study (EOS) Visit 27 (Day 560/Week 80);
- The following main outcome measure was added: Proportion of patients with at least one reduction in asthma controller medication from Visit 15 to EOS (Visit 27);
- Supportive measures were added: Proportion of patients with at least one reduction in background medication by categories (ie, discontinuation of LAMA, LTRA, LABA, theophylline; reduction in ICS dose [HD-ICS, MD-ICS, LD-ICS or anti-inflammatory reliever]) at EOS (Visit 27);

- Characteristics of patients with 0 vs ≥2 reductions in controller medication for patients on maintenance OCS at Visit 15:
- For patients on maintenance OCS at Visit 15:
  - Proportion achieving 50/75/90/100% reduction in OCS dose at EOS (Visit 27);
  - Proportion achieving OCS dose ≤5mg at EOS (Visit 27);
  - Change in OCS dose from Visit 15 to Visit 27 (EOS).

Supportive measures to meet other efficacy objectives have been expanded to include change in pre-bronchodilator forced expiratory volume [pre-BD FEV_1] and weekly mean morning peak expiratory flow [PEF]; and the degree of change reported by the patient (PGI-C) and Investigator (CGI-C).

Statistical methods for the Open label ANDHI IP substudy have been updated.

Section 1.4 (Study design): updated study design figure to reflect actual enrolment FEV_1.

Section 2.3 (Exploratory objectives): the main outcome variable for the Open label ANDHI IP Substudy has been reworded and supportive measures added as previously indicated.

Section 4 (Study plan and timing of procedures): Text added to address the possible need for alternative study procedures due to coronavirus disease 2019 (COVID-19) and referring readers to detailed information in new Appendix F. GINA step assessment row has been deleted from Table 3.

Section 4.4.1 (Visit 13 [Week 24]): Open label ANDHI IP substudy enrolment visit and first open-label benralizumab dose): adapted GINA treatment step assessment bullet has been deleted.

Section 4.5.1 (Background asthma medication reduction visits in the clinic): Visit 15, Visit 17, Visit 19, Visit 21, and Visit 23): GINA step assessment bullets have been deleted.

Section 4.5.5 (Approach to background medication reduction in eligible patients): modified CCI [redacted]

Section 4.6.2 (Visit 27 [Week 80]: End of ANDHI IP Substudy [EOS]): GINA step assignment bullet has been deleted.

Section 4.7 (Premature investigational product discontinuation, or early withdrawal from study [IPD/WD] from the ANDHI IP substudy): GINA step assignment bullet has been deleted.

Section 5.2.1 (Assigning adapted GINA status): Text has been modified to clarify adapted GINA step category assessments will be performed programmatically.

Section 8.4 (Outcome measures): Added text to clarify "baseline" in ANDHI IP substudy.

Section 8.6.1 (Summary of the ANDHI IP substudy objectives and relation to the ANDHI controlled study): The main outcome variable has been updated as described previously; analysis methods are updated, and the list of efficacy endpoints included in other efficacy analyses are expanded.

Section 8.6.3 (Definition of analysis sets for ANDHI IP): The definition of the main efficacy set has been amended to include all enrolled patients who received at least one dose of open label benralizumab and are not receiving maintenance OCS for asthma at Visit 15. Two additional analysis sets have been added:

- OCS efficacy analysis set, which will include all enrolled patients who received at least 1 dose of open label benralizumab, attended Visit 15 of the ANDHI IP substudy and are receiving maintenance OCS for asthma at Visit 15.

- The direct transitioning efficacy analysis set is defined as all patients in the main efficacy analysis set who receive their benralizumab dose at Visit 13 within a 60-day window of their last IP dose (benralizumab or placebo) in the ANDHI double-blind study.

All analyses will be presented by overall and by ANDHI double-blind treatment group and repeated by asthma control status at EOS (Visit 27).

Section 8.7 (Definition of Baselines): Baseline definitions were updated and in particular, the following definitions added:

- Baseline for the ANDHI IP substudy was revised to align with revisions to the SAP such that in the case of morning PEF, the average of the last 7 consecutive days prior to Visit 15 with less than 4 missing daily diary entries will be used as baseline. Only PEF scores on or after Visit 14 will be considered for the baseline derivation.

- For the safety analyses, measurements taken at Visit 13 will be used as baseline (ie, for vital signs).

- For blood eosinophil counts Visit 4 (from ANDHI double-blind [DB] study) will be used as baseline.

- Section 8.7.1.1 (Main ANDHI IP substudy objective: assessing reduction of the patients' standard of care background asthma controller regimen): The main outcome variables and measures for the ANDHI IP substudy have been updated and descriptions of supportive measures were added.)

Section 8.7.1.2 (Calculation or derivation of other efficacy variables in the ANDHI IP substudy): clarified analyses for patients in the direct transitioning efficacy analysis set.

Section 8.8.1 (Analysis of the main efficacy variables for the ANDHI IP substudy): The main outcome variables have been updated. Descriptions of analyses for the main and supportive measures were added.

Section 8.8.2 (Analysis of other efficacy variables): Analyses have been updated and use of the direct transitioning efficacy analysis set specified for the analyses looking at change from ANDHI DB (Visit 4) baseline.

Section 11 (LIST OF REFERENCES): added reference to GINA 2020.

Appendix D (Guidance on Assigning Adapted GINA Step Based on Asthma Concomitant Medications): replaced Appendix D with new version based on more recent GINA step guidelines including new Table 8 presenting modified GINA step assignment for the purpose of the ANDHI IP substudy.

Appendix E: added new table "OCS equivalency table for asthma patients".

Appendix F: new Appendix F added to include details of handling study conduct changes due to COVID-19.

Appendix G: signature pages, formerly Appendix F, are now Appendix G.

Version 3.0, amendment 2, 18 July 2018

Changes to the protocol are summarized below:

Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document. In addition, changes have been made to section heading numbers and table cross-references, where necessary, due to amendments detailed in this document.

Protocol synopsis

- Study design has been updated to include a 56-week open label ANDHI in Practice (ANDHI IP) substudy upon the completion of the 24-week double-blind period of the ANDHI study. Patients who do not

participate in the open label ANDHI IP substudy, or who do not transition into the open label period will complete the follow-up (FU) Visit 12 for final safety assessment at Day 182 (Week 26). Patients who transition into the open label ANDHI IP substudy prior to the FU Visit 12, will receive the first open label dose of benralizumab at Visit 13 on Day 168 and complete the End of ANDHI IP Substudy (EOS) Visit 27 at week 80.

- The estimated date of last patient completed was updated from Q1 2019 to approximately Q3 2020.

- The objectives and outcome measures for the open label ANDHI IP substudy have been included:

– The main objective of the open label ANDHI IP substudy is to assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen while maintaining asthma control. The proportions and distribution of the number of adapted GINA step category the patient changes from Visit 15 to the EOS Visit 27 will be measured.

– Other objective is to assess standard asthma efficacy measures for benralizumab treated patients who reduce their standard of care asthma controller regimen. The change in continuous asthma efficacy measures (eg, ACQ6 and Saint George Respiratory Questionnaire (SGRQ)) and clinically significant asthma exacerbations from Visit 15 to EOS Visit 27 will be measured. The change in continuous asthma efficacy measures from Visit 4 to EOS Visit 27 will also be measured.

– Safety objective of the open label ANDHI IP substudy is to assess the safety and tolerability of benralizumab during treatment period. The adverse events (AEs), physical examination, vital signs during the open label benralizumab treatment period (Visit 13 to Visit 27) will be measured.

- The study period has been updated from a maximum of 32 weeks to 88 weeks to reflect the inclusion of the open label ANDHI IP substudy. Patients who transition into the open label ANDHI IP substudy prior to the FU Visit 12 will receive the first open label dose of benralizumab at Visit 13 on Day 168 and complete the EOS Visit 27 at Week 80.

- The administration of benralizumab sc has been updated to reflect the inclusion of the open label ANDHI IP substudy. All patients in the open label ANDHI IP substudy will received benralizumab sc at Day 168 (Week 24), Day 196 (Week 28), Day 224 (Week 32), Day 280 (Week 40), Day 336 (Week 48), Day 392 (Week 56), Day 448 (Week 64), and Day 504 (Week 72).

- Statistical methods have been updated to reflect the inclusion of the open label ANDHI IP substudy. In the open label ANDHI IP substudy, the main efficacy analysis of GINA step reduction and other efficacy analyses will be summarized descriptively. For the main efficacy analysis patients using maintenance OCS at the Visit 15 will be excluded from the primary analysis, based on the assumption that complete OCS cessation will be uncommon given the duration of the treatment period. The proportions of patients achieving increasing number of adapted GINA category reduction(s) are defined as the number of patient with at least X number of steps of reductions in adaptive GINA category, where X is ranging from 1 to 4. The cumulative and actual reductions will both be presented by baseline adapted GINA step category with nominal 95% confidence intervals derived using the exact Clopper-Pearson method.

Section 1.2 (Rational for study design, doses and control group): the rational for the inclusion of the open label ANDHI IP substudy as part of ANDHI study has been added.

Section 1.3 (Benefit/risk and ethical assessment): the potential risks of open label ANDHI IP substudy have been included. During the open label ANDHI IP substudy, protocol guided reductions in the level of background asthma medication could potentially be associated with loss of asthma control. To mitigate this risk, the patient's overall level of asthma control must be stable to improving at any given reduction visit based on regular ACQ6 assessments (via an electronic patient-reported outcome [ePRO] device), with an overall ACQ6 score of <1.5 (where a score ≥1.5 is indicative of inadequately controlled asthma), to be eligible for background medication reduction. CCI [redacted] Investigators may defer any scheduled dose reduction, based on their overall, documented clinical assessment that it would not be in the patients' best interest. Dose reductions commence only after the patient has received the 3rd open label dose of benralizumab, with attempts at per protocol reductions occurring no more frequently than every 2 months, at scheduled benralizumab dosing visits. Interim telephone contacts, between dose reduction visits, are also scheduled to assess the patient's status. Peak expiratory flow (PEF) monitoring with alerts for sustained worsening will be maintained during the open label period.

Section 1.4 (Study design): study design has been updated to reflect the inclusion of open label ANDHI IP substudy. Study flow chart for ANDHI IP substudy has been added.

Section 2.3 (Exploratory objectives): the objectives and outcome measures have been added for the open label ANDHI IP substudy.

Section 2.4 (Safety objectives): the safety objectives and outcome measures have been added for the open label ANDHI IP substudy.

Section 3.1.1 (Inclusion criteria for the ANDHI study): the text of Inclusion #7 (a) has been updated to clarify the rationale of airway reversibility testing. The patient should complete

the per protocol reversibility testing during the screening period as above as screening reversibility is an important baseline disease state characteristic. If the patient does not meet this criterion at Visit 2 the airway reversibility assessment must be repeated at a separate Visit 3. If at Visit 3 the patient again does not meet screening reversibility but meet one of the alternate criteria below (b to e) the patient can be considered as eligible per Inclusion #7.

Section 3.1.2 (Inclusion criteria for the open label ANDHI IP substudy): subsection has been added specifying the inclusion criteria of the open label ANDHI IP substudy. The patients must have completed ANDHI EOT Visit 11 and written informed consent must be obtained prior to any related procedures being performed in the open label ANDHI IP substudy. Patients who have received any approved or investigational targeted biologic for the treatment of asthma (eg, commercial mepolizumab, reslizumab, benralizumab) may be included if the last dose is ≥2 months of Visit 13.

Section 3.2.2 (Exclusion criteria [open label ANDHI IP substudy]): additional exclusion criteria for the open label ANDHI IP substudy has been added. Each exclusion criterion should be reviewed in all potential participants, including those who transition directly from the double-blind period and those with a delay between completing the EOT Visit 11 and the first open label visit (Visit 13).

Section 3.3 (Subject enrolment and randomization): the text for ANDHI IP substudy has been included. All patients entering ANDHI IP substudy will receive active benralizumab 30 mg sc in an open label fashion. Patients and site staff will remain blinded to randomized treatment assignment in ANDHI. Enrolment in the ANDHI IP open label substudy will stop after the last ANDHI controlled patient completes their EOT Visit 11.

Section 3.5 (Methods for assigning treatment groups): the text to reflect the ANDHI IP substudy has been included. All patients in the ANDHI IP substudy will receive active benralizumab 30 mg sc in an open label fashion.

Section 3.6 (Methods for ensuring blinding): the text to reflect the ANDHI IP substudy was included. At the time of enrolment of patients into the open label ANDHI IP substudy, the treatment status will not be known and will remain blinded until such time as the 24-week double-blind period of the ANDHI is unblinded. During the open label period, benralizumab will be provided in a labelled accessorized pre-filled syringe.

Section 3.10 (Restrictions during the open label ANDHI IP substudy): additional guidance for management of concomitant asthma medication and on the days of scheduled lung function assessments specific to the open label ANDHI IP substudy has been added.

Section 3.11 (Discontinuation of investigational product): the text to reflect the ANDHI IP substudy has been included.

Section 3.12 (Criteria for withdrawal): the text to reflect ANDHI IP substudy has been included.

Section 4 (Study plan and timing of procedures): the study plan for the open label ANDHI IP substudy, Visit 13 to Visit 27, has been included in Table 3.

Section 5.1 (Efficacy assessments): the text of efficacy assessments has been updated to reflect the ANDHI IP substudy.

Section 5.2 (Efficacy assessments in the open label ANDHI IP substudy): the efficacy assessments for the ANDHI IP substudy have been included to address the assigning adapted GINA status.

Section 5.3 (Safety assessments): the safety assessments for ANDHI IP substudy have been included. During the open label period, urine beta-human chorionic gonadotropin (hCG) test will be performed at the study center for women of childbearing potential (WOCBP) at all dosing Visits: Visit 13, Visit 14, Visit 15, Visit 17, Visit 19, Visit 21, Visit 23, Visit 25, and at Visit 27 EOS/IPD/WD, using a dipstick. Urine tests should be performed before IP administration at treatment visits. A positive urine test must be confirmed by a serum beta hCG test.

Section 5.4.1 (Daily asthma measurements): the text to reflect the ANDHI IP substudy has been included. Patients will be dispensed an ePRO device at Visit 2 and at Visit 13 as needed for patients who enrolled in the ANDHI IP substudy after the FU Visit 12 and may have returned their devices, which will allow home measurement of PEF and recording of Asthma Daily Diary data.

Section 5.4.1.1 (Peak expiratory flow assessment at home): For patients entering the ANDHI IP substudy, only morning PEF (and not evening) will be obtained through Visit 27.

Section 5.8.4 (Blood eosinophil counts): the text of blood eosinophil counts assessments has been added to reflect assessments from the ANDHI IP substudy. Blood eosinophil counts will be followed periodically as a biomarker relevant to the benralizumab mechanism of action. Blood eosinophil counts will be assessed centrally.

Section 6.3 (Recording of adverse events): the text of adverse events recording has been updated to reflect the ANDHI IP substudy.

Section 7.7 (Concomitant and other treatments): the text of concomitant treatment has been updated to reflect the ANDHI IP substudy.

Section 8 (Statistical analysis by AstraZeneca): statistical considerations for the ANDHI IP substudy have been included. Detailed statistical measures have been updated in Section 8.1 Statistical considerations, Section 8.6 Statistical analysis pertaining to the open label

ANDHI IP substudy, Section 8.7 Outcome measure for analyses for the ANDHI IP substudy, and Section 8.8 Methods for statistical analyses for the ANDHI IP substudy.

Section 9.3 (Study timetable and end of study): the study timetable and end of study has been updated to reflect the addition of the ANDHI IP substudy.

Appendix D has been added to provide guidance on assigning adapted GINA steps based on asthma concomitant medications for the purpose of ANDHI IP substudy.

Appendix E was updated to reflect the most updated GINA 2018 guideline for inhaled corticosteroids (ICS) equivalency tables for asthma patients age 12 and older.

Version 2.0, amendment 1, 04 January 2018

Changes to the protocol are summarized below:

Whole document: Formatting, grammatical and minor editorial changes have been made throughout the document. In addition, changes have been made to section heading numbers and table cross-references, where necessary, due to amendments detailed in this document.

Protocol synopsis (Study sites and number of patients planned):

- The total estimated number of patients to be randomized was updated from approximately 800 with 1:1 randomization ratio for benralizumab:placebo to approximately 630 with a 2:1 randomization of benralizumab:placebo. This change is expected to mitigate early challenges around recruiting sufficient numbers of appropriately severe eosinophilic asthma patients to the study. This change preserves the number of patients receiving active benralizumab treatment and reduces the number of patients exposed to placebo, while retaining statistical power to detect a treatment difference for both asthma exacerbation reduction and SGRQ improvement (97% and 87% respectively). The revised powering remains consistent with a level that would assure robust conclusions and scientific exchange. This change is reflected throughout the synopsis and protocol.

- The estimated date of first patient enrolled was updated from Q2 2017 to Q3 2017, as this date is now known (this update was also made in Section 9.3 [Study timetable and end of study]).

- The approximate number of study centers was updated from 275 to 270.

Section 1.1 (Background and rationale for conducting this study): The text was updated with efficacy results from Phase III studies that were recently published. These data support the inclusion of patients with baseline blood eosinophil counts of ≥150 cells/μL if they have other evidence of a severe eosinophilic asthma phenotype. These newer data inform the updated blood eosinophil inclusion criterion for this study (see Section 3.1 changes).

Section 1.4 (Study design), Figure 1: the figure was updated to reflect the change in inclusion criterion 8 (see below), and an explanatory footnote added.

Section 3.1 (Inclusion criteria):

- Inclusion criterion 7 was updated to specify additional indicators of variable lung function. Reversibility to short-acting bronchodilator can be difficult to demonstrate in patients with severe asthma using high dose ICS + other controllers during the relatively short study screening period. Therefore, additional measures of variable airway obstruction have been added consistent with GINA 2017 guidance, BOX 1-2: *Diagnostic criteria for asthma in adults, adolescents and children*. These criteria were also used in the registration trials for the currently marketed asthma biologic mepolizumab. These additional measures include:

  – Documented historical reversibility testing.

  – Peak flow variability (further details have been added in Section 5.1.3).

  – Improvement in FEV_1 after a therapeutic trial of asthma therapy. A therapeutic trial of systemic corticosteroids is elevated for this study as patients with eosinophilic asthma have been shown to be particularly responsive to this modality (Sousa AR, Marshall RP, Warnock LC, Bolton S, Hastie A, Symon F, et al. Responsiveness to oral prednisolone in severe asthma is related to the degree of eosinophilic airway inflammation. Clin Exp Allergy. 2017 Jul;47[7]:890-899).

  – Airway hyper-responsiveness as demonstrated by standard bronchial challenge testing.

- Inclusion criterion 8 was updated to allow inclusion of patients with a blood eosinophil count of ≥150 to <300 cells/μL, if they meet at least 1 of 5other clinical criteria at the time of enrolment associated with an eosinophilic asthma phenotype and that have been associated with an enhanced response to benralizumab in recently published analyses. Asthma exacerbation reduction, lung function and symptom improvements were demonstrated in the overall ≥150 cells/μL, with baseline oral corticosteroid (OCS) dependence, history of nasal

polyposis, adult onset of asthma, more frequent exacerbations, and low lung function predictive of an enhanced treatment response (Fitzgerald et al 2017). In an independent study, benralizumab was shown to be highly effective in OCS-dependent asthma patients with a blood eosinophil count ≥150 cells/μL (Nair et al 2017).

- Inclusion criterion 9 was updated to include other acceptable methods of birth control, per a request from Swedish health authorities.

Section 3.3 (Eligibility criteria to be assessed at Visit 4 prior to randomization): Visit 4 eligibility criterion #3 was updated to correct a logical flaw that inadvertently resulted in screen failing some patients with severe uncontrolled eosinophilic asthma who partially improved their FEV_1 during run-in, but still had qualifying low lung function at randomization (ie, FEV_1 <80% of predicted as per inclusion #6). The proposed change will allow randomization of patients with either a pre-BD FEV_1 that remains <80% of predicted, or that is not increased from the qualifying pre-BD FEV_1 value at Visit 2 by more than 20%.

Section 3.6 (Methods for assigning treatment groups): Text was added reflecting the updated randomization ratio of 2:1 for benralizumab:placebo.

Section 3.8 (Methods for unblinding): Text was added to describe the process for emergency unblinding, per a request from Swedish health authorities.

Section 4 (Study plan and timing of procedures, Table 2), Section 4.2.1 (Randomization [Visit 4] Day 0), Section 4.2.8 (EOT [Visit 11; Week 24] Day 168, premature investigational product discontinuation, or early withdrawal from study), Section 5.7 (Biomarker analysis): it has been clarified that samples taken for biomarker analyses are optional. A footnote (footnote k) has been added to Table 2 to this effect (subsequent footnotes have been re-lettered accordingly), and text has been added to Sections 4.2.1, 4.2.8, and 5.7 to clarify the optional nature of the biomarker samples.

Section 4 (Study plan and timing of procedures, Table 2), Section 4.2.2 (Visit 5 [Week 2] Day 14), Section 4.2.5 (Visit 8 [Week 12] Day 84): The frequency of interim biomarker assessments has been reduced at EOT (assessments at Visits 5 and 8 removed). This change is based on their exploratory nature, and will result in fewer blood draws and a lower burden for patients, while still allowing assessment of any treatment effect.

Section 4 (Study plan and timing of procedures; footnotes of Tables 1 and 2), Section 4.1 (4.1 Screening/Enrolment period), Section 4.1.3 (Screening/run-in visit [Visit 3] Day -14), Section 4.2.1 (Randomization [Visit 4] Day 0): Text and footnotes were added and updated to clarify that if all eligibility criteria assessed at Visit 1 and Visit 2 are satisfied, Visit 3 can occur on the same day as Visit 2, and that the period between Visit 3 and Visit 4 (Randomization) should be a minimum of 12 days.

Section 4 (Study plan and timing of procedures; footnotes of Table 1), Section 4.1.1 (Enrolment [Visit 1] Day -42) and Section 4.1.2 (Screening/run-in visit [Visit 2] Day -28): Text was added to reflect the updates to inclusion criterion 8 (eosinophil count).

Section 4 (Study plan and timing of procedures; footnotes Table 2), Section 4.2.1 (4.2.1 Randomization [Visit 4] Day 0): Text has been added to reflect the changes to the Visit 4 eligibility criterion #3.

Section 4.1.4 (Re-screening): Text was added indicating that, where amendments to specific eligibility criteria of the study may result in some patients becoming eligible under the new criteria, re-screening of patients that have screen failed in the past based on Version 1 of these criteria may be re-screened under the amended criteria.

Section 5.1.3 (Peak expiratory flow assessment at home): Additional details were added regarding excessive diurnal peak flow variability (>10%) to support the addition of "peak flow variability" as an indicator of variable lung function in inclusion criterion 7 (Section 3.1).

Section 5.1.4.7 (Sino-Nasal Outcome Test 22 Item): At the request of ethics committees in Belgium, additional text has been added providing additional rationale for the nasal polyposis substudy.

Section 6.4 (Reporting of serious adverse events): Text was added providing further information on the reporting of suspected unexpected severe adverse reactions (SUSARs).

Section 8 (Statistical analyses by AstraZeneca) and subsections: The statistical analyses sections were updated to align with the Statistical Analysis Plan. This includes:

- Clarification of analysis set definitions
- Further details for derivation of annual asthma exacerbation rate
- Updating baseline for SNOT-22 to Visit 3 (from Visit 4) for consistency with the rest of protocol
- Shift tables were removed from the summaries to be presented for PGI-C, CGI-C, and PSIA responses
- The covariates for analysis of several efficacy endpoints were updated

Section 8.2 (Sample size estimate): The text was updated with details of the new randomization ratio for benralizumab:placebo and the power estimations for the primary and secondary endpoints. Additionally, the expected difference between treatment groups in change from baseline in SGRQ was updated from "4" to ">4" for clarification.

Appendix C (Anaphylaxis: signs and symptoms, management), Section 4.1 (Immediate intervention): the guidelines for immediate intervention were updated to correct a typographical error: the administration of epinephrine every 5 to 15 minutes was updated from “IV” (intravenously) to “intramuscularly”.

Version 1.0, 10 March 2017
Initial creation

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 Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI)

Study sites and number of patients planned

This study will be conducted in approximately 270 study centers globally. The target is to randomize approximately 630 patients.

Study period		Phase of development
Date of first patient enrolled	Q3 2017	Phase IIIb
Estimated date of last patient completed	Approximate Q3 2020	

Study design

This is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the efficacy and the safety of repeat dosing of benralizumab 30 mg subcutaneous (sc) versus placebo on top of standard of care asthma therapy in patients with severe uncontrolled asthma. Approximately 630 patients with peripheral blood eosinophil counts ≥150 cells/μL will be randomized 2:1 to receive benralizumab 30 mg sc or matched placebo for 24 weeks. After enrolment, eligible patients will enter an up to 42-day screening/run-in period. Patients who meet eligibility criteria will be randomized 2:1 on Day 0 to receive either benralizumab or placebo every 56 days (every 8 weeks) through Week 16, with end of treatment (EOT) at Day 168 (Week 24). At the completion of the 24-week double-blind period of the ANDHI study, eligible patients in benralizumab and placebo arm may enter a 56-week open label period (ANDHI *in Practice* [ANDHI IP] substudy), in which concomitant asthma therapies will be tapered as directed by the protocol in those patients who achieve and maintain asthma control (defined as ACQ6 score <1.5 and no clinically significant asthma exacerbations that required a burst of systemic corticosteroid or a hospitalization due to asthma between reduction visits) with add-on benralizumab.

The initial dose of benralizumab will be followed by a single loading dose of benralizumab 30 mg sc or placebo at Day 28 (Week 4) consistent with tested Phase III dosing regimen. This dose and regimen was previously confirmed to be effective in Phase III asthma studies with an overall safety profile similar to placebo and conforms to the anticipated posology for regulatory approval. Patients who do not participate in the open label ANDHI IP substudy, or who do not transition into the open label period will complete the follow-up (FU) Visit 12 for final safety assessment at Day 182 (Week 26). Patients who transition into the open label ANDHI IP substudy prior to the FU Visit 12, will receive the first open label dose of

benralizumab at Visit 13 on Day 168 and complete the End of ANDHI IP Substudy (EOS) Visit 27 at Week 80.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the effect of benralizumab on the rate of asthma exacerbations	The annualized rate of asthma exacerbations between benralizumab and placebo (treatment period 24 weeks)

Key Secondary Objectives:	**Outcome Measure:**
To determine the effect of benralizumab on patient-reported disease specific quality of life	The change from baseline (Visit 4) in Saint George Respiratory Questionnaire (SGRQ) to the EOT; Day 168/Week 24)

Secondary Objectives:	**Outcome Measure:**
To determine the effect of benralizumab on lung function	The change from baseline (Visit 4) in forced expiratory volume in first second (FEV1) over the treatment period (up to and including Day 168/Week 24)
To determine the effect of benralizumab on patient-reported asthma control	The change from baseline (Visit 4) in Asthma Control Questionnaire 6 (ACQ6) to the EOT (Day 168/Week 24)
To determine the effect of benralizumab on time to first asthma exacerbation	Time to first asthma exacerbation (treatment period 24 weeks)
To determine the effect of benralizumab on lung function at home	The change from run-in baseline morning peak expiratory flow (PEF) to the EOT (Day 168/Week 24)
To determine the effect of benralizumab general quality of life and health status	The change from baseline (Visit 4) Social Functioning (SF)-36v2 to the EOT (Day 168/Week 24)
To evaluate patient impression of overall asthma severity (patient global impression of severity [PGI-S])	The change from baseline (Visit 4) in PGI-S to the EOT (Day 168/Week 24)
To evaluate patient impression of change in the overall asthma status from baseline as reported by the patient (patient global impression of change [PGI-C]) and clinician (clinician global impression of change [CGI-C])	The degree of change reported by the patient (PGI-C) and Investigator (CGI-C) expressed as a proportion of each of the 7 possible responses to the EOT (Day 168/Week 24)

To determine the effect of benralizumab on the patient's predominant symptoms (Predominant Symptom and Impairment Assessment; PSIA)	The degree of change reported by the patient in their predominant symptom to the EOT (Day 168/Week 24)
To determine the effect of benralizumab on disease specific health-related quality of life in patients with doctor diagnosed chronic sinusitis with nasal polyposis	The change from baseline (Visit 3) in the sino-nasal outcome test (SNOT-22) score to the EOT (Day 168/Week 24)

Exploratory Objectives:	**Outcome Measure:**
To determine the effect of eosinophil depletion with benralizumab on: Biomarker components of known asthma inflammatory pathways or airway remodeling (including periostin, DPP4, YKL-40 and MMPs) Biomarker surrogates of eosinophilic inflammation/activation (including, eosinophil granule proteins)	The change from baseline (Visit 4) in circulating biomarkers to each pre-specified scheduled assessment during the treatment period
To determine the effect of benralizumab on the patient's level of asthma control based standard asthma guidance recommendations	The proportion of time that that the patient's asthma is well-controlled based on composite diary measures

Objectives of the Open Label ANDHI IP Substudy	**Outcome Measures:**
Main objective: To assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen while maintaining asthma control [a]	**Main outcome variables:** Number of reductions in asthma controller medications from Visit 15 to the end of study (EOS) Visit 27 (Day 560/Week 80) Number of adapted[b] GINA step category reductions from baseline at Visit 15 to the EOS Visit 27 (Day 560/Week 80). **Main outcome measures:** -Proportion of patients with at least one reduction in asthma controller medication from Visit 15 to EOS (Visit 27); - Proportions of patients with the number of adapted[b] GINA step category reductions from Visit 15 to EOS (Visit 27) ≥ X, where X is ranging from 1 to 4. - Distribution of the number of adapted[b] GINA step reductions from Visit 15 to EOS (Visit 27) (X) where X is ranging from 0[c] to 4 **Supportive Measures:** - Proportion of patients with at least one reduction in background medication by categories (ie, discontinuation of LAMA, LTRA, LABA, theophylline; reduction in ICS dose [HD-ICS, MD-ICS, LD-ICS or anti-inflammatory reliever]) at EOS (Visit 27) - Characteristics of patients with 0 vs ≥2 reductions in controller medication - For patients on maintenance OCS at Visit 15[d]: Proportion achieving 50/75/90/100% reduction in OCS dose at EOS (Visit 27); Proportion achieving OCS dose ≤5mg* at EOS (Visit 27); Change in OCS dose* in OCS dose from Visit 15 to Visit 27 (EOS).

[a] Maintaining asthma control is defined as Asthma Control Questionnaire 6 (ACQ-6) <1.5 and no clinically significant asthma exacerbations that required a burst of systemic corticosteroid or a hospitalization due to asthma between consecutive visits or the 8 weeks prior.
[b] Does not consider add-on benralizumab as part of the assessment.
[c] X=0 includes no change and any increase in adapted GINA step category.
[d] Patients using maintenance OCS at Visit 15 will be excluded from the main analysis, based on the assumption that complete OCS cessation will be uncommon given the duration of the treatment period
GINA Global initiative for asthma.
* Prednisone equivalent dose.

Other Efficacy Objectives:	**Supportive Measures**
To assess standard asthma efficacy measures for benralizumab treated patients when reducing their standard of care asthma controller regimen	- Change in continuous asthma efficacy measures (including ACQ6, SGRQ, pre-bronchodilator forced expiratory volume [pre-BD FEV_1] and weekly mean morning peak expiratory flow [PEF]) from Visit 15 to the EOS Visit 27 (Day 560/Week 80). - Change in continuous asthma efficacy measures (including ACQ6, SGRQ, FEV_1 and morning PEF) from Visit 4 to the EOS Visit 27 (Day 560/Week 80). - Degree of change reported by the patient (PGI-C) from Visit 13 and Investigator (CGI-C) from Visit 4 to the EOS Visit 27 (Day 560/Week 80). - Clinically significant[a] asthma exacerbations from Visit 15 to the EOS Visit 27 (exacerbation count and time to first exacerbation).

[a]Clinically significant asthma exacerbations means that it requires a burst of systemic corticosteroid or a hospitalization.
ACQ-6 Asthma Control Questionnaire 6; SGRQ St George's Respiratory Questionnaire; pre-BD FEV_1 Pre-bronchodilator Forced Expiratory Volume in first second; PEF Peak Expiratory Flow; PGI-C patient global impression of change; CGI-C clinician global impression of change.

Safety Objectives:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab	Adverse events (AEs), laboratory variables, physical examination

Safety Objectives of the Open Label ANDHI IP Substudy:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab during treatment period	AEs, physical examination, vital signs during the open label benralizumab treatment period (Visit 13 to Visit 27).

Target patient population

Male and female patients with severe uncontrolled asthma will be enrolled. All patients will have had ≥2 asthma exacerbations while on maintenance ICS plus another asthma controller that required treatment with systemic corticosteroids (intramuscular [IM], intravenous [IV], or oral) in the 12 months prior to Visit 1. In addition, a target goal is to recruit a minimum of 40% of patients with ≥3 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids (IM, IV, or oral) in the 12 months prior to Visit 1.

In order to achieve the assumed exacerbation rates used to determine sample size and therefore have sufficient power in the study, it is expected that approximately 40% of patients

will have ≥3 exacerbations in the 12 months prior to Visit 1. Therefore, enrolment of patients with only 2 exacerbations in the 12 months prior to Visit 1 may be halted if this subgroup within a site or region reaches approximately 60% of randomized patients.

Duration of treatment

After enrolment, eligible patients will enter an up to 42-day screening/run-in period. Patients who meet eligibility criteria will enter a 24-week treatment period and receive 30 mg benralizumab or placebo at Day 0, Day 28 (±3 days), Day 56 (±3 days), and Day 112 (±3 days). An EOT Visit will be conducted at Day 168 (+7 days) and a FU visit will be conducted at Day 182 (±7 days). Patients who transition into the open label ANDHI IP substudy prior to the FU Visit 12, will receive the first open label dose of benralizumab at Visit 13 on Day 168 and complete the EOS Visit 27 at week 80.

The total planned study duration for each patient considering the run-in, double-blind and open label study periods is a maximum of 88 weeks.

Investigational product, dosage and mode of administration

Benralizumab 30 mg/mL solution for injection in an accessorized pre-filled syringe (APFS) will be administered at the study center subcutaneously (sc) for 4 doses: Day 0 (Week 0), Day 28 (Week 4), Day 56 (Week 8), and Day 112 (Week 16). A matching placebo will be used as comparator. In the open label ANDHI IP substudy, all patients will receive benralizumab sc at Day 168 (Week 24), Day 196 (Week 28), Day 224 (Week 32), Day 280 (Week 40), Day 336 (Week 48), Day 392 (Week 56), Day 448 (Week 64), and Day 504 (Week 72).

Statistical methods

Approximately 630 patients randomized to benralizumab or placebo at a ratio of 2:1 (ie, 420 benralizumab treated and 210 placebo-treated patients) are needed for this study based on the primary and secondary objectives of the study to determine the effect of benralizumab on the rate of asthma exacerbations and on the patient's SGRQ score.

Patients who meet eligibility criteria will be randomized 2:1 on Day 0 to receive either benralizumab or placebo.

Efficacy analyses for the main study will be performed using the full analysis set, which consists of all patients randomized and receiving any investigational product (IP).

The primary analysis method for the primary endpoint, the annualized rate of asthma exacerbations between benralizumab and placebo (treatment period 24 weeks), will be compared between the 30 mg benralizumab group and placebo using a negative binomial model and the full analysis set. The response variable in the model will be the number of asthma exacerbations over the 24-week treatment period. The model will include covariates of treatment group, number of exacerbations in the year before the study, center/region and the use of maintenance oral corticosteroids ([OCS] yes/no). The logarithm of the FU time will be used as an offset variable in the model. The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and 2-sided

p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will also be presented. The same analysis will be performed by hospitalization and/or emergency room visit.

Efficacy analyses for the chronic rhinosinusitis with nasal polyposis substudy will include the subset of patients who are included in the substudy assessing rhinosinusitis health status by SNOT-22 and who received any IP.

In the open label ANDHI IP substudy, the main efficacy analysis set will include all patients who received at least one dose of open label benralizumab, and are not receiving maintenance OCS for asthma at Visit 15. The main efficacy analysis of any reduction in asthma controller medications, GINA step category reduction and other efficacy analyses will be summarized descriptively. For the main efficacy analysis patients using maintenance OCS at the Visit 15 will be excluded from the analysis, based on the assumption that complete OCS cessation will be uncommon given the duration of the treatment period. The main outcome measures for the open label substudy are the proportion of patients with at least one reduction in asthma medication controller, proportions and distribution of patients achieving increasing numbers of adapted GINA categories reductions, presented overall and by ANDHI DB treatment group and by asthma control status at EOS (Visit27

For the variables assessing OCS reduction the analysis will be based on those patients who received at least one dose of open label Benralizumab and are on maintenance OCS at V15.

For all summaries, proportions will be estimated with nominal 95% CIs derived using the exact Clopper-Pearson method.

Continuous variables (i.e. FEV1, SGRQ, ACQ6, etc) will be analyzed for patients who directly transitioned from the double-blind ANDHI study to the open-label ANDHI in Practise (time since last IP administration <16 weeks).

All safety variables will be summarized descriptively. The safety analysis will be performed using the safety analysis set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACQ	Asthma Control Questionnaire
ACQ6	Asthma Control Questionnaire 6
ACQ-IA	Asthma Control Questionnaire – Interviewer Administered
ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANDHI DB	ANDHI double-blind (DB)
ANDHI IP	ANDHI in Practice
APFS	Accessorized pre-filled syringe
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BMI	Body Mass Index
CGI-C	clinician global impression of change
CI	Confidence Interval
CMS	Central Monitoring Services
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of investigational product due to Adverse Event
DILI	Drug Induced Liver Injury
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EOS	End of ANDHI IP Substudy
EOT	End of Treatment
ERS	European Respiratory Society

Abbreviation or special term	Explanation
FEV_1	Forced expiratory volume in first second
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
GH	General health perceptions
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL-5	Interleukin-5
IM	Intramuscular
IP	Investigational product
IPD	Premature IP Discontinuation
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β2 agonists
LAMA	Long-acting muscarinic antagonists
LTRA	Leukotriene receptor antagonists
MCID	Minimal clinically important difference
MCS	Mental health component summary score
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental health
NRS	Numeric rating scale
OCS	Oral corticosteroids
GMP	Good manufacturing practice
HL	Hy's Law
PCS	Physical component summary score
PEF	Peak expiratory flow
PGI-C	Patient global impression of change

Abbreviation or special term	Explanation
PGI-S	Patient global impression of severity
PHL	Potential Hy's Law
PI	Principal Investigator
PN	Predicted normal
Pre-BD	Pre-bronchodilator
PF	Physical Functioning
PPE	Personal protective equipment
PRO	Patient-reported outcome
PSIA	Predominant Symptom and Impairment Assessment
RE	Role limitations due to emotional problem
RP	Role limitations due to Physical Health
SABA	Short-acting β2 agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SF	Social functioning
SGRQ	Saint George Respiratory Questionnaire
SNOT-22	Sino-nasal Outcome Test
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin
ULN	Upper limit of normal
VT	Vitality
WD	Early study withdrawal visit
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a syndrome characterized by airway inflammation, reversible airway obstruction, and airway hyper-responsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma continues to be a major health concern worldwide, with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 to 450 million people worldwide by 2025 (Masoli et al 2004, To et al 2012).

Despite treatment per management guidelines, (Global Initiative for Asthma GINA 2018 NAEPP 2007) up to 50% of patients have asthma that is not well-controlled (Bateman et al 2010). This results in considerable impact on quality of life, disproportionate use of healthcare resources, and adverse reactions from regular systemic steroid use. Therefore, there remains an unmet medical need for patients whose asthma is not controlled by existing therapies.

The observed variability in clinical response to currently available asthma therapies appears to be related, in part, to distinctive inflammatory phenotypes (Wenzel 2012). In particular, asthma associated with eosinophilic inflammation in the airway (often referred to as eosinophilic asthma) is common (approximately 40% to 60% of asthmatics), and the degree of eosinophilia is associated with key clinical features of disease severity including low lung function, symptoms, and the risk of future asthma exacerbations (Bousquet et al 1990, Lieberman et al 2010, Di Franco et al 2003, Horn et al 1975, Price et al 2015, Zeiger et al 2014).

Interleukin-5 (IL-5) is a key cytokine essential for eosinophil trafficking and survival (Molfino et al 2011). Benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5Rα) on the target cell, which is expressed on the surface of eosinophils and basophils (Takatsu et al 1994, Toba et al 1999). Afucosylation confers enhanced antibody-dependent cellular cytotoxicity (ADCC) which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2010). Single and repeated doses of benralizumab in mild to severe asthma patients results in rapid and sustained depletion of blood eosinophils; repeat doses of benralizumab subcutaneously (sc) also markedly reduced airway wall and sputum eosinophil levels (Busse et al 2010, Laviolette et al 2013; Pham et al 2016).

The clinical efficacy of benralizumab 30 mg sc was confirmed in 2 large Phase III global safety and efficacy trials in patients on high dose inhaled corticosteroids/long-acting β2 agonists (ICS/LABA) and blood eosinophil counts ≥300 cells/μL (Bleeker et al 2016, Fitzgerald et al 2016). In these studies, benralizumab was dosed every 8 weeks for approximately 1 year and produced significant decreases in asthma exacerbations (up to 51%), and improvements in forced expiratory volume in first second (FEV_1; up to 159 mL) and total daily asthma symptom scores in both trials. There was no apparent advantage to more frequent dosing (every 4 weeks) in these studies. Of note, the Phase 3 program also studied the efficacy

of benralizumab in patients with blood eosinophil counts <300 cells/µL and in an oral corticosteroid (OCS)-dependent asthma population (Fitzgerald et al 2017, Goldman et al 2017, Nair et al 2017). The results of these pre-specified and pooled analyses demonstrate broad efficacy in patients with blood eosinophil levels ≥150 cells/µL, and also support an enhanced response to benralizumab treatment when certain identifiable clinical features of the eosinophilic asthma phenotype are present. These features include OCS dependence, a history of frequent exacerbations, nasal polypsis, later onset of disease, and low lung function.

The goal of this randomized, double-blind, placebo-controlled Phase IIIb study is to further investigate the effect of benralizumab (30 mg) administered sc on asthma exacerbations in patients with severe asthma and to extend our understanding of asthma control (particularly the onset of clinical effect) in patients with an eosinophilic asthma phenotype.

1.2 Rationale for study design, doses and control groups

This is a Phase IIIb, randomized, double-blind, placebo-controlled study designed to further investigate the efficacy of benralizumab (30 mg) administered sc in severe asthma patients with eosinophilic asthma based on an elevated blood eosinophil count and who remain uncontrolled despite standard of care therapy(-ies). The 30 mg sc dose and every 8 week regimen (with a loading dose at Week 4) was shown to be effective across multiple measures of asthma control in this population, with an overall safety profile similar to placebo. Based on the previous Phase III experience, approximately 630 patients studied over a 24-week treatment period will be sufficient to detect differences between benralizumab and placebo for asthma exacerbation rate and the key secondary endpoint of Saint George Respiratory Questionnaire (SGRQ).

After being held constant during the double-blind period, concomitant asthma therapies will be tapered in patients who elect to enter the open label ANDHI *In Practice* [ANDHI IP] substudy. Current asthma treatment guidance advises the stepping down of asthma controller medications once asthma control has been achieved (GINA 2018**,** GINA 2020). In clinical practice, reduction of standard of care background asthma treatment medications, in patients whose asthma becomes controlled following the addition of an asthma biologic like benralizumab, is anticipated to be an increasingly common scenario. Oral corticosteroids, ICS, and LABA each have potential safety and tolerability issues. It would be a potential benefit to patients if benralizumab treatment could enable reduction in these therapies, while allowing patients to maintain asthma control. Whether treatment with benralizumab can enable patients to reduce their standard of care asthma controller regimen while maintaining asthma control has not been previously evaluated.

1.3 Benefit/risk and ethical assessment

Benralizumab is being studied in severe asthma where there are few treatment options for patients whose asthma remains uncontrolled on high dose ICS/LABA and/or OCS (GINA 2018). In adult patients whose asthma was poorly controlled by high dose ICS/LABA therapy, benralizumab 30 mg every 8 weeks produced improvements in multiple measures of

asthma control including the annual rate of asthma exacerbations, lung function symptoms, and Asthma Control Questionnaire (ACQ) scores in 2 Phase III trials each approximately 1 year in duration (Bleeker et al 2016, Fitzgerald et al 2016). Longer-term safety studies are presently ongoing.

Potential risks:

- Serious hypersensitivity reactions (including anaphylaxis) are important potential risk of a biologic therapy such as benralizumab; anaphylaxis may be life-threatening. Risk minimization includes a 2-hour observation period at the clinical site following study drug administration to assess and treat any acute event that might occur.
- Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA include decreased drug efficacy and hypersensitivity reactions. There was no apparent impact of ADA on overall benralizumab safety or efficacy in the Phase III safety and efficacy trials.
- During the open label ANDHI IP substudy, protocol guided reductions in the level of background asthma medication could potentially be associated with loss of asthma control in some patients. To mitigate this risk, the patient's overall level of asthma control must be stable to improving at any given reduction visit based on regular ACQ6 assessments (via an electronic patient-reported outcome [ePRO] device), with an overall ACQ6 score of <1.5 (where a score ≥1.5 is indicative of inadequately controlled asthma), to be eligible for background medication reduction. CCI [redacted] Investigators may defer any scheduled dose reduction, based on their overall, documented clinical assessment that it would not be in the patients' best interest. Dose reductions commence only after the patient has received the 3rd open label dose of benralizumab, with attempts at per protocol reductions occurring no more frequently than every 2 months, at scheduled benralizumab dosing visits. Interim telephone contacts, between dose reduction visits, are also scheduled to assess the patient's status. Peak expiratory flow (PEF) monitoring with alerts for sustained worsening will be **maintained** during the open label period.
- Potential for immunosuppression:
  - The overall incidence of any infection in the completed Phase III studies was similar to placebo, without any evidence of opportunistic infection.
  - 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. There was no apparent impact of benralizumab treatment on the incidence of helminthic parasitic infections in competed Phase III trials (none reported). Risk minimization measures herein include exclusion of patients with untreated parasitic infection, in conjunction with the performance of routine pharmacovigilance activities.

– The presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors; however, both clinical and non-clinical data are mixed in this regard. The incidence of malignant neoplasms in the completed Phase III trials was <1% and similar to placebo, with no evidence of clustering of any particular or unusual tissue types. Malignancies will be monitored throughout the trial via routine pharmacovigilance.

The efficacy and safety data obtained to date support a favorable benefit/risk profile of benralizumab in severe asthma patients who manifest an eosinophilic phenotype.

A detailed assessment of the overall risk/benefit of benralizumab is given in the Investigator's Brochure.

1.4 Study design

This is a Phase IIIb, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the efficacy and the safety of repeat dosing of benralizumab 30 mg sc versus placebo on top of standard of care asthma therapy in patients with severe uncontrolled asthma. All patients will have had ≥2 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids (intramuscular [IM], intravenous [IV], or oral) in the 12 months prior to Visit 1; a minimum of 40% of patients will have had ≥3 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids (IM, IV, or oral) in the 12 months prior to Visit 1. Approximately 630 patients with peripheral blood eosinophil counts ≥150 cells/μL will be randomized to receive benralizumab 30 mg sc or matched placebo.

After enrolment at Visit 1, eligible patients will enter an up to 42-day screening/run-in period. Patients who meet eligibility criteria will be randomized 2:1 on Visit 4 (Day 0) to receive either benralizumab or placebo every 56 days (every 8 weeks) through Visit 9 (Week 16), with EOT Visit 11 at Day 168 (Week 24). The initial dose of benralizumab will be followed by a single loading dose of benralizumab 30 mg sc or placebo at Visit 6 (Day 28/Week 4) consistent with the tested Phase III dosing regimen. This dose and regimen was previously confirmed to be effective in Phase III asthma studies with an overall safety profile similar to placebo and conforms to the anticipated posology for regulatory approval.

At the completion of the 24-week double-blind period of the ANDHI study, eligible patients may enter a 56-week open label ANDHI IP substudy, in which concomitant asthma therapies will be tapered as directed by the protocol.

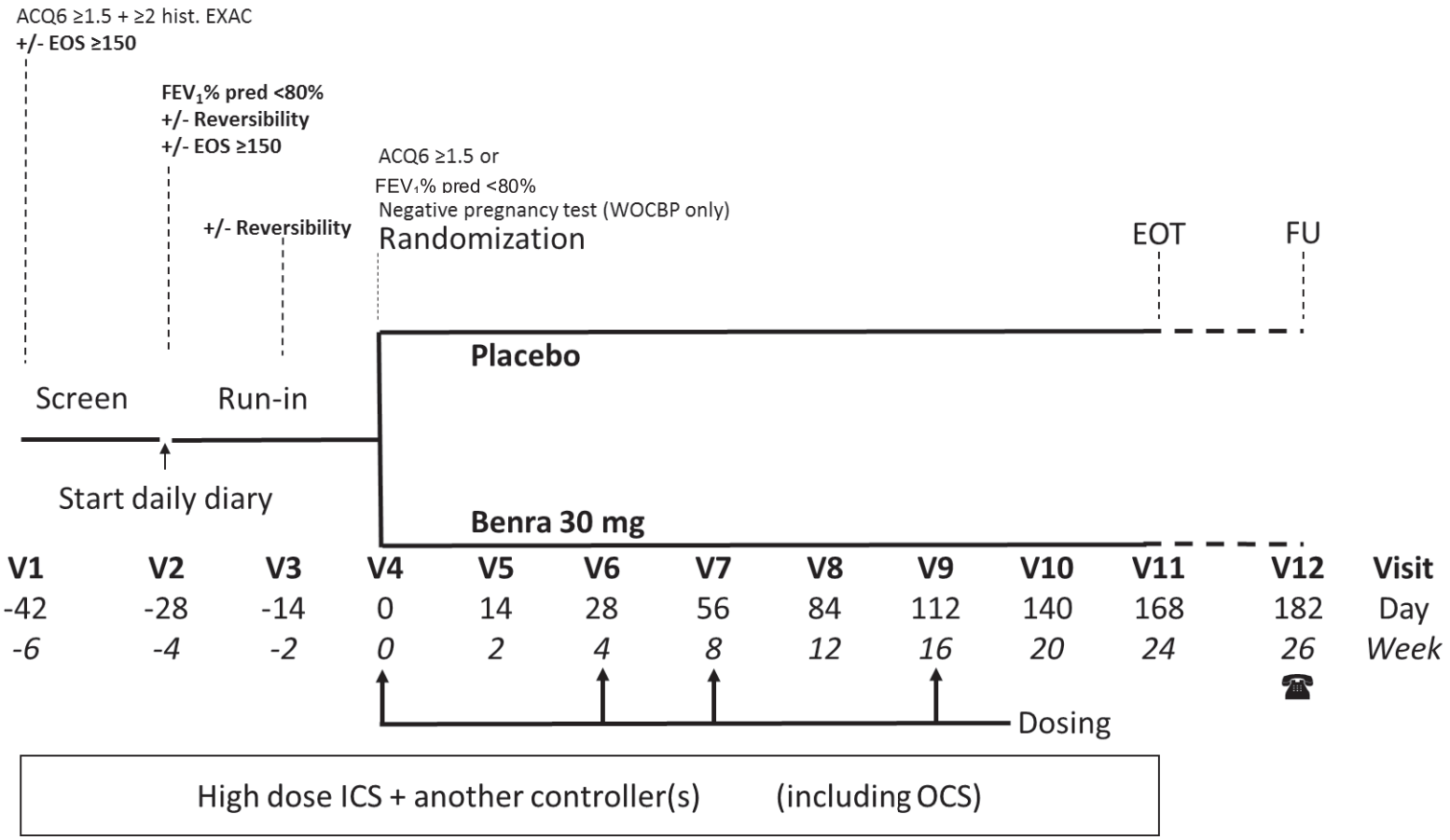
- For those who transition directly into the open label ANDHI IP substudy, Visit 13 is on the same day as the ANDHI EOT Visit 11.

- Patients who transition into the open label ANDHI IP substudy prior to FU Visit 12, will receive the first open label dose of benralizumab at Visit 13 and will complete the EOS visit at Week 80.

- Those who do not enter the open label ANDHI IP substudy will have the FU visit 12 and then leave the study.

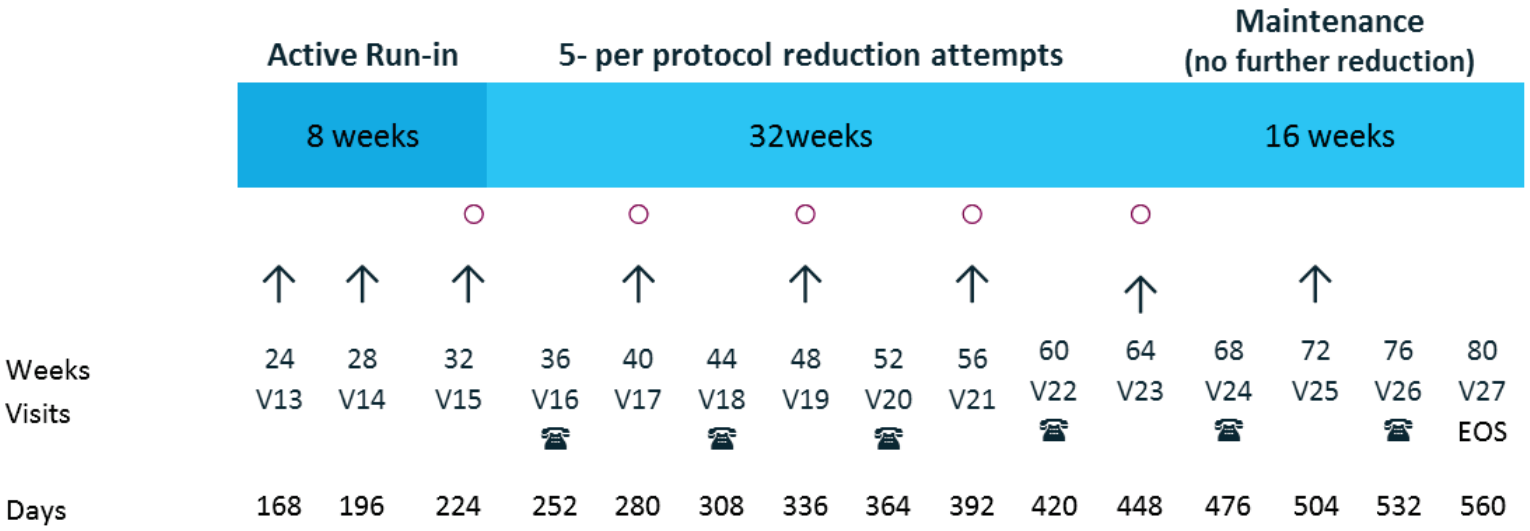
- Patients who completed the ANDHI FU Visit 12 are not excluded from participation in the ANDHI IP substudy.

Figure 1 Double-blind period flow chart



Patients with a peripheral blood eosinophil count of ≥150 to <300 cells/µL have to fulfill additional clinical criteria described in inclusion criterion 8 (Section 3.1), patients with a peripheral blood eosinophil count of ≥300 cells/µL do not need to meet the additional criteria.
ACQ6 asthma control questionnaire 6; Benra benralizumab; EOS eosinophil; EOT end of treatment; EXAC exacerbation; FEV_1 forced expiratory volume in first second; FU follow-up; ICS inhaled corticosteroid; V visit; WOCBP women of childbearing potential.; ☎ telephone visit.

Figure 2 ANDHI IP open label substudy flow chart



EOS End of ANDHI IP Substudy

○ Per protocol background reduction attempts based on asthma control

↑ Open label benralizumab dosed

☎ Telephone visits

2 STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To determine the effect of benralizumab on the rate of asthma exacerbations	The annualized rate of asthma exacerbations between benralizumab and placebo (treatment period 24 weeks)

2.2 Secondary objectives

Key Secondary Objectives:	**Outcome Measure:**
To determine the effect of benralizumab on patient-reported disease specific quality of life	The change from baseline (Visit 4) in SGRQ to the EOT (Day 168/Week 24)

Secondary Objectives:	**Outcome Measure:**
To determine the effect of benralizumab on lung function	The change from baseline (Visit 4) in forced expiratory volume in first second (FEV_1) over the treatment period (up to and including Day 168/Week 24)
To determine the effect of benralizumab on patient-reported asthma control	The change from baseline (Visit 4) in Asthma Control Questionnaire 6 (ACQ6) to the EOT (Day 168/Week 24)
To determine the effect of benralizumab on time to first asthma exacerbation	Time to first asthma exacerbation (treatment period 24 weeks)
To determine the effect of benralizumab on lung function at home	The change from run-in baseline morning PEF to the EOT (Day 168/Week 24)
To determine the effect of benralizumab general quality of life and health status	The change from baseline (Visit 4) Social Functioning (SF)-36v2 to the EOT (Day 168/Week 24)
To evaluate patient impression of overall asthma severity (patient global impression of severity [PGI-S])	The change from baseline (Visit 4) in PGI-S to the EOT (Day 168/Week 24)
To evaluate patient impression of change in the overall asthma status from baseline as reported by the patient (patient global impression of change [PGI-C]) and	The degree of change reported by the patient (PGI-C) and Investigator (CGI-C) expressed as a proportion of each of the 7 possible responses to the EOT (Day 168/Week 24)

clinician (clinician global impression of change [CGI-C])	
To determine the effect of benralizumab on the patient's predominant symptoms (Predominant Symptom and Impairment Assessment; PSIA)	The degree of change reported by the patient in their predominant symptom to the EOT (Day 168/Week 24)
To determine the effect of benralizumab on disease specific health-related quality of life in patients with doctor diagnosed chronic sinusitis with nasal polyposis	The change from baseline (Visit 3) in the sino-nasal outcome test (SNOT-22) score to the EOT (Day 168/Week 24)

2.3 Exploratory objectives

Exploratory Objectives:	**Outcome Measure:**
To determine the effect of eosinophil depletion with benralizumab on: • Biomarker components of known asthma inflammatory pathways or airway remodeling (including periostin, DPP4, YKL-40 and MMPs) • Biomarker surrogates of eosinophilic inflammation/activation (including, eosinophil granule proteins)	The change from baseline (Visit 4) in circulating biomarkers to each pre-specified scheduled assessment during the treatment period
To determine the effect of benralizumab on the patient's level of asthma control based standard asthma guidance recommendations	The proportion of time that that the patient's asthma is well-controlled based on composite diary measures

Objectives of the Open Label ANDHI IP Substudy	**Outcome Measures:**
Main objective: To assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen while maintaining asthma control [a]	**Main outcome variables:** Number of reductions in asthma controller medications from Visit 15 to the end of study (EOS) Visit 27 (Day 560/Week 80) Number of adapted[b] GINA step category reductions from baseline at Visit 15 to the EOS Visit 27 (Day 560/Week 80). **Main outcome measures:** -Proportion of patients with at least one reduction in asthma controller medication from Visit 15 to EOS (Visit 27); - Proportions of patients with the number of adapted[b] GINA step category reductions from Visit 15 to EOS (Visit 27) ≥ X, where X is ranging from 1 to 4. - Distribution of the number of adapted[b] GINA step reductions from Visit 15 to EOS (Visit 27) (X) where X is ranging from 0[c] to 4 **Supportive Measures:** - Proportion of patients with at least one asthma controller medication reduction by categories (ie, discontinuation of LAMA, LTRA, LABA, theophylline; reduction in ICS dose [HD-ICS, MD-ICS, LD-ICS or anti-inflammatory reliever]) at EOS (Visit 27) - Characteristics of patients with 0 vs ≥2 reductions in controller medication - For patients on maintenance OCS at Visit 15[d]: Proportion achieving 50/75/90/100% reduction in OCS dose at EOS (Visit 27); Proportion achieving OCS dose ≤5mg* at EOS (Visit 27); Change in OCS dose* in OCS dose from Visit 15 to Visit 27 (EOS).

[a] Maintaining asthma control is defined as Asthma Control Questionnaire 6 (ACQ-6) <1.5 and no clinically significant asthma exacerbations that required a burst of systemic corticosteroids between Visit 25 and EOS (Visit 27)

[b] Does not consider add-on benralizumab as part of the assessment.

[c] X=0 includes no change and any increase in adapted GINA step category.

[d] Patients using maintenance OCS at Visit 15 will be excluded from the primary analysis, based on the assumption that complete OCS cessation will be uncommon given the duration of the treatment period GINA Global initiative for asthma. * Prednisone equivalent dose.

Other Efficacy Objectives: To assess Standard asthma efficacy measures for benralizumab treated patients when reducing their standard of care asthma controller regimen	**Supportive measures** - Change in continuous asthma efficacy measures (including ACQ6, SGRQ, pre-bronchodilator forced expiratory volume [pre-BD FEV_1] and weekly mean morning peak expiratory flow [PEF]) from Visit 15 to the EOS Visit 27 (Day 560/Week 80). - Change in continuous asthma efficacy measures (including ACQ6, SGRQ, FEV_1 and morning PEF,) from Visit 4 to the EOS Visit 27 (Day 560/Week 80). - Degree of change reported by the patient (PGI-C) from Visit 13 and Investigator (CGI-C) from Visit 4 to the EOS Visit 27 (Day 560/Week 80). - Clinically significant[a] asthma exacerbations from Visit 15 to the EOS Visit 27 (exacerbation count and time to first exacerbation).

[a]Clinically significant asthma exacerbations means it requires a burst of systemic corticosteroid or a hospitalization.
ACQ-6 Asthma Control Questionnaire 6; SGRQ St George's Respiratory Questionnaire; pre-BD FEV_1 Pre-bronchodilator Forced Expiratory Volume in first second; PEF Peak Expiratory Flow; PGI-C patient global impression of change; CGI-C clinician global impression of change.

2.4 Safety objectives

Safety Objectives:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab	Adverse events (AEs), laboratory variables, physical examination

Safety Objectives of the Open Label ANDHI IP Substudy:	**Outcome Measure:**
To assess the safety and tolerability of benralizumab during treatment period	AEs, physical examination, vital signs during the open label benralizumab treatment period (Visit 13 to Visit 27).

3 SUBJECT SELECTION, ENROLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

3.1.1 For inclusion in the ANDHI study patients should meet the following criteria:

1. Written informed consent for study participation must be obtained prior to any study related procedures being performed and according to international guidelines and/or applicable European Union (EU) guidelines.

2. Female and male patients aged 18 to 75 years inclusively at the time of Visit 1 with a history of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS plus asthma controller, for at least 12 months prior to Visit 1 (see Appendix E for medium and high daily ICS doses by formulation).

   – Other acceptable asthma controllers include a long-acting bronchodilator (LABA or long-acting muscarinic antagonists [LAMA]), a leukotriene inhibitor, theophylline preparations or maintenance OCS (daily or every other day OCS requirement in order to maintain asthma control; maximum total daily dose 20 mg prednisone or equivalent).

3. Documented current treatment with high daily doses of ICS plus at least 1 other asthma controller for at least 3 months prior to Visit 1; see inclusion criterion 2 for acceptable other asthma controllers.

   – For ICS/LABA combination preparations, highest-strength maintenance doses approved in the given country will meet this criterion.

   – If the ICS and the other asthma controller therapies are given by separate inhalers, then the patient must be on a high daily ICS dose (see Appendix E for high daily ICS doses by formulation).

4. History of at least 2 asthma exacerbations while on ICS plus another asthma controller (see inclusion criterion 2 for examples) that required treatment with systemic corticosteroids (IM, IV, or oral) in the 12 months prior to Visit 1. For patients receiving corticosteroids as a maintenance therapy, the corticosteroid treatment for the exacerbation is defined as a temporary increase of their maintenance dose.

   NOTE: In order to achieve the assumed exacerbation rates used to determine sample size and therefore have sufficient power in the study, it is expected that approximately 40% of patients will have ≥3 exacerbations in the 12 months prior to Visit 1. Therefore, enrolment of patients with only 2 exacerbations in the 12 months

prior to Visit 1 may be halted if this subgroup within a site or region reaches approximately 60% of randomized patients.

5. ACQ6 score ≥1.5 at Visit 1.

6. Screening pre-bronchodilator (pre-BD) FEV_1 of <80% predicted at Visit 2

Note: Spirometry testing should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.9.2), the test should be postponed to another day prior to Visit 3 to improve the chances of achieving a qualifying FEV_1 that is not affected by bronchodilator medication.

7. Evidence of asthma as documented by excessive variability in lung function by satisfying ≥1 of the criteria below:

(a) Airway reversibility (FEV_1 ≥12%) using a short-acting bronchodilator demonstrated at Visit 2 or Visit 3.

Note: The patient should complete the per protocol reversibility testing during the screening period as above as screening reversibility is an important baseline disease state characteristic. If the patient does not meet this criterion at Visit 2 the airway reversibility assessment must be repeated at a separate Visit 3. If at Visit 3 the patient again does not meet screening reversibility but meet one of the alternate criteria below (b to e) the patient can be considered as eligible per Inclusion #7.

(b) Airway reversibility to short-acting bronchodilator (FEV_1 ≥12%) documented* during the 12 months prior to enrolment Visit 1.

(c) Daily diurnal peak flow variability of >10% when averaged over 7 continuous days during the study run-in period (see Section 5.1.3).

(d) An increase in FEV_1 of ≥12% and 200 mL after a therapeutic trial of systemic corticosteroid (eg, OCS), given outside of an asthma exacerbation, documented* in the 12 months prior enrolment Visit 1.

(e) Airway hyper-responsiveness (methacholine: PC20 of <8 mg/mL, histamine: PD20 of <7.8 µmol, mannitol: decrease in FEV_1 as per the labeled product instructions) documented* in the 24 months prior to randomization Visit 4.

*Source documentation for tests of variable lung function outside of per protocol reversibility testing should include the official pulmonary function report where applicable and/or clear notation in the patient's medical record. Documentation must be filed in the patient's source documents prior to randomization.

8. Peripheral blood eosinophil count either:

– ≥300 cells/µL assessed by central laboratory at either Visit 1 or Visit 2

OR

– ≥150 to <300 cells/μL assessed by central laboratory at either Visit 1 or Visit 2, **IF** ≥1 of the following 5 clinical criteria (a to e) is met:

(a) Using maintenance OCS (daily or every other day OCS requirement in order to maintain asthma control; maximum total daily dose 20 mg prednisone or equivalent) at screening

(b) History of nasal polyposis

(c) Age of asthma onset ≥18 years

(d) Three or more documented exacerbations requiring systemic corticosteroid treatment during the 12 months prior to screening

(e) Pre-bronchodilator forced vital capacity <65% of predicted, as assessed at Visit 2 (note that screening pre-BD FEV_1 Inclusion Criterion #6 must still be satisfied)

9. Women of childbearing potential (WOCBP) must use at least 1 acceptable and effective form of birth control (confirmed by the Investigator), eg, male or female condom with or without spermicide; a cap, diaphragm or sponge with spermicide; total sexual abstinence when this is in line with the preferred and usual lifestyle of the patient (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception); a vasectomized sexual partner; Implanon®; female sterilization by tubal occlusion; any effective Intrauterine device/Levonorgestrel Intrauterine system; Depo-Provera™ injections; oral contraceptive; and Evra Patch™ or Nuvaring™. Women of childbearing potential must agree to use birth control, as defined above, from enrolment, throughout the study duration and until 16 weeks (approximately 5 half-lives) after last dose of investigational product (IP). Women of childbearing potential must also have negative serum pregnancy test result on Visit 1.

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

– Women <50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and if follicle stimulating hormone (FSH) levels are in the postmenopausal range.

– Women ≥50 years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

11. All male patients who are sexually active must agree to use a double barrier method of contraception (condom with spermicide) from the first dose of IP until 16 weeks after their last dose.

12. Weight of ≥40 kg.

3.1.2 For inclusion in the open label ANDHI IP substudy patients should meet the following criteria:

1. Patients study must have completed ANDHI EOT Visit 11.

2. Written informed consent must also be obtained prior to any study related procedures being performed in the open label ANDHI IP substudy.

3. Patients who have received any approved or investigational targeted biologic for the treatment of asthma (eg, commercial mepolizumab, reslizumab, benralizumab) may be included if the last dose is ≥ 2 months of Visit 13.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled (patients who meet specific exclusion criteria can be re-screened once at the discretion of the Investigator [see Section 4.1.4 for details]):

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, chronic obstructive pulmonary disease [COPD], bronchiectasis, pulmonary fibrosis, cystic fibrosis), or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

2. Acute upper or lower respiratory infections within 30 days prior to the date informed consent is obtained or during the screening/run-in period.

3. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

   – Affect the safety of the patient throughout the study.

   – Influence the findings of the studies or their interpretations.

- Impede the patient's ability to complete the entire duration of study.

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

5. A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained that has not been treated with, or has failed to respond to, standard of care therapy.

6. Any clinically significant abnormal findings in physical examination, vital signs, hematology, or clinical chemistry during screening period, which in the opinion of the Investigator may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to complete entire duration of the study.

7. Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion of the Investigator may put the patient at risk or interfere with study assessments.

8. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained.

9. A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.

10. Current smokers or former smokers with a smoking history of ≥10 pack years. A former smoker is defined as a patient who quit smoking ≥6 months prior to Visit 1.

11. Current malignancy, or history of malignancy, except for:

    - Patients who have had non-melanoma skin cancers or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent is obtained.

    - Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent is obtained.

12. Approved or off-label use of systemic immunosuppressive medications within 3 months prior to the date informed consent is obtained. These include but are not limited to small molecules such as methotrexate, cyclosporine, azathioprine, and immunosuppressive/immunomodulating biologics such as tumor necrosis factor (TNF) blockers. Regular use of systemic (oral) corticosteroids is also excluded except for the indication of asthma.

13. Concurrent biologics for asthma are not allowed except for stable allergen immunotherapy (defined as a stable dose and regimen at the time of Visit 1). Acceptable washout periods for other asthma biologics:

    – Other eosinophil lowering products indicated for asthma (including mepolizumab or reslizumab): at least 4 months.

    – Prior omalizumab use: at least 1 month.

14. Previously received benralizumab (MEDI-563).

15. Receipt of any investigational medication as part of a research study within approximately 5 half-lives prior to randomization.

16. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level >3 times the upper limit of normal (ULN) confirmed during screening period.

17. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained.

18. Receipt of live attenuated vaccines 30 days prior to the date of randomization; other types of vaccines are allowed.

19. Planned surgical procedures during the conduct of the study.

20. Currently breastfeeding or lactating women.

21. Previous randomization in the present study.

22. Concurrent enrolment in another interventional or post-authorization safety study.

23. AstraZeneca staff involved in the planning and/or conduct of the study.

24. Employees of the study center or any other individuals involved with the conduct of the study or immediate family members of such individuals.

3.2.1 Eligibility criteria to be assessed at Visit 4 prior to randomization.

1. A negative urine pregnancy test in WOCBP prior to administration of IP.

2. ACQ6 ≥1.5.

3. A Pre-BD FEV_1 that either:

    – Is not increased from the qualifying pre-BD FEV_1 value at Visit 2 by >20%

    OR

- Remains <80% of predicted.

4. None of the following during the screening/run-in period prior to randomization Visit 4:

   - Upper respiratory tract infection.
   - Asthma exacerbation that required treatment with systemic corticosteroids.
   - An increase in regular maintenance dose of OCS.

Procedures for withdrawal of incorrectly enrolled patients: see Section 3.12.

3.2.2 Exclusion criteria for the open label ANDHI IP substudy

Patients should not enter the open label ANDHI IP substudy if any of the following exclusion criteria are fulfilled. Each exclusion criterion should be reviewed in all potential participants, including those who transition directly from the double-blind period and those with a delay between completing the EOT Visit 11 and the first open label visit (Visit 13).

1. Patients who participated in the double-blind period, but failed to complete the ANDHI EOT Visit 11. Patients who completed the ANDHI FU Visit 12 are not excluded from participation in the ANDHI IP substudy.

2. Unable to commit to the monthly visits as required by the protocol, or unable to commit to undergoing protocol guided reductions in asthma therapy, as directed by the Investigator.

3. Patients who experienced a severe or serious treatment-related AE during the double-blind period and, and those whom Investigator judges it is not in the patient's best interest to extend possible treatment with benralizumab.

4. Approved or off-label use of systemic immunosuppressive medications within 3 months prior to the first open label visit (Visit 13). These include but are not limited to small molecules such as methotrexate, cyclosporine, azathioprine, and immunosuppressive/immunomodulating biologics such as tumor necrosis factor (TNF) blockers. Regular use of systemic OCS is also excluded except for the indication of asthma.

5. Receipt of live attenuated vaccines 30 days prior to the first visit in the open label ANDHI IP substudy (Visit 13); other types of vaccines are allowed.

6. Planned surgical procedures during the conduct of the study.

7. Positive urine pregnancy test at Visit 13, or currently breastfeeding or lactating women.

3.3 Subject enrolment and randomization

The Investigator(s) should keep a patient screening log listing of those who have entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed

2. Assign a potential patient a unique enrolment number at the time of screening, beginning with 'E#' via interactive web/voice response system (IWRS/IVRS)

3. Determine patient eligibility. See Sections 3.1 and 3.2.

4. Assign an eligible patient a unique randomization code via IWRS/IVRS on the day of randomization

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused.

Patients will be allocated to treatment arms in a 2:1 ratio (benralizumab:placebo) and according to the stratification factors listed in Section 3.5. Specific information concerning the use of the IWRS/IVRS will be provided in the separate manual. In addition to the eligibility criteria in Sections 3.1 and 3.2, patients should be assessed against the criteria in Section 3.2.1 before being randomized. Randomized patients who discontinue from IP administration will not be replaced.

All patients entering ANDHI IP substudy will receive active benralizumab 30 mg sc in an open label fashion. Patients and site staff will remain blinded to randomized treatment assignment in ANDHI.

Enrolment in the ANDHI IP open label substudy will stop after the last ANDHI controlled patient completes their EOT Visit 11.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study. Patients who meet specific exclusion criteria can be re-screened once at the discretion of the Investigator (see Section 4.1.4).

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the medical monitor immediately, and a discussion should occur between the medical monitor, the AstraZeneca

clinical lead and the Investigator regarding whether to continue or discontinue the patient from treatment. The medical monitor must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Patients will be randomized to benralizumab or to placebo in a 2:1 ratio, and stratified by:

- Previous exacerbations (2 exacerbations in 12 months prior to Visit 1; ≥3 exacerbations in 12 months prior to Visit 1),
- Maintenance OCS use (use, non-use),
- Region (North America, rest of world).

See Section 3.1 for definition of qualifying exacerbations. In order to achieve the assumed exacerbation rates used to determine sample size and therefore have sufficient power in the study, it is expected that approximately 40% of patients will have ≥3 exacerbations in the 12 months prior to Visit 1. Therefore, enrolment of patients with only 2 exacerbations in the 12 months prior to Visit 1 may be halted if this subgroup within a site or region reaches approximately 60% of randomized patients.

Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization.

In the ANDHI IP substudy all patients will receive active product in an open label fashion (see Section 3.3).

3.6 Methods for ensuring blinding

The 24-week double-blind period of the ANDHI study will be conducted in a double-blind fashion. AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of the patients or in their clinical evaluation will not be aware of the treatment allocation. At the time of enrolment of patients into the open label ANDHI IP substudy, the treatment status will not be known and will remain blinded until such time as the 24-week double-blind period of the ANDHI is unblinded.

Placebo solution will be visually matched with benralizumab solution. Both benralizumab and placebo will be provided in an accessorized pre-filled syringe (APFS).

During the open label period, benralizumab will be provided in a labelled APFS.

3.6.1 Maintaining the blind to the patient's blood eosinophils counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. In order to mitigate potential unblinding on this basis, per protocol hematology will be run by the central laboratory. From Visit 4 on, eosinophil, basophil, and monocyte counts will be redacted from any central laboratory reports sent to investigative sites to prevent the Principal Investigator (PI)/designee,

the medical monitor, or AstraZeneca, from deducing the 'eosinophil + basophil' contribution to the complete blood count.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center. When emergency unblinding is required, sites will complete their transaction in the system; if the system is down, the codes can be accessed via the toll-free customer care number for the respective country (access at http://support.perceptive.com/support/home.aspx/phones)

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator must document and report the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

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

3.8 Asthma medication restrictions during the screening/run-in period

After enrolment, the patient should continue their usual asthma controller medication regimen (including allergen immunotherapy) without change during the run-in and screening period.

3.9 Restrictions during the double-blind period

3.9.1 Asthma medication restrictions

(a) Use of short-acting bronchodilators

- As needed, use of short-acting bronchodilators for relief of acute asthma symptoms is permitted throughout. Regularly scheduled use of bronchodilators such as short-acting β-2 receptor agonists (SABA; eg, albuterol [salbutamol]) and antimuscarinics (eg, ipratropium) is discouraged from enrolment and throughout the study duration.

(b) Use of long-acting bronchodilators including LABAs and LAMAs

- Regularly scheduled use of LABA and LAMAs that were part of the patient’s usual asthma controller regimen at baseline are allowed.

- Use as a reliever (eg, Symbicort Maintenance and Reliever Treatment) is not allowed from enrolment and throughout the study duration.

(c) **Changes to the patient's usual asthma controller medications are discouraged during the double-blind period of the study.** Any changes deemed essential for patient safety or any other reason should be brought to the attention of the medical monitor. The rationale for any change in the patient's usual controller medication should be documented in the source as well as in the medication Case Report Form (CRF).

(d) **Asthma exacerbations** should be treated with oral or other systemic corticosteroids according to standard practice.

3.9.1.1 Other medication restrictions

(a) Use of immunosuppressive medications is not allowed except maintenance use of OCS for asthma if present at baseline and rescue use of systemic corticosteroids (oral, IV, or IM) to treat an asthma exacerbation. Topical administration of immunosuppressive medication may be allowed at the discretion of the Investigator.

(b) Receipt of live attenuated vaccines during the treatment period, and for 16 weeks (approximately 5 half-lives) after the last dose of the IP is not allowed.

3.9.2 Restrictions on the days of scheduled lung function assessments

(a) General restrictions:

- Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.
- Patients should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.

(b) Restrictions to the patient's background medication: Patients should withhold their usual asthma therapies on the day(s) when lung function testing is being performed:

- Short-acting bronchodilators (eg, albuterol [salbutamol] or ipratropium) should be withheld for at least 6 hours before spirometry.
- Twice daily long-acting bronchodilator (LABA or LAMA)-containing therapies should be withheld for 12 to 24 hours and once daily long-acting bronchodilator -containing therapies for >24 hours before spirometry.
- Leukotriene receptor antagonists (LTRA) should be restricted for >24 hours.
- Twice daily theophyllines should be withheld for at least 12 to 24 hours and once daily for >24 hours before spirometry assessments.

If the patient has taken rescue SABA within 6 hours of the planned center visit spirometry, they should either:

– Remain at the center until the 6-hour withholding time has been reached (as long as that does not exceed the 2-hour spirometry window [see Section 5.1.1]) OR

– Return on another day within the visit window.

3.9.3 Other restrictions

(a) Fertile and sexually active patients or their partners should use effective contraceptive methods throughout the study and at least for 16 weeks (approximately 5 half-lives) after last administration of the IP. Male patients should refrain from fathering child or donating sperm from the time of informed consent, and for 16 weeks (approximately 5 half-lives) after last dose of IP (see Inclusion criteria 9 and 10)

(b) Patients must abstain from donating blood and plasma from the time of informed consent, and for 16 weeks (approximately 5 half-lives) after last dose of IP.

3.10 Restrictions during the open label ANDHI IP substudy

3.10.1 Asthma medication restrictions

Medication restrictions in Section 3.9 above apply to the double-blind period of the study through EOT Visit 11. Additional guidance for management of concomitant asthma medication specific to the open label ANDHI IP substudy period appears in Sections 4.4 (ANDHI IP substudy run-in period), Section 4.5 (background standard of care asthma controller reduction period), and Section 4.6 (background standard of care asthma controller maintenance period).

3.10.2 Restrictions on the days of scheduled lung function assessments

(c) General restrictions:

– Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.

– Patients should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.

(d) Restrictions to the patient's background medication: Patients should withhold their usual asthma therapies on the day(s) when lung function testing is being performed:

– Short-acting bronchodilators (eg, albuterol [salbutamol] or ipratropium) should be withheld for at least 6 hours before spirometry.

– Twice daily long-acting bronchodilator (LABA or LAMA)-containing therapies should be withheld for 12 to 24 hours and once daily long-acting bronchodilator -containing therapies for >24 hours before spirometry.

- Leukotriene receptor antagonists (LTRA) should be restricted for >24 hours.
- Twice daily theophyllines should be withheld for at least 12 to 24 hours and once daily for >24 hours before spirometry assessments.

If the patient has taken rescue SABA within 6 hours of the planned center visit spirometry, they should either:

- Remain at the center until the 6-hour withholding time has been reached (as long as that does not exceed the 2-hour spirometry window [see Section 5.1.1]) OR
- Return on another day within the visit window.

3.11 Discontinuation of investigational product

Patients will be discontinued from IP in the following situations:

- Patient decision. At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.12), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs
- An AE that in the opinion of the Investigator contraindicates further dosing.
- Severe non-compliance with the Clinical Study Protocol (CSP).
- Lost to FU.
  - The patient is considered lost to follow-up when any of the following attempts of contact are failed: 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail; or 1 unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations.
- Risk to patient outweighs benefit as judged by the Investigator or AstraZeneca
- Pregnancy
- Development of any study specific criteria for discontinuation:
  - Anaphylactic reaction to the IP
  - Development of helminth parasitic infestations requiring hospitalization

– An asthma-related event requiring mechanical ventilation

3.11.1 Procedures for discontinuation of a patient from investigational product (double-blind period)

All patients who prematurely discontinue IP prior EOT (Visit 11) should return to the study center and complete the procedures described for the premature IP Discontinuation (IPD) Visit (see Section 4.2.8) within 4 weeks ±3 days after the last dose of IP; the reason for discontinuation must be documented on the eCRF.

Patients who are discontinued from IP should be encouraged to remain in the study and complete all subsequent scheduled study visits, procedures, and assessments through study completion. Note that in this case, the IPD visit replaces the nearest regular visit.

If the patient is not willing to participate further in the study after the IPD visit, the patient should be withdrawn from the study and also complete the FU visit (see Section 4.3.1).

If a patient is withdrawn from the study, see Section 3.12.

3.11.2 Procedures for discontinuation of a patient from investigational product (open label ANDHI IP substudy)

All patients who prematurely discontinue IP should complete the procedures described for the ANDHI IP substudy premature IPD AND early withdrawal from study visit (WD) (see Section 4.7) within 4 weeks ±3 days after the last dose of IP; the reason for discontinuation must be documented on the electronic case report form (eCRF). For details on study withdrawal see Section 3.12.

3.12 Criteria for withdrawal

3.12.1 Eligibility criteria not fulfilled

This includes patients who do not fulfill the inclusion criteria (see Section 3.1) or who meet an exclusion criterion (see Section 3.2) during the screening period, or who meet an exclusion criterion (see Section 3.2.2) prior to Visit 13, or who fail to meet Visit 4 randomization criteria (see Section 3.2.1).

3.12.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment. Patients who withdraw early should attend an early study withdrawal visit (WD; see Section 4.2.8 and Section 4.7 for ANDHI IP substudy).

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his/her enrolment/randomization code cannot be reused. Withdrawn patients will not be replaced. Subsequent to

discontinuation of IP, the Investigator will advise the patient on other treatment options, as appropriate.

3.13 Discontinuation of the study

The study may be stopped if, in the judgement of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or that are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for discontinuation, all data available for the patient at the time of discontinuation must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4 STUDY PLAN AND TIMING OF PROCEDURES

The study plan for the screening/run-in period (Visit 1 up to Visit 4) is shown in Table 1 and the study plan for randomization, treatment and FU (Visit 4 through Visit 12) is shown in Table 2. Please refer to Section 4.1 and Section 4.2 for further details regarding the screening and treatment periods, respectively.

The study plan for the open label ANDHI IP substudy, Visit 13 to Visit 27, appears in Table 3 below. Please refer to Section 4.4 to Section 4.7 for more information regarding the open label period.

In the event of a pandemic, COVID-19 resurgence or other unforeseen disaster, specific contingencies and alternative processes will be implemented to manage patient safety, and to manage protocol-specified procedures, laboratory/diagnostic testing, data collection, and IP drug administration. Study decisions will be based on country and site level guidelines/restrictions for continuing use of the investigational product for patients already participating in the trial and the need to change patient monitoring. Since study participants may not be able to come to the investigational site for protocol specified visits, alternative methods for safety assessments (eg, phone contact, virtual visit, alternative location for assessment, including local labs) and IP administration may be implemented to assure the safety of study participants. Efficacy assessments when necessary and feasible to minimize risks to study integrity may be implemented by alternative methods (study staff visits or home health nurse to another clinic location or patient's home, telemedicine, and telephone visits).

Regulatory guidance and documentation practices as detailed in the guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic will be used. See Appendix F for details.

Table 1 Study plan - Run-in period; Visit 1 to Visit 3

Assessment/Activity	Refer to	Enrolment	Run-in	
		Visit 1	Visit 2	Visit 3
		D -42	D -28 (±2 days)[a]	D -14 (±2 days)[b]
General procedures:				
Informed consent	10.4	X		
Inclusion/exclusion criteria	3.1.1,3.2,3.2.1	X	X	X
Demographics	4.1.1	X		
Medical and asthma history	4.1.1	X		
Patient-Reported Outcome assessments:				
ACQ6	5.1.4.2	X[c]		
PSIA	5.1.4.6			X[d]
Safety assessments:				
Complete physical examination	5.3.2	X		
Vital signs	5.3.4		X	X
Weight, height, BMI	5.4.2	X		
ECG	5.3.3	X		
Adverse events	6		X	X
Concomitant medication	3.9.1, 3.9.1.1, 7.7	X[e]	X	X
Laboratory assessments:				
Clinical chemistry	5.3.1	X		
Hematology (full)[c]	5.3.1	X		
Hematology for eosinophil count (WBC + differential)	5.3.1		X[f]	
Serum pregnancy test	5.3.1.1	X		
Serology (HIV-1, HIV-2)	5.3.1.2	X		
FSH	5.3.1.1	X[g]		
Lung function assessments:				
Spirometry (Pre-BD FEV_1)	5.1.2		X[h]	
Reversibility (post-BD FEV_1)	5.1.2.1		X[i]	X[i]

Table 1 Study plan - Run-in period; Visit 1 to Visit 3

Assessment/Activity	Refer to	Enrolment	Run-in	
		Visit 1	Visit 2	Visit 3
		D -42	D -28 (±2 days)[a]	D -14 (±2 days)[b]
Asthma Daily Diary assessments:				
Dispensing of home spirometry equipment, Asthma Daily Diary and patient-reported outcome device	5.4.1		X	
Assessment of PEF at home[j]	5.4.1.1		Every morning and every evening	
Asthma control assessments[j]	5.4.1.2 to 5.4.1.4		Every morning and every evening	
Regular asthma medication compliance[j]	5.4.1		Daily	
Substudy Patients that report Chronic Rhinosinusitis with Nasal Polyps as part of their Medical History:				
SNOT-22	5.1.4.7			X

[a] Visit 2 may be scheduled within the 14 days following Visit 1, at a time when hematology and chemistry results are available to the Investigator to determine if there are any safety concerns related to clinical laboratory results, and if the blood eosinophil inclusion ≥300 cells/µL (or ≥150 to <300 cells/µL with additional clinical criteria met per inclusion criterion 8) has been met.

[b] Visit 3 may be scheduled within the 14 days following of Visit 2. If all eligibility criteria assessed at Visit 1 and Visit 2 are satisfied, Visit 3 can occur on the same day as Visit 2, or at any time in the 14 days after Visit 2.

[c] All patients must meet an ACQ6 score ≥1.5 at Visit 1. If this criterion is not met the patient must be screen failed and will not be allowed to re-screen.

[d] PSIA Parts 1 and 2 to be performed at Visit 3 (see Section 5.1.4.6).

[e] Special attention to requisite background medication for inclusion (Inclusion criterion 3).

[f] Inclusion criterion 8 (eosinophil count ≥300 cells/µL [or ≥150 to <300 cells/µL with additional clinical criteria met], see Section 3.1) can be met at Visit 1 or Visit 2. If this criterion happens to be met at Visit 1, the Visit 2 WBC + differential may be omitted.

[g] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months.

[h] Qualifying pre-BD FEV_1 (<80% predicted) must be met at Visit 2. If the patient did not comply with the requisite asthma medication hold for lung function testing (see Section 3.9.2), the test should be postponed to another day prior to Visit 3 to improve the chances of achieving a qualifying FEV_1 that is not affected by bronchodilator medication.

[i] The patient must satisfy reversibility testing at Visit 2 or Visit 3. If the patient did not comply with the requisite asthma medication hold for lung function testing (see Section 3.9.2), the test should be postponed to another day within the visit window to improve the chances of achieving a qualifying reversibility that is not affected by bronchodilator medication. If the reversibility is not met at Visit 2 or Visit 3 THEN the alternate criteria listed under Inclusion 7 may be considered.

[j] Assessment of PEF at home, asthma control assessments, and the recording of adherence to regularly scheduled asthma medication should be started on the evening of the day of Visit 2. Peak expiratory flow, asthma symptom score, rescue medication and background medication should be recorded morning and evening, night-time awakenings due to asthma should be recorded in morning. Adherence to regularly scheduled asthma medication should be recorded once daily. During on-site visits, sites should check and reinforce patient use of Asthma Daily Diary for recording PEF and asthma control assessments.

ACQ6 Asthma Control Questionnaire 6; BMI Body Mass Index; D Day; ECG electrocardiogram; FEV_1 forced expiratory volume in first second; FSH Follicle stimulating hormone; HIV Human Immunodeficiency virus; PEF: peak expiratory flow; pre-BD pre-bronchodilator; post-BD post-bronchodilator; PSIA Predominant Symptom and Impairment Assessment; SNOT-22 sino-nasal outcome test; W Week; WBC whole blood count; WOCBP women of childbearing potential.

Table 2 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 12

		Treatment							EOT	IPD/ WD	FU	UNS[a]
	Visit Day	**V4 D0[b]**	**V5 D14**	**V6 D28**	**V7 D56**	**V8 D84**	**V9 D112**	**V10 D140**	**V11 D168**		**V12 ☎ D182[c]**	
	Window (days)[d]		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±7**	**N/A**
Assessment/ activity	**Week**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**26**	
	Refer to											
General procedures:												
Inclusion/ exclusion criteria	3.1.1, 3.2, 3.2.1	X										
Randomization	3.5, 4.2	X										
Asthma exacerbation assessment[e]	5.1.1		X	X	X	X	X	X	X	X		
Patient and clinician Reported Outcome assessments:												
ACQ6	5.1.4.2	X[f]	Assessed at home every 7 days[g]		Assessed at home every 28 days[g] X				X	X		
SGRQ	5.1.4.1	X		X		X			X	X		
SF-36 v2	5.1.4.3	X				X			X	X		
PGI-S	5.1.4.4	X	Assessed at home every 7 days[g]		Assessed at home every 28 days[g]				X	X		
PGI-C	5.1.4.5		Assessed at home every 7 days[g]		Assessed at home every 28 days[g]				X	X		
CGI-C	5.1.4.5		X	X	X	X	X	X	X	X		
PSIA	5.1.4.6	X	Assessed at home every 7 days[h]					X[h]	X	X		

Table 2 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 12

		Treatment							EOT	IPD/ WD	FU	UNS[a]
	Visit Day	**V4 D0[b]**	**V5 D14**	**V6 D28**	**V7 D56**	**V8 D84**	**V9 D112**	**V10 D140**	**V11 D168**		**V12 ☎ D182[c]**	
	Window (days)[d]		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±7**	**N/A**
Assessment/ activity	**Week**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**26**	
	Refer to											
Substudy in patients that report chronic rhinosinusitis with nasal polyps as part of their medical history:												
SNOT-22	5.1.4.7			X		X			X	X		
Safety assessments:												
Complete physical examination	5.3.2	X							X	X		
Brief physical examination	5.3.2			X	X		X					X[a]
Vital signs	5.3.4	X		X	X		X		X	X		X[a]
Adverse events	6	AEs to be collected from Visit 1 onwards										X[a]
Concomitant medication	3.9.1, 3.9.1.1, 7.7	X	X	X	X	X	X	X	X	X	X	X[a]
Laboratory assessments:												
Hematology (full)	5.3.1								X	X		

Table 2 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 12

		Treatment							EOT	IPD/ WD	FU	UNS[a]
	Visit Day	**V4 D0[b]**	**V5 D14**	**V6 D28**	**V7 D56**	**V8 D84**	**V9 D112**	**V10 D140**	**V11 D168**		**V12 ☎ D182[c]**	
	Window (days)[d]		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±7**	**N/A**
Assessment/ activity	**Week**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**26**	
	Refer to											
Hematology for eosinophil count (WBC + differential)[i]	5.3.1	X	X	X	X	X	X	X				
Clinical chemistry	5.3.1								X	X		
Urine pregnancy test, dipstick[j]	5.3.1.1	X		X	X	X	X	X	X	X		
Lung function assessments:												
Spirometry (pre-BD FEV_1)	5.1.2	X[f]	X	X	X	X			X	X		
Biomarker assessment:												
Total IgE and Phadiatop	5.4.3	X										
Blood for asthma biomarkers[k]	5.8	X							X	X		
Asthma Daily Diary assessments:												
Assessment of PEF at home[l]	5.4.1.1	Every morning and every evening throughout treatment period										

Table 2 Study Plan - Randomization, treatment period, follow-up; Visit 4 to Visit 12

		Treatment							EOT	IPD/ WD	FU	UNS[a]
	Visit Day	**V4 D0[b]**	**V5 D14**	**V6 D28**	**V7 D56**	**V8 D84**	**V9 D112**	**V10 D140**	**V11 D168**		**V12 ☎ D182[c]**	
	Window (days)[d]		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±7**	**N/A**
Assessment/ activity	**Week**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**		**26**	
	Refer to											
Asthma control assessments[l]	5.4.1.2 to 5.4.1.4	Every morning and every evening throughout treatment period										
Regular asthma medication compliance[l]	5.4.1	Daily										
Investigational Product administration:												
Benralizumab/ placebo[m]	7.2, 7.5, 7.6	X[m]		X[m]	X[m]		X[m]					

[a] 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 mandatory for each UNS visit.

[b] The period between Visit 3 and Visit 4 (Randomization) must not be shorter than 12 days (ie, 14 days ±2 days).

[c] Visit 12 (Day 182, FU) is an optional telephone visit for patients not entering the ANDHI IP substudy: the patient does not need to attend the study site. Telephone visits should be scheduled at the previous on-site Visit.

[d] All visits are to be scheduled from the date of randomization, not from the date of previous visit, except for early discontinuation from IP (see Section 3.11 for details).

[e] The patient must be queried regarding any worsening of asthma that resulted in initiation of systemic corticosteroids (oral, intravenous or intramuscular), and/or urgent care visit or a hospitalization. The detail should be captured on the EXAC CRF.

[f] The patient must have an ACQ6 score ≥1.5 and a pre-BD FEV_1 that is either is not increased from the qualifying pre-BD FEV_1 value at Visit 2 by >20%, **or** remains <80% of predicted. If not, the patient must be screen failed and cannot be re-screened.

[g] During the treatment period, ACQ6 and PGI-S will be assessed on-site at Visit 4, and then at home by patients every 7 days (±2 days) for 28 days (until Visit 6). PGI-C will be completed at home every 7 days (±2 days) following Visit 4 for 28 days (until Visit 6). From Visit 6 to EOT, PGI-C, and PGI-S will be assessed at home by patients every 28 days (±2 days).

[h] During the treatment period, PSIA (Part 3, see Section 5.1.4.6) will be assessed on-site at Visit 4, and then at home by patients every 7 days (±2 days) for 16 weeks (until Visit 9). After Visit 9, PSIA will be assessed at home by patients at Visit 10 (±2 days) and EOT (or IPD/WD).

[i] Blood eosinophil count will be assessed in central laboratory as a part of the central hematology panel but eosinophil, basophil, and monocyte count will be redacted from the reports available for investigative sites from the day of randomization onwards to maintain the blind.

[j] For WOCBP only.

[k] If the patient consents to optional blood samples for biomarker analysis being taken.

[l] Peak expiratory flow, asthma symptom score, and rescue medication should be recorded morning and evening, night-time awakenings due to asthma should be recorded in morning. Adherence to regularly scheduled asthma medication should be recorded once daily. During on-site visits, sites should check and reinforce patient use of Asthma Daily Diary for recording PEF and asthma control assessments.

[m] After IP administration the patient should be observed for a minimum of 2 hours at the clinical site in case of any acute drug reactions.

ACQ6 Asthma Control Questionnaire 6; AE adverse event; ANDHI IP ANDHI in Practice; CGI-C Clinician Global Impression of Change; CRF case report form; D Day; EOT End-of-treatment; EXAC: exacerbation; FEV_1 forced expiratory volume in first second; FU follow-up; IgE Immunoglobulin E; IPD investigational product Discontinuation; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PEF: peak expiratory flow; pre-BD pre-bronchodilator; PSIA Predominant Symptom and Impairment Assessment; SF-36v2 Short Form 36-item Health survey, version 2 (acute recall); SGRQ St. George's Respiratory Questionnaire; SNOT-22 sino-nasal outcome test; UNS Unscheduled visit; V Visit; WD early study withdrawal visit; Wk Week; WBC whole blood count; WOCBP Women of childbearing potential; ☎ telephone visit.

Table 3 Study Plan – open label ANDHI IP Substudy; Visit 13 to Visit 27

		Run-in		Background asthma controller reduction (Section 4.5)								Maintenance (Section 4.6) (no further reduction)			EOS	IPD/ WD	UNS[k]
	Visit	**V13**	**V14**	**V15**	**V16** ☎	**V17**	**V18** ☎	**V19**	**V20** ☎	**V21**	**V22** ☎	**V23**	**V24** ☎	**V25**	**V26** ☎	**V27**		
	Day[l]	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**		
	Window (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Assessment/ activity	**Weeks[l]**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**		
Informed consent	Section 3.1.2	X																
Inclusion/ exclusion criteria	Section 3.1.2, 3.2.2	X																
Medical history		X[a]																
Concomitant medication	Section 7.7	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma medication reduction attempts	Section 4.5.5			X		X		X		X		X						
Asthma treatment compliance assessment and reminder[c]	Section 4.5.2				X		X		X		X		X		X			
Dispense and train: ePRO device/PEF meter		X[d]	X[d]															
ACQ6[e]	Section 5.1.4.2	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SGRQ[e]	Section 5.1.4.1			X		X		X		X		X		X		X	X	

Table 3 Study Plan – open label ANDHI IP Substudy; Visit 13 to Visit 27

		Run-in		Background asthma controller reduction (Section 4.5)								Maintenance (Section 4.6) (no further reduction)			EOS	IPD/ WD	UNS[k]
	Visit	**V13**	**V14**	**V15**	**V16** ☎	**V17**	**V18** ☎	**V19**	**V20** ☎	**V21**	**V22** ☎	**V23**	**V24** ☎	**V25**	**V26** ☎	**V27**		
	Day[l]	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**		
	Window (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Assessment/ activity	**Weeks[l]**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**		
PGI-C[e]	Section 5.1.4.5				X	X	X	X	X	X	X	X				X	X	
CGI-C	Section 5.1.4.5					X		X		X		X				X	X	
Asthma exacerbation assessment[f]	Section 5.1.1		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Brief physical examination	Section 5.3.2	X[b]	X	X		X		X		X		X		X				X
Vital signs[g]	Section 5.3.4	X[b]	X	X		X		X		X		X		X		X	X	X
Adverse events	Section 6	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (dipstick)[h]	Section 5.3.1.1	X[b]	X	X		X		X		X		X		X		X	X	
Pre-bronchodilator Spirometry	Section 5.1.2	X[b]		X		X		X		X		X		X		X	X	
Morning Peak expiratory flow[d]	Section 5.4.1.1	Morning PEF																

Table 3 Study Plan – open label ANDHI IP Substudy; Visit 13 to Visit 27

		Run-in		Background asthma controller reduction (Section 4.5)								Maintenance (Section 4.6) (no further reduction)			EOS	IPD/ WD	UNS[k]
	Visit	**V13**	**V14**	**V15**	**V16** ☎	**V17**	**V18** ☎	**V19**	**V20** ☎	**V21**	**V22** ☎	**V23**	**V24** ☎	**V25**	**V26** ☎	**V27**		
	Day[l]	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**392**	**420**	**448**	**476**	**504**	**532**	**560**		
	Window (days)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Assessment/ activity	**Weeks[l]**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**		
Blood sample for blood eosinophil count[i]	Section 5.8.4			X				X				X				X	X	
Benralizumab 30mg sc[j]	Section 7.2,7.5, 7.6	X	X	X		X		X		X		X		X				

a. Medical history should be reviewed in patients who enrolled into the open label ANDHI IP substudy after completing FU visit 12. Any new medical conditions that occurred since completion of the double-blind period should be entered as medical history.

b. Complete this assessment for patients who do not transition directly from the double-blind to open label ANDHI IP substudy (ie, on the Day of the ANDHI EOT Visit 11).

c. Verify that the patient has accomplished the background medication reduction prescribed at the last clinic visit (if applicable). If the patient has not adopted the recommended step down for a non-clinical issue, the site must evaluate the issue and help mitigate logistical obstacles.

d. Dispense ePRO device/PEF meter as needed for patients for those patients who did not transition directly from the double-blind to open label period and returned their device. This should be accomplished at Visit 13. Patients directly transitioning should continue morning PEF from Visit 13 and PROs, as scheduled, for the open label ANDHI IP substudy.

e. Patient-reported outcomes assessed via the ePRO device.

f. The exacerbation CRF must be completed for any asthma worsening meeting the per protocol definition of an asthma exacerbation (ie, requiring an OCS burst, an emergency room visit for asthma requiring systemic corticosteroid, or a hospitalization for asthma).

g. Vital signs to be collected include pulse rate, body temperature, respiration rate, and blood pressure measurements.

h. A positive urine test result must be confirmed by a serum beta hCG test.

i. Blood eosinophil counts will be assessed centrally.

j. After IP administration the patient should be observed for a minimum of 2 hours at the clinical site in case of any acute drug reactions. All patients will receive benralizumab 30mg sc in an open label fashion.

k. 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 mandatory for each UNS visit.

[l.] Numbering of days and weeks refer to the time elapsed since baseline Visit 4, assuming direct transition into the ANDHI IP substudy. For transitioned patients with gap between Visit 11 and Visit 13 the number of days and weeks reflect the time elapsed since baseline Visit 4 during their participation in the ANDHI, regardless the time gap between Visit 11 and Visit 13.

ACQ6 Asthma Control Questionnaire 6; CGI-C Clinical Global Impression of Change; D Day; EOS end of ANDHI IP Substudy; ePRO electronic patient-reported outcome; FU follow-up; GINA Global Initiative for Asthma; IP investigational product; IPD investigational product discontinuation; N/A not applicable; PEF Peak expiratory flow; PGI-C Patient Global Assessment for Change; SGRQ Saint George Respiratory Questionnaire, UN unscheduled visit; W Week, WD early study withdrawal visit; ☎ telephone visit.

4.1 Double-blind Screening/Enrolment period

The Screening/run-in period combined is up to 42 days in duration, and may be shorter depending on how rapidly patients satisfy the requisite eligibility criteria.

Sufficient time between Visit 1 and Visit 2 (up to 14 days) should be allowed to ensure Visit 1 eligibility criteria are assessed and reviewed, including review of the eosinophil count and safety laboratory parameters. Once all Visit 1 assessments have been completed, Visit 2 can be scheduled for patients eligible to proceed to Visit 2, and can occur less than 14 days after Visit 1.

Similarly, while the run-in period (Visit 2 to Visit 4) may be up to 4 weeks duration (±2 days), if all eligibility criteria assessed at Visit 1 and Visit 2 are satisfied, Visit 3 can occur on the same day as Visit 2, or at any time in the 14 days after Visit 2.

The period between Visit 3 and Visit 4 must not be shorter than 12 days (ie, 14 days ±2 days).

4.1.1 Enrolment (Visit 1) Day -42

Each potential patient will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit (see Table 1).

Patient must sign the Informed Consent Form (ICF) prior to any Visit 1 procedures and prior to being instructed to withhold any non-study medication. Registration of patient's enrolment via IWRS/IVRS should occur on the day of ICF signature.

Visit 1 assessments are primarily concerned with confirmation of the asthma disease state and the requisite level of control and severity based on ACQ6 score, historical asthma exacerbations, and background medications. Demographic data collected will include date of birth/age, sex, race, and ethnicity.

A record of physician-diagnosed asthma is required in source documentation prior to enrolment. A patient's verbal history suggestive of asthma symptoms, but without supporting documentation, is not sufficient to satisfy this inclusion criterion.

The following procedures are to be performed and/or data to be collected at Visit 1 (please refer to Table 1 for details):

- Informed consent process
- Confirmation of eligibility criteria
- Demographics (including date of birth/age, sex, race, and ethnicity)

- Medical and asthma history, including historical exacerbations and prior medication use.

Note:

– At least 2 asthma exacerbations requiring treatment with systemic steroid (eg, oral, IV, or IM) within the 12 months prior to enrolment are required for study inclusion and must be documented in the source documentation and verified by the clinical research associate. Acceptable source documentation includes a chart note of the event details, the actual hospital or urgent care center record and/or a copy of the prescription record for rescue OCS. If adequate documentation of at least 2 exacerbations requiring systemic corticosteroid cannot obtained during the screening period, the patient should be screen failed.

– Additional events (beyond the requisite 2) must be recorded in the CRF and should be documented in the source if at all possible, or may be documented at enrolment.

- ACQ6 ≥1.5. If this criterion is not met the patient must be screen failed and will not be allowed to re-screen
- Complete physical examination
- Height/Weight/Body Mass Index (BMI)
- Electrocardiogram
- Concomitant medication review
- Central laboratory assessments (including clinical chemistry, full hematology testing, serum pregnancy test, FSH [if needed], and serology for HIV-1, HIV-2)

– Peripheral blood eosinophil count value of ≥300 cells/μL (or ≥150 to <300 cells/μL with additional clinical criteria met, see inclusion criterion 8) must be met at either Visit 1 or Visit 2.

4.1.2 Screening/run-in visit (Visit 2) Day -28

Visit 2 defines the start of the formal run-in period, and may be scheduled within the 14 days following Visit 1, at a time when hematology and chemistry results are available to the Investigator to determine:

- If there are any safety concerns related to the Screening clinical laboratory results, and
- If the blood eosinophil inclusion ≥300 cells/µL (or ≥150 to <300 cells/µL with additional clinical criteria met, see inclusion criterion 8) has been met at Visit 1.

The following procedures are to be performed and/or data to be collected at Visit 2 (please refer to Table 1 for details):

- Confirmation of eligibility criteria
- Assessment of vital signs
- Collection of AEs
- Concomitant medication review
- Dispense and train patient on the use of home spirometry equipment and Asthma Daily Diary for daily PEF, asthma control assessments, and to record adherence with their regularly scheduled asthma medication

– Patients will be instructed to start daily assessment of PEF (morning and evening; see Section 5.4.1.1), asthma control assessments (morning and evening; see Sections 5.4.1.2 to 5.4.1.4), and to record their level of adherence with their regularly scheduled asthma medication (once daily) from the evening of the day of Visit 2 onwards.

- If a peripheral blood eosinophil count value of ≥300 cells/µL (or ≥150 to <300 cells/µL with additional clinical criteria met, see inclusion criterion 8) was not met at Visit 1, the test should be repeated at this Visit (hematology for eosinophil count: WBC + differential). If this criterion was met at Visit 1, a repeat test is not necessary.
- Spirometry –qualifying pre-BD FEV_1 (<80% predicted) must be met at Visit 2. Spirometry testing should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.9.2). If the patient did not comply with the requisite asthma medication hold for lung function testing, the test should be postponed to another day prior to Visit 3 to improve the chances of achieving a qualifying FEV_1 that is not affected by bronchodilator medication.

- Reversibility testing –qualifying reversibility criterion (≥12%) must be met at Visit 2 or Visit 3. If the reversibility is not met at Visit 2 or Visit 3 then the alternate criteria listed under Inclusion 7 may be considered. Reversibility testing should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.9.2). If the patient did not comply with the requisite asthma medication hold for lung function testing, the test should be postponed to another day within the visit window to improve the chances of achieving a qualifying reversibility that is not affected by bronchodilator medication.

4.1.3 Screening/run-in visit (Visit 3) Day -14

Visit 3 may be scheduled within 14 days of Visit 2. If all eligibility criteria assessed at Visit 1 and Visit 2 are satisfied, Visit 3 can occur on the same day as Visit 2, or at any time in the 14 days after Visit 2.

The following procedures are to be performed and/or data to be collected at Visit 3 (please refer to Table 1 for details):

- Confirmation of eligibility criteria
- Assessment of vital signs
- The following patient-reported outcome assessments:

– PSIA (Parts 1 and 2; see Section 5.1.4.6)

- Collection of AEs
- Concomitant medication review
- Reversibility testing if not already met at Visit 2. Reversibility testing should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.9.2). If the patient did not comply with the requisite asthma medication hold for lung function testing, the test should be postponed to another day within the visit window to improve the chances of achieving a qualifying reversibility that is not affected by bronchodilator medication.

Note: If reversibility ≥12% is not met at Visit 2 or Visit 3 then the alternate criteria listed under Inclusion 7 may be considered.

- For patients that report ongoing chronic rhinosinusitis with nasal polyps as part of their medical history participating in the substudy:

– SNOT-22

4.1.4 Re-screening

Re-screening of patients is allowed once only, at the Investigator's discretion, for patients:

- Who meet one or more of the following exclusion criteria: 2, 12, 13, 15, 17, or 18.
- Who experience an exacerbation of their asthma during screening that requires OCS or a change in their background controller regimen. In this circumstance the patient can be re-screened (only once) after they have fully recovered and their background medication regimen has been stable for 30 days.
- Patient inclusion criteria #7 (reversibility) and #8 (screening blood eosinophil) (see Section 3.1.1), and randomization criterion #3 (allowable pre-BD FEV_1; see Section 3.2.1) were amended in Version 2 of this protocol; these amendments may affect the potential eligibility of some previously screen failed patients. Therefore, patients that have screen failed in the past based on Version 1 of these criteria may be re-screened once under the amended version 2 criteria, at the discretion of the Investigator. Patients that are re-screened under this provision will follow the criteria outlined in this section for re-screening if applicable.

Patients must meet ACQ6 ≥1.5 at Visit 1. If this criterion is not met the patient must be screen failed and will not be allowed to re-screen.

Re-screened patients should re-sign informed consent on the re-screening Visit 1. All procedures from screening/run-in period should be repeated.

4.2 Double-blind treatment period

The treatment period lasts 24 weeks and consists of 8 on-site study visits (Visit 4 to Visit 12).

Patients confirmed to be eligible will be randomized at Day 0 (Visit 4).

Patients will be randomized to either placebo or benralizumab 30 mg, with treatment on-site at randomization, Week 4 (Visit 6), Week 8 (Visit 7) and Week 16 (Visit 9).

Several assessments will be performed by the patient at home during the treatment period:

- Peak expiratory flow, asthma symptom score, and rescue medication should be recorded morning and evening, night-time awakenings due to asthma should be recorded in the morning. Adherence to regularly scheduled asthma medication should be recorded once daily. During on-site visits, sites should check and reinforce patient use of Asthma Daily Diary (see Section 5.4.1).

- ACQ6, PGI-S will be assessed at Visit 4 on-site, then by patients at home once every 7 days (±2 days) until Visit 6. After Visit 6, ACQ6 and PGI-S will be assessed by patients at home once every 28 days (±2 days) until EOT (or IPD/WD).

- PGI-C will be completed at home every 7 days (±2 days) following Visit 4 for 28 days (until Visit 6). After Visit 6, PGI-C will be assessed by patients at home once every 28 days (±2 days) until EOT (or IPD/WD).

- During the treatment period, PSIA (Part 3; see Section 5.1.4.6) will be assessed on-site at Visit 4, and then at home by patients every 7 days (±2 days) for 16 weeks (until Visit 9). After Visit 9, PSIA will be assessed at home by patients at Visit 10 (±2 days) and EOT (or IPD/WD).

After Visit 4, when patients are due to complete PSIA, PGI-C, PGI-S or ACQ6 on an on-site visit day, patients can choose to bring in their electronic devices and complete the assessments at the site during the visit.

Patients with doctor diagnosed chronic rhinosinusitis with nasal polyposis that is ongoing at baseline and who elect to participate in the substudy will have SNOT-22 assessments at Week 4 (Visit 6), Week 12 (Visit 8), and EOT/IPD/WD.

Scheduled assessments for EOT, IPD, and WD are the same (see Section 4.2.8).

Patients who discontinue IP early (see Sections 3.11.1) should return to the study center and complete the procedures described for the IPD Visit (see Section 4.2.8) within 4 weeks ±3 days after the last dose of IP. Patients who are discontinued from IP should be encouraged to remain in the study and complete all subsequent scheduled study visits, procedures, and assessments through study completion. Note that in this case, the IPD visit replaces the nearest regular visit.

Patients who discontinue IP early (see Sections 3.11.1) and are not willing to continue to participate in the study should attend a WD visit (see Section 4.2.8). Follow-up should be performed (see Section 4.3.1).

Completion or early termination of the treatment will be registered via IWRS/IVRS for each patient.

4.2.1 Randomization (Visit 4) Day 0

The period between Visit 3 and Visit 4 must not be shorter than 12 days (ie, 14 days ±2 days).

The following procedures are to be performed and/or data to be collected at Visit 4 (please refer to Table 2 for details):

- Adherence to all criteria listed in Section 3.2.1 must be confirmed prior to randomization

– Patients confirmed to be eligible will be randomized via IWRS/IVRS.

- Spirometry – qualifying pre-BD FEV_1 must be met to proceed (ie, not increased from the qualifying pre-BD FEV_1 value at Visit 2 by >20%, or remains <80% of predicted). Spirometry testing must only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the medication hold is not met, the test should be postponed to another day within the visit window to improve the chances of achieving a qualifying FEV_1 (according to randomization criterion 3 [see Section 3.2.1]) that is not affected by bronchodilator medication.

- The following patient-reported outcome assessments:

– ACQ6 (**score must be ≥1.5 for patients to be randomized**, see Sections 3.2.1 and 5.1.4.2)

– SGRQ, SF-36v2 (see Section 5.1.4.3), PGI-S (see Section 5.1.4.4), and PSIA (see Section 5.1.4.6)

- Complete physical examination
- Assessment of vital signs
- Collection of AEs
- Concomitant medication review
- The following laboratory tests:

– Peripheral blood eosinophil count

– Urine pregnancy test (WOCBP only)

– Total immunoglobulin E (IgE) and Phadiatop

– Asthma biomarkers (if the patient consented to optional biomarker samples)

- Administration of IP/placebo

After IP administration the patient should be observed for a minimum of 2 hours at the clinical site in case of any acute drug reactions.

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.2 Visit 5 (Week 2) Day 14

The following procedures are to be performed and/or data to be collected at Visit 5 (please refer to Table 2 for details):

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Collection of AEs
- Concomitant medication review
- The following laboratory test:

– Hematology for eosinophil count

- Spirometry – pre-BD FEV_1. Spirometry should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4 and should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the patient does not meet these criteria:

(a) If the patient has taken rescue SABA within 6 hours of the scheduled visit the patient should either remain at the center until the 6-hour withholding time for a short-acting bronchodilator has been reached (as long as that does not exceed the 2-hour spirometry window) OR

(b) The test should be postponed to another day within the visit window.

(c) If neither (a) nor (b) are feasible options for the patient, the patient may proceed with the test; however, an out of window spirometry deviation must be noted in the source along with any flag provided on the central spirometry report.

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.3 Visit 6 (Week 4) Day 28

The following procedures are to be performed and/or data to be collected at Visit 6 (please refer to Table 2 for details):

- The following patient-reported outcome assessments:

– SGRQ (see Section 5.1.4.1)

– For patients in the chronic rhinosinusitis with nasal polyps substudy: SNOT-22

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Brief physical examination
- Assessment of vital signs
- Collection of AEs
- Concomitant medication review
- The following laboratory tests:

– Hematology for eosinophil count

– Urine pregnancy test (WOCBP only)

- Spirometry – pre-BD FEV_1. Spirometry should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4 and should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the patient does not meet these criteria, see options listed for Visit 5 (Section 4.2.2).
- Administration of IP/placebo

After IP administration the patient should be observed for a minimum of 2 hours at the clinical site in case of any acute drug reactions.

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.4 Visit 7 (Week 8) Day 56

The following procedures are to be performed and/or data to be collected at Visit 7 (please refer to Table 2 for details):

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Brief physical examination
- Assessment of vital signs
- Collection of AEs
- Concomitant medication review
- The following laboratory tests:

– Hematology for eosinophil count

– Urine pregnancy test (WOCBP only)

- Spirometry – pre-BD FEV_1. Spirometry should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4 and should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the patient does not meet these criteria, see options listed for Visit 5 (Section 4.2.2).
- Administration of IP/placebo

After IP administration the patient should be observed for a minimum of 2 hours for the appearance of any acute drug reactions.

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.5 Visit 8 (Week 12) Day 84

The following procedures are to be performed and/or data to be collected at Visit 8 (please refer to Table 2 for details):

- The following patient-reported outcome assessments:

– SGRQ (see Section 5.1.4.1), SF-36v2 (see Section 5.1.4.3)

– For patients in the chronic rhinosinusitis with nasal polyps substudy: SNOT-22

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Collection of AEs
- Concomitant medication review
- The following laboratory tests:

– Hematology for eosinophil count

– Urine pregnancy test (WOCBP only)

- Spirometry – pre-BD FEV_1. Spirometry should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4 and should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the patient does not meet these criteria, see options listed for Visit 5 (Section 4.2.2).
- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.6 Visit 9 (Week 16) Day 112

The following procedures are to be performed and/or data to be collected at Visit 9 (please refer to Table 2 for details):

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Brief physical examination
- Assessment of vital signs
- Collection of AEs
- Concomitant medication review
- The following laboratory tests:

– Hematology for eosinophil count

– Urine pregnancy test (WOCBP only)

- Administration of IP/placebo

After IP administration the patient should be observed for a minimum of 2 hours at the clinical site in case of any acute drug reactions.

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.7 Visit 10 (Week 20) Day 140

The following procedures are to be performed and/or data to be collected at Visit 10 (please refer to Table 2 for details):

- The following clinician reported outcome assessment:

– CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)
- Collection of AEs
- Concomitant medication review
- The following laboratory test:

– Hematology for eosinophil count

– Urine pregnancy test (WOCBP only)

- Patients should be reminded to complete morning and evening Asthma Daily Diary assessments, morning and evening PEF measurements, and periodic questionnaires at home according to the schedule in Table 2.

4.2.8 End of treatment (Visit 11; Week 24) Day 168, premature investigational product discontinuation, or early withdrawal from study

The following procedures are to be performed and/or data to be collected at Visit 11 EOT/IPD/WD visit (please refer to Table 2 for details):

- Discontinuation of IP (IWRS/IVRS)
- The following patient-reported outcome assessments:

– SGRQ (see Section 5.1.4.1), SF-36v2 (see Section 5.1.4.3), PGI-S (see Section 5.1.4.4), ACQ6 (see Section 5.1.4.2), PGI-C (see Section 5.1.4.5), PSIA (see Section 5.1.4.6)

If the visit is an EOT or WD visit, the patient should perform their final PGI-S, ACQ6 and PGI-C assessments at the clinic if they have not already completed them at home. If they forgot their diary, they may still compete the final assessments at home, and within the prescribed diary window.

- For patients in the chronic rhinosinusitis with nasal polyps substudy: SNOT-22

- The following clinician reported outcome assessment:

- CGI-C (see Section 5.1.4.5)

- Asthma exacerbation assessment (see Section 5.1.1)

- Complete physical examination

- Assessment of vital signs

- Collection of AEs

- Concomitant medication review

- The following laboratory tests:

- Full hematology testing

- Clinical chemistry

- Urine pregnancy test (WOCBP only)

- Asthma biomarkers (if the patient consented to optional biomarker samples)

- Spirometry – pre-BD FEV_1. Spirometry should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4 and should only be performed if the patient meets the asthma medication hold for lung function testing (see Section 3.11.2). If the patient does not meet these criteria, see options listed for Visit 5 (Section 4.2.2).

- Subsequent to discontinuation of IP, the Investigator will advise the patient on other treatment options, as appropriate.

- Details for Visit 12 (FU telephone visit) will be confirmed with the patient.

4.3 Double-blind Follow-up period

4.3.1 Follow-up (Visit 12) Day 182

Patients who complete the double-blind randomized treatment period and do not directly transition to the ANDHI IP substudy will have a telephone FU visit (Visit 12). Patients who transition directly into the open label ANDHI IP substudy at Visit 11 will not complete the Day 182 FU visit. Additionally, the ICF will ask that patients continue study assessments for the whole double-blind treatment period, including FU, even if they discontinue study treatment prematurely.

Completion of the FU visit 12 does not exclude patients from the ANDHI IP substudy; however, enrolment in the open label ANDHI IP substudy will stop after the last ANDHI controlled patient completes their EOT Visit.

The following procedures are to be performed and/or data to be collected at Visit 12 (please refer to Table 2 for details):

- Collection of AEs
- Concomitant medication review

4.4 ANDHI IP substudy enrolment and open label benralizumab run-in period

All eligible patients who completed the EOT Visit 11 of the double-blind period may be enrolled in the open label ANDHI IP substudy. The open label run-in period (Visit 13 to Visit 15) serves to introduce benralizumab to previous placebo patients from ANDHI double-blind study prior to entering the reduction phase. In directly transitioning patients who were treated with benralizumab during the ANDHI double-blind study, the run-in represents a continuation of their active treatment. The patients' prior treatment status in ANDHI will not be known and all patients will receive open label benralizumab, including the loading dose.

The first open label visit (Visit 13) assessments and procedures may be conducted on the same day as the double-blind EOT Visit 11 (directly transitioning patients), after all of the EOT assessments have been completed; otherwise, the patient may initiate the open label Visit 13 at a later date.

Enrolment in the ANDHI IP open label substudy will stop after the last ANDHI controlled patient completes their EOT Visit 11.

4.4.1 Visit 13 (Week 24): Open label ANDHI IP substudy enrolment visit and first open label benralizumab dose

Each patient will provide written informed consent prior to any study specific procedures within the open label ANDHI IP substudy (see Table 3). Registration of open label substudy enrolment via IWRS/IVRS should occur on the day of Visit 13.

The following procedures are to be performed and/or data to be collected at Visit 13.

- Confirm informed consent for the open label ANDHI IP substudy
- Confirmation of eligibility criteria (Section 3.1.2 and Section 3.2.2)
  - Dispense electronic patient-reported outcome (ePRO) device and peak flow meter, as needed in patients who may have already returned their devices
- Administration of benralizumab

The following assessments need only be performed as part of the first open label visit, Visit 13, when this occurs one or more days after Visit 11, the EOT Visit of the double-blind concomitant medications

- ACQ6 assessment using the ePRO device
- Medical history review
- Brief physical exam, vital signs
- Concomitant medication
- Collection of AEs
- Pre-bronchodilator spirometry
- Morning PEF
- Urine pregnancy test must always be performed on the day of first dose, prior to dosing

4.4.2 Visit 14 (Week 28): Open label run-in visit and second IP dose

The following procedures are to be performed and/or data to be collected at Visit 14 (please refer to Table 3 for details):

- Asthma exacerbation assessment
- ACQ6 assessment using the ePRO device

- Brief physical examination
- Vital signs
- Collection of AEs
- Concomitant medication
- Reminder: PEF must always be performed every morning before taking usual asthma medication
- Urine pregnancy test: must always be performed prior to dosing
- Administration of benralizumab

4.5 Background standard of care asthma controller reduction period (Begins Week 32)

4.5.1 Background asthma medication reduction visits in the clinic: Visit 15, Visit 17, Visit 19, Visit 21, and Visit 23

The following procedures are to be performed according to Table 3

- ACQ6 assessment (performed at Visit 15, Visit 16, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23)
- SGRQ assessment (performed at Visit 15, Visit 17, Visit 19, Visit 21, Visit 23)
- PGI-C assessment (performed at Visit 16, Visit 17, Visit 18, Visit 19, Visit 20, Visit 21, Visit 22, Visit 23)
- CGI-C assessment (performed at Visit 17, Visit 19, Visit 21, Visit 23)
- Asthma exacerbation assessment
- Brief physical examination and vital signs (performed at Visit 15, Visit 17, Visit 19, Visit 21, Visit 23)
- Urine pregnancy test (performed before dosing at Visit 15, Visit 17, Visit 19, Visit 21, Visit 23)
- Pre- bronchodilator spirometry (performed at Visit 15, Visit 17, Visit 19, Visit 21, Visit 23)
- Blood eosinophil count (performed at Visit 15, Visit 19, Visit 23)
- Collection of AEs

- Concomitant medication
- Administration of benralizumab
- Reduce the patient's background asthma controller regimen by one step if they meet the eligibility criteria outlined in Section 3.2.2.
- The recommended categorical reductions are given in Section 4.5.5, Table 4)
- A new prescription should be issued (ideally called directly into pharmacy) if the patient's current formulation is not amenable to the indicated reduction (eg, by reducing number of puffs of and ICS or ICS/LABA). The patient must be given written instructions regarding changes to their controller regimen, and should remain on the new regimen until the next clinic visit assessment, barring any interim worsening (see below)

Reminder: PEF must always be performed every morning before taking usual asthma medication

Please see Table 3 for additional details.

4.5.2 Interim status checks by telephone: Visit 16, Visit 18, Visit 20, and Visit 22

Further reductions in background medication should not be attempted at the interim telephone visits; however, background asthma controller medications may be stepped back up for a sustained increase in asthma symptoms as clinically indicated. The telephone visits will serve as status check on the following:

- Asthma compliance assessment and reminder: verify that the patient has accomplished the background medication reduction prescribed at the last clinic visit (if applicable). If the patient has not adopted the recommended step the reason should be listed on the CRF. If the failure to step-down was for a non-clinical issue (eg, did not get prescription filled), the site must evaluate the issue and help mitigate logistical obstacles.
- Assess the interim stability of the patients' asthma, with particular consideration given to any interim clinically significant asthma exacerbation requiring systemic corticosteroid. Any meaningful deterioration in the ACQ6 score (ie, ≥0.5 units) since from the patients most recent scheduled visit will be available for review and should also be considered. The patient's background medication should be returned to the previous step or higher step (s) if asthma control is determined to be meaningfully worse (see Section 4.5.6, Table 4).
- PGI-C assessment.
- Concomitant medication.
- Collection of AEs.

Please see Table 3 for additional details.

4.5.3 Peak flow alerts for potential loss of control during the reduction (and maintenance) periods

The site and the patient will be alerted if the AM PEF decreases by > 20% from the Visit 15 for ≥3 consecutive days. The patient must be contacted and evaluated by the site when a PEF alert is triggered.

4.5.4 Asthma controller therapy reduction algorithms

There are 5 scheduled per protocol reductions of the patients' standard of care background medication at Visit 15, Visit 17, Visit 19, Visit 21 and Visit 23 (spaced every 2 months) with the first reduction at the Visit 15, with subsequent attempts based on asthma control and exacerbation history since the previous reduction visit. Patients will be considered eligible for background medication reduction at every bi-monthly visit when all criteria below are met.

Criteria for Background Controller Medication Reduction at Visit 15 (all criteria must be met)

1. ACQ6 <1.5
2. No interim clinically significant exacerbation since the patient's last visit that required an OCS burst (or an increase in the patients' maintenance OCS dose) or a hospitalization for asthma
3. Investigator agrees that there is no clinical or other reason not to reduce*

Criteria for Background Controller Medication Reduction at Visit 17, Visit 19, Visit 21, and Visit 23 (all criteria must be met)

1. ACQ6 <1.5
2. No clinically meaningful deterioration in ACQ6 score since the patient's last clinic visit value (ie, change in ACQ6 from the most recent clinic visit value is < +0.5 units)
3. Since the patient's last clinic visit, no interim clinically significant exacerbation that requires an OCS burst (or an increase in the patients' maintenance OCS dose) or a hospitalization for asthma
4. Investigator agrees that there is no clinical or other reason not to reduce.*

*Background medication reductions **must be applied** when the asthma control and exacerbation criteria are met, unless the Investigator cites a specific clinical or other reason for not stepping down at a that time. The reason for not reducing background medication must be recorded in the CRF.

4.5.5 Approach to background medication reduction in eligible patients

Per protocol standard of care background medication reduction attempts are scheduled every 2 months during the reduction period. Consistent with the inclusion criteria for ANDHI, most patients enrolled in the ANDHI IP substudy are expected to currently be using an ICS/LABA combination ± other controllers (eg, LAMA, LTRA, theophylline, or OCS) at ANDHI IP

substudy baseline (Visit 15). A smaller proportion of patients may currently be using an ICS with an another non-LABA controller (s).

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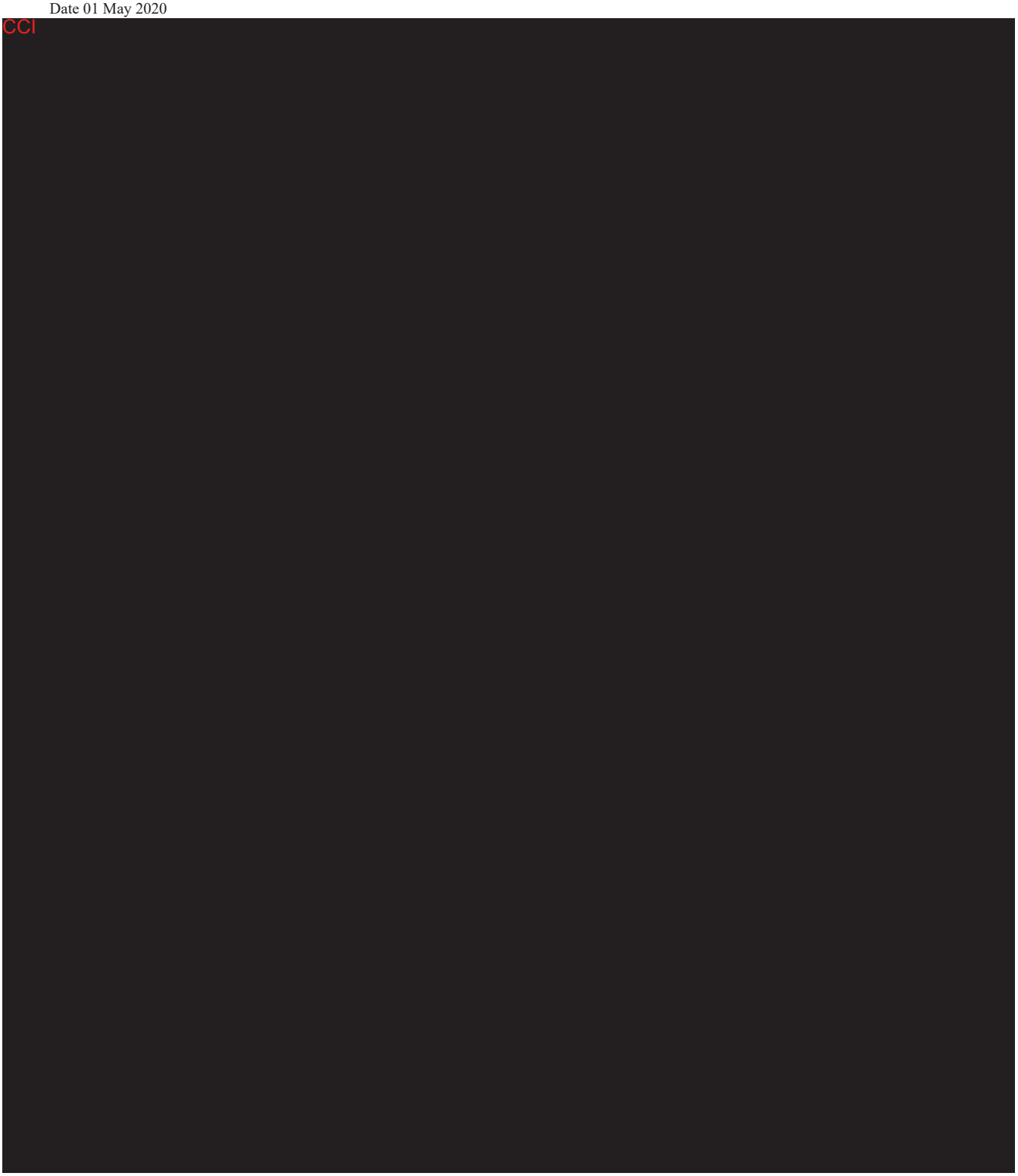

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4.5.6 Approach to worsening asthma control during the reduction period

The approach for controlling worsening asthma assessed either at the scheduled clinic visit or occurring in the interim between clinic visits, that does not respond to as needed short-acting bronchodilators includes either:

1. Step-up back up to a previously effective level of standard of care background asthma controller medication (see Table 4), OR
2. Receive a burst of OCS if clinically indicated for a severe exacerbation of asthma symptoms, OR
3. Both 1 and 2, as clinically indicated.

Patients who step up as a result of interim worsening, may resume per protocol background medication reductions when stable, at the Investigator's discretion.

4.6 Background standard of care asthma controller maintenance period (Begins after Visit 23 to Visit 27 [EOS])

4.6.1 Visit 23 (Week 64): No further background reduction period begins

No further attempts to reduce the patient's background asthma controller medications should be made after the day of Visit 23 through the EOS Visit 27; however, the patient's controllers may be stepped up if clinically indicated.

Benralizumab will continue to be dosed (Visit 23). Telephone Visits 22 and Visit 24 will serve as interim status checks to make sure that any indicated medication reduction at Visit 23 has been accomplished and that the patient's asthma is stable

Please see Table 3 for additional details.

4.6.2 Visit 27 (Week 80): End of ANDHI IP Substudy (EOS)

The following procedures are to be performed and/or data to be collected at Visit 27/EOS (please refer to Table 3 for details). At this Visit, Investigators should assess the adequacy of the asthma treatment regimen planned after study completion and discuss with the patient's treating clinician as appropriate.

- ACQ6 assessment
- SGRQ assessment
- PGI-C assessment

- CGI-C assessment
- Asthma treatment compliance assessment and reminder
- Asthma exacerbation assessment
- Brief physical examination
- Vital signs
- Collection of AEs
- Concomitant medication
- Urine pregnancy test
- Pre-bronchodilator spirometry
- PEF
- Blood eosinophil count

4.6.3 Approach to worsening asthma control during the maintenance period

The approach for controlling worsening asthma during the maintenance period as assessed either at the scheduled clinic visit or occurring in the interim between visits, that does not respond to as needed short-acting bronchodilators, is the same as for the reduction period:

1. step-up to a previously effective level of standard of care background asthma controller medication (see Table 4), OR
2. receive a burst of OCS if clinically indicated for a severe exacerbation of asthma symptoms, OR
3. both 1 and 2, as clinically indicated.

4.7 Premature investigational product discontinuation, or early withdrawal from study (IPD/WD) from the ANDHI IP substudy

The following procedures are to be performed and/or data to be collected at IPD/WD visit (please refer to Table 3 for details):

- Discontinuation of IP and complete IWRS/IVRS transaction
- ACQ6 assessment
- SGRQ assessment
- PGI-C assessment

- CGI-C assessment
- Asthma exacerbation assessment
- Brief physical examination
- Vital signs
- Collection of AEs
- Concomitant medication
- Asthma treatment compliance assessment and reminder
- Urine pregnancy test
- Pre-bronchodilator Spirometry
- Blood eosinophil count

5 STUDY ASSESSMENTS

The INFORM system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the CRF as specified in the CSP and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed CRF. A copy of the completed electronic CRFs will be archived at the study site.

5.1 Efficacy assessments

Efficacy assessments during the double-blind period and open label ANDHI IP substudy are described here. Additional information regarding efficacy assessments in the open label period is presented in Section 5.2.

5.1.1 Asthma exacerbations

Patients will be assessed for asthma exacerbations at on-site visits from Visit 5 until Visit 11 during double-blinded period, and Visit 15 until Visit 27 during the open label ANDHI IP substudy. Patients will be queried regarding any worsening of asthma that resulted in initiation of systemic corticosteroids (oral, IV, or IM), and/or urgent care visit or a hospitalization. The detail should be captured on the EXAC CRF.

For the purpose of the protocol, an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.

- An emergency room/urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per above).

- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

Worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or to the Investigator, or as indicated by an electronic diary alert based on a week with a pre-specified change in at least 2 of the following daily asthma control measures:

- Decrease in morning peak flow ≥15% on at least 2 successive days compared with previous 7 days

- An increase in total asthma symptom score of at least 2 units on at least 2 successive days compared with the average score for the previous 7 days

- A greater than 50% increase in number of occasions of rescue medication on at least 2 successive days compared with the average use for the previous 7 days

During the open label ANDHI IP substudy, the electronic diary alert is based on worsening PEF only. The site and the patient will be alerted if the AM PEF decreases by >20% from the Visit 15 baseline for ≥ 3 consecutive days. The patient must be contacted and evaluated by the site when a PEF alert is triggered. (Section 4.5.3)

The ePRO device will be programmed to alert both the patient and study center when pre-specified worsening thresholds are crossed.

Further details on asthma control measures are provided in Section 5.4.1.

Reasonable attempts should be made by the Investigator to bring the patient into the study center for evaluation of any asthma worsening, particularly when it results in additional treatment being prescribed. Study center evaluations for asthma worsening may occur as an unscheduled visit or as part of an ordinary center visit if the worsening happens to be coincident with a scheduled visit window; treatments initiated based on telephone contacts only should be noted in the source and relevant CRFs. A copy of the medical record should be

obtained for exacerbations evaluated and treated at non-study centers (eg, by the primary care healthcare professional or at an emergency department/hospital) and details entered into the exacerbation CRF in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the CRF.

The rules for determining the number and duration of asthma exacerbations during this study are presented in Section 8.4.1.1.

The patient may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the patient to do so.

5.1.2 On-site lung function assessments

General requirements

Lung function (FEV_1) at the study center will be measured by spirometry using equipment provided by central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Patients should withhold their SABA medication(s) for at least 6 hours prior to all scheduled lung function assessments. Twice daily LABA- or LAMA-containing therapies should be withheld for 12 to 24 hours and once daily LABA- or LAMA-containing therapies for >24 hours before spirometry. LTRA should be restricted for >24 hours and twice daily theophyllines should be withheld for at least 12 to 24 hours and once daily for >24 hours before spirometry assessments.

Options for handling patients who have inadvertently taken their asthma medication within the restricted window are described in Section 3.9.2.

Time of day for scheduled center visit spirometry

Spirometry testing should be initiated in the morning between 6:00 AM and 11:00 AM according to the schedule provided in Table 1 and Table 2. All post-randomization spirometry assessments should be performed within ±2 hours of the time at which the baseline pre-BD FEV_1 spirometry was performed at Visit 4.

Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the center. Forced expiratory maneuvers 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 maneuver from enrolment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the maneuver. Mouthpieces of the same dimension and shape should be used by the patient from enrolment throughout the study.

The forced expiratory maneuver (FEV_1) should start with a maximal inspiration and then 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 maneuver. 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 center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement for FEV_1, and the percentage of predicted normal (PN) value (Quanjer et al 2012) will be recorded.

Order of administration of usual asthma controller medication and IP relative to scheduled pre-bronchodilator spirograms.

The patient's usual morning asthma controller therapy and IP must not be given until after the pre-BD spirometry is complete.

Record keeping

A signed and dated copy of the pre-BD printout must be kept at the study center for source data verification. The printout must be marked with the study code, patient enrolment code, date and time of measurement, and visit number.

Spirometry references

The Global Lung Function Initiative equations will be used to determine the PN values and are pre-programmed into your spirometer (Quanjer et al 2012).

FEV_1 expressed as percent of the PN value will be calculated as follows:

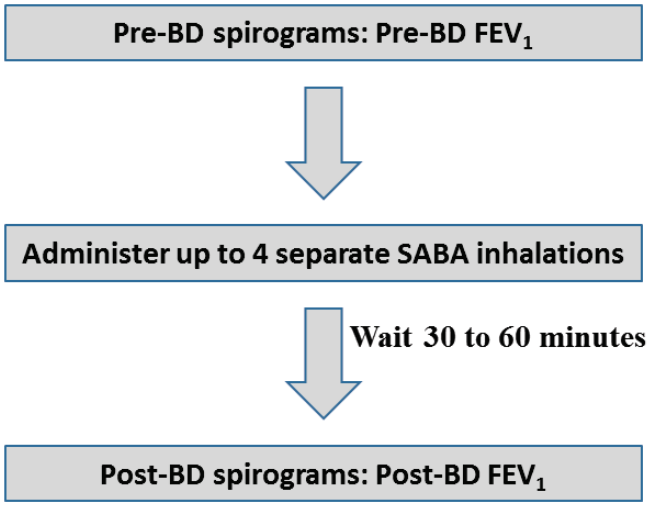
$$FEV_1\% \text{ of } PN = FEV_1 \text{ measured}/FEV_{1PN} \times 100$$

5.1.2.1 Reversibility testing

The procedure described in this section refers to the reversibility testing that can be performed at Visit 2 or Visit 3. If the reversibility is not met at Visit 2 or Visit 3 then the alternate criteria listed under Inclusion 7 may be considered.

Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 4 inhalations. It is highly recommended to use a spacer device for this procedure to ensure adequate delivery of bronchodilator to the airway. The algorithm for reversibility testing is outlined in Figure 3.

Figure 3 Reversibility testing algorithm



1. Verify with the patients the medication restrictions to allow the reversibility assessment have been met
2. After a gentle and complete expiration, albuerol, salbuterol, or levalbuterol is inhaled in one breath to TLC from a spacer device. The breath is then held for 5 to 10 seconds before the patient exhales. Four separate inhalations are delivered at approximated 30-second intervals. Post-BD spirometry should be performed 30 to 60 minutes later.
3. If the patient has not met reversibility criteria at Visit 2, a further attempt to demonstrate reversibility is allowed at Visit 3.

FEV_1 forced expiratory volume in first second; Post-BD post-bronchodilator; Pre-BD pre-bronchodilator; TLC total lung capacity; SABA Short-acting bronchodilators.

5.1.3 Peak expiratory flow assessment at home and calculation for peak flow variability inclusion

Details of PEF measurement are provided in Section 5.4.1.1.

Excessive diurnal peak flow variability >10% averaged over any 7 continuous days during the run-in period is one of the acceptable indicators of variable lung function for study inclusion (see Section 3.1). The result will be calculated centrally and will be made available to the site via the vendor portal. The average diurnal PEF variability is calculated from the twice daily PEF as ([day's highest minus day's lowest])/mean of the day's highest and the day's lowest) averaged over any 7 consecutive days during the run-in period. This value will be calculated programmatically as part of the PEF run-in for the patient and can be accessed via the eDiary portal.

5.1.4 Patient- and clinician reported outcomes

The ACQ6 will be assessed using an ePRO device at the site at Visit 1 and Visit 4 as part of the study inclusion criterion, and at the patient's home thereafter as an efficacy assessment. The PGI-S and PSIA will also be completed on the ePRO device on-site at Visit 4, then at home thereafter. The PGI-C will be completed at home subsequent to Visit 4. Assessments will be according to the schedules in Table 1 and Table 2 for double-blind period and in Table 3 for the open label ANDHI IP substudy.

The SGRQ, SF-36v2, SNOT-22 and CGI-C will be completed at on-site visits electronically. Assessments will be according to the schedules in Table 1 and Table 2 for double-blind period and in Table 3 for the open label ANDHI IP substudy.

5.1.4.1 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 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with a minimal clinically important difference (MCID). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

5.1.4.2 Asthma Control Questionnaire 6

The ACQ6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and SABA use) omitting the FEV_1 measurement from the original ACQ score.

Patients are asked to recall how their asthma has been during the previous week by responding to one bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ6 score is the mean of the responses. Mean scores of ≤0.75 indicate well-controlled asthma, scores between 0.75 and <1.5 indicate partly controlled asthma, and a score ≥1.5 indicates not well-controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

5.1.4.3 Short Form 36-item Health survey, version 2 (acute recall)

The Short Form 36-item Health survey, Version 2 (acute recall) (SF-36v2) is a 36-item, self-report survey of functional health and well-being, with 1-week recall period (QualityMetric 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks patients to rate how their current state of health compared to their state of health 1 year ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). Psychometrically-based physical and MH component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and MH-related quality of life.

Two types of thresholds have been developed for interpretation of SF-36v2 scores (Table 5). The first type is suitable for comparing group mean scores and is generally referred to as the MCID. The second type is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (QualityMetric 2011).

Table 5 Threshold values for the SF-36v2 scale and summary measures

	SF-36v2 score									
Threshold	**PCS**	**MCS**	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
Group difference	2	3	3	3	3	2	2	3	4	3
Individual change	3.4	4.6	4.3	3.4	6.2	7.2	6.2	6.9	4.5	6.2

BP Bodily Pain; GH General Health Perceptions; MCS mental health component summary; MH Mental Health; PCS physical component summary; PF Physical Functioning; RE Emotional Problems; RP Role Limitations due to Physical Health; SF Social Functioning; SF-36v2 Short Form 36-item Health survey, Version 2; VT Vitality.

5.1.4.4 Patient Global Impression of Severity assessments

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

5.1.4.5 Clinician and Patient Global Impression of Change assessments

The CGI-C and PGI-C instruments are used for an overall evaluation of response to treatment. The Investigator (clinician) and the patient will be asked to rate the degree of change in the overall asthma status compared to the start of treatment, ie, randomization visit. A 7-point rating scale will be used: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Changes; 5=Minimally Worse; 6=Much Worse and 7=Very Much Worse.

The CGI-C should be completed before other study assessments and IP administration per the schedule provided in Table 2 for double-blind period and in Table 3 for open label ANDHI IP substudy.; PGI-C is completed at home by the patient on the ePRO device.

5.1.4.6 Predominant symptom and impairment assessment

The objective of this assessment is to capture the degree to which patient-stated bothersome symptoms and impairments change over time. This is achieved by generating an individualized profile of symptoms and impairments ranked in order of importance by the patient (to be performed at Week 0). The initial PSIA (Part 1) asks patients to review a list of 8 concepts (including cardinal asthma symptoms, activities, awakenings, triggers) and select those which are typically bothersome. Part 2 of the initial PSIA asks patients to rank the concepts they selected in Part 1 in order of importance: from most important (ie, value of 1) to least important. The initial PSIA assessment produces a rank order list of bothersome concepts which will be evaluated in subsequent administrations. Part 3 of the PSIA, administered throughout the study period, will ask the patient to record the severity of each selected symptom or impairment using an 11-point numeric rating scale (NRS) where '0' ='did not experience' and '10' = 'worst I can imagine').

The PSIA administered throughout the study period will be individualized per the patient ranking. Every 7 days for the first 16 weeks of the treatment period patients will be asked to record the severity of the symptoms/impairments previously selected using the 11-point NRS. During this 16-week period patients will also be asked to record the degree to which each selected symptom changed since starting treatment using a 7-point change scale (eg, much worse, worse, a little worse, no change, a little better, better, much better). From Week 16 until EOT, patients will only complete the severity assessment (11-point NRS) every 28 days. Change items will not be administered following Week 16.

5.1.4.7 Sino-Nasal Outcome Test 22 Item

Nasal polyposis is typically characterized by eosinophilic inflammation (Fokkens et al 2012). The presence of nasal polyposis by patient medical history has recently been associated with an enhanced asthma treatment response to benralizumab (Fitzgerald et al 2017); however the effect of benralizumab on nasal polyp disease itself is unknown.

Patients with baseline chronic rhinosinusitis with nasal polyposis will participate in a substudy. The rhinosinusitis health status and quality of life of the patients will be assessed using the 22-item SNOT-22.

The SNOT-22 is a further modification of the SNOT-20 (Piccirillo et al 2002), where the scoring has been simplified by removing the importance rating. In addition to the normal 20-item version of the SNOT, 2 additional items were measured, nasal blockage, and loss of sense of taste and smell. The 22-question SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110 (higher scores indicate poorer outcomes); a MCID of 8.90 has been established (Hopkins et al 2009).

The SNOT-22 should be completed by the patient before other study assessments and IP administration per the schedule provided in Table 2**.**

5.2 Efficacy assessments in the open label ANDHI IP substudy

5.2.1 Assigning adapted GINA status

The main efficacy analysis of the ANDHI IP substudy is to evaluate the per protocol reduction of the patients' background asthma medication after initiating benralizumab, by adapted GINA step. We have qualified the GINA step assessment as 'adapted' for the purpose of this substudy, as it ignores the fact that patients are currently treated with an add-on biologic, which is step 5 by convention (GINA 2020). The adapted GINA status for the purpose of this substudy will be determined programmatically according to the concomitant medication-based algorithm described in the GINA 2020 guidelines in Appendix D.

5.3 Safety assessments

5.3.1 Laboratory safety assessments

Safety laboratory tests (see Table 6 for list of hematology and clinical chemistry parameters) will be performed at screening by a central laboratory. For information on methods of collection, assessment, labelling, storage, and shipment of samples please refer to the separate Laboratory Manual. Safety samples will be collected in accordance with the schedules provided in Table 1 and Table 2.

Clinical chemistry will be performed during the double-blind period at Visit 1 (Day -42) and at EOT/IPD. Clinical chemistry may be performed at subsequent visits as clinically indicated at the discretion of the Investigator, but will not be scheduled routinely. The circumstances around additional testing, or request for other safety tests, should be brought to the attention of the medical monitor.

Hematology will be performed at all on-site visits during the double-blind period and will include a blood sample for the eosinophil count; additional hematologic assessments will be obtained at screening and EOT (full hematology). During the open label ANDHI IP substudy period, hematology samples for eosinophil measurement will be performed centrally at selected Visits (Table 3).

Table 6 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Hematocrit	Alkaline phosphatase (ALP)
Hemoglobin (Hb)	Aspartate transaminase (AST)
Mean corpuscular volume (MCV)	Alanine transaminase (ALT)
Platelet count	Blood urea nitrogen (BUN)
Red blood cell (RBC)	Calcium
White blood cell (WBC) count with differential[a]	Chloride
	Creatinine
	Gamma-GT (gamma-glutamyl transpeptidase)
	Glucose
	Phosphorus
	Potassium
	Sodium
	Bilirubin, total
	Cholesterol, total
	Uric acid
	ALP

[a] Eosinophils, basophils and monocytes counts will be redacted from central laboratory reports except for Visit 1 and/or 2 as applicable (see Section 3.6).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3×ULN **or** total bilirubin (TBL) ≥2×ULN at any point post-randomization, please refer to Appendix B 'Actions required in cases of combined increase of Aminotransferase and TBL – Hy's Law (HL)', for further instructions.

5.3.1.1 Pregnancy test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in Table 1 and Table 2 for the double-blind period and in Table 3 for the open label ANDHI IP substudy.

- Serum beta-human chorionic gonadotropin (hCG): To be done at screening Visit 1 for WOCBP (analyzed at central laboratory).

- FSH: To be done at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months.

- Urine hCG: To be performed at the study center for WOCBP at Visit 4, Visit 6, Visit 7, Visit 8, Visit 9, Visit 10, and EOT (Visit 12)/IPD/WD, using a dipstick. Urine tests should be performed before IP administration at treatment visits. A positive urine test result must be confirmed by a serum beta hCG test.

- During the open label ANDHI IP substudy period, urine hCG test is performed at the study center for WOCBP at all dosing Visits: Visit 13, Visit 14, Visit 15, Visit 17, Visit 19, Visit 21, Visit 23, Visit 25, and at Visit 27 EOS/IPD/WD, using a dipstick. Urine tests should be performed before IP administration at treatment visits. A positive urine test must be confirmed by a serum beta hCG test.

5.3.1.2 Serology

HIV-1 and HIV-2 antibodies: To be done only at enrolment (Visit 1); test to be performed at the central laboratory.

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

5.3.2 Physical examination

Physical examination will be done in accordance with the schedules provided in Table 1 and Table 2 for the double-blind period and in Table 3 for the open label ANDHI IP substudy.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 6.3.

5.3.3 Electrocardiogram

Electrocardiograms are to be performed locally at Visit 1 to assess eligibility for this study, and then as clinically indicated during the treatment period.

A 12-lead ECG 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, and administration of the asthma-related medications and IP).

The Investigator or authorized delegate will be responsible for the overall interpretation as normal or abnormal; in case of an abnormal ECG the Investigator will assess the clinical significance of any potential ECG findings. In case of discrepancy between the Investigators interpretation and that provided by the ECG machine (if applicable), the Investigator's interpretation takes precedence and should be noted on the printout and recorded in the CRF. Two identical copies of the ECG will be produced, quality checked, and kept in case of further

need for re-evaluation. The ECG printouts will be signed and dated by the Investigator and stored at the study center.

ECG data and evaluation will be recorded in the CRF.

5.3.4 Vital signs

5.3.4.1 Pulse and blood pressure

Vital signs (pulse, blood pressure, respiration rate, and body temperature) are to be obtained in accordance with schedule provided in Table 1 and Table 2 for the double-blind period and in Table 3 for the open label ANDHI IP substudy.

Vital signs must be taken prior to IP administration, and, if possible, before blood drawing and usual asthma controller medication. Vital signs should also be taken prior to any spirometry, including bronchodilator administration if applicable for that visit.

5.3.4.2 Body temperature

Body temperature is to be recorded in degrees Celsius.

5.4 Other assessments

5.4.1 Daily asthma measures

Patients will be dispensed an ePRO device at Visit 2 and at Visit 13 as needed for patients who enrolled in the ANDHI IP substudy after the FU Visit 12 and may have returned their devices, which will allow home measurement of PEF and recording of Asthma Daily Diary data. Training in the correct use of the ePRO device will be provided when dispensed.

The Asthma Daily Diary will be completed each day from the evening of Visit 2 to the morning of Visit 11 and will serve to alert the patient to signs of worsening of asthma and to contact their physician (please refer to Section 5.1.1).

The Investigator/authorized delegate will check and reinforce patient's adherence to the Asthma Daily Diary at each visit as shown in Table 1 and Table 2. Further training on home PEF measurements will be provided as necessary.

The Asthma Daily Diary will include the following daily recordings:

- **Morning and evening home PEF data (**obtained from the home peak flow meter; see Section 5.4.1.1)
- Adherence to regularly scheduled asthma medication (once daily)

- Asthma control assessments:

  – Asthma symptom score in the morning and in the evening (see Section 5.4.1.2)

  – Number of times (occasions) that the patient needed to use their rescue medication in the morning and in the evening (see Section 5.4.1.3)

  – Nights with awakenings due to asthma and that required use of the rescue inhaler (see Section 5.4.1.4)

5.4.1.1 Peak expiratory flow assessment at home

Patients will measure PEF each morning after awakening and before taking their morning asthma medications, and each evening. Measurements should be taken at approximately the same time each day from Visit 2 until Visit 11, and recorded in the Asthma Daily Diary. For patients entering the ANDHI IP substudy, only morning PEF (and not evening) will be obtained from Visit 13 through EOS Visit 27.

The peak flow manoeuvre is similar to the forced expiratory manoeuvre described previously:

- The patient should ideally be standing or otherwise seated in an upright position.
- They should be instructed to breath in as deeply as possible.
- Place the peak flow meter in the mouth with the tongue under the mouthpiece and the lips closed tightly around it.
- Blow out as hard and fast as possible.
- After a few normal breaths, repeat the process 2 more times.

5.4.1.2 Asthma symptom score

Asthma symptom score (Bleeker et al 2016, Fitzgerald et al 2016) during night-time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary, from Visit 2 to Visit 11. Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night-time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

5.4.1.3 Rescue medication

The number of times (occasions) rescue medication inhalations and nebulizer treatments are taken will be recorded by the patient in the Asthma Daily Diary twice daily from Visit 2 to Visit 11. The number of occasions rescue medication inhalations and nebulizer treatments taken between the morning and evening lung function assessments will be recorded in the evening. The number of rescue medication inhalations and nebulizer treatments taken between

the evening and morning lung function assessments will be recorded in the morning. Rescue medication usage is captured in the daily diary as the number times (occasions) that the patient used his/her inhaler irrespective of number of puffs taken. Nebulizer use is the same as one occasion of rescue medication use.

5.4.1.4 Night-time awakenings due to asthma

From Visit 2 to Visit 11, night-time awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response. A night-time awakening due to asthma symptoms must have also resulted in rescue medication use, otherwise, it should not be recorded as an awakening due to asthma.

5.4.2 Weight and height

Weight and height will be measured, and BMI calculated in accordance with schedules provided in Table 1.

The patient's weight will be recorded in kilograms; height will be recorded in centimeters.

Weight and height measurements will be performed in light clothing and with shoes off.

5.4.3 Total Immunoglobulin E and allergen-specific Immunoglobulin E (Phadiatop)

A blood sample for assessment of total IgE and a qualitative assessment for the presence of allergen-specific IgE (ImmunoCAP Phadiatop) will be collected at randomization (Visit 4).

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

5.5 Pharmacokinetics (Not applicable)

5.6 Pharmacodynamics

5.6.1 Collection of samples

Samples for the analysis of peripheral blood eosinophils will be analyzed in a central laboratory as part of the routine hematology assessment (complete blood count).

5.7 Genetics (Not applicable)

5.8 Biomarker analysis

Optional blood samples will be collected if the patient consents, and may be analyzed for exploratory biomarkers including asthma biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes, and toxicity.

5.8.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient’s Last Visit, after which they will be destroyed. The results of this biomarker research will be

reported either in the Clinical Study Report (CSR) itself or as an addendum, or separately in a scientific report or publication.

5.8.2 Labelling and shipment of biological samples

The PI ensures that samples are labelled and shipped in accordance with the Laboratory Manual.

5.8.3 Chain of custody of biological samples

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

The PI at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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 documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

5.8.4 Blood eosinophil counts

Blood eosinophil counts will be followed periodically as a biomarker relevant to the benralizumab mechanism of action. Blood eosinophil counts will be assessed centrally (see Table 3).

5.8.5 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, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

If a patient withdraws consent to the use of donated biological samples, the patient may continue in the study, following all other procedures.

The PI:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented

- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6 SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 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 unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, 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 treatment has been administered.

6.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the FU period (through Day 182 [±7 days]). For patients who complete the open label ANDHI IP substudy, AE's will be collected through EOS Visit 27 (Day 560/Week 80).

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patients' last study Visit (at FU Visit 12 in the double-blind period or at EOS Visit 27 in the open label period) are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. 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.

In patients who directly transition to the open label ANDHI IP substudy, CRF follow-up data of unresolved AE's at Visit 11 will continue to be documented in the CRF.

6.3.3 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 (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- 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
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will 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 will also be assessed for other medication and study procedures. Note that 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 A.

6.3.5 Adverse events based on signs and symptoms

All AEs 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 CRF. 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.

6.3.6 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and/or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

In this study hematology is assessed throughout the treatment period; however, clinical chemistry is only obtained at screening and at the EOT Visit 11. The Investigator should obtain interim laboratory testing, as clinically indicated, to evaluate any treatment emergent AE. The Investigator should keep the medial monitor apprised of any additional standard clinical laboratory testing; the need for any specialized testing including imaging should be discussed with the medical monitor.

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.

6.3.7 Hy's Law

In this study, clinically chemistry is scheduled during screening and the EOT (of double-blinded period and open label period); interim assessments during the treatment period are obtained only as clinically indicated. Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3×ULN together with TBL ≥2×ULN may need to be reported as SAEs. Please refer to Appendix B for further instruction on cases of increases in liver biochemistry and evaluation of HL.

6.3.8 Disease under Study (DUS)

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness, and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Section 6.2
- The patient discontinues the study due to the sign or symptom

- The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

After randomization, asthma exacerbations should be recorded in the exacerbation CRF. If the exacerbation fulfills any of the above criteria, the sign or symptom should also be recorded as an AE.

6.4 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 CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 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 FU is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any FU information on a previously reported SAE within 1 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 INFORM, an automated email alert is sent to the designated AstraZeneca representative.

If the INFORM system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The Sponsor or Contract Research Organization (CRO) (depending on the country) is responsible for reporting SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening events within 7 days (with any follow-up information to be reported within a further 8 calendar days), and within 15 days for all other serious reports.

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that approved the trial.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File. For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidances. The reference document for definition of expectedness/listedness is the investigator's brochure (IB) for the AstraZeneca drug.

6.5 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

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 in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 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 (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks (approximately 5 half-lives) following the last dose.

Pregnancy of the patients' partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (approximately 5 half-lives) after the last administration of IP.

6.7 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 study drug 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 recognized 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, wrong syringe provided to site staff

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated
- Drug not stored as instructed eg, kept at room temperature when it should be kept in the fridge
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 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 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of hypersensitivity reactions

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available at the clinical research site where IP is administered. Study personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix C.

Anaphylaxis will be defined as a serious reaction that is rapid in onset (minutes to hours) and that may result in death (Sampson et al 2006). Anaphylaxis to an IP that the patient has not been previously exposed to (such as benralizumab) is deemed highly likely when Sampson criterion 1 is fulfilled. Sampson criteria 2 and 3 are also listed for completeness:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, AND AT LEAST 1 of the following: a) respiratory compromise or b) reduced blood pressure or symptoms of end-organ dysfunction

2. Two or more of the following that occur rapidly after exposure to a *likely allergen for that patient* including: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms

3. Reduced blood pressure after exposure

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 a minimum of 2 hours for the appearance of any acute drug reactions.

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

7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

All IP will be manufactured in accordance with Good Manufacturing Practice (GMP).

Benralizumab and placebo administered in the study will be a clear to opalescent, colorless to yellow solution. IP will be supplied by AstraZeneca.

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	30 mg/mL solution for injection in APFS, 1 mL fill volume	MedImmune
Placebo	Matching placebo solution for injection in APFS, 1 mL fill volume	MedImmune

7.2 Dose and treatment regimens

The IP will be administered at the study center on dosing visits and within visit windows as specified in Table 2 and Table 3.

Before investigational product administration

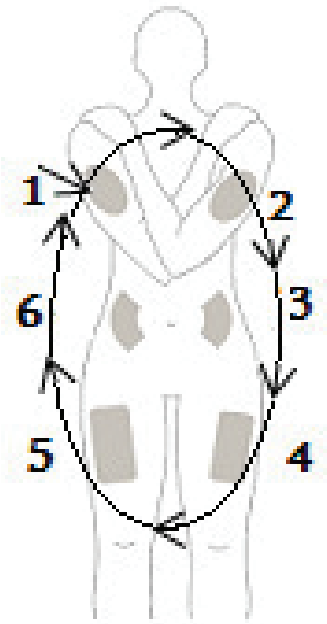
Prior to each IP administration:

- Investigator/authorized delegate will assess injection site as per standards of medical care.
- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 5.3.1.1).

Investigational product administration

The IP will be administered by the Investigator/authorized delegate. It is advised that the site of injection of the IP be rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 4).

Figure 4 Injection sites and rotation scheme



In the case when rotation of the injection site is not favorable for the patient and/or Investigator, the reason should be recorded in the source documents. The injection site of the IP should be recorded in the source documents and CRF at each treatment visit.

Further details on IP administration are provided to study centers. Investigational product administration must be carried out in line with the instruction.

After investigational product administration

After IP administration the patient should be observed for a minimum of 2 hours in case of any acute drug reactions.

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 (eg, viral illnesses)
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration

7.3 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines of each country participating in the study. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language as required.

The label will include the following information:

- Study code
- Investigational product/study drug dosage form, route of administration, and quantity of dosage units
- kit ID
- P Lot ID
- Expiry date
- Investigator Name (to be written on the label)
- E-code (to be written in the label)
- Sponsor name and contact details
- Directions for use
- Storage condition
- Standard statements required by regulatory authorities

7.4 Storage

Benralizumab/placebo is to be stored at the study center in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The IP must be kept in the original outer container and under conditions specified on the label (between 2 to 8°C [36 to 46°F], protected from the light).

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

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

Damaged IP should be documented via IWRS/IVRS (refer to IWRS/IVRS manual for further details).

7.5 Compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

The IP will be administered at the study center on dosing visits and within visit windows as specified in Table 2 and Table 3.

7.6 Accountability

The study drug provided for this study will be used only as directed in this CSP.

The study site staff will account for investigational study products dispensed and used in this study.

The monitor will account for investigational study products received at the site, unused study drugs, and for appropriate destruction. Certificates of delivery, destruction and/or return should be signed.

In the case of a malfunctioning APFS, the center should contact the study monitor to initiate a product complaint process according to applicable guidelines.

7.7 Concomitant and other treatments

Information about any treatment in the 3 months prior to the date of the informed consent, and all the concomitant treatments given during the study with reason for the treatment will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and

Table 2 for the double-blind period and in Table 3 for the open label ANDHI IP substudy.) and recorded in the CRF.

Note: To satisfy inclusion criterion 3 (Section 3.1.1), the history of treatment with asthma therapies at the protocol designated doses prior to Visit 1 should be documented in source and recorded in the CRF.

7.7.1 Other concomitant treatment

Medication other than that described in Section 3.9, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

8 STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until the primary database lock and CSP violators identified.
- Analyses for both periods of the study will be performed by AstraZeneca or its representatives.
- The primary database lock for the double-blind phase will be once all patients have completed the double-blind EOT Visit 11 of the study. A second database lock will be carried out once all patients entered in the open label ANDHI IP substudy have completed that part of the study.
- Two comprehensive Statistical Analysis Plans (SAPs) (for the double-blind and open label periods) will be finalized prior to unblinding of the data from the double-blind period of the study.
- Sections 8.2 to 8.5 primarily describe the statistical considerations for the double-blind treatment period of the study.
- Section 8.6 describes the statistical considerations for the open label period of the study.

8.2 Sample size estimate

The study is powered for the primary objective (to determine the effect of benralizumab on asthma exacerbations) through the primary endpoint (Annual Exacerbation Rate Reduction) as well as for the key secondary objective (to determine the effect of benralizumab on patient-reported disease specific quality of life) through the key secondary endpoint (the change from baseline to EOT in SGRQ up until and including the Week 24 visit).

Previous benralizumab Phase III asthma exacerbation studies (Bleeker et al 2016, Fitzgerald et al 2016) indicate that an annual placebo rate of 1.25 (and a negative binomial shape dispersion parameter of 1.2) and a 40% reduction between benralizumab and placebo may be expected. It seems furthermore reasonable to expect a difference of >4 points between benralizumab and placebo in the change from baseline SGRQ.

Under these assumptions, a 630-patient study randomized to benralizumab or placebo at a ratio of 2:1 (ie, 420 benralizumab treated and 210 placebo-treated patients) has approximately 97% power with respect to the primary endpoint and 87% power with respect to the key secondary endpoint (assuming a 2-sided significance level in both cases; see Section 8.5.1).

The sample size was estimated using nQuery+nTerim version 4.0.

8.3 Definitions of analysis sets

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

All patients randomized and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the Intention-to-treat (ITT) principle. Patients who withdraw consent, and assent when applicable, to participate in the study will be included up to the date of their study termination.

8.3.3 Chronic rhinosinusitis with nasal polyposis substudy analysis set

This analysis set is defined as the subset of patients with doctor diagnosed chronic rhinosinusitis and nasal polyposis included in the substudy assessing rhinosinusitis health status by SNOT-22 and who received any IP.

8.3.4 Safety analysis set

The safety analysis set will include all patients randomized who received any IP. Patients will be classified according to the treatment they actually received. A patient who has on one, or several occasions, received active treatment will be classified as active (eg, benralizumab 30 mg sc). Any deviations from the randomized treatment will be listed and considered when interpreting the safety data. All safety analyses will use this analysis set according to treatment taken.

8.4 Outcome measures for analyses

Definition of baseline

In general, the last measurement prior to the first dose of study treatment will serve as the baseline measurement. If time is collected, assessments performed the same day but at a time prior the first dose of study treatment will be included in baseline definition. If there is no value prior to the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

Visit 4 is the planned baseline visit, for all assessments carried out at a center, except for physical examination, PEF and SNOT-22. The baseline visit for physical examination will be Visit 1. The baseline for PEF is the average PEF over the last 7 days of the run-in period prior to randomization. The baseline for SNOT-22 is Visit 3.

The pre-BD FEV_1 measurement recorded at Visit 4 will be used as baseline FEV_1. If the Visit 4 pre-BD measurement is missing, the last non-missing pre-BD value before Visit 4 will be used as baseline instead.

Change from baseline will be calculated as the post-baseline assessment value minus the baseline assessment value. If either value is missing, then the change from baseline value will be missing.

In the ANDHI IP substudy, baseline for the analysis of the number of adapted GINA step category reductions will be the start of Visit 15 (before any reduction attempts) to the EOS Visit 27 (Day 560/Week 80).

8.4.1 Calculation or derivation of efficacy variables

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after randomization at Visit 4 to the conclusion of EOT Visit 11, inclusive.

8.4.1.1 Asthma exacerbations

Annualized rate of exacerbation over the 24-week treatment period will be the primary efficacy variable. An asthma exacerbation is defined as a worsening of asthma that leads to any of the criteria for asthma exacerbations detailed in Section 5.1.1.

8.4.1.1.1 Annualized rate of asthma exacerbations

In order to calculate the number of exacerbations experienced by a patient during the 24-week treatment period, the following rules will be applied:

- The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of a temporary increase in a stable OCS background dose, or start date of hospital admission, whichever occurs the earlier.

- The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable OCS background dose, or the date of discharge from a hospital, whichever occurs the later.

- Additional systemic corticosteroid treatments, emergency room/urgent care visits requiring use of systemic corticosteroids, or inpatient hospitalization due to asthma occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted for as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

- Maximum FU time for a patient is approximately 24 weeks; defined as the time from randomization to the date of Visit 11. For a patient lost to FU, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

For the production of summary statistics, the annual exacerbation rate in each treatment group will be calculated using the time-based approach below:

Annual Exacerbation Rate = 365.25*Total Number of Exacerbations / Total duration of FU within the treatment group (days)

In the statistical analysis, the logarithm of the patient's corresponding FU time will be used as an offset to adjust for patients having different exposure times during which the events occur.

8.4.1.1.2 Time to first exacerbation

Time from randomization to the first asthma exacerbation is a secondary efficacy variable and is derived as follows:

Start Date of first asthma exacerbation − Date of Randomization + 1.

The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the date of their last visit for the 24-week treatment period, or at the time point after which an exacerbation could not be assessed (for lost to FU patients).

8.4.1.2 St. George's Respiratory Questionnaire

The change in total score in SGRQ from baseline (Visit 4) will be assessed with the change to EOT being the key secondary variable. The SGRQ domain (symptoms, activity, impacts) scores will be calculated and summarized to evaluate the relative contribution of each domain to the total score.

8.4.1.3 Pre-bronchodilator forced expiratory volume in first second

The change in pre-BD FEV_1 from baseline (Visit 4) over the treatment period up to and including the EOT (Day 168/Week 24) and to other post-randomization visits will be secondary efficacy variables.

8.4.1.4 The Short Form 36-Item Health Survey, version 2 [Acute Recall]

The mean difference between benralizumab and placebo for the change from baseline to EOT in the following SF-36v2 component and domain scores will be efficacy variables:

- Physical component summary score (PCS)
- Mental health component summary score (MCS)
- Domain Scores:

– PF, RP, BP, GH, VT, SF, RE, and MH

The difference between benralizumab and placebo in the proportion of responders as defined in Table 5 will be additional efficacy variables.

8.4.1.5 Asthma Control Questionnaire 6

The change in score in ACQ6 from baseline (Visit 4) to post-randomization visits (including EOT) will be a secondary efficacy variable.

8.4.1.6 Patient Global Impression of Severity

The PGI-S is a single question asking the patient to rate the severity of their symptoms using a 6-point categorical response scale (0=no symptoms, 5=very severe symptoms). The change from baseline (Visit 4) in PGI-S score to post-randomization visits will be a secondary efficacy variable.

8.4.1.7 Patient and Clinician Global Impression of Change

The CGI-C and PGI-C – both secondary efficacy variables – are used for an overall evaluation of response to treatment. The Investigator (clinician) and the patient will be asked separately to rate the degree of change in the overall asthma status compared to the start of treatment, ie, randomization visit. A 7-point rating scale will be used: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Changes; 5=Minimally Worse; 6=Much Worse, and 7=Very Much Worse.

8.4.1.8 Predominant symptom and impairment assessment

Section 5.1.4.6 contains the description and recording of the patient's predominant symptoms. Change from baseline to the post-randomization visits assessments will be secondary efficacy variables.

8.4.2 Chronic rhinosinusitis with nasal polyposis substudy

The change in total SNOT-22 score from baseline Visit 3 to EOT Visit 11 will be a secondary efficacy variable for those in the chronic rhinosinusitis with nasal polyposis substudy.

8.4.3 Peak expiratory flow assessment at home

Morning and evening PEF assessments are described in Section 5.4.1; both are secondary efficacy variables.

8.4.4 Calculation or derivation of safety variable(s)

8.4.4.1 Safety variables

The following safety data will be collected: vital signs, physical examination and ECG, hematology, clinical chemistry, reported AEs and SAEs.

8.5 Methods for statistical analyses

Demographics and patient characteristics will be summarized by treatment group using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) and using the full analysis set. The analysis of the primary and secondary endpoints will include all data captured during the 24-week double-blind treatment period, defined as the period after randomization at Visit 4 and the conclusion of the EOT Visit, inclusive. In this context and in accordance with the principle of ITT, it is intended to collect complete data for all patients for the whole 24-week double-blind treatment period, including FU, even if they discontinue study treatment prematurely.

Descriptive statistics will also be provided for safety and efficacy data. Unless otherwise stated, the data analysis includes patients in the full analysis set. Descriptive statistics on continuous variables will be summarized by treatment group using n, mean, standard deviation, minimum, median and maximum, while categorical data were summarized using frequency counts and percentages. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used for the safety analysis, and the values collected for efficacy variables will be allocated to protocol-scheduled visits based on assigned windows. When assessing minimum/maximum increases or decreases during the study, all assessments, including unscheduled assessments will be used. For analysis assessing change from baseline, only patients with both baseline and at least 1 evaluable post-baseline measure will be included.

The prior medications, categorized according to the AstraZeneca Drug Dictionary, will be summarized by treatment group as frequency and percentage of patients reporting usage.

The concomitant medication will be categorized according to the AstraZeneca Drug Dictionary. The frequency and percentage of patients taking concomitant medications and non-drug therapies during the treatment period will be summarized by drug class and drug name using the Anatomical Therapeutic Chemical (ATC) code.

8.5.1 Testing strategy to account for multiplicity considerations

To account for multiplicity to test one primary variable and one key secondary variable, the following hierarchical testing strategy to control for the overall type-1 error (0.05) will be adopted:

- Initially, test the annualized asthma exacerbation rate at the 5% level
- If annualized asthma exacerbation rate is positive (ie, the p-value for the primary analysis is less than or equal to 0.05) then test SGRQ at the 5% level

8.5.2 Analysis of the primary variable

The primary efficacy variable is the annualized rate of asthma exacerbations.

The exacerbation rate on benralizumab will be compared to the exacerbation rate on placebo using a negative binomial model and the full analysis set. The response variable in the model will be the number of asthma exacerbations over the 24-week treatment period. The model will include covariates of treatment group, number of exacerbations in the year before the study, center/region and the use of maintenance OCS (yes/no). The logarithm of the FU time will be used as an offset variable in the model. The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and 2-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will also be presented. The same analysis will be performed for the patients with hospitalization and/or emergency room visit.

8.5.3 Analysis of the secondary variables

8.5.3.1 Analysis of the key secondary efficacy variable

The key secondary efficacy variable is change from baseline (Visit 4) in SGRQ to the EOT Visit 11 (Week 24).

The change from baseline (Visit 4) in SGRQ at the EOT Visit 11 will be compared between the 30 mg benralizumab group and placebo using a repeated measures analysis on patients with a baseline SGRQ and at least 1 post-randomization SGRQ in the full analysis set. The dependent variable will be the change from baseline in SGRQ at the post-baseline protocol-specified visits (up to the EOT Visit). Treatment group will be fitted as the explanatory variable, the use of maintenance OCS, number of exacerbations in the year before the study, center/region, visit and treatment×visit interaction as fixed effects and baseline SGRQ as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead.

8.5.3.2 Analysis of other secondary efficacy variables

Other secondary efficacy variables include:

- The change from baseline (Visit 4) in FEV_1 over the treatment period (up to and including Week 24)

The change from baseline (Visit 4) in FEV_1 over the treatment period (up to and including Week 24) will be compared between the 30 mg benralizumab group and placebo using a repeated measures analysis on patients with a baseline pre-BD FEV_1 and at least 1 post-randomization pre-BD FEV_1 in the full analysis set. The dependent variable will be the change from baseline in pre-BD FEV_1 at all post-baseline protocol specific visits. Treatment group will be fitted as the explanatory variable, the use of maintenance OCS, number of exacerbations in the year before the study, center/region, visit and treatment*visit interaction as fixed effects and baseline pre-BD FEV_1 as a covariate. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead.

- Change from baseline to each post-randomization assessment in FEV_1

From the model above, contrasts will be used to obtain estimates of the treatment differences at each time point separately up to and including the EOT.

- Time to first asthma exacerbation

Time to first asthma exacerbation will be analyzed using a Cox proportional hazards model with the covariates treatment, OCS use, number of exacerbations in the year before the study, and center/region.

- Change from baseline in ACQ6

From a model similar to the one used for FEV_1 contrasts will be used to obtain estimates of the treatment differences at each time point separately up to and including the EOT.

- Change from run-in baseline in morning and evening PEF

From a model similar to the one used for FEV_1 contrasts will be used to obtain estimates of the treatment differences at each time point separately up to and including the EOT.

- Change from baseline in SGRQ

From a model similar to the one used for FEV_1, contrasts will be used to obtain estimates of the treatment differences at each time point separately up to and including the EOT.

- Change from baseline in SF-36v2 (acute) PCS, MCS, and domain scores

From a model similar to the one used for FEV_1 contrasts will be used to obtain estimates of the treatment differences at each time point separately up to and including the EOT.

- Change from baseline in PGI-S

Patients showing an improvement on the PGI-S at the EOT will be analyzed using a logistic regression model with covariates of treatment, baseline PGI-S, the use of maintenance OCS, number of exacerbations in the year before the study, and center/region. The percentage and number of patients in each change category will be summarized over time. In addition, the number and percentage of patients within each change category demonstrating how patients change their categories throughout the study will be presented.

- PGI-C at each assessment post-randomization

Patients with a PGI-C much improved and very much improved will be analyzed using a logistic regression model with covariates of treatment, the use of maintenance OCS, number of exacerbations in the year before the study, and center/region. The percentage and number of patients in each category will be summarized over time. In addition, the number and percentage of patients within each category demonstrating how patients change their categories throughout the study will be presented.

- CGI-C at each assessment post-randomization

Patients with a CGI-C much improved and very much improved will be analyzed using a logistic regression model with covariates of treatment, the use of maintenance OCS, number of exacerbations in the year before the study, and center/region. The percentage and number of patients in each category will be summarized over time. In addition, the number and percentage of patients within each category demonstrating how patients change their categories throughout the study will be presented.

- PSIA at each assessment post-randomization

The patient's top (top 3 ranked) PSIA symptoms or impairment recorded as better, much better or no symptom or impairment will be analyzed using a logistic regression model with covariates of treatment, the use of maintenance OCS, number of exacerbations in the year before the study, and center/region. The percentage and number of patients in each category will be summarized over time. In addition, the number and percentage of patients within each category demonstrating how patients change their categories throughout the study will be presented. Other descriptive presentations of these data will be performed as pre-specified in the SAP.

As supportive analyses to the repeated measures analyses the responder variables for SGRQ, SF-36v2, ACQ6, and SGRQ component and domain scores will be analyzed as for the PGI-C, CGI-C and PGI-S endpoints.

8.5.3.3 Analysis for the chronic rhinosinusitis with nasal polyposis substudy

The change from baseline at each time point for the SNOT-22 score will be compared between benralizumab and placebo using a repeated measures analysis. As supportive analyses to the repeated measures analyses the number and percentage of SNOT-22 responders will be analyzed by the reported MCID for this tool.

8.5.3.4 Analysis of safety variables

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number of patients with events and percentages will be tabulated by preferred term and system organ class. An event that occurred once or more times during the study treatment period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all patients in the Safety set. Adverse events will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a patient report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the patient's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation, and commonly occurring AEs will be summarized in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to study discontinuation will be summarized for each treatment group as applicable.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarized.

Vital sign data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarized.

Baseline ECG data will be summarized according to status normal or abnormal, and if abnormal: clinically significant YES or NO. The diagnosis for all abnormal ECGs will be listed. There are no scheduled treatment period ECG assessments.

8.5.4 Subgroup analysis

Full details of any subgroup analyses will be pre-specified in the SAP.

8.5.5 Interim analysis

No interim analyses are planned.

8.5.6 Sensitivity analysis

Full details of any sensitivity analysis will be pre-specified in SAP.

8.5.7 Exploratory analysis

8.5.7.1 Analysis of biomarker data

Biomarker data will be analyzed and reported separately to the CSR.

8.5.7.2 Analysis of asthma control assessments

The proportion of time that the patient achieves target asthma control (eg, well-controlled weeks) will be analyzed using control definitions aligned with asthma guidance.

(GINA 2018; Reddel et al 2009) and based on a composition of daily diary measures (see Section 5.4.1).

Details of the analysis of asthma control assessments (see Sections 5.4.1.2 to 5.4.1.4) in support of the primary analysis will be pre-specified in the SAP.

8.6 Statistical analyses pertaining to the open label ANDHI IP substudy

8.6.1 Summary of the ANDHI IP substudy objectives and relation to the ANDHI controlled study

The open label ANDHI IP substudy of the main ANDHI study is designed to assess the potential for benralizumab treated patients to reduce their standard of care asthma controller regimen while maintaining asthma control. The ANDHI IP substudy will be managed under a separate SAP from the ANDHI controlled study. The ANDHI controlled study will be analyzed and distributed as described above in Sections 8.1 through 8.5 once all ANDHI data are collected and cleaned including a freezing of these data. The results of the ANDHI IP substudy will be reported by way of addendum to the ANDHI CSR.

The main outcome variables for the ANDHI IP substudy are the number of reductions in asthma controller medications and the number of adapted GINA step category reductions by the patient from Visit 15 to EOS (Visit 27). The main outcome measures are: the proportion of patients with at least one reduction in asthma controller medication from Visit 15 to EOS (Visit 27); the proportions of patients with the number of adapted GINA step category reductions ≥X, where X is ranging from 1 to 4; and the distribution of the number of adapted GINA step reductions where X is ranging from 0 to 4 (where 0 includes no change and any increase in adapted GINA step category).

The main outcome measures will be summarized overall and by ANDHI double-blind (DB) treatment group (benralizumab versus placebo) and repeated by asthma control status at EOS (Visit 27). For all of these summaries, proportions will be estimated with nominal 95% CIs derived using the exact Clopper-Pearson method. Specific reductions in ICS dose category

(high to medium/low dose; medium to low dose); and discontinuation of LAMA, LTRA, LABA or theophylline will also be quantified.

Selected asthma efficacy measures from the ANDHI DB phase (eg, ACQ6, SGRQ, pre-bronchodilator forced expiratory volume [pre-BD FEV_1] and weekly mean morning peak expiratory flow [PEF]), will be assessed from Visit 15 of ANDHI IP substudy and from the baseline of ANDHI controlled study (Visit 4) though EOS Visit 27. Baseline characteristics will be compared for subgroups of patients of particular interest: those never achieving sufficient asthma control to attempt reductions; and those achieving ≥2 reductions in asthma controller medications.

8.6.2 Sample Size Estimate for ANDHI IP substudy

The ANDHI IP substudy is not formally powered; all patients from the ANDHI study meeting the inclusion/exclusion criteria of this open label substudy will be eligible to enroll. Approximately 630 patients are expected to be randomized into the ANDHI study, however the actual number of patients rolling over into the open label period is not known.

Based on main outcome variable defined in Section 8.6.1, we estimate that 50% of patients with severe eosinophilic asthma will achieve at least one adapted GINA step reduction by the EOT. This assumption is based on the observation that approximately 60% of benralizumab Q8W patients in the Phase 3 exacerbation trials improved their ACQ6 score by at least the minimal clinically important difference (MCID) of 0.5 so would therefore be amenable to at least one background medication dose reduction.

Table 7 provides the expected precision for various sample sizes in terms of the width of the nominal 95% CIs (Clopper-Pearson); for example, if 300 patients are enrolled it is expected that the 95% CIs will span no more than 5.8% between the observed proportion and confidence limits (when observed proportion is 50%).

Table 7 Expected distance to lower/upper 95% confidence limits (Clopper-Pearson) from observed proportion of patients reducing their standard of care asthma controller regimen for the cumulative or actual number of adaptive GINA steps while maintaining asthma control

Proportion observed	Expected distance from observed proportion to lower/upper 95% confidence limits		
	N = 200	N=300	N = 500
5%	2.6% / 4.0%	2.2% / 3.1%	1.7% / 2.3%
10%	3.8% / 5.0%	3.2% / 4.0%	2.5% / 3.0%
20%	5.3% / 6.2%	4.4% / 5.0%	3.4% / 3.8%

30%	6.3% / 6.9%	5.1% / 5.5%	4.0% / 4.2%
40%	6.8% / 7.1%	5.6% / 5.8%	4.3% / 4.4%
50%	7.1% / 7.1%	5.8% / 5.8%	4.5% / 4.5%
60%	7.1% / 6.8%	5.8% / 5.6%	4.4% / 4.3%
70%	6.9% / 6.3%	5.5% / 5.1%	4.2% / 4.0%

Note: The N represented in the Table 7 span different assumptions around numbers of patients who might elect to enroll into ANDHI IP substudy.

8.6.3 Definition of analysis sets for ANDHI IP substudy

The main efficacy analysis set for the ANDHI IP substudy will include all enrolled patients who received at least one dose of open label benralizumab, attended V15 and are not receiving maintenance OCS for asthma at Visit 15 irrespective of their protocol adherence and continued participation in the study. A patient will be classified as receiving maintenance OCS at Visit 15 if the OCS started prior to or on the date of Visit 15 and was ongoing or stopped at Visit 15. Of note, patients using OCS as a rescue/reliever for an asthma exacerbation (and not as part of a maintenance regimen) at the time of Visit 15 will be included in the main efficacy analysis set. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

The main efficacy analyses for the ANDHI IP substudy will be based on the main efficacy analysis set.

The rationale for excluding maintenance OCS patients from the main and other efficacy analyses is based on the assumption that complete OCS cessation will be uncommon during ANDHI IP substudy period given the relatively short duration of the reduction period and so would not inform the primary or secondary efficacy objectives.

Supportive analyses will be carried out using a separate OCS dependent efficacy analysis set, which will include all enrolled patients who received at least 1 dose of open label benralizumab, attended Visit 15 of the ANDHI IP substudy and are receiving maintenance OCS for asthma at Visit 15.

The direct transitioning efficacy analysis set is defined as all patients in the main efficacy analysis set who receive their benralizumab dose at Visit 13 within a <16-week window of their last IP dose (benralizumab or placebo) in the ANDHI double-blind study.

Additional analysis sets may be defined in the SAP.

The safety analysis set will include all patients enrolled into the ANDHI IP open label substudy who received at least 1 dose of open label IP. All baseline characteristics (including demographics and medical history) and safety analyses will use this analysis set.

8.7 Outcome measures for analyses for the ANDHI IP substudy

Definition of baseline

There are 3 baseline visits that will be considered for analyses in this substudy:

- Most main and supportive efficacy analyses will use the last measurement prior to the start of the background asthma controller reduction phase at Visit 15 as the baseline measurement. Note, however, that the last prior measurement must not include any values from the ANDHI DB phase. In the case of morning PEF, the average of the last 7 consecutive days prior to Visit 15 with less than 4 missing daily diary entries will be used as baseline. Only PEF scores on or after Visit 14 will be considered for the baseline derivation. If there is no value prior to the start of the background asthma controller reduction phase, then the baseline value will not be imputed and will be set to missing.

- For the supportive efficacy analyses that assess changes in continuous asthma efficacy measures (including ACQ6, SGRQ, FEV_1 and morning PEF) from Visit 4 to the EOS Visit 27, changes will be taken from the ANDHI DB study baseline (Visit 4).

- For the safety analyses, measurements taken at Visit 13 will be used as baseline (ie, for vital signs).

- For blood eosinophil counts Visit 4 (from ANDHI DB study) will be used as baseline.

Change from baseline will be calculated as the post-baseline assessment value minus the baseline assessment value. If either value is missing, then the change from baseline value will be missing.

8.7.1 Calculation or derivation of efficacy variables for ANDHI IP substudy

8.7.1.1 Main ANDHI IP substudy objective: assessing reduction of the patients' standard of care background asthma controller regimen

The main outcome variables for the ANDHI IP substudy are the number of reductions in asthma controller medications and the number of adapted GINA step category reductions from the baseline at Visit 15 to the EOS Visit 27. The outcome measures are the proportion of patients with at least one reduction in asthma controller medication from Visit15 to EOS (Visit 27), proportions and distribution of patients achieving increasing numbers of adapted GINA category reductions from Visit 15 to EOS (Visit 27), presented overall, by ANDHI DB treatment group and repeated by asthma control status at EOS (Visit 27). A supportive measure is the proportion of patients with at least one asthma controller medication reduction by categories (ie, discontinuation of LAMA, LTRA, LABA or theophylline; reduction in inhaled ICS dose [HD-ICS/LABA to MD-ICS/LABA, MD-ICS/LABA to LD-ICS/LABA] and LD-ICS/LABA to LD-ICS and LD-ICS maintenance to ICS reliever at EOS Visit 27).

For patients receiving maintenance OCS for asthma at Visit 15, the following measures will be reported:

- Proportions of patients achieving 50/75/90/100% reduction in OCS dose from baseline (Visit 15) at EOS (Visit 27);
- Proportion achieving an OCS dose ≤5mg (prednisone equivalent dose) at EOS (Visit 27);
- Change and percentage change in OCS dose from baseline (Visit 15).

As an additional supportive analysis, patient characteristics at ANDHI baseline will be summarized for 2 subgroups of particular interest: patients who do not achieve asthma control at any of the 5 reduction visits (and so are ineligible to reduce); and patients who achieve ≥2 reductions in asthma controller medications (as described in detail in Section 3.2.1 of the SAP addendum) and remain controlled at EOS (Visit 27). Characteristics will include baseline demographics and respiratory history.

8.7.1.2 Calculation or derivation of other efficacy variables in the ANDHI IP substudy

Calculation of other efficacy variables from the ANDHI IP substudy Visit 15 through EOS Visit 27 including ACQ6, SGRQ, pre-bronchodilator FEV_1, weekly mean morning PEF, asthma exacerbation rate (and other exacerbation-related measures), CGI-C and PGI-C in asthma status will be performed as for ANDHI (see Sections 8.4). A similar approach will be used for changes from Visit 4 for patients in the direct transitioning efficacy analysis set.

8.8 Methods for statistical analyses for the ANDHI IP substudy

The analyses of demographics and patient characteristics are the same as in the ANDHI controlled study.

The primary objective of the ANDHI IP substudy is to describe the potential of benralizumab treated patients to reduce their background standard of care asthma controller regimen while maintaining asthma control. Given this, the principal baseline for main and other outcome variables is set to the first background medication reduction visit (Visit 15); the ANDHI baseline Visit 4 and subsequent controlled visit assessments will also be considered for additional context. There is no pre-design hypothesis or pre-determined tests or adjustment for multiplicity. The main outcome of the study will be point estimates with associated 95% CIs.

Descriptive statistics will also be provided for safety and efficacy data as discussed above for the ANDHI controlled study (Section 8.5).

8.8.1 Analysis of the main efficacy variable for the ANDHI IP substudy

The proportion of patients achieving at least one reduction in asthma controller medication from Visit 15 to EOS (Visit 27) will be summarized for the main efficacy analysis set.

Cumulative proportions of patients with at least X adapted GINA step reductions, where X ranges from 1 to 4 (ie ≥1, ≥2, ≥3, and 4 step reductions), from Visit 15 to EOS (Visit 27), will be summarized for the main efficacy analysis set.

The proportion of patients who achieve each number of GINA step reductions X (where X ranges from 0 to 4; and 0 includes no change and any increase in adapted GINA step category) will be summarized for the main efficacy analysis set.

All the above analyses will be presented overall and by ANDHI DB treatment group, and repeated by asthma control status at Visit 27.

A summary of the number of step reductions made by the number of opportunities to reduce (ie, where asthma was controlled as defined in Section 3.2.1 of the ANDHI IP SAP addendum and the PI determined the patient was eligible for reduction) will be provided for the main efficacy analysis set.

Additionally, the main efficacy variables will be analyzed using logistic regression modelling, including ANDHI DB treatment group (benralizumab or placebo) and baseline adapted GINA step (baseline step categories 2, 3, 4 or 5) as independent variables and with any reduction in asthma controller medication (Y/N) and the number of GINA category reductions (0 vs ≥1; ≤1 vs ≥2; ≤2 vs ≥3; ≤3 vs 4) as the response variables. The results of the analyses will be presented as odds ratios with associated 95% CI. The analysis will be provided for the main efficacy analysis set.

Asthma controller medication reductions and GINA step reduction details (number of reductions per patient; baseline adapted GINA step category and ANDHI treatment group) will also be listed.

8.8.1.1 Supportive analyses

In addition to the analyses of the main outcome variable, supportive analyses will be performed as described below.

Reduction of asthma controller medication:

The proportion (with 95% CI) of patients achieving any reduction in asthma controller medication at EOS (Visit 27) will be presented overall and by ANDHI DB treatment group, and repeated by asthma control status at Visit 27, for the main efficacy analysis set. Nominal 95% CIs will be derived using the exact Clopper-Pearson method. Proportions (with 95% CIs) achieving discontinuations / reductions in component medications will also be presented.

- For patients who were receiving LABA at Visit 15, the number and proportion (with 95% CIs) of patients discontinuing LABA by EOS (Visit 27).

- For patients who were receiving LAMA at Visit 15, the number and proportion (with 95% CIs) of patients discontinuing LAMA by EOS (Visit 27).

- For patients who were receiving LTRA at Visit 15, the number and proportion (with 95% CIs) of patients discontinuing LTRA by EOS (Visit 27).

- For patients who were receiving theophylline at Visit 15, the number and proportion of patients (with 95% CIs) discontinuing theophylline by EOS (Visit 27).

- For patients who were receiving ICS (as single / combination therapy) at Visit 15, the number and proportion (with 95% CIs) of patients achieving a ≥1 category reduction in ICS dose (i.e. from high to medium/low or medium to low) at EOS (Visit 27) from baseline (Visit 15).

- For patients who were receiving maintenance ICS (as single/combination therapy) at Visit 15, the number and proportion (with 95% CIs) of patients reducing to reliever ICS use by EOS (Visit 27).

Reduction of OCS dose for those on maintenance OCS at Visit 15:

The number and proportion (with 95% CIs) of patients achieving 50% / 75% / 90% / 100% reduction in OCS dose at EOS (Visit 27) from baseline (Visit 15) will be presented for the OCS-dependent efficacy analysis set. In addition, the number and proportion (with 95% CI) of patients achieving an OCS dose ≤5 mg (prednisone equivalent dose) at EOS (Visit 27) will be presented for the OCS-dependent efficacy analysis set. Nominal 95% CIs will be derived using the exact Clopper-Pearson method.

Summary statistics for absolute change in OCS dose from baseline (Visit 15) will be also presented at each intermediate visit (ie, Visit 17, 19, 21 and 23) for the OCS-dependent efficacy analysis set. Absolute dose changes will be calculated as prednisone equivalent doses.

8.8.2 Analysis of other efficacy variables

In order to further understand the effect that reducing the patients' background asthma medications may have on overall asthma control after benralizumab is initiated, certain asthma efficacy measures initiated in ANDHI will continue to be assessed during the open label ANDHI IP substudy period.

The other outcome measures will be analyzed descriptively and include change in ACQ6 and change in SGRQ from Visit 15 to Visit 27; PGI-C and CGI-C scores at scheduled visits between Visit 16 and Visit 27 (see Table 3), change in FEV_1 and PEF from Visit 15 to Visit 27, and number of asthma exacerbations between Visit 15 and Visit 27 (including annualised rate and time to first exacerbation).

To give further context into the effect of reduction of background asthma medication on asthma control, some outcome measures (including ACQ6 and SGRQ) will be assessed in continuously exposed patients (patients transitioning directly into the ANDHI IP substudy) from ANDHI controlled study baseline (Visit 4) until EOS Visit 27, including all intermediate scheduled measurements. This analysis will use the direct transitioning efficacy analysis set.

8.8.3 Analysis of safety variables.

All safety variables will be summarized descriptively, both overall and according to benralizumab treatment history in ANDHI. The safety analysis will be performed using the safety analysis set.

9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and IQVIA will review related documents with the investigational staff and also train them in any study specific procedures and INFORM, IWRS/IVRS, PROs, and other systems to be utilized.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.2 Monitoring of the study

During the study, an IQVIA representative will have contact with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the CSP, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The IQVIA monitor will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as ‘the last visit of the last patient undergoing the study’. Patients who do not participate in the open label ANDHI IP substudy, or who do not transition directly into the open label ANDHI IP substudy (on the same day as the double-blind EOT Visit 11), will complete a FU visit for final safety assessment at Day 182 (Week 26) and the final study visit will be the telephone FU visit (see Section 4.3.1).

For patients who participate in the ANDHI IP substudy, the final study visit will be at EOS Visit 27 (Day 560).

The study started in Q3 2017 and is expected to end approximately by Q3 2020.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with benralizumab.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by IQVIA, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at IQVIA.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious adverse event (SAE) reconciliation

Serious Adverse Event reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory (ies) internal or external to AstraZeneca.

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An IEC/IRB should approve the final CSP, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the CSP should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final CSP, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRB and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator’s Study File
- Ensure a copy of the signed ICF is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

Separate, optional, informed consent will be taken for the participation of qualifying patients for participation in the chronic rhinosinusitis with nasal polyposis substudy.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

If there are any substantial changes to the CSP, then these changes will be documented in a new version of the study protocol.

The new version of the CSP is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of CSPs.

AstraZeneca will distribute any new versions of the CSP to each PI(s). For distribution to Ethics Committee see Section 10.3.

If a change to a CSP requires a change to a center's ICF, AstraZeneca and the center's Ethics Committee are to approve the revised ICF before the revised form is used.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the CSP, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact the study monitor immediately if contacted by a regulatory agency about an inspection at the center.

11 LIST OF REFERENCES

Bateman et al 2010

Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: The relationship between current control and future risk. American Academy of Allergy, Asthma & Immunology. 2010;125(3):600-08.

Bleeker et al 2016

Bleecker ER, Fitzgerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β 2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. The Lancet 2016;388(10056):2115-2127.

Busse et al 2010

Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck B, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti–IL-5 receptor a antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol.
2010 Jun;125(6):1237-44.

Bousquet et al 1990

Bousquet J, Chanez P, Lacoste JY, Barnéon G, Ghavanian N, Enander I, et al. Eosinophilic inflammation in asthma. N Engl J Med. 1990 Oct 11;323(15):1033-9.

Di Franco et al 2003

Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Bacci E, Dente FL, et al. Analysis of sputum cell counts during spontaneous moderate exacerbations of asthma in comparison to the stable phase. J Asthma. 2003 Apr;40(2):155-62.

Fitzgerald et al 2016

Fitzgerald JM, Bleecker ER, Nair P, Korn S, Ohta K., Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. The Lancet 2016;388(10056):2128-2141.

Fitzgerald et al 2017

FitzGerald JM, Bleecker ER, Menzies-Gow A, Zangrilli JG, Hirsch I, Metcalfe P, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med. 2017 Sep 8. pii: S2213-2600(17)30344-2.

Fokkens et al 2012

Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012 Mar;50(1):1-12.

Goldman et al 2017

Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017 Sep;33(9):1605-1613.

GINA 2018

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) Updated 2018. Available from: URL: http://ginasthma.org.

GINA 2020

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) Updated 2020. Available from: URL: http://ginasthma.org.

Hopkins et al 2009

Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009 Oct;34(5):447-54.

Horn et al 1975

Horn BR, Robin ED, Theodore J, Van Kessel A. Total eosinophil counts in the management of bronchial asthma. NEJM. 1975;292(22):1152-1155.

Jones et al 1991

Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. RespirMed. 1991;85 Suppl B:25-31.

Jones et al 2009

Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Leidy NK. Development and first validation of the COPD Assessment Test. Eur Respir J 2009, 34: 648–654.

Juniper et al 2006

Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006 Apr;100(4):616-21.

Kolbeck et al 2010

Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti–IL-5 receptor a mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. J Allergy Clin Immuno. 2010, Jun;125(6):1344-53.

Laviolette et al 2013

Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA, Effects of benralizumab on airway eosinophils in asthma with sputum eosinophilia. J Allergy Clin Immunol. 2013 Nov;132(5):1086–1096.e5.

Lieberman et al 2010

Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010 Sep;126(3):477-80.e1-42.

Masoli et al 2004

Masoli M, Holt S, Weatherall M, Beasley R. The dose-response relationship of inhaled corticosteroids in asthma. Curr Allergy Asthma Rep. 2004 Mar;4(2):144-8.

Miller et al 2005

Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function Testing. Eur Respir J 2005;26(1):153-61.

Molfino et al 2011

Molfino NA, Gossage D, Kolbeck R, Parker JM, Geba GP. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. Clin Exp Allergy. 2011;42;712-37.

NAEPP 2007

NAEPP 2007, National Asthma Education Prevention Program. Expert Panel Report 3:Guidelines for the Diagnosis and Management of Asthma. Available: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

Nair et al 2017

Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017 Jun 22;376(25):2448-2458.

Pham et al 2016

Pham T, Damera G, Newbold P, Ranade K 2016. Reductions in eosinophil biomarkers by benralizumab in patients with asthma. Respiratory medicine. 2016;111;21-29.

Piccirillo et al 2002

Piccirillo JF, Merritt MG, Richards ML. Psychometric and clinimetric validity of the 20-item Sino-Nasal Outcome Test (SNOT-20). Otolaryngology--Head and Neck Surgery. 2002;126(1);41-47.

Price et al 2015

Price DB, Rigazio A, Campbell JD, Bleeker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. The Lancet Respiratory Medicine. 2015;3(11), pp. 849-858.

QualityMetric 2011

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

Quanjer et al 2012

Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, Culver B, et al. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. 2012 Dec;40(6):1324-43.

Reddel et al 2009

Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009 180(1):59-99.

Sampson et al 2006

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

Takatsu et al 1994

Takatsu K, Takaki S, Hitoshi Y. Interleukin-5 and its receptor system: implications in the immune system and inflammation. Adv Immunol. 1994;57:145-90.

To et al 2012

To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. 2012. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC public health. 2012;12(1):p.1.

Toba et al 1999

Toba K, Koike T, Shibata A, Hashimoto S, Takahashi M, Masuko M, et al. Novel technique for the direct flow cytofluorimetric analysis of human basophiles in unseparated blood and

bone marrow, and the characterization of phenotype and peroxidase of human basophiles. Cytometry. 1999 Mar 1;35(3):249-59.

Wenzel 2012

Wenzel S E. Asthma phenotypes: the evolution from clinical to molecular approaches. 2012 May 4;18(5):716-25.

Zeiger et al 2014

Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Gossage D, et al, 2014. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. J Allergy Clin Immunol: In Practice. 2014;2(6):741-750.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

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).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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 intervention

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, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention 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 anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization.

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of 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 etiology such as the underlying disease, other drugs, 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 recognized 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 limited or insufficient information in the case, it is likely that 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.

Appendix B Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3×Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

AST or ALT ≥3×ULN **together with** TBL ≥2×ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

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

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4. Follow-up

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' FU and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used.

- Complete the 3 Liver CRF Modules as information becomes available.

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply

- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue FU and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  - If there is no significant change no action is required

  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in 4.2 Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix C Anaphylaxis: Signs and Symptoms, Management

1. INTRODUCTION

As with any antibody, allergic reactions to dose administration are possible. The clinical criteria for defining anaphylaxis for this study are listed in Section 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

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

2. CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS

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, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST 1 OF THE FOLLOWING

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, 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, generalized hives, itch-flush, swollen lips-tongue-uvula).

(b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, 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): Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that patient’s baseline.

3. SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- 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
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps, and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

4. MANAGEMENT OF ACUTE ANAPHYLAXIS

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.

4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place patient in recumbent position and elevate lower extremities.

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

(c) Consider nebulized β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (eg, dopamine).

(f) Consider glucagon for patient taking β-blocker.

(g) Consider atropine for symptomatic bradycardia.

(h) Consider transportation to an emergency department or an intensive care facility.

(i) For cardiopulmonary arrest during anaphylaxis, high dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from Sampson et al 2006

5 REFERENCES

Johansson et al 2004
Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004; 113(5): 832-6

Appendix D Guidance on Assigning Adapted GINA Step Based on Asthma Concomitant Medications

- The table below will be used to map the patient's current asthma controller regimen to the appropriate adapted GINA step (this will be done programmatically and the table is provided for reference only)
- Note that the TOTAL daily dose of ICS, or any background use of OCS, are the most influential determinant of the patients' adapted GINA classification. ICS and OCS equivalency tables are provided below based on total daily dose (Table 8)

Table 8 Assigning adapted GINA[a] steps for the purpose of ANDHI IP

<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Benralizumab sc 30 mg every 8 weeks</td></tr>
<tr><td rowspan="4">No maintenance asthma controller regimen</td><td>Low daily dose ICS[b] as monotherapy</td><td>Low daily dose ICS/LABA</td><td>Medium daily dose ICS/LABA</td><td>High daily dose ICS/LABA</td></tr>
<tr><td>An LTRA[c] as monotherapy</td><td>Medium daily dose ICS as monotherapy</td><td>High daily dose ICS as monotherapy</td><td>Any maintenance OCS</td></tr>
<tr><td>Theophylline as monotherapy[e]</td><td>Low daily dose ICS + an LTRA</td><td></td><td></td></tr>
<tr><td></td><td>Low daily dose ICS + Theophylline[e]</td><td></td><td></td></tr>
<tr><td colspan="5">As needed asthma reliever regimen consistent with local practice,eg as needed SABA[d], as needed or low dose ICS-formoterol or low dose ICS taken whenever SABA is taken.</td></tr>
</table>

[a]This table lists only those controller and reliever classes essential to determining the adapted GINA 2020 step for programming purposes(e.g. LAMAs are not listed)
[b] ICS – inhaled corticosteroid,
[c] LTRA - Leukotriene inhibitor (eg, montelukast, zileuton);
[d] SABA – short-acting beta agonist,
[e] Theophylline is discussed in GINA 2020 Step 2 and Step 3 as 'not recommended' and 'less efficacious' options, respectively. Theophylline preparations were allowed in ANDHI and included in the table as a contingency.

Appendix E ICS/OCS equivalency tables

ICS equivalency tables for asthma patients age 12 and older[a]

Adults and adolescents (12 years and older)			
	Daily dose (mcg) – expressed as metered dose		
Drug	**Low**	**Medium**	**High**
Beclometasone dipropionate (CFC)	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>1000-2000	>2000

CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroids; pMDI: pressurized metered dose inhaler; n.a.: not applicable.
[a.] Adapted from GINA 2020.

OCS equivalency table for asthma patients

Oral corticosteroid	Approximate equivalence dose (mg)
Prednisone	10
Prednisolone	10
Cortisone	50
Hydrocortisone	40
Methylprednisolone	8
Betamethasone	1.2
Dexamethasone	1.5
Deflazacort	12

Appendix F Guidance on changes to study conduct due to pandemic, COVID-19 resurgence or other unforeseen disaster

Due to the disruptions caused by unforeseen crises such as the coronavirus disease 2019 (COVID-19) pandemic on the day-to-day activities of many people around the world including individuals involved in this study, either as study or site personnel or as study participants, changes to the conduct of the study may be required on a temporary or permanent basis, as described in the guidance in this appendix.

Because many study patients are currently or may become unable to visit the clinical sites for normal monitoring and due to the chronic nature of the indication being studied in this clinical trial, the study sponsor, AstraZeneca, has put in place a number of provisions to mitigate risks to clinical trial conduct arising as a consequence of the coronavirus outbreak and ensure patient safety during this unprecedented situation.

As the priority is the safety of our patients, it is necessary to implement these urgent safety measures so that we can maintain surveillance of any potential effects the therapy may have.

Investigational study sites must comply with local public health rules. A record must be kept of when specific COVID-19 local guidelines have been implemented, and AstraZeneca or their representative must be notified with details of the local guidance and dates of implementation for any alternative approaches as soon as possible.

Every effort should be made to follow the CSP. Protocol deviations beyond those measures outlined in this appendix cannot be preapproved. Any protocol deviations resulting from the COVID-19 situation should be recorded and prefixed with “COVID-19”.

Remote site monitoring will replace on-site monitoring visits when on-site monitoring visits are restricted per local guidance and this will continue until on-site visits can be resumed.

If a study participant is unable to attend clinic visits, and/or receive study intervention, the site staff should keep in close contact with the patient(s), preferably through telephone calls, to maintain awareness of their status.

Email communications from the IQVIA Central Monitoring Services (CMS), the ANDHI Portal and newsletters are to be checked for the latest guidance on these processes.

On-site visits for IP administration

On-site visits are to be conducted whenever it is possible to do so without putting patients or site personnel at undue risk, however such visits are to be kept as short as possible. Flexibility of ±15 Days in on-site visit window is permitted due to COVID-19; out-of-window visits due to COVID-19 must be reported by the site to the CRA and documented in writing via e-mail. This information will also be shared with the Medical Monitor by the local study team.

The IP, benralizumab 30 mg Q8W, is an approved biologic which has been shown to provide clinical benefits to severe eosinophilic asthmatic patients and therefore continuation of

treatment is intended to reduce the risk of asthma exacerbations of these patients. However, the risk versus benefit for patients must be considered for patients who may come in for on-site IP administration. Exceptionally, one missed IP dose will be accepted. New provisions for patient transportation via taxi to and from sites are being implemented (see "Possibility of reimbursement of exceptional expenses" below for details).

Remote (telephone) visits

If the scheduled on-site clinic visit is not possible, a telephone visit is to be done instead, and any assessments for that study visit that require the patient to be physically present at the study site (eg, FEV1 assessments and blood draws) will be skipped. During telephone visits, the usual clinic visit CRFs (eg, EXACA, AMRA) are to be completed including reason(s) for no reduction in an otherwise controlled patient and concomitant medications. In addition, a form-level free text comment should be entered, eg, "A clinic visit was not possible due to COVID-19 concerns, the visit was conducted by phone." Compliance is to be recorded and patients are to be reminded to continue entering information in their e-diary.

Under these circumstances, clinic visit assessments that require patient presence (eg, FEV1 assessment, blood draws) can be skipped; this information is to be recorded as described above. The procedures for conducting remote telephone visits are presented in Annex F1 of this appendix.

The ANDHI newsletter and website are to be checked for the latest guidance on conducting visit assessments including ePROs, and how to return devices to the site post study.

For patients who are able to do so and who are considered to be eligible, these remote visits may also include patient self-administration of IP; see "Self-administration of IP" below for details.

Conducting of study spirometry assessments during COVID-19

Concern has been raised that pulmonary function testing could represent a potential avenue for COVID-19 transmission due to the congregation of patients with lung disease and because of the potential for coughing and droplet formation surrounding pulmonary function testing procedures. It is therefore recommended that pulmonary function testing be limited to only those tests that are essential for immediate treatment decisions, that the type of pulmonary function testing be limited to the most essential tests when possible, and that measures to protect both the staff and individuals being tested should be put in place. Protective measures include personal protective equipment (PPE) that limits aerosolized droplet acquisition for staff and enhanced cleaning of the testing space such as wiping down surfaces with appropriate cleaners. Use of PPE should be considered in discussions with the infection control team.

Decisions regarding the conduct of pulmonary function tests need to balance the potential risks against the need for assessment of lung function to make treatment decisions.

Investigators and site staff are encouraged to consult the following resource for the most up-to-date guidance:
https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/novel-coronavirus.php

Electronic PRO collection process during COVID-19

Due to the COVID-19 situation, it may be necessary to collect certain ePRO questionnaires via telephone or video call instead of at an on-site visit. For such telephone visits, the following process is to be followed for administering the questionnaires over telephone in the local language. Site staff must read and understand the latest guidance on the process for contacting patients and completing the relevant questionnaires. Documentation that all site staff contacting patients by telephone have read and understood this guidance is to be filed in the Investigator Site File.

The provision has been made for the remote administration of the following ePRO questionnaires:

1. Asthma Control Questionnaire – Interviewer Administered (ACQ_IA; replacing ACQ6)
2. SGRQ
3. PGI-C (English version).

Exceptions to the method for obtaining Informed Consent

In cases where it will be necessary to obtain additional informed consent to receive IP at home and/or to self-administer IP or other changes to study procedures vis-à-vis those detailed in the initial ICF, and where this cannot be done using the customary signed ICF or ICF addendum, alternative procedures will be considered for obtaining it. Despite the implementation of these alternative procedures (eg, telephone contacts, followed by confirmation e-mails or validated electronic systems), the written consent will be obtained as soon as the situation permits, on the first occasion when the patient will be able to return to the clinical site. In the case of temporary verbal consent, the presence of an impartial witness is required to certify that the consent has been given and to put the date and signature on the informed consent document. It will be up to the Investigator to approve the method of selection of the impartial witness.

Home IP Delivery and administration

If necessary because on-site visits are no longer feasible, the administration of IP at the patient's home or other location by the Investigator, nurse, qualified site staff, or other caregiver can be considered. Details of off-site administration of IP are provided in Annex F1 of this CSP appendix.

Self-administration of IP

Alternatively, in certain cases it may be appropriate for patients to self-administer IP with per-patient prior approval from the sponsor. The overall risk associated with self- subcutaneous injection of IP was assessed as acceptable by the Study Sponsor for those patients who, in the Investigator's judgment, are considered to be suitable and able to do so. To minimize the risk,

prior to drug administration the participant will be provided with paper instruction as well as video training. The investigator or nurse will observe the study participant during the drug administration. Constant follow up with site staff will be maintained to ensure subject safety. Details of patient self-administration of IP are provided in Annex F1 to this appendix.

Investigational Medicinal Product (IP) Management

If an alternative delivery method of IP from the site to study patients is agreed upon, this is to be implemented using a suitable courier service. See Annex F1 for details on home IP delivery and self-administration for outline of full process.

Suitable remote communication mechanisms with the interested parties must be assured and adequate documentation of such procedures must be maintained. Such procedures may include, for example, telephone and/or video calls in order to check on the health of the patient, compliance with the IP prior to additional dispensing, confirming correct delivery and accounting of the IP, and to instruct patients on IP administration.

In the case of the use of specialized courier for the transport of IP to the patient's home, the use of personal data will be guaranteed according to the current legislation on privacy and will not be shared with the Sponsor.

Prior to doing this, study sites will be instructed to acquire verbal agreement from the patient, verification of correct shipping address and to confirm the patient's availability to receive the shipment.

The patient will receive a confirmation of receipt for IP that they are to sign and which will be filed in the site source documentation.

All possible costs due for the delivery of the IP to the subject (eg, specific courier) will be reimbursed to the site by the Sponsor.

Recording of AEs/SAEs in Relation to COVID-19

All AEs/SAEs should be reported in line with instructions for safety reporting documented in Section 6.3 of this CSP.

For patients experiencing signs and symptoms indicating infection, an attempt must be made to determine the infectious organism and the AE must be recorded accordingly. If a patient presents with clinical signs and symptoms consistent with COVID-19, a test must be requested where possible.

- If test is positive, record "COVID-19 confirmed" in the Adverse Event Field.
- If test is negative, record the AE/SAE signs and symptoms and/or other diagnosis in the Adverse Event Field(s).
- If test is not available and signs and symptoms, as judged by the investigator, are highly suspicious of COVID-19 infection, record "COVID-19 suspected" in the Adverse Event Field.

If other concurrent diagnoses, eg, pneumonia, please record as separate AEs.

If an AE/SAE is associated with COVID-19, the investigator should determine whether the participant's investigational product should continue, be interrupted, or stopped in accordance with Section 3.11 of this CSP.

Participant safety is paramount and the investigator should continue to reassess the risk/benefit of continued study involvement for each study participant.

Closure of a study site for containment measures from COVID-19

In the event that a site is impacted by the evolving COVID-19 pandemic in a way that results in an inability to perform study activities, AstraZeneca or their representative is to be notified as soon as possible.

In the event that a study site must close to the public for COVID-19 containment measures or where the experimental staff is unable to follow the patients, patients could be transferred to another active study site if practicable. Such a transfer may be either permanent or temporary based on the contingent situation and the patient's status. Adequate documentation must be made available and the procedure proving the transfer will be adequately archived among the study documentation. The procedure of transfer must be agreed upon with Sponsor prior its implementation.

Possibility of reimbursement of exceptional expenses

If additional expenses related to study participation must be borne by patients in order to implement urgent measures for their own safety, the Sponsor/CRO will reimburse these expenses subject to prior approval by the CRA. In order to avoid unnecessary direct contacts between subjects and study personnel, the preferable method will be the dispatch of receipts or delivery (when possible) by the subject to the study site which will accordingly invoice this amount to the Sponsor/CRO in order to reimburse expenses. Such expenses must be adequately documented.

In such cases, a "Letter of commitment" for payment/reimbursement will be sent to the study site, to supplement the existing contract between the parties.

The Principal Investigator and his staff will carefully record the actions taken in the source documentation.

Changes to Statistical Analyses

Additional sensitivity and supportive analyses to assess the impact of COVID-19 on the main and other efficacy endpoints may be defined. Full details will be included in the SAP.

Appendix G Signatures

ASTRAZENECA SIGNATURE

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI)

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development Site Representative

PPD

AstraZeneca

29 / May / 20

Date
(Day Month Year)

ASTRAZENECA SIGNATURE

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