Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3250C00065
Version	4
Date	17 October 2020

PONENTE: A Multicenter, Open-label, Phase 3b Efficacy and Safety Study of Benralizumab 30 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Patients with Severe Eosinophilic Asthma on High-Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy

Sponsor:

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EudraCT Number: 2018-000170-30

VERSION HISTORY

Version 4.0, 17 October 2020
This amendment includes the addition of a long-term follow-up visit 12 to 18 months after end of PONENTE treatment period where we will retrospectively collect data to understand changes in OCS dose and other background asthma therapy, and occurrence of asthma exacerbations under real-world conditions. We will also evaluate the recovery from adrenal insufficiency (AI) and the long-term impact of OCS reduction achieved during PONENTE study on the glucocorticoid toxicity. Appendix K has been created to describe all details related to the PONENTE Long Term Follow Up Visit substudy and consequently, the following sections include a reference to the newly created Appendix K: • *CSP Synopsis* • *Section 1.1 – Background and rationale for conducting this study* • *Section 1.4 – Study design* • *Section 2 – Study Objectives* • *Section 3 – Patient Selections, Enrollment, Restrictions, Discontinuation, and Withdrawal* • *Section 5 – Study Assessments* • *Section 6 – Safety Reporting and Medical Management* • *Section 7.8 – Concomitant and other treatments* • *Section 8.2 – Sample size estimate* • *Section 8.3 – Safety analysis set* • *Section 8.4 – Outcome measures for analyses* • *Section 8.5 – Methods for statistical analyses* *CSP Synopsis:* Added synopsis of the Ponente long term follow up substudy. *CSP Synopsis:* In the Primary objective regarding a ≥90%, ≥75%, and ≥50% reduction, added > 0% reduction. *List of Abbreviations and Definition of Terms:* Added abbreviations for coronavirus disease 2019 (COVID-19),, and Standard Operating Procedures (SOP). *Figure 1:* Updated to include the long term follow up visit 12- to 18-months after end of PONENTE treatment period. Removed text regarding fixed-visits only related to benralizumab dosing; as this may be confusing in context of the long term follow up substudy. *Section 2.1 Primary objective:* In the Primary objective regarding a ≥90%, ≥75%, and ≥50% reduction, added > 0% reduction.

Section 4 - Study plan and timing of procedures:

- Added new subsection, *4.4 PONENTE Long Term Follow Up Substudy,* to describe the addition of an long term follow up period to the PONENTE study, high-level objectives, and to refer to new Appendix K for details.
- Added new subsection, *4.5 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis*. The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.

Section 6.3.1 – Hy's Law: Added clarification that any potential Hy's Law case should be reported as SAE promptly (even before all other possible causes of liver injury have been excluded). This was added after direct feedback from a regulatory authority/ethics committee

Section 8.1 – Statistical considerations: Added clarification that there will be a second and separate SAP for the PONENTE Long Term Follow Up substudy

Section 8.5.3 – Analysis of safety outcomes: Corrected information regarding spaghetti plots will be for patients with Partial AI (not indeterminate results).

Section 11 – List of References: Added new reference to GINA 2020 -this is the current GINA report at the start of the long term follow up substudy. Previous reference to GINA 2018 will remain, as this was the version when the enrollment phase of the main study was active.

Appendix D – Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law: In Subsection 4.2 – potential Hy's Law criteria met, added clarification that any potential Hy's Law case should be reported as SAE promptly (even before all other possible causes of liver injury have been excluded). This was added after direct feedback from a regulatory authority/ethics committee

Appendix K: added new appendix – *PONENTE Long Term Follow Up Visit Substudy* to include details of the Long Term Follow Up visit. At this visit we will retrospectively collect changes in OCS dose and other background asthma as well as occurrence of asthma exacerbations since the PONENTE follow-up visit. In addition, we will assess recovery from AI in those patients who had partial or complete AI at the end of PONENTE study, and we will also assess the long term impact of the OCS dose reduction on glucocorticoid toxicity by means of GTI. Eligible patients who consent to have a Long Term Follow Up visit will be

treated according to standard practice; any changes to the maintenance asthma regimen are allowed, including further reductions of OCS as recommended in the GINA report. Consent for PONENTE Long Term Follow Up can be obtained at any time from the EOT visit to before the Long Term Follow Up visit. *Appendix L:* new appendix, *Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis*. The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption. *Whole document:* • Deleted mention of the supplemental protocol, as this mention has been replaced with the addition of the long term follow up substudy • 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.
Version 3.0, 06 November 2019
CSP Synopsis – Study Design: Clarified the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarified that the morning cortisol test is used to identify patients with normal cortisol levels or complete AI only; for indeterminate results, patients must undergo more specific testing via the ACTH stimulation test. *CSP Synopsis – Study Design:* updated terminology to clarify that for patients with cortisol levels below normal range and above the Complete AI range, "indeterminate results" replaced "Partial AI" in the case of morning cortisol tests; "Partial AI" is only used in the case of ACTH stimulation tests. The term "intermediate" is removed throughout. *CSP Synopsis – Study Design:* Added an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase, for patients who have Partial AI after the repeat morning cortisol test. *CSP Synopsis – Study Design Maintenance Phase:* Added a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Maintenance phase, for patients who have Complete AI or Partial AI at the end of the OCS Reduction phase.

CSP Synopsis: Added recommendation for patients who have Complete AI or Partial AI at the end of the Maintenance phase to be followed-up by an endocrinologist or other appropriate specialist, per Investigator discretion.

CSP Synopsis: All reference to the sputum substudy has been deleted. The sub-study was terminated due to low enrollment rate. Sputum samples already collected at the time of this amendment will not be analyzed, and will be destroyed.

CSP Synopsis – Exploratory Objective: Removed mention of sputum-related outcome measures from table listing exploratory objectives

CSP Synopsis –Statistical Methods: Added information that a database lock and analysis of all relevant data collected through end of OCS reduction phase may be performed after all patients have completed the OCS reduction phase Replaced "way of diagnosis," with "method of diagnosis."

Table of Contents: Updated all sections and page numbers to reflect new subsection(s)

Section 1.2 – Rationale for study design, doses, and control groups: Added mention of a supplemental protocol, which may be conducted to evaluate additional safety endpoints.

Section 1.4.3 – OCS Reduction phase (Week 4 onwards): Added clarifications on the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarified that the morning cortisol test is used only to identify patients with normal cortisol levels or complete AI only; for indeterminate results, patients must undergo more specific testing via the ACTH stimulation test.

Section 1.4.3 – OCS Reduction phase (Week 4 onwards): Updated terminology to clarify cortisol levels from morning cortisol test vs from ACTH stimulation test: for patients with cortisol levels below normal range and above the Complete AI range, "indeterminate results" replaced "Partial AI" in the case of morning cortisol tests; "Partial AI" is only used in the case of ACTH stimulation tests. The term "intermediate" is removed throughout.

Section 1.4.3 – OCS Reduction phase (Week 4 onwards): Added an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase, for patients who have Partial AI after the repeat morning cortisol test.

Section 1.4.4 – Maintenance Phase: Added a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Maintenance phase, for patients who have Complete AI or Partial AI at the end of the OCS Reduction phase.

Section 1.4.5 – Premature Discontinuation and Follow-Up Contact: Added recommendation for patients who have Complete AI or Partial AI at the end of the Maintenance phase to be followed-up by an endocrinologist or other appropriate specialist.

Section 1.4.6 – Sputum Sampling for Exploratory Biomarkers: made this section not applicable due to protocol amendment.

Figure 1: Added Footnote '7,' to describe the additional follow-up recommended for patients who have Complete AI or Partial AI at the end of the Maintenance phase

Section 2.4 – Exploratory Objectives: Removed mention of sputum-related outcome measures from table

Section 3.1 – Inclusion criteria: For inclusion criterion #3, the text was updated to clarify that *one* method of highly effective form of birth control must be used, and trade names were removed, based on feedback from prior regulatory submissions.

Section 3.2 – Exclusion Criteria: - For exclusion criterion #19, the following wording*: Influence the findings of the study or the interpretation* was replaced with: *Confound the study result; or would impact the scientific validity of the data outcome,* based on feedback from prior regulatory submissions.

Section 4 – Study Plan and Timing of Procedures – Table 1: Sputum induction row and Footnote 'n' updated to note that the sputum study is no longer applicable due to protocol amendment.

Section 4 – Study Plan and Timing of Procedures - Table 1: Footnote 'q' updated to remove sputum collection.

Section 4 – Study Plan and Timing of Procedures - Table 1: In the Morning cortisol testing row, an additional test was added to the "Maintenance Phase benralizumab visit" and "EOT visit" columns. Footnote 'r' was added.

Section 4.2.1 – Induction phase: Deleted mention of baseline sputum sample collection

Section 4.2.2 – OCS Reduction Phase: Added clarifications on the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarified that the morning cortisol test is used to identify patients with normal cortisol levels or complete AI only; for indeterminate results, patients must undergo more specific testing via the ACTH stimulation test.

Section 4.2.2 – OCS Reduction Phase: Updated terminology to clarify cortisol levels from morning cortisol test vs from ACTH stimulation test: for patients with cortisol levels below normal range and above the Complete AI range, "indeterminate results" replaced "Partial

AI" in the case of morning cortisol tests; "Partial AI" is only used in the case of ACTH stimulation tests. The term "intermediate" is removed throughout.

Section 4.2.2 – OCS Reduction Phase: Added an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase, for patients who have Partial AI after the repeat morning cortisol test.

Section 4.2.3 – Maintenance phase: Added a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Maintenance phase, for patients who have Complete AI or Partial AI at the end of the OCS Reduction phase.

Section 4.3 – Follow-up period: Added recommendation for patients who have Complete AI or Partial AI at the end of the Maintenance phase to be followed-up by an endocrinologist or other appropriate specialist.

Section 5.1.2 – OCS dose titration: Added clarifications on the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarified that the morning cortisol test is used to identify patients with normal cortisol levels or complete AI only; for indeterminate results, patients must undergo more specific testing via the ACTH stimulation test.

Section 5.1.2 – OCS dose titration: Updated terminology to clarify cortisol levels from morning cortisol test vs from ACTH stimulation test: for patients with cortisol levels below normal range and above the Complete AI range, "indeterminate results" replaced "Partial AI" in the case of morning cortisol tests; "Partial AI" is only used in the case of ACTH stimulation tests. The term "intermediate" is removed throughout.

Section 5.2.1 – HPA axis evaluation: Added clarifications on the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarified that the morning cortisol test is used to identify patients with normal cortisol levels or complete AI only; for indeterminate results, patients must undergo more specific testing via the ACTH stimulation test.

Section 5.2.1 – HPA axis evaluation: Updated terminology to clarify cortisol levels from morning cortisol test vs from ACTH stimulation test: for patients with cortisol levels below normal range and above the Complete AI range, "indeterminate results" replaced "Partial AI" in the case of morning cortisol tests; "Partial AI" is only used in the case of ACTH stimulation tests. The term "intermediate" is removed throughout.

Figure 2 – HPA axis evaluation: Footnote was updated to also reflect the additional HPA-axis assessments.

5.2.1.1 - Morning cortisol test (done at "OCS ≤ 5mg/day [morning cortisol]" visit): Added additional assessments to be conducted at the end of the OCS Reduction phase and OCS Maintenance phases. Added recommendation for patients with Complete AI or Partial AI at the end of the Maintenance phase, to be referred to an endocrinologist or other appropriate specialist per Investigator discretion.

5.2.1.2 – *ACTH stimulation test*: Added additional assessments to be conducted at the end of the OCS Reduction phase and OCS Maintenance phases. Added recommendation for patients with Complete AI or Partial at the end of the Maintenance phase, to be referred to an endocrinologist or other appropriate specialist per Investigator discretion.

Section 5.2.3 – Sputum collection and biomarkers: Section updated to note that the sputum substudy is no longer applicable due to protocol amendment.

Section 5.2.7 – Glucocorticoid toxicity index: Added clarification that only a subset of the domains from the composite GTI will be assessed in the PONENTE study.

Section 6.4 – Reporting of serious adverse events: Added new subsection, *6.4.1 Regulatory Reporting Requirements for SAEs* to reflect changes to the AstraZeneca global protocol template.

Section 8.4 – Outcome measures for analyses: Under the third Secondary efficacy Outcome variable, added "initial morning cortisol test," as an additional timepoint for reporting ACQ-6 scores.

Section 8.5.1 – Analysis of the primary variables: Added that patients who do not achieve 100% reduction in their daily OCS dose, the reason for no further reduction will be listed

Section 8.5.2.2 – ACQ-6: Added clarification to timepoint at which OCS dose equals 5mg.

Section 8.5.3 – Analysis of safety outcomes: Added the following, "Spaghetti plots may be produced for patients with indeterminate AI throughout the OCS reduction phase, showing cortisol levels over time."

Section 8.5.4 – Subgroup analysis: Updated the baseline OCS subgroups to the following 3 categories: Patients with baseline OCS dose >10 mg/day, >5 mg/day to ≤10 mg/day, and 5 mg/day

Section 8.5.4 – Subgroup analysis: Updated the baseline serum eosinophil count subgroups as in to the following 3 categories: Patients with baseline blood eosinophil count:

- <150/µL and ≥150/µL;
- <300/µL and ≥300/µL; and
- <150, ≥150 to <300, and ≥300 cells/µL

Section 8.5.5 – Interim review and Analysis: updated section title, and added details on the additional database lock which may occur after all patients have completed the OCS reduction phase.

Section 8.5.7 – Exploratory analysis: added the following: Baseline blood eosinophil counts may be further investigated by summarizing vs. baseline OCS dose and/or by region/country.

Section 8.5.7 – Exploratory analysis: deleted mention of sputum

Section 11 – List of References: Deleted Bafadhel et all 2012, and Pizzichini et al 1996, which related to the sputum study

Appendix D – Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law: Updated text throughout the appendix to reflect changes to the AstraZeneca global protocol template, specifically in sections 1, 3, 4.2, 5, 6, and 7. A new reference has also been added in this appendix.

Version 2.0, 15 January 2019

Title Page: Added EudraCT number.

CSP Synopsis: Added headers to tables.

CSP Synopsis – Study design: Added clarification that serum prednisone/prednisolone testing is only for patients who were not already on prednisone/prednisolone prior to Visit 1

CSP Synopsis – Study Design: Deleted text 'from 3 months before screening' when referencing ICS/LABA in order to correct and align with rest of CSP. Text replaced with 'as is defined in Section 3.1 (Inclusion Criteria)'.

CSP Synopsis – Induction phase: Clarified the timeframe of the induction phase

CSP Synopsis – Cortisol levels confirm AI: Clarified that repeat cortisol testing will only occur on one occasion.

CSP Synopsis – Maintenance phase: added clarification that if a patient experiences an exacerbation during the maintenance phase, this period will not be extended.

CSP Synopsis – Primary Objectives: Removed "average" from the key supportive outcome measures when describing the daily OCS dose.

CSP Synopsis – Secondary Objective #2: Removed "timepoint at which OCS dose equals 5mg" from the outcome measures.

CSP Synopsis – Safety Objective #2: Removed "severe" when describing asthma exacerbation rate.

CSP Synopsis – Duration of Treatment: Removed "Week 0 to Week 4" and clarified that the induction phase is 4 weeks in duration.

CSP Synopsis – Statistical Methods: Replaced "The proportion and confidence interval of the primary outcome measures will be estimated using the Clopper-Pearson formula for overall patients and for at least the following prespecified subgroup: baseline OCS dose level, baseline eosinophil count, and duration of chronic OCS dose. The endpoints will be evaluated independently." with "The proportion and 95% confidence interval for each of the primary outcome measures will be estimated for all patients in the full analysis set and for at least the following prespecified subgroups based on: baseline OCS dose level, baseline eosinophil count, and duration of chronic OCS dose. The endpoints will be evaluated independently. All confidence intervals will be estimated using the Clopper-Pearson exact method".

CSP Synopsis – Statistical Methods: Text describing the plans for conducting the interim review was clarified. The location of where the interim review would be detailed was updated from "SAP" to "separate interim review plan". Interim "analysis" was changed to interim "review" throughout CSP.

List of Abbreviations & Definition of Terms: Abbreviations for ACO, 'COPD', EGPA, and HES added in line with Exclusion 1 update.

Section 1.1 – Background and rationale for conducting this study: The following text was removed as this is specific to the US label - "Benralizumab (Fasenra®) is indicated for the add-on maintenance treatment of patients 12 years of age and older and with severe eosinophilic asthma."

Section 1.2 – Rationale for study design, doses, and control groups: Clarified the previous study referenced here is the ZONDA study.

Section 1.4 – Study Design: Added sub-sections to organize this section. Added clarification on the duration of each study period (Enrollment Weeks -2 to Week -1, Induction phase Week 0 to Week 3, OCS Reduction phase Week 4 onwards). This change was also implemented globally throughout the document.

Section 1.4.1 – Study Design - Enrollment period: Clarified that at Visit 1 (screening visit) the serum prednisone/prednisolone laboratory test is only for patients switching from other

OCS, and clarified when benralizumab is to be administered. Added text clarifying when the screening period may be extended.

Section 1.4.2 – Study Design - Induction phase: Clarified the benralizumab and OCS dosing during this period, and added instruction on how to proceed if an exacerbation occurs during this phase.

Section 1.4.3 – Study Design (OCS reduction phase): Added text to clarify benralizumab dosing. Added text to clarify that HPA axis integrity will be assessed at the start of the reduction phase (Visit 3, "4 weeks after the first dose of benralizumab and before initiation of the OCS reduction") for all patients on a baseline OCS dose of 5 mg/day. Also added text to clarify that the first OCS dose reduction can occur at Visit 3 after the dose of benralizumab at the site.

Section 1.4.4 – Maintenance phase: added clarifications to indicate that worsening of asthma control will be determined by the investigator based on the cortisol/ACTH stimulation results, the duration of the maintenance phase and the procedure should a subject experience an asthma exacerbation (if exacerbation, the length of the maintenance phase will not be extended and the patient will continue on 3 doses of benralizumab Q8W).

Figure 1 – Study flow chart: Updated to clarify the following:

- when benralizumab is to be administered
- the OCS reduction phase will vary for a variety of factors detailed in the figure
- information regarding the IPD visit for patients who discontinue treatment early

Section 1.5.1 – Scientific Committee: The charter details roles of scientific committee also.

Section 2.1 – Primary Objective: Removed “average” from the key supportive outcome measures when describing the daily OCS dose.

Section 2.2 – Secondary Objective #2: Removed “timepoint at which OCS dose equals 5mg” from the outcome measures.

Section 2.3 – Safety objectives: Deleted “severe” from “annualized severe asthma exacerbation rate”

Section 3.1 – Inclusion criteria: The following text was added to inclusion 3 for clarity - “[periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception].” The following text was updated for clarification: “a vasectomized sexual partner, female sterilization by tubal occlusion, any effective intrauterine device (e.g copper IUD, levonorgestrel intrauterine system), depot injections or

implanted contraception (e.g. Depo-Provera™, Implanon®), oral contraceptive, and contraceptive patches or vaginal rings (e.g. Evra Patch™, Xulane™, or NuvaRing®)."

Section 3.1 – Inclusion criteria: Inclusion 5 was updated to clarify that patients must have a smoking history of 20 pack years or less.

Section 3.1 – Inclusion criteria: Inclusion 7 was updated to clarify definition of high-dose ICS includes: budesonide/formoterol HFA ≥ 640/18/ per day or equivalent , fluticasone propionate DPI > 500/day or equivalent, or authorized generics for these products; see Appendix E and GINA 2018 guidelines for more recommendations); and that for ICS monotherapy preparations, or ICS/LABA combination preparations not mentioned in GINA (e.g. newer formulations), the highest approved maintenance dose in the local label will also meet this ICS criterion. Additionally, in countries where the high-dose ICS is not available (e.g. only the medium-dose ICS is available in that country), the highest approved maintenance dose in the local label will also meet this ICS criterion. Inclusion 7 was also updated to note that ICS can also be given via nebulized solution for inhalation.

Section 3.2 – Exclusion Criteria: Abbreviations were included within exclusion 1 to enhance ability to search CSP for certain conditions; and asthma-COPD overlap [ACO] was added an as example of clinical important pulmonary disease other than asthma.

Section 3.2 – Exclusion Criteria: Clarified Exclusion 8 to indicate that a history of positive HIV test (not a baseline HIV test; as baseline HIV test is not a part of study procedures) is also exclusionary.

Section 3.2 – Exclusion Criteria: Clarified Exclusion 11 that interventional clinical trials (not all clinical trials) is an exclusion.

Section 3.2 – Exclusion Criteria: Updated Exclusion 15 (prior benralizumab in present study) to clarify that patients may not re-enter the study after completion or premature discontinuation.

Section 3.2 – Exclusion Criteria: Added the following new exclusion criteria to enhance patient safety and to better align with prior studies:

19. 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 study or the interpretation
    - Impede the subject's ability to complete the entire duration of study.
20. Any clinically significant abnormal findings in physical examination, medical history, vital signs, hematology, clinical chemistry, or urinalysis during the enrollment 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.

21. History of cancer. Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, 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 was 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 was obtained

Section 3.2 – Exclusion Criteria: Added new Exclusion (#22) to allow for an extension of screening period up to 3 months for other (non-asthma related) disease flare-up or AE/SAE which occurs during the screening period and requires temporary use of systemic corticosteroids. This extension is not allowed when OCS is used for related diseases, such as rhinitis or nasal polyposis; in this case, the OCS use is an exclusion. See Section 7.8 Table 6 for more detail.

Section 3.2 – Exclusion Criteria: Added new Exclusion (#23) to clarify that current night-shift workers are not allowed into the study.

Section 3.5 – Restrictions: Clarified that SABA rescue medication will be permitted throughout the study and that ICS (not LABA if taken separately) should be withheld prior to cortisol/ACTH stimulation testing.

Section 3.6 – Discontinuation of study drug and criteria for withdrawal: Update was made to how a lost to follow-up (LTFU) patient will be defined in order to reduce prevalence of LTFU patients.

Section 4 – Study Plan and Timing of Procedures – Table 1: Table headers and Footnote ‘k’ updated to clarify Week numbers for the study periods, and for the PGIC timepoints.

Section 4 – Study Plan and Timing of Procedures - Table 1: The header for the "OCS </= 5mg/day" visit was updated with text to designate this the "morning cortisol visit."

Section 4 – Study Plan and Timing of Procedures - Table 1: Footnote ‘d’ updated to clarify calls/visits during OCS reduction period.

Section 4 – Study Plan and Timing of Procedures - Table 1: Footnote ‘m’ updated to clarify that prednisone testing is only done for patients who switch to prednisone/prednisolone at V1.

Section 4 – Study Plan and Timing of Procedures - Table 1: Footnote ‘n’ updated to clarify the timing of sputum sample collection; and to mention that this includes spirometry

Section 4 – Study Plan and Timing of Procedures - Table 1: Footnote ‘q’ added to clarify additional types of visits to be classified as Unscheduled visits.

Section 4.1 – Enrollment period (header): Text was removed as length of screening period was listed incorrectly.

Section 4.1.1 – Screening Visit: Clarified in the title that the screening visit is Visit 1 and starts Week -2. Text was added to clarify prednisone/prednisolone testing and to clarify that for patients switching to prednisone/prednisolone and who thus require a delay in the laboratory tests, Visit 2 can be done up to 2 weeks after collection of laboratory samples.

Section 4.1.1 – Screening Visit: Text added to clarify that patients experiencing acute upper/lower respiratory infection that requires antibiotics or antiviral medication during screening will be granted an extension to the screening period of up to 3 months.

Section 4.1.1 – Screening Visit: Text was added to clarify that patients experiencing non-asthma related events requiring temporary increase (bolus/burst) of systemic steroids may be granted an extension to the screening period of up to 3 months, if approved by the AstraZeneca Physician.

Section 4.1.2 – Rescreening: Text added to confirm that rescreening is allowed only once for each patient.

Section 4.2.1 – Induction phase: Added clarifications regarding timing of induction phase, timing of baseline sputum sample collection and that PGIC will completed weekly only during the induction phase.

Section 4.2.2 – OCS reduction phase: Added text to clarify when reduction phase starts, that there are 8 weeks between the 3rd and 4th dose of benralizumab, and that HPA axis integrity will be assessed at the start of the reduction phase (Visit 3) for all patients on a baseline OCS dose of 5 mg/day. Text also added to clarify which ACQ-6 score should be used if baseline result is missing.

Section 4.2.3 – Maintenance phase: Text added to clarify the following:

- that replacement/additional asthma treatment may be prescribed at EOT visit, per Investigator discretion.
- the duration of the maintenance phase will vary based on when the patient enters the maintenance phase, relative to the dosing cycle of benralizumab
- the length of the maintenance will not change due to an asthma exacerbation
- the registration of completion of treatment will be captured in IWRS/IVRS

Section 4.3 – Follow-up Period: The following text was added for clarity - “The follow-up contact can be done either on-site or via telephone contact.”

Section 5.1.2 - OCS dose titration: Added text to clarify how to start the initial OCS reduction if: 1. Table 2 instructs to reduce dose by 5mg increments, but the initial OCS dose is < 5mg to the nearest dosing level, and 2. Table 2 instructs to reduce the initial dose by 2.5 mg increments, but the initial dose is < 2.5 to the next dosing level.

Section 5.1.2 Table 2 – OCS down-titration approaches: Table was updated to show the correct down-titration method, in line with the OCS down-titration table in the protocol Synopsis. Correction is in the column titled **7.5 mg** ('Q4W' was corrected to 'Q2W'). Corrected text is "2.5 mg Q2W until reaching a dose of 7.5 mg/day". Footnote 'a' was updated to clarify that 'Risk AI' means cortisol testing confirmed with ACTH stimulation testing and if complete AI, no modification to the OCS dose will occur.

Section 5.2.1.1 – Asthma worsening or asthma exacerbation preventing OCS down-titration: Text added to clarify which ACQ-6 score should be used if baseline result is missing.

Section 5.2.1 – HPA axis evaluation: Moved the following from section 5.2.1.1 "For the morning cortisol test, the last OCS dose should be taken 24 hours prior to testing. Additionally, patients must not take ICS (or ICS/LABA if in single inhaler) treatment on the morning of the cortisol testing (for patients taking a once-daily ICS/LABA formulation, e.g. fluticasone furoate/vilanterol; patients must not take the treatment the night prior or the morning of the cortisol testing). If a patient requires a short course of macrolides, antivirals, or azoles, there must be a window of ≥1 week prior to the testing of cortisol levels (see Section 7.8).

Section 5.2.1 – HPA axis evaluation: Clarified that details related to values for normal, partial and complete AI for females using oral estrogen-containing contraceptives or oral estrogen-containing hormone replacement therapy are provided in the laboratory manual.

Section 5.2.1.1 – Morning cortisol and *Section 5.2.1.2 – ACTH stimulation test:* Sections revised to add further detail and clarification to both the initial and repeat cortisol and ACTH stimulation testing process along with actions on OCS titration based on results.

Section 5.2.1, Figure 2 – HPA axis evaluation: figure footnotes to clarify actions after retesting.

Section 5.2.1.2 – ACTH stimulation test: The following text was removed - "An injection of 250 µg tetracosactide depot will be given intravenously". This text was replaced by - "An injection of the fast-acting ACTH stimulant will be given intravenously".

Section 5.2.1.2 – ACTH stimulation test: The following text was added for clarity: "Please refer to the package insert of the product used locally for further guidance on preparation and administration"

Section 5.2.1.2 – ACTH stimulation test: The following text was added: "In the event of any issues with availability of the product used for the ACTH stimulation test, please consult with AZ study physician for further guidance".

Section 5.2.3 – Management of asthma exacerbations, Maintenance phase: Clarified that the length of the maintenance phase will not be extended should the patient experience an exacerbation

Section 5.2.4 – Laboratory safety assessments Table 4: Added glucose to the laboratory safety variables table as this is required for assessment of adrenal insufficiency. Clarified text for absolute leukocyte count is white blood cell count with differential.

Section 5.3.2 – Prednisone/prednisolone levels: Text was added to this section to clarify the prednisone/prednisolone testing is only done for patients who are switching to prednisone/prednisolone at V1.

Section 5.3.4.1 Patient-reported outcomes (Patient Global Impression of Change assessment): The text was corrected to reflect the new PGIC standards. Text was also added to clarify the timing of PGIC collection (in line with Table 1 – Study Plan).

Section 5.7.3 – Sputum collection and biomarkers: Section updated to align timing of sputum collection in Treatment with text throughout CSP (after approximately 24 weeks of benralizumab treatment).

Section 5.7.3 - Sputum collection and biomarkers: Added new subsection, "Spirometry," to clarify that spirometry is included in the sputum induction procedure, is included only for patient safety during the procedure, and that spirometry results will neither be captured nor analyzed.

Section 5.7.3 Sputum collection and biomarkers: Added a new subsection, "order of administration of usual asthma controller medication and investigational product relative to scheduled spirometry," to give details on when to dose patient, and also to note that detailed sputum collection procedures are in a separate sputum manual.

Section 6.6 Pregnancy: Subsection 6.6.2 'Paternal exposure' added along with the following text: "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 study drug until 16 weeks (approximately 5 half-lives) after the last administration of study drug."

Section 7.2 – Dose and treatment regimens (Conditions that will require rescheduling of study drug administration): "The patient, in the opinion of the Investigator, is experiencing an acute

or emerging asthma exacerbation" was removed as one of the conditions requiring study drug rescheduling.

Section 7.2 – Dose and treatment regimens (Conditions that will require rescheduling of study drug administration): The following text was added to clarify action for potential out of window dosing - "Every possible effort should be made to bring the patient in within the allowed visit window and study drug should be administered at that visit. If this is not possible, the AZ study physician should be contacted to discuss further."

Section 7.3 – Management of study drug-related reactions: Removed "lung function" as an example of a pre-assessment as lung function is not a CSP-required assessment.

Section 7.8 – Concomitant and other treatments: Text updated to clarify that information is collected in eCRF for treatments received 3 months prior (versus 6 months prior) and that information is collected through follow-up period. The following text was also added "The as-needed use of short-acting bronchodilators for relief of acute asthma symptoms is permitted throughout the study" and removed table referencing short-acting bronchodilators.

Section 7.8 – Concomitant and other treatments: Added Table 5 "Medication Restrictions" and Table 6 "Prohibited Medications" headers to existing tables.

Section 7.8 Concomitant and other treatments: Deleted table summarizing Rescue usage and instead summarized in text at the top of this section.

Section 7.8 Concomitant and other treatments

Table 5: Clarification added regarding withholding of high-dose ICS for morning cortisol/ACTH stimulation test.

Section 7.8 – Concomitant and other treatments Table 6: updated to define short course of marcolides, antivirals, and azole therapies as "≤ 2 weeks".

Section 7.8 – Concomitant and other treatments Table 6: Added new row with new washout periods for marketed respiratory biologics (as follows) and clarified pre-existing row is in reference to non-respiratory marketed biologics or any investigational biologics.

> Any marketed respiratory biologic treatment (eg, omalizumab, mepolizumab, reslizumab, benralizumab) is not allowed 4 months or 5 half-lives (whichever is longer) prior to the date informed consent is obtained and throughout the entire treatment period.
>
> - For patients who have previously not tolerated or have not responded to marketed mepolizumab, omalizumab or reslizumab (as assessed by the treating physician), a shorter washout period of ≥ 30 days between the last dose of mepolizumab, omalizumab or reslizumab and the first dose of open label Benralizumab (Visit 2), is allowed.
>
> - Patients who have previously received benralizumab still require a complete washout prior to date of informed consent; those who have not tolerated or have not responded to benralizumab would not be a candidate for this study.

Section 7.8 – Concomitant and other treatments Table 6: Added clarifications to immunosuppressive medications, to allow short course of OCS for non-asthma related disease flare ups; at any time during the study and to indicate that the prohibited period for any non-respiratory marketed or any investigational biologics

Section 8.1 – Statistical considerations: Removed text referencing sputum collection as a subgroup.

Section 8.1 – Statistical considerations: Updated text from 'synthetic control arm' to 'external data sources' when referring to what will be used to assess certain changes seen in patients and clarified where it will be described.

Section 8.2 – Sample size estimate: Provided further clarification regarding the sample size estimate in relation to the primary outcome measure and 95% confidence interval

Section 8.2 – Sample size estimate Table 7: Updated the values of expected distance between observed proportion and confidence limit.

Section 8.4 – Outcome Measures for Analyses: Removed "average" from the key supportive outcome variables to the primary efficacy outcome variables when describing the daily OCS dose.

Section 8.4 – Outcome Measures for Analyses: Removed "timepoint at which OCS dose equals 5mg" from the secondary efficacy outcome variables.

Section 8.4 – Outcome Measures for Analyses: Removed "severe" when describing asthma exacerbation rate in the safety outcome variables.

Section 8.5.1 – Analysis of the primary variable: Provided further clarification regarding the analysis of the primary variable using the Clopper-Pearson exact method

Section 8.5.2.1 – Time to 1st OCS increase; section header was renamed; updated to describe analysis method for measuring the time to 1st OCS increase

Section 8.5.2.2 – ACQ-6: '+' signs added for clarification, to indicate that deterioration is a change from baseline in an ACQ-6 score of at least +0.5.

Section 8.5.2.4 – PGIC: The text was corrected to reflect the new PGIC standards, and to better align with Table 1.

Section 8.5.3 – Analysis of safety outcomes: Removed "severe" when describing how the annualized rate of asthma exacerbations will be summarized

Section 8.5.4 – Subgroup analysis: Updated the baseline serum eosinophil count subgroups as ≥300/μL and <300/μL

Section 8.5.5 – Interim analysis: Text describing the plans for conducting the interim review was clarified. The location of where the interim review would be detailed was updated from "SAP" to "separate interim review plan". Interim "analysis" was changed to interim "review" throughout.

Section 10.4: Text updated to clarify that genetic consent is a separate consent but not necessarily a separate form.

Appendix C – Informed consent: Text updated to clarify that genetic consent is a separate consent but not necessarily a separate form.

Appendix E (Estimated daily doses for inhaled corticosteroids): Updated the "inhaled corticosteroid" section of the table to match the current GINA 2018 guidelines. Updated the "inhaled corticosteroid in ICS/LABA combination" to match highest dose per local labels of major markets; GINA 2018 does not specifically address ICS/LABA comparable doses.

Appendix E (Estimated daily doses for inhaled corticosteroids): Updated in footnotes to clarify references, and to add additional clarification from GINA 2018 on how to interpret data. Also added clarification that, "this protocol also allows clinically comparable doses of newer products, including authorized generics. High-dose ICS via nebulized solution for inhalation is also allowed. For products not listed in this table, the highest approved maintenance ICS or ICS/LABA dose in the local country label will meet the protocol-defined criterion for 'high-dose ICS.'"

Appendix F - Estimated OCS dose therapy equivalence: Added footnote that for other OCS products or doses not listed, to see local label of OCS product or online calculators.

Appendix G - Prednisone/Prednisolone Doses <5 mg in Relation to Available Tablet Strengths: Administered number of tablets to achieve a 3 mg daily dose with 5 mg tablets was corrected. Made corrections to dosing conversions throughout, added rows for 0.5mg and 1.5mg.

Appendix H – Glucocorticoid Toxicity Index: Added in-text headers to make it clear that Appendix H spans several pages.

Adjustments made throughout:

- For general administrative purposes (i.e. headers, formatting) and grammatical corrections
- To clarify the timeframe of screening and induction phases
- To clarify that patients who are already taking prednisone/prednisolone at Visit 1 do not require the serum prednisone/prednisolone laboratory test
- To clarify that baseline visit is Visit 2

• To clarify that repeat morning cortisol testing is done only once • To clarify that for patients who are on a baseline OCS dose of 5 mg/day, HPA axis integrity will be assessed after 4 weeks at 5mg/day, at the start of the reduction phase (Visit 3). • To clarify that the duration of the maintenance phase will depend on when the patient enters the maintenance phase relative to the dosing cycle of benralizumab. • Created consistency in the language for sputum (that sputum will be done for a subset of up to approximately 100 patients at selected clinical sites). • Added clarification that there are 8 weeks between the 3rd and 4th benralizumab doses
Version 1.0, 12 April 2018
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

PONENTE: A Multicenter, Open-label, Phase 3b Efficacy and Safety Study of Benralizumab 30 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Patients with Severe Eosinophilic Asthma on High-Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy

International Coordinating Investigator

Study sites and number of patients planned

The target number of patients entering treatment for this study is approximately 600 patients at approximately 180 study sites worldwide.

Study design

This is an open-label, multicenter study designed to evaluate the efficacy and safety of reducing oral corticosteroid (OCS) use after initiation of a 30 mg dose of benralizumab administered subcutaneously (SC) every 4 weeks (Q4W) up until the third dose of benralizumab and then every 8 weeks (Q8W) thereafter in patients with severe eosinophilic asthma who are receiving high-dose inhaled corticosteroids (ICS)/long-acting β_2 agonists (LABAs) and OCS with or without additional asthma controller(s).

After they sign the informed consent form, patients will undergo a screening visit (Visit 1) to assess eligibility criteria and laboratory tests. All patients who are not already taking prednisone/prednisolone as their OCS treatment will be switched to prednisone/prednisolone, and the laboratory tests will be delayed 3 to 7 days to include prednisone/prednisolone testing. Patients who are already taking prednisone/prednisolone at Visit 1 do not require the serum prednisone/prednisolone laboratory test (see Table 1). Patients still fulfilling inclusion/exclusion criteria at Visit 2 (Week 0) will enter the study and receive open-label benralizumab.

The benralizumab treatment period is divided into 3 phases:

- **Induction phase (starting Week 0):** Patients who are receiving benralizumab treatment should remain stable on their baseline (Visit 2) OCS dose during this 4-week phase.
- **OCS reduction phase (Week 4 onwards):** Patients will reduce their dosage of OCS according to the schema defined below for each baseline OCS dose until they reach 5 mg/day.

Table A OCS Titration Schema Until Reaching 5 mg/day

Baseline OCS dose	OCS down-titration schema until reaching 5 mg/day (without worsening of asthma)
>20 mg/day	Reductions of 5 mg every 1 week until reaching a dose of 20 mg/day; followed by reductions of 5 mg every 2 weeks (Q2W) until a dose of 10 mg/day is reached; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
>10 to ≤20 mg/day	Reductions of 5 mg Q2W until reaching a dose of 10 mg/day; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
>7.5 to ≤10 mg/day	Reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day followed by reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
>5 to ≤7.5 mg/day	Reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day

For all patients, hypothalamic-pituitary-adrenal (HPA) axis integrity will be evaluated after 4-weeks on 5 mg/day and prior to tapering down the OCS dose (for patients with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase).

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the patient has:

- Normal cortisol levels
- Complete adrenal insufficiency (AI)

Cortisol levels from the morning cortisol test that are below normal range and above the Complete AI range are considered “Indeterminate;” and require additional testing as described below.

Secondly, the adrenocorticotropic hormone (ACTH) stimulation test (ie, Synacthen®, Cortrosyn™) is done within approximately 1 week in the subset of patients with indeterminate results from the morning cortisol test [see also Section 5.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the patient has:

- Normal cortisol levels
- Complete AI
- Partial AI

Depending on the morning cortisol level results and the presence of cortisol level values indicating AI, the patient will continue per the following guidance:

- Cortisol levels within normal range:
    - Patient exhibits absence of signs and/or symptoms of AI: continue OCS down-titration by 2.5 mg Q4W
    - Patient exhibits signs and/or symptoms of AI: continue OCS down-titration at a slower pace (1 mg Q4W)
- Cortisol levels are indeterminate: Patient will undergo the ACTH stimulation testing (Section 5.2.1.2). Decisions regarding how to continue OCS down-titration will be based on the results of the ACTH stimulation testing (see Table B)

Table B ACTH Stimulation Testing

	ACTH stimulation test results		
	Normal	**Partial AI**	**Complete AI**
OCS down-titration	Reduction of 2.5 mg Q4W	Reduction of 1 mg Q4W	Continue on same OCS dose
Repeat morning cortisol test for further OCS down-titration	No need	2 months later	3 months later (see below)

– Cortisol levels confirm complete AI: OCS dose will remain the same without further reduction until there is evidence of recovery from the complete AI. The test will be repeated on one occasion 3 months later, and patients will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards

If a patient experiences an exacerbation or an asthma deterioration, OCS dose reductions should stop. After recovery from the first exacerbation or asthma deterioration, the patient will be allowed to proceed with another attempt to reduce OCS dose; however, this must follow a lower speed of OCS down-titration (reductions Q4W). However, in case of a second exacerbation or asthma deterioration, no further OCS dose reduction will be allowed, and the patient will continue on the same OCS dose or will return to a one-step higher dose level (or more as considered necessary by the Investigator), and the patient will then enter the maintenance phase. Further details are provided in Sections 5.2.2 and 5.2.3.

At each clinic/phone call visit, in addition to the information provided by the patient on his/her asthma disease, investigators will have access to the patient's weekly Asthma Control Questionnaire 6 (ACQ-6) scores and compliance with maintenance asthma therapy (completed by means of an electronic patient-reported outcome device [ePRO] to evaluate whether the patient's condition has significantly deteriorated [ie, increase in ACQ-6 score of ≥0.5 from Visit 2, ie, before benralizumab administration]) and will make the final decision to further reduce the OCS dose until the patient

reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control. Approximately 1-2 weeks prior to end of the OCS reduction phase, the patients who have Partial AI after the repeat morning cortisol test, will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase.

- **Maintenance phase:** This phase will last approximately 24 to 32 weeks from the time the patient reaches a complete withdrawal of OCS without worsening of asthma control. The maintenance phase could be initiated earlier if OCS dose reduction fails due to clinical deterioration or if the patient does not recover from AI. The length of the maintenance phase will vary depending on when the patient enters the maintenance phase. During this phase, patients will continue benralizumab Q8W for 3 doses, and then the End of Treatment (EOT) visit will be scheduled 8 weeks (± 7 days) after the last dose of benralizumab. Patients who have Complete AI or Partial AI at the end of the OCS Reduction phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to end of the OCS Maintenance phase. If a patient experiences an exacerbation during the maintenance phase, this period will not be extended.

Patients should be maintained on their currently prescribed ICS plus LABAs with or without other asthma controller therapy, without change, as is defined in Section 3.1 (Inclusion Criteria) until the EOT visit.

All patients who prematurely discontinue study drug/investigational product or discontinue from the study should return to the study center and complete the procedures described for the Premature Investigational Product Discontinuation (IPD) visit within 4 weeks (± 7 days) after the last dose of benralizumab.

For all patients dosed with benralizumab, a follow-up contact will be scheduled 12 weeks (± 7 days) after their last dose of benralizumab. Patients who have Partial AI or Complete AI at the end of the Maintenance phase should be followed-up by an endocrinologist or other appropriate specialist, if deemed necessary by the Investigator.

PONENTE Long Term Follow Up Visit Substudy

After completion of the EOT visit procedures, eligible patients may consent to a long term follow up visit that will occur 12- to 18-months after completion of the main PONENTE study. The objectives of this long term follow up visit are to retrospectively collect changes in OCS dose and other background asthma therapy and to further assess recovery from AI in a real-world setting. Between the EOT visit of the main PONENTE study and the long term follow up, patients will be treated according to standard practice; for example, any changes to maintenance asthma regimens are allowed, including further reductions of OCS as recommended in the GINA report (GINA 2020).

See Appendix K: for details on eligibility for and endpoints of the PONENTE Long Term Follow Up Visit substudy.

Objectives and Endpoints

Primary Objective	Endpoints/Outcome Variables
To assess the ability to reduce OCS dose in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Primary outcome measures** • Patients who achieve 100% reduction in daily OCS dose that is sustained over at least 4 weeks without worsening of asthma • Patients who achieve 100% reduction or a daily OCS dose ≤5 mg, if reason for no further OCS reduction is AI, that is sustained over at least 4 weeks without worsening of asthma **Key supportive outcome measures** • Patients who achieve a daily OCS dose of ≤5 mg that is sustained over at least 4 weeks without worsening of asthma • Patients who achieve a ≥90%, ≥75%, ≥50%, and >0% reduction in daily OCS dose, sustained over at least 4 weeks without worsening of asthma • Change from baseline in daily OCS dose (mg) from start of OCS reduction to end of the OCS reduction phase

Secondary Objective	Outcome Measure
To assess the sustained reduction of daily OCS dose while not losing asthma control during approximately 6 months after the end of OCS down-titration (maintenance phase) in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • Change in daily OCS dose from the end of OCS reduction phase to the end of the maintenance phase (EOT visit) • Time to first increase in OCS dose during the maintenance phase, after achieving the minimum OCS dose during the OCS reduction phase
To assess the effect of OCS down-titration protocol on asthma control in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • ACQ-6 scores at baseline (Visit 2), Visit 3, end of OCS reduction phase, and monthly from end of OCS reduction phase to end of maintenance phase (EOT visit) • Change from baseline in ACQ-6 to Visit 3, end of OCS reduction phase, and end of maintenance phase (EOT visit) • Responder analysis of ACQ-6 scores from Visit 2 through end of maintenance phase

Secondary Objective	Outcome Measure
To assess the effect of OCS down-titration protocol on quality of life in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • Change from baseline (Visit 2) in St. George's Respiratory Questionnaire (SGRQ) total scores to the end of maintenance phase (EOT visit) • Responder analysis of SGRQ total scores at the end of maintenance phase

Safety Objective	Outcome Measure
To evaluate the occurrence of AI when reducing OCS	**Key outcome measure** • Patients with complete AI
To assess the effect of OCS down-titration protocol on asthma exacerbations in adult patients with severe asthma treated with benralizumab 30 mg SC	**Key outcome measures** • Annualized asthma exacerbation rate • Annualized asthma exacerbation rate leading to hospitalization or emergency room visit
To assess the safety and tolerability of benralizumab in patients who reduce their chronic OCS dose	• Adverse events/Serious adverse events • Laboratory parameters and vital signs
To evaluate corticosteroid toxicity after OCS reduction	• Glucocorticoid toxicity index

Exploratory Objective	Outcome Measure
To investigate the contribution of genomic variants to the study outcomes	• Association of common and rare genomic variants with patient responses
To assess early improvements in asthma status during the first 4 weeks of benralizumab treatment before initiation of OCS reduction	• Patient Global Impression of Change
To assess the impact of OCS down-titration on blood eosinophil levels	**Key outcome measure** • Change from baseline blood eosinophils
To investigate biomarkers for predicting response to benralizumab	**Key biomarker parameters** • Serum samples at baseline for protein biomarkers • Plasma for eosinophil-derived neurotoxin

Target patient population

Male and female patients aged ≥18 years with diagnosed asthma and requiring continuous treatment with high-dose ICS (high-dose ICS at the highest approved dose in a country) plus LABAs for ≥6 months. Patients must be on chronic treatment with OCS (equivalent to a prednisone dose of ≥5 mg/day) for ≥3 months prior to study entry. The OCS dose must be stable for ≥4 weeks prior to study entry. Patients must have peripheral blood eosinophil counts of ≥150 cells/μL as assessed by a central laboratory at Visit 1 or documented eosinophil count of ≥300 cells/μL in the past 12 months.

Duration of treatment

Patients will start receiving open-label benralizumab at Visit 2 (Week 0) and will enter the 4 week induction phase, where they will remain stable on their baseline OCS dose during this period.

The OCS reduction phase will start at Visit 3 (Week 4) and will be completed depending on the baseline OCS dose, the occurrence of asthma exacerbation or asthma worsening, and the integrity of the HPA axis (which will guide the speed of OCS down-titration for patients taking doses of <5 mg/day). After OCS down-titration, patients will continue to receive treatment with benralizumab 30 mg Q8W for approximately 24 to 32 weeks (the maintenance phase). The maintenance phase will end with an EOT visit conducted 8 weeks after the last dose of benralizumab. A follow-up contact will be conducted 12 weeks following the last dose of benralizumab.

The total planned study duration is flexible and will vary for each individual patient depending on the factors previously mentioned. The expected duration can range from approximately 32 weeks (eg, a patient with a baseline OCS dose of 5 mg) to approximately 48 weeks (eg, a patient with a baseline OCS dose of 40 mg), assuming the patient has completely withdrawn OCS without the occurrence of an asthma exacerbation, completes the study, and morning cortisol levels do not indicate risk for AI.

Study drug, dosage, and mode of administration

Benralizumab 30 mg/mL solution for injection in an accessorized prefilled syringe will be administered at the study center SC Q4W up until the third dose of benralizumab and then Q8W thereafter (8 weeks between the 3rd and 4th benralizumab doses).

Statistical methods

The study includes two primary endpoints: 1) Patients who can reduce their daily OCS dose by 100% and 2) Patients who can reduce their daily OCS dose by 100% or reduce to a dose ≤5 mg if the reason for no further OCS reduction is AI; both endpoints to be sustained over at least 4 weeks without worsening of asthma. The proportion and 95% confidence interval for each of the primary outcome measures will be estimated for all patients in the full analysis set and for at least the following prespecified subgroups based on: baseline OCS dose level, baseline eosinophil count, and duration of chronic OCS dose. The endpoints will be evaluated independently. All confidence intervals will be estimated using the Clopper-Pearson exact method.

The full analysis set, which will include all patients who receive any dose of benralizumab, is defined based on an intention-to-treat approach. All efficacy and safety analyses will be analyzed using the full analysis set.

The changes in OCS daily dose, ACQ-6 scores, and SGRQ scores will be summarized in descriptive statistics. Asthma control and SGRQ responders will be summarized in count and percentage.

As this study is primarily descriptive in nature, no statistical multiplicity adjustment will be made over different endpoints or subgroups.

As the study does not include any predefined confirmatory tests, the sample size is based on the ability to provide sufficient precision in point estimates. The primary outcome, the observed proportion of patients who successfully down-titrated their doses, is expected to be equal to or greater than 50%. A total sample size of 600 patients is expected to provide 95% confidence intervals for a single proportion extending approximately 4.1% from the point estimate of a 50% success rate.

One interim review may be performed after approximately 90-100 patients have completed (or have had the opportunity to complete) their OCS down-titration; further details will be described in a separate interim review plan.

An additional database lock and analysis of all relevant data collected through the end of the OCS reduction phase, may be performed after the final patient has had the opportunity to complete the OCS reduction phase. The purpose of this analysis is to generate a sub-set of the pre-planned analysis outputs of all relevant data for all patients up to the end of the OCS reduction phase. Further details will be outlined in the Statistical Analysis Plan (SAP). The number and percentage of patients diagnosed with AI will be tabulated overall and by the method of diagnosis.

The PONENTE long term follow up visit substudy is designed to understand the clinical management of OCS and other background asthma maintenance medications in a real-world setting following completion of the maintenance phase of PONENTE study. Outcome measures include the proportion of patients who achieve 100% reduction (and other pre-defined percentage reductions) in OCS use and other background asthma maintenance medications from the PONENTE baseline to the end of the PONENTE Long Term Follow Up. Proportions will be presented with nominal 95% confidence intervals estimated using the Clopper-Pearson exact method. Results will be presented for all patients who sign informed consent to continue into the PONENTE Long Term Follow Up and will be repeated by exposure to (i) any biologic and (ii) commercial Benralizumab during the PONENTE Long Term Follow Up. No formal hypothesis will be tested and no multiplicity adjustment will be applied in the statistical analysis.

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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
ACO	Asthma-COPD overlap
ACQ-6	Asthma Control Questionnaire 6
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AI	Adrenal insufficiency
ALT	Alanine aminotransferase
APFS	Accessorized prefilled syringe
AST	Aspartate aminotransferase
BP	Blood pressure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic case report form
EDN	Eosinophil-derived neurotoxin
EGPA	Eosinophilic granulomatous polyangiitis
ePRO	Electronic patient-reported outcome device
EOT	End of Treatment
FAS	Full analysis set
GC	Glucocorticoid
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
GTI	Glucocorticoid toxicity index
HCG	Human chorionic gonadotropin
HES	Hypereosinophilic syndrome
HL	Hy's Law
HPA	Hypothalamic-pituitary-adrenal
ICH	International Conference on Harmonisation
ICF	Informed consent form
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E

Abbreviation or special term	Explanation
IL-5	Interleukin-5
IL-5Rα	Interleukin-5 receptor alpha subunit
IPD	Investigational product discontinuation
International Coordinating investigator	If a study is conducted in several countries, the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally.
IVRS	Interactive voice response system
IWRS	Interactive web response system
LABA	Long-acting β_2 agonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroids
PGIC	Patient Global Impression of Change
PHL	Potential Hy's Law
PRO	Patient-reported outcome
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedures
TBL	Total bilirubin
ULN	Upper limit of normal
WBDC	Web-based data capture
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 is a leading cause of morbidity 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).

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centered around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs), with the addition of long-acting β_2 agonists (LABAs) in patients with more severe asthma (NAEPP 2007, GINA 2018). Approximately 5% to 10% of persons with asthma have a severe form of disease that is usually managed with high-dose inhaled glucocorticoids (GCs) and bronchodilators (Bateman et al 2010, Chung et al 2014). Within this group, 32% to 45% of persons rely on frequent or maintenance use of oral GC therapy (Moore et al 2007, Shaw et al 2015, Miloslavsky et al 2017). Biologics targeting interleukin-5 (IL-5) and immunoglobulin E (IgE) are now included in international treatment guidelines as an add-on treatment to patients uncontrolled with LABA/ICS treatment (GINA 2018).

Although oral GC therapy can be effective at treating several inflammatory diseases, it adversely affects health-related quality of life (Sweeney et al 2016) and is associated with several side effects, including osteoporosis, hypertension, and depression (Dinsen et al 2013). Chronic use of oral GCs suppresses the hypothalamic-pituitary-adrenal (HPA) axis (Broersen et al 2015) and prevents cortisol production (Neogi et al 2010, Nicholas et al 2018). Upon withdrawal of GCs, restoration of the HPA axis may take a longer time, thus leading to adrenal insufficiency (AI) in approximately 48.7% of patients (Dinsen et al 2013, Broersen et al 2015). Symptoms of AI are nonspecific and can include fatigue and nausea and, in severe cases, acute adrenal crisis; however, the suppression of a cortisol-induced stress response can be fatal in physiologically traumatic situations such as during surgery, bodily injury, or severe systemic infections (Alves et al 2008, Dinsen et al 2013, Johnson et al 2014, Joseph et al 2016). It is therefore important to monitor patients for AI while down-titrating their oral GC dose, especially once the patient has reached a physiological dose, which is defined as approximately 5 mg per day of oral prednisone (Alves et al 2008).

Interleukin-5 is a key cytokine involved in the differentiation and maturation of eosinophils from hematopoietic stem cells in the bone marrow, their mobilization and migration from the bone marrow to the blood, and their activation and survival in tissue (Blanchard and Rothenberg 2009). The receptor for IL-5 (IL-5Rα [IL-5 receptor alpha subunit]) is exclusively expressed on eosinophils and basophils.

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5Rα on the target cell (Takatsu et al 1994, Toba et al 1999, Tedeschi et al 2018).

The purpose of this global study is to assess the potential for reducing the use of maintenance oral corticosteroids (OCS) in patients with severe eosinophilic asthma who are OCS-dependent. Patients will receive benralizumab 30 mg on an open-label basis, and, 4 weeks after the first benralizumab dose, investigators will initiate the tapering of the OCS dose while not losing asthma control and managing signs/symptoms of AI. Primary effectiveness will be determined by the ability of patients to reduce their OCS dose to 0 mg/day without losing asthma control or to reach the lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control.

At the end of the PONENTE EOT visit, patients will be invited to participate in a long term follow up visit sub-study to further assess changes in asthma maintenance therapy in an a real-world setting, i.e., according to the treatment prescribed by their healthcare provider. Additionally, there will be assessment of recovery from AI as well as assessment of glucocorticoid toxicity by means of GTI. See Appendix K for details on the background and rationale of the PONENTE Long Term Follow Up visit substudy.

1.2 Rationale for study design, doses, and control groups

The treatment options for patients who remain uncontrolled on high-dose ICS/LABA are extremely limited; one of the treatment options is the addition of OCS to the current treatment (GINA 2018). However, regular intake of OCS can lead to a number of adverse events (AEs) and, as a result, can decrease quality of life for these patients (Kwong et al 1987).

In the ZONDA study, benralizumab significantly reduced the median final oral GC doses from baseline by 75%, as compared with a reduction of 25% in the placebo group (Nair et al 2017), and 56% of patients who received benralizumab were able to have a 100% reduction in their OCS dose. However, this study had some limitations, and there are medical questions still to be addressed. Patients who were receiving baseline prednisone doses above 12.5 mg were not allowed to completely withdraw from OCS as the study duration did not allow for this. Also, the adequacy of the speed of the OCS down-titration and whether it can be performed faster than the down-titration regimen used in the ZONDA study (Nair et al 2017) remains unclear. Finally, the maintenance phase was limited to 4 weeks after last OCS dose reduction, so it is uncertain as to whether benralizumab benefits are maintained after OCS down-titration or withdrawal.

Furthermore, patients who are receiving higher doses of OCS or who have been on prolonged OCS therapy at baseline may potentially experience secondary AI upon complete/inappropriate withdrawal of OCS due to HPA axis suppression. Patients may also experience steroid withdrawal or deprivation symptoms and reactivation/relapse of underlying disease (Alves et al 2008). This has not yet been evaluated in previous studies.

This study will recruit patients who are receiving chronic treatment with OCS for ≥3 months prior to study entry and receiving stable doses of OCS for ≥4 weeks prior to study entry. Additionally, patients must have peripheral blood eosinophil counts of ≥150 cells/μL, as assessed by the central laboratory at Visit 1, or documented eosinophil counts of

≥300 cells/μL in the past 12 months. These historical eosinophil values will help to identify patients with eosinophilic phenotypes, as patients on OCS may have reduced eosinophils.

The purpose of this trial is to assess the potential for reducing the use of maintenance OCS in systemic corticosteroid–dependent asthma patients treated with benralizumab 30 mg (who have severe refractory eosinophilic asthma). This study will allow patients to reduce their OCS dose to 0 mg/day or to the lowest OCS dose that is physiologically possible (given the possibility of AI in this population of patients) and will assess whether a faster OCS down-titration compared with what has been previously studied (Nair et al 2017) is appropriate. Patients will enter the maintenance phase of approximately 24 to 32 weeks after their OCS dose has been reduced to 0 mg/day (or to the lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control), which will assess the ability of benralizumab to maintain clinical benefits after OCS withdrawal.

Patients will receive open-label benralizumab 30 mg/mL solution for injection in an accessorized prefilled syringe (APFS). It will be administered subcutaneously (SC) at the study site as every-4-week (Q4W) dosing up until the third dose of benralizumab (Visits 2 to 4) and then every-8-week (Q8W) dosing thereafter. This dose is aligned with the current prescribing information for benralizumab, and an open-label design allows for a real-world assessment of OCS down-titration as it relates specifically to benralizumab effectiveness.

1.3 Benefit/risk and ethical assessment

There are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS/LABA (GINA 2018). The evidence base for oral add-on therapies (ie, OCS, leukotriene inhibitors, and xanthenes) is extremely limited. Tiotropium is a long-acting bronchodilator that has recently been shown to produce improvement in lung function and exacerbation risk (pooled data) in patients with severe asthma, with inconsistent effects on other measures of asthma control (Juniper et al 2005, Juniper et al 2006, Kerstjens et al 2012).

Biologics targeting IL-5 and IgE are now included in international treatment guidelines as an add-on treatment to patients uncontrolled with ICS/LABA treatment (GINA 2018). In adult patients whose asthma was poorly controlled on high dose ICS/LABA and chronic OCS (with or without other controller medications), benralizumab significantly reduced the median OCS doses from baseline by 75%, as compared with a reduction of 25% in the oral GC doses in the placebo group. The odds of a reduction in the oral GC dose were 4.12 times higher with benralizumab than with placebo, respectively ($P<0.001$) (Nair et al 2017).

There is the risk of an asthma exacerbation or worsening due to withdrawal of OCS in OCS-dependent patients. However, data from the ZONDA study shows benefits in exacerbation reduction as the rate of exacerbations in OCS-dependent asthmatics treated with benralizumab who are withdrawn from OCS was 70% lower than the rate in those who are not treated with benralizumab (placebo) (Nair et al 2017).

Development of antidrug antibodies to benralizumab has been documented without an apparent clinical impact. Theoretical risks of developing antidrug antibodies include hypersensitivity reactions (eg, anaphylaxis or immune complex disease) and decreased drug efficacy.

Blood eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The identified (injection-site reaction) and potential (hypersensitivity reactions/anaphylaxis, malignancies, and serious infections [especially helminthic ones]) risks of benralizumab are discussed in detail in the latest version of the Investigator's Brochure.

Furthermore, there is a risk of AI when OCS is completely or inappropriately withdrawn (Alves et al 2008, Dinsen et al 2013, Johnson et al 2014, Joseph et al 2016) in:

- Patients who are on prolonged OCS therapy.
- Patients who are treated with a high dose of OCS at baseline.
- During periods of stress to the body when a cortisol-induced response is critical to maintain homeostasis, eg, during acute intercurrent illness, following trauma, and during surgery and childbirth.

The symptoms of chronic AI include many nonspecific symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, tiredness, and depression. In severe cases, a life-threatening event of acute adrenal crisis may occur (Alves et al 2008). The study will include close monitoring of the risk of AI by assessing HPA axis integrity in patients who have reached OCS doses equal to 5 mg/day and for patients who have baseline OCS doses equal to 5 mg/day. A detailed assessment of the overall risks/benefits of benralizumab in patients with asthma is given in the Investigator's Brochure.

1.4 Study design

This is an open-label, multicenter study designed to evaluate the efficacy and safety of reducing OCS use after initiation of a 30-mg dose of SC benralizumab administered with Q4W dosing up until the third dose of benralizumab (Visits 2 to 4) and then Q8W thereafter in approximately 600 adult patients with severe eosinophilic asthma who are receiving high-dose ICS/LABA and OCS with or without additional asthma controller(s). Each patient must have been receiving an average daily dose equivalent to ≥5 mg of prednisone for the last 3 months before study entry.

Please see Appendix K for details on the study design of the PONENTE Long Term Follow Up Substudy.

1.4.1 Enrollment Period (starting Week -2):

After patients sign the informed consent form (ICF), patients will undergo a Screening visit (Visit 1) to assess eligibility criteria and laboratory tests. All patients who are not already taking prednisone/prednisolone as their OCS treatment will be switched to prednisone/prednisolone, and the laboratory tests (including serum prednisone/prednisolone) will be delayed 3 to 7 days. Patients who are already taking prednisone/prednisolone at Visit 1 do not require the serum prednisone/prednisolone laboratory test (see Table 1). Additionally, an extension of the screening period up to 3 months is allowed to ensure that a patient recovers from any asthma exacerbation or acute upper/lower respiratory infection (refer Section 4.1.1 for more details). Patients still fulfilling inclusion/exclusion criteria at Visit 2 (Week 0) will enter the study and receive open-label benralizumab.

The treatment period is divided into 3 phases: induction, reduction, and maintenance (Figure 1). The duration of the benralizumab treatment period will be dependent on the baseline OCS dose, the occurrence of asthma exacerbation(s) or asthma worsening, and the integrity of the HPA axis, which will guide the speed of OCS down-titration below 5 mg/day. However benralizumab treatment will start at Visit 2, continue throughout the Reduction phase, and will end after 3 doses in the Maintenance Phase.

1.4.2 Induction phase (starting Week 0):

Patients in the induction phase will start their first dose of benralizumab at Visit 2 and should remain stable on their baseline OCS dose during this 4-week phase. If an asthma exacerbation occurs during the induction phase, the patient will be managed per Section 5.2.3.

1.4.3 OCS Reduction phase (Week 4 onwards):

Benralizumab dosing

Patients will receive Q4W benralizumab up until the 3rd dose (8 weeks between the 3rd and 4th benralizumab dose). Benralizumab will then continue Q8W through the end of the Reduction phase and continue to the Maintenance phase.

OCS reduction

Patients will reduce their dosage of OCS according to the schema defined for each baseline OCS dose until they reach 5 mg/day (Section 5.1.2).

For all patients, hypothalamic-pituitary-adrenal (HPA) axis integrity will be evaluated after 4-weeks on 5 mg/day and prior to tapering down the OCS dose (for patients with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase)

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the patient has:

- Normal cortisol levels
- Complete AI

Cortisol levels from the morning cortisol test that are below normal range and above the Complete AI range are considered "Indeterminate;" and require confirmation via additional testing described below.

Secondly, the adrenocorticotropic hormone (ACTH) stimulation test (ie, Synacthen®, Cortrosyn™) is done within approximately 1 week in the subset of patients with indeterminate results from the morning cortisol test [see also Section 5.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the patient has:

- Normal cortisol levels
- Complete AI
- Partial AI.

The OCS reduction will continue until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control. The first OCS dose reduction may occur at Visit 3 after the dose of benralizumab at the site. Investigators should monitor the occurrence of asthma exacerbation(s) or asthma deterioration. After recovery from the first exacerbation or asthma deterioration, the patient will be allowed to proceed with another attempt to reduce OCS dose; however, this must follow a lower speed of OCS down-titration (reductions Q4W). However, in case of a second exacerbation or asthma deterioration, no further OCS dose reduction will be allowed, and the patient will continue on the same OCS dose or will return to a one-step higher dose level (or more as considered necessary by the Investigator), and the patient will then enter the maintenance phase.

Approximately 1-2 weeks prior to end of the OCS reduction phase, the patients who have Partial AI after the repeat morning cortisol test, will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase.

1.4.4 Maintenance phase:

This phase will start from the time the patient reaches a complete withdrawal of OCS (or lowest possible OCS dose) without worsening of asthma control and as determined by the Investigator (based on the cortisol/ACTH stimulation results). The maintenance phase could be initiated earlier if OCS dose reduction failed due to clinical deterioration or because the patient did not recover from AI.

The length of the maintenance phase will last approximately 24 to 32 weeks. The duration of the maintenance treatment phase will depend on when the patient enters the maintenance phase relative to the dosing cycle of benralizumab. During this phase, patients will continue benralizumab Q8W for 3 doses, and then the End of Treatment (EOT) visit will be scheduled 8 weeks (± 7 days) after the last dose of benralizumab.

Patients who have Complete AI or Partial AI at the end of the OCS Reduction phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1- 2 weeks prior to end of the OCS Maintenance phase.

If an asthma exacerbation occurs during the maintenance phase, the length of the maintenance phase will not be extended.

1.4.5 Premature Discontinuation and Follow-Up Contact:

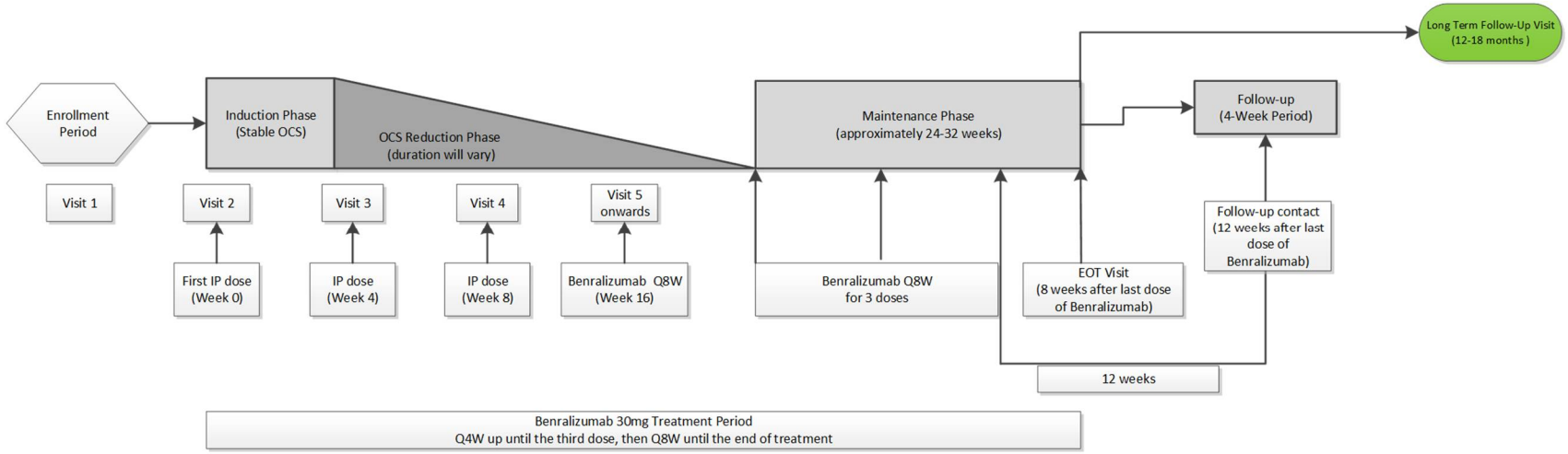
All patients who prematurely discontinue study drug/investigational product or who discontinue from the study should return to the study center and complete the procedures described for the Premature Investigational Product Discontinuation (IPD) visit within 4 weeks (± 7 days) after the last dose of benralizumab.

For all patients dosed with benralizumab, a follow-up contact will be scheduled 12 weeks (± 7 days) after their last dose of benralizumab. Patients who have Complete AI or Partial AI at the end of the Maintenance phase should be followed-up by an endocrinologist or other appropriate specialist, if deemed necessary by the Investigator.

1.4.6 Sputum Sampling for Exploratory Biomarkers:

Not applicable due to protocol amendment.

Figure 1 Study flow chart



1. The duration of the OCS reduction phase will vary based on asthma exacerbations, asthma worsening, HPA integrity, or other safety issues altering the OCS titration schedule.
2. For patients who have reached OCS doses equal to 5 mg/day, HPA axis integrity will be assessed at the end of a 4-week period on 5 mg/day (8-9 am morning cortisol level), followed by a ACTH stimulation test within approximately 1 week, in case of indeterminate result. For those patients who had a baseline OCS dose equal to 5 mg/day, HPA axis integrity will be assessed 4 weeks after first dose of benralizumab administration and before initiation of the OCS reduction phase
3. The maintenance phase will start from the time the patient reaches a complete withdrawal of OCS (or lowest possible OCS dose per Section 1.4.3) without worsening of asthma control and as determined by the Investigator (based on the cortisol/ACTH stimulation results). This period will last approximately 24 to 32 weeks from the time the patient reaches a complete withdrawal of OCS (0 mg) or the lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control. The length of the maintenance phase may vary depending on the when the patient enters the maintenance phase. During this phase, patients will continue benralizumab Q8W for 3 doses and then the EOT visit will be scheduled 8 weeks (± 7 days) after the last dose of benralizumab.
4. End of the study will be different for individual patients and will depend on baseline OCS dose, occurrence of asthma exacerbation or asthma worsening, and HPA axis integrity.
5. Patients who discontinue treatment early will undergo the Premature IPD visit within 4 weeks (± 7 days) after the last dose of benralizumab.
6. A follow-up contact will occur 12 weeks (± 7 days) after the last dose of benralizumab, discontinuation of study drug, or discontinuation from the study. All patients who prematurely discontinue study drug or discontinue from the study should return to the study center and complete the procedures described for the Premature IPD visit within 4 weeks (± 7 days) after the last dose of benralizumab.
7. Patients who have Partial AI or Complete AI at the end of the Maintenance phase, should be followed-up by an endocrinologist or other appropriate specialist, if deemed necessary by the Investigator.
8. Patients who enroll in the long term follow up substudy during the EOT visit will still undergo the final 4-week follow-up visit. ICF for the PONENTE Long Term Follow Up substudy must be obtained any time from EOT of the main PONENTE study and to prior to any activities of the PONENTE Long Term Follow Up visit.

1.5 Study governance and oversight

1.5.1 Scientific Committee

A Scientific Committee consisting of internal AstraZeneca and external experts (pulmonologists, allergists, and endocrinologists) who have been involved in the design of the clinical study will advise the sponsor on changes to the study design and provide recommendations on issues related to the study conduct, if required. In addition, the committee will be involved in the review and interpretation of the study results. The Scientific Committee will be governed by a charter, detailing roles and responsibilities and processes.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective	Endpoints/Outcome Variables
To assess the ability to reduce OCS dose in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Primary outcome measures** • Patients who achieve 100% reduction in daily OCS dose that is sustained over at least 4 weeks without worsening of asthma • Patients who achieve 100% reduction or a daily OCS dose ≤5 mg, if reason for no further OCS reduction is AI, that is sustained over at least 4 weeks without worsening of asthma **Key supportive outcome measures** • Patients who achieve a daily OCS dose of ≤5 mg that is sustained over at least 4 weeks without worsening of asthma • Patients who achieve a ≥90%, ≥75%, ≥50%, and >0% reduction in daily OCS dose, sustained over at least 4 weeks without worsening of asthma • Change from baseline in daily OCS dose (mg) from start of OCS reduction to end of the OCS reduction phase

2.2 Secondary objectives

Secondary Objective	Outcome Measure
To assess the sustained reduction of daily OCS dose while not losing asthma control during approximately 6 months after the end of OCS down-titration (maintenance phase) in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • Change in daily OCS dose from the end of OCS reduction phase to the end of the maintenance phase (EOT visit) • Time to first increase in OCS dose during maintenance phase, after achieving the minimum OCS dose during the OCS reduction phase
To assess the effect of OCS down-titration protocol on asthma control in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • Asthma Control Questionnaire 6 (ACQ-6) scores at baseline (Visit 2), Visit 3, end of OCS reduction phase, and monthly from end of OCS reduction phase to end of maintenance phase (EOT visit) • Change from baseline in ACQ-6 to Visit 3, end of OCS reduction phase, and end of maintenance phase (EOT visit) • Responder analysis of ACQ-6 scores from Visit 2 through end of maintenance phase
To assess the effect of OCS down-titration protocol on quality of life in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg SC	**Key outcome measure** • Change from baseline (Visit 2) in St. George's Respiratory Questionnaire (SGRQ) total scores to the end of maintenance phase (EOT visit) • Responder analysis of SGRQ total scores at the end of maintenance phase

2.3 Safety objectives

Safety Objective	Outcome Measure
To evaluate the occurrence of AI when reducing OCS	**Key outcome measure** • Patients with complete AI
To assess the effect of OCS down-titration protocol on asthma exacerbations in adult patients with severe asthma treated with benralizumab 30 mg SC	**Key outcome measures** • Annualized asthma exacerbation rate • Annualized asthma exacerbation rate leading to hospitalization or emergency room visit
To assess the safety and tolerability of benralizumab in patients who reduce their chronic OCS dose	• Adverse events/Serious adverse events • Laboratory parameters and vital signs
To evaluate corticosteroid toxicity after OCS reduction	• Glucocorticoid toxicity index (GTI)

2.4 Exploratory objectives

Exploratory Objective	Outcome Measure
To investigate the contribution of genomic variants to the study outcomes	• Association of common and rare genomic variants with patient responses
To assess early improvements in asthma status during the first 4 weeks of benralizumab treatment before initiation of OCS reduction	• Patient Global Impression of Change (PGIC)
To assess the impact of OCS down-titration on blood eosinophil levels	**Key outcome measure** • Change from baseline blood eosinophils
To investigate biomarkers for predicting response to benralizumab	**Key biomarker parameters** • Serum samples at baseline for protein biomarkers • Plasma for eosinophil-derived neurotoxin

Please refer to Appendix K for the objectives of the PONENTE Long Term Follow Up Substudy.

3. PATIENT SELECTION, ENROLLMENT, 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

For inclusion in the study, patients should fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures
2. Female or male aged ≥18 years at the time of Visit 1
3. Women of childbearing potential (WOCBP) must agree to use one highly effective form of birth control (confirmed by the Investigator) from 48inimizin throughout the study duration and within 16 weeks after last dose of IP. Highly effective forms of birth control include:

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

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Sexual abstinence, i.e. refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.)
- Vasectomized sexual partner provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success

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 amenorrhoeic for 12 months prior to the planned start date of the induction phase without an alternative medical cause. The age-specific requirements that apply are as follows:

- Women <50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle-stimulating hormone levels in the postmenopausal range
- Women ≥50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment

4. Weight of ≥40 kg
5. Nonsmokers, current smokers, or former smokers with a smoking history of ≤20 pack-years at Visit 1
6. Peripheral blood eosinophil count of ≥150 cells/μL assessed by central laboratory at Visit 1 or documented eosinophil count of ≥ 300 cells/μL in the past 12 months
7. History of physician-diagnosed asthma that requires continuous treatment with high-dose ICS (high-dose ICS is budesonide/formoterol HFA ≥640/18 per day or equivalent, fluticasone propionate DPI > 500/day or equivalent, or authorized generics for these products; see Appendix E and GINA 2018 guidelines for more recommendations) plus a LABA for at least 6 months prior to Visit 1. The ICS and LABA can be contained within a combination product or given by separate inhalers. The ICS can also be given via nebulized solution for inhalation:

- In order to aid the dose assessment, ICS equivalents for high-dose fluticasone propionate dry powder, as published by the Global Initiative for Asthma (GINA) guidelines, are presented in Appendix E
- For ICS monotherapy preparations, or ICS/LABA combination preparations not specifically mentioned in GINA (e.g. newer formulations, authorized generics), the highest approved maintenance dose in the local label will also meet this ICS criterion. Additionally, in countries where the high-dose ICS or ICS/LABA is not available (e.g. only the medium-dose ICS or ICS/LABA is available in that country), the highest approved maintenance dose in the local label will also meet this ICS criterion

Note: Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline) are allowed.

8. Chronic OCS therapy equivalent to a daily dose of at least 5 mg of prednisone for at least 3 continuous months directly preceding Visit 1 (to be documented in medical records)

   Note: Alternate intake of OCS (ie, every other day) or other frequency is allowed provided the average daily dose is equivalent to at least 5 mg of prednisone and the patient is switched to a daily intake of prednisone/prednisolone at Visit 1. Systemic corticosteroid doses administered by any route other than oral cannot be used to determine the average daily dose preceding Visit 1

9. Patient should be on a stable OCS dose for at least 4 weeks prior to Visit 1. To aid the dose assessment, a guide for OCS dose equivalence is presented in Appendix F. Patients must agree to switch to study-required prednisone/prednisolone as their OCS for the duration of the study

See Appendix K for inclusion/exclusion criteria, and restrictions related to the PONENTE Long Term Follow Up substudy.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Clinically important pulmonary disease other than asthma (eg, active lung infection, chronic obstructive pulmonary disease [COPD], asthma-COPD overlap [ACO] bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha-1 antitrypsin deficiency, primary ciliary dyskinesia) or have ever been diagnosed with pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatous polyangiitis [EGPA], hypereosinophilic syndrome [HES])
2. Known history of allergy or reaction to the study drug formulation

3. History of anaphylaxis to any biologic therapy
4. 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
5. Asthma exacerbation requiring use of systemic corticosteroids, increase in maintenance dose of OCS, or acute upper/lower respiratory infection that requires antibiotics or antiviral medication within 30 days prior to Visit 2 (first benralizumab dose)

   An extension of the screening period up to 3 months is allowed to ensure that a patient recovers from any asthma exacerbation or acute upper/lower respiratory infection (refer Section 4.1.1 for more details)
6. Intention to use any concomitant medication that is not permitted by this protocol or failure to undergo the required washout period for a particular prohibited medication

   Explanatory note: Refer to Section 7.8 for washout periods of prohibited medications
7. History of alcohol or drug abuse within 12 months prior to the date informed consent is obtained
8. History of known immunodeficiency disorder, including history of a positive HIV test
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥3 × upper limit of normal (ULN) confirmed at Visit 1
10. Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent is obtained
11. Concurrent enrollment in another interventional clinical trial
12. AstraZeneca staff involved in the planning and/or conduct of the study
13. Employees of the study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals
14. Currently pregnant, breastfeeding, or lactating
15. Received previous treatment with benralizumab in the present study (patients may not re-enter the study after completion or premature discontinuation).
16. Coincident primary adrenal failure (Addison's disease) or irreversible secondary hypoadrenalism due to another independent cause (eg, pituitary tumor or its treatment)
17. Coexistent inflammatory conditions for which chronic OCS doses are part of their maintenance treatment such as, but not limited, giant cell arteritis or polymyalgia rheumatica
18. Exclusion from genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
    - Previous allogeneic bone marrow transplant

- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection

19. 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
    - Confound the study results; or would impact the scientific validity of the data outcome. Impede the subject's ability to complete the entire duration of study
20. Any clinically significant abnormal findings in physical examination, medical history, vital signs, hematology, clinical chemistry, or urinalysis during the enrollment 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.
21. History of cancer. Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, 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 was 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 was obtained
22. Any other (non-asthma related) disease flare-up or AE/SAE during the screening period that requires the temporary use of systemic corticosteroids, increase in maintenance OCS, or requires antibiotics or antiviral medication within 30 days prior to Visit 2 (first benralizumab dose). However, an extension of 3 months of the screening period is allowed to ensure that a patient recovers from any non-asthma related disease flare-up or AE/SAE. See Section 7.8 Table 6 for more detail.
23. Current night-shift workers.

See Appendix K for inclusion/exclusion criteria, and restrictions related to the PONENTE Long Term Follow Up substudy.

Procedures for withdrawal of incorrectly enrolled patients are discussed in Section 3.4.

3.3 Patient enrollment

Investigators will keep a record of patients considered for and included in the study. This prescreening/screening log will be evaluated periodically by AstraZeneca or its delegates during routine monitoring visits.

The Investigators will do the following:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed
2. Assign each potential patient a unique enrollment number, beginning with 'E#' via an interactive web/voice response system (IWRS/IVRS)
3. Determine patient eligibility. See Sections 3.1 and 3.2

Specific information concerning the use of the IWRS/IVRS will be provided in a separate manual.

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

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. Patients who are enrolled but are subsequently found not to meet all the eligibility criteria must be withdrawn from the study. If a patient who does not meet all the eligibility criteria is incorrectly started on treatment, the Investigator should inform the AstraZeneca Physician immediately. A discussion should occur between the AstraZeneca Physician and the Investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca Physician must ensure all decisions are appropriately documented.

3.5 Restrictions

After enrollment, the patient should continue their usual asthma controller medication regimen without change during the study. Any changes deemed essential for patient safety or any other reason should be brought to the attention of the Medical Monitor or AstraZeneca Physician. The rationale for any change in the patient's usual controller medication should be documented in the source as well as in the medication electronic case report form (eCRF). Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice. Section 7.8 describes the concomitant medications allowed and prohibited during the study period.

Treatment with prednisone/prednisolone should be withheld until the morning of serum cortisol measurement/ACTH stimulation test as defined below:

- Prednisone/prednisolone: 24 hours prior to morning cortisol level testing
- High-dose ICS: No ICS (or ICS/LABA if in single inhaler) treatment on the morning of the cortisol testing

The visit should be rescheduled if the above medications are not withheld properly (note: SABA rescue is allowed throughout the study). Use of ICS/LABA as a reliever (eg, Symbicort

Maintenance and Reliever Treatment) that was part of the patient's usual asthma controller regimen at baseline is allowed; however, it should also be withheld before cortisol testing as described above. Any maintenance therapy such as long-acting muscarinic antagonists used prior to study entry should not be changed during the study.

3.5.1 Other restrictions

- Fertile and sexually active patients and their partners must use highly effective contraceptive methods throughout the study and at least for 16 weeks (5 half-lives) after last administration of the study drug
- Patients must abstain from donating blood or plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of study drug

3.6 Discontinuation of study drug and criteria for withdrawal

Patients may be discontinued from study drug in the following situations:

- Patient decision—the patient is free at any time to discontinue treatment, without prejudice to further treatment
- Severe noncompliance with the Clinical Study Protocol
- Eligibility requirement found not to be fulfilled
- Pregnancy
- AE that, in the opinion of the Investigator, contraindicates further dosing
- Lost to follow-up when the following three attempts at contact have failed:
  - Three (3) attempts of either phone calls, faxes, or emails
  - Having sent 1 registered letter/certified mail
  - One unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed by local regulations
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the study drug
  - Development of helminth parasitic infestations requiring hospitalization
  - An asthma-related event requiring mechanical ventilation

3.6.1 Procedures for discontinuation of a patient from study drug

A patient who decides to discontinue study drug will always be asked about the reason(s) and the presence of any AEs.

All patients who prematurely discontinue study drug should return to the study center and complete the procedures described for the IPD visit within 4 weeks (± 7 days) after last study drug administration. The reason for premature discontinuation of study drug should be

documented in the source documentation and recorded in the eCRF. Patients will be required to return to the study center one last time at 12 weeks (± 7 days) after the last dose of study drug for final study-related assessments (see Table 1).

3.6.2 Screen failures

Screen failures are patients who do not fulfill the inclusion criteria (see Section 3.1) or who meet an exclusion criterion (see Section 3.2) during the enrollment period. These patients should have the reason for study withdrawal recorded as 'screen failure' (the potential patient does not meet one or more criteria required for participation in a trial; this reason for study withdrawal is only valid for not enrolled patients).

3.6.3 Withdrawal of informed consent

Patients are free to withdraw from the study at any time (study drug and assessments), without prejudice to further treatment.

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. The patient will return the electronic patient-reported outcome device (ePRO).

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

If the patient agrees, he/she will be asked to return to the study site to complete procedures described for the IPD visit and follow-up visits (Table 1).

4.3.1.1 Withdrawal of consent for genetic research

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

3.7 Discontinuation of the study

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

- Meet individual stopping criteria or 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 termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF.

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

Table 1 Study plan – Treatment period and follow-up

Assessment*	Protocol section	Screening (starting Week -2)	Induction phase (starting Week 0)	OCS reduction phase (Week 4 onwards)			Maintenance phase[e]		IPD	Follow-up[g]	Unscheduled visit [q]
		V1	V2 +7 days	Benralizumab dosing visit[a] (V3 onwards)	OCS ≤5 mg/day (Morning Cortisol Visit)[b]	Phone call[d]	Maintenance Phase benralizumab visit	EOT[f]			
				± 7 days	± 7 days[c]		± 7 days	± 7 days	± 7 days	± 7 days	
Written informed consent	10.4	X									
Demographics[h]	4.1.1	X									
Verify inclusion/exclusion criteria	3.1/3.2	X	X								
Medical/surgical and asthma history	4.1.1	X									
Complete physical examination	5.2.5.1	X									
Brief physical examination	5.2.5.2		X	X	X		X	X	X		X
Weight and height[i]	5.3.1	X			X			X	X		
ACQ-6[j] and maintenance medication assessment	5.3.4.1		X	<<Weekly from Visit 2 until EOT visit>>					X		X
SGRQ	5.3.4.1		X					X	X		
PGIC[k]	5.3.4.1		X	X							

Table 1 Study plan – Treatment period and follow-up

Assessment*	Protocol section	Screening (starting Week -2)	Induction phase (starting Week 0)	OCS reduction phase (Week 4 onwards)			Maintenance phase[e]		IPD	Follow-up[g]	Unscheduled visit [q]
		V1	V2 +7 days	Benralizumab dosing visit[a] (V3 onwards)	OCS ≤5 mg/day (Morning Cortisol Visit)[b]	Phone call[d]	Maintenance Phase benralizumab visit	EOT[f]			
				± 7 days	± 7 days[c]		± 7 days	± 7 days	± 7 days	± 7 days	
Train on and dispense ePRO	5.3.4.1		X								
Check ePRO compliance	5.3.4.1			X	X	X	X	X	X		X
Vital signs	5.2.6	X	X	X	X		X	X	X		X
Serum chemistry	5.2.4	X			X			X	X		
Hematology	5.2.4	X			X			X	X		
Serum pregnancy test and FSH test[l]	5.2.4.1/ 3.1	X						X	X		
Urine pregnancy test	5.2.4.1		X	X	X		X				
Prednisone/ prednisolone levels[m]	5.3.2	X									
Serum for total IgE	5.3.3	X									
Serum for Phadiatop test	5.3.3	X									
Blood sample for genomic analysis	5.6	X									

Table 1 Study plan – Treatment period and follow-up

Assessment*	Protocol section	Screening (starting Week -2)	Induction phase (starting Week 0)	OCS reduction phase (Week 4 onwards)			Maintenance phase[e]		IPD	Follow-up[g]	Unscheduled visit [q]
		V1	V2 +7 days	Benralizumab dosing visit[a] (V3 onwards)	OCS ≤5 mg/day (Morning Cortisol Visit)[b]	Phone call[d]	Maintenance Phase benralizumab visit	EOT[f]			
				± 7 days	± 7 days[c]		± 7 days	± 7 days	± 7 days	± 7 days	
Plasma for eosinophil-derived neurotoxin	5.7.2	X						X	X		
Serum for biomarkers	5.7.1	X			X						
Sputum induction[n]	5.7.3	Not applicable due to protocol amendment									
Morning cortisol testing[c]	5.2.1.1				X		X[r]	X[r]			
AI symptom evaluation	5.2.1/ 5.2.1.2				X						
Glucocorticoid toxicity index	5.2.7		X		X			X	X		
Assessment of asthma exacerbations	5.2.2/ 5.2.3	X	X	Ongoing based on investigators' indication			X	X	X	X	X
OCS dose reduction [o]	5.1.2			Ongoing based on investigator's indication							
Adverse events	6.1	X	X	X	X	X	X	X	X	X	X
Concomitant medication	7.8	X	X	X	X	X	X	X	X	X	X

Table 1 Study plan – Treatment period and follow-up

Assessment*	Protocol section	Screening (starting Week -2)	Induction phase (starting Week 0)	OCS reduction phase (Week 4 onwards)			Maintenance phase[e]		IPD	Follow-up[g]	Unscheduled visit [q]
		V1	V2 +7 days	Benralizumab dosing visit[a] (V3 onwards)	OCS ≤5 mg/day (Morning Cortisol Visit)[b]	Phone call[d]	Maintenance Phase benralizumab visit	EOT[f]			
				± 7 days	± 7 days[c]		± 7 days	± 7 days	± 7 days	± 7 days	
Switch to prednisone/ prednisolone	Appen-dix G	X									
Administration of benralizumab	4.2		X	X	X[p]		X				

[a] Benralizumab dosing will be administered as Q4W dosing up until the third dose of benralizumab (Visits 2 to 4) and Q8W for each subsequent dose (8 weeks between the 3rd and 4th benralizumab dose).

[b] For patients who have reached OCS doses equal to 5 mg/day, HPA axis integrity will be assessed after 4 weeks have passed on 5 mg/day (8-9 am morning cortisol level, followed by an ACTH stimulation test within approximately 1 week, in case of partial AI). For those patients who had baseline OCS doses equal to 5 mg/day, HPA axis integrity will be assessed 4 weeks after first dose of benralizumab administration and before initiation of the OCS reduction phase.

[c] Benralizumab administration should be delayed/advanced to match the visit where HPA axis evaluation will be tested, provided the period between benralizumab administration is no longer than 10 weeks.

[d] During the OCS reduction phase, the Investigator and/or an authorized delegate should call the patient for his/her OCS reduction. OCS reduction could also coincide with a benralizumab dosing visit, or unscheduled visit (due to other clinical issue, per Investigator discretion).

[e] Maintenance phase will last approximately 24 to 32 weeks from the time the patient reaches a complete withdrawal of OCS without worsening of asthma control. The length of the maintenance phase will vary depending on when the patient enters the maintenance phase.

[f] The EOT visit will occur 8 weeks (± 7 days) after the last dose of benralizumab. Patients who prematurely discontinue study drug should return to the study site and complete the procedures described for the Premature IP Discontinuation Visit (IPD) within 4 weeks (± 7 days) after the last dose of benralizumab.

[g] For all patients who receive benralizumab, a follow-up contact will be scheduled 12 weeks (± 7 days) after their last dose of benralizumab.

[h] Demographic information includes date of birth, age, sex, race, and ethnicity (as per local regulations).

[i] Height to be measured only at screening

[j] Patients will complete the ACQ-6 weekly (± 2 days) from Visit 2 until EOT using the ePRO.

[k] The PGIC will be completed on a weekly (± 2 days) basis (starting at Week 0) during the first month of treatment using the ePRO.

[l] FSH will be analyzed at the screening visit to confirm postmenopausal status only in women <50 years of age who have been amenorrhoeic for ≥12 months.

[m] Done only for patients who switch to prednisone/prednisolone at V1. If this test is required, the laboratory tests should be delayed (for all parameters, not just prednisone levels) by 3 to 7 days after having switched the OCS and V2 can be done up to 2 weeks after collection of laboratory samples. Prednisone/prednisolone levels should be measured approximately 1 to 2 hours after prednisone/prednisolone intake on the same day.

[n] Not applicable due to protocol amendment

[o] The OCS reduction will continue until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control.

[p] Benralizumab administration to follow Q8W periodicity, so it may or may not occur at the same time as morning cortisol testing.

[q] The following instances should also be captured as an UNS visit: 1) unscheduled blood collection (ex. Hy's Law); 2) replacement genetic blood sample in case of DNA extraction failure.

[r] Patients who have Partial AI after the repeat morning cortisol test, will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the OCS Reduction phase. Patients who have Complete AI or Partial AI at the end of the OCS Reduction phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the OCS Maintenance phase (prior to EOT visit).

*for the PONENTE Long Term Follow Up Substudy, please refer to Appendix K.

4.1 Enrollment period

4.1.1 Screening visit – Visit 1 (Week -2)

Each patient will provide written informed consent prior to any study-specific procedures and will undergo assessments applicable for each visit as outlined in Table 1. Registration of the patient's enrollment via IWRS/IVRS should occur on the day that Visit 1 procedures are performed.

At screening, consenting patients will be assessed to ensure that they meet all eligibility criteria. Visit 1 assessments are primarily concerned with assessment of eligibility (inclusion/exclusion criteria), including asthma disease state, requisite level of severity based on background medications and eosinophil count.

Demographic information, including date of birth, age, sex, race, and ethnicity, will be collected during the screening visit as per local regulations. All patients who are not already taking prednisone/prednisolone as their OCS treatment will be switched to prednisone/prednisolone. Testing of prednisone/prednisolone levels will be done only for patients who switch to prednisone/prednisolone. If this test is required, all laboratory tests should be delayed by 3 to 7 days after having switched the OCS (Appendix F). Prednisone/prednisolone levels should be measured approximately 1 to 2 hours after prednisone/prednisolone intake on the same day.

At the screening visit, blood samples will be collected for assessments such as laboratory tests, genomic analysis, serum biomarkers, total IgE, Phadiatop test, EDN, eosinophil count, etc., as mentioned in Table 1. Current, regular use of a high-dose ICS and LABA for ≥6 months prior to enrollment will be recorded. Additionally, patients must be on chronic daily OCS therapy (equivalent to ≥5 mg/day of prednisone) for ≥3 continuous months directly preceding Visit 1, and this must be documented in the medical records. Inhaled corticosteroids and LABAs may have been administered as either a fixed dose or 2 separate inhalers and must be consistent with the highest approved maintenance dose in the local country (Inclusion Criterion 6). A stable dose of OCS must have been maintained for ≥4 weeks prior to Visit 1.

Patients can proceed directly to Visit 2 once central laboratory results are received, and all eligibility requirements are confirmed. Visit 2 should be done up to 2 weeks after Visit 1. For patients switching to prednisone/prednisolone at V1 and who thus require a delay in laboratory tests, Visit 2 can be done up to 2 weeks after the collection of laboratory samples. Patients will continue to receive treatment with their current ICS/LABA and other controller(s) (if applicable) with no changes.

If the patient experiences an asthma exacerbation during screening that requires evaluation in an urgent care center or emergency department, hospitalization, or temporary increase (bolus/burst) of systemic steroids, they will not be screen failed, but an extension of the screening period up to 3 months will be allowed to ensure that the patient recovers from the asthma exacerbation and the OCS dose is stabilized. Additionally, if a patient experiences acute upper/lower respiratory infection that requires antibiotics or antiviral medication during

screening, then they also will not be screen failed and an extension of the screening period of up to 3 months will be allowed. If the patient recovers from the asthma exacerbation or acute upper/lower respiratory infection and is stable for ≥2 weeks, then the patient will be allowed to continue in the study. Patients must enter the treatment phase within 3 months of screening; if it has been longer than 3 months, then the patient may be rescreened.

If the patient experiences a non-asthma related event requiring temporary increase (bolus/burst) of systemic steroids, an extension of the screening period of up to 3 months may be allowed (AZ study physician can be consulted if required).

Patient's eligibility should be evaluated at the screening visit with the relevant documentation entered in the source and eCRF.

4.1.2 Rescreening

Rescreening of patients for any reason will be allowed only once for each patient and only upon approval of the AstraZeneca Physician. Patients will keep the same e-code.

4.2 Open-label treatment period

The open-label treatment period is divided into 3 phases based on the OCS dose adjustment: induction phase (Section 4.2.1), reduction phase (Section 4.2.2), and maintenance phase (Section 4.2.3). Patients will complete the ACQ-6 and maintenance medication assessment weekly using the ePRO throughout the treatment period (see Section 5.3.4 for details).

4.2.1 Induction phase

The induction phase will start at Visit 2 (Week 0) and will continue until the day prior to Visit 3. Inclusion and exclusion criteria will be confirmed at Visit 2 and the patient will complete the ACQ-6, maintenance medication assessment, and SGRQ on the ePRO, prior to benralizumab administration, to establish baseline scores. Additionally, during the induction phase only, patients will complete the Patient Global Assessment of Change (PGIC) on a weekly basis on the ePRO in addition to weekly completion of the ACQ-6 and maintenance medication assessments. All patients who meet eligibility criteria and enter the study will receive open-label benralizumab. The first dose of the study drug will be administered SC as Q4W dosing at Visit 2. Patients will be observed at the site for 2 hours after dosing. During this time, patients will remain on their regular asthma controller medications, and no dose adjustments to OCS will be made. Patients who experience asthma exacerbations that require evaluation in an urgent care center or emergency department, hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) will be managed as per Section 5.2.3.

4.2.2 OCS Reduction phase

The reduction phase will start at Visit 3 (Week 4) after the dose of benralizumab, and subsequent OCS dose reductions will occur according to the schema defined for each baseline OCS dose until patients reach a 5 mg/day dose (Table 2).

The study drug will be administered SC as Q4W dosing up until the third dose of benralizumab (therefore at Visits 3 and 4 during the OCS reduction phase) and then Q8W thereafter (8 weeks between the 3rd and 4th benralizumab dose). Patients will be observed at the site for 2 hours after dosing for the first 3 study drug administrations (therefore at Visits 3 and 4 during the OCS reduction phase) and for 1 hour after subsequent study drug administrations for any acute drug reactions.

For all patients, HPA axis integrity will be evaluated after 4-weeks on 5 mg/day and prior to tapering down the OCS dose (for patients with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase)

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the patient has:

- Normal cortisol levels
- Complete AI

Cortisol levels from the morning cortisol test that are below normal range and above the Complete AI range are considered "Indeterminate;" and require additional testing described below.

Secondly, the ACTH stimulation test (ie, Synacthen®, Cortrosyn™) is done within approximately 1 week in the subset of patients with indeterminate results from the morning cortisol test [see also Section 5.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the patient has:

- Normal cortisol levels
- Complete AI
- Partial AI

Dose reduction of OCS should be interrupted if the patient suffers an asthma exacerbation (Section 5.2.3) or in case the Investigator considers the patient to be having a significant deterioration of his/her asthma disease (Section 5.1.2.1). After the OCS bolus/burst to treat an exacerbation is completed, or after recovery from an asthma deterioration, the Investigator may either return the OCS dose to a one-step higher dose level (or more if considered necessary by the Investigator) than what was prescribed when the exacerbation or asthma worsening occurred or continue with the same OCS dose, which must be maintained at a stable dosage for at least two weeks.

After recovery from the first exacerbation or asthma deterioration, the patient will be allowed to proceed with another attempt to reduce their OCS dose; however, the patient will follow a lower speed for OCS down-titration (reductions Q4W; Table 3).

In case of a second exacerbation or asthma deterioration, no further OCS dose reduction will be allowed, and the patient will remain on the same OCS dose or return to a one-step higher dose level (or more as considered necessary by the Investigator) than what was prescribed

when the exacerbation/worsening occurred. The OCS dose reduction phase will then be terminated, and the patient will enter the maintenance phase. Further details are provided in Section 5.2.3.

Patients who experience asthma exacerbations that require evaluation in an urgent care center or emergency department, hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) will be managed as per details in Section 5.2.3.

To help investigators evaluate the occurrence of a significant asthma deterioration, investigators will have access to the patient's weekly ACQ-6 scores (completed by means of an ePRO). A significant deterioration is defined as a worsening in ACQ-6 score of at least 0.5 from value at Visit 2. If the ACQ-6 score at Visit 2 is missing, the 1st score recorded post-Visit 2 and pre-OCS reduction may be used as baseline for the 0.5-point increase (note, however, that it will not be used to impute the baseline value for ACQ-6 analysis). Investigators should consider this information together with any other information reported by patients on signs/symptoms of the disease as well as compliance with maintenance asthma therapy. Based on the totality of the information, investigators can decide whether the patient can continue with the OCS dose reduction until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control. The other patient-reported outcomes (PROs) will be carried out per the schedule in Table 1.

The length of the benralizumab treatment period will depend on the baseline OCS dose, occurrence of asthma exacerbation(s) or asthma worsening, and whether the patient experiences AI. Procedures specific for the visits are listed in Table 1. Restrictions as set out in Section 3.5 will continue to apply throughout the treatment period.

From Visit 3 onwards, the dose of OCS may be reduced only when conditions listed in Section 5.1.2 are met. The reductions will occur at an interval according to the titration schedule. The first OCS dose reduction can occur at Visit 3 after the dose of benralizumab at the site.

Patients will reduce OCS following confirmation from the Investigator/study site personnel at site visits or via telephone calls. Phone calls can be scheduled as required to assess the occurrence of exacerbations, asthma control (ACQ-6 scores), AEs, and concomitant medication use. Additional site visits can be scheduled for patients in case of poor asthma control.

Table 2 depicts the proposed dose reduction schedule, provided the patient does not experience an exacerbation, worsening of asthma control, or AI. In case of asthma exacerbation or worsening, the dose reduction schedule will be longer (Table 3) and will vary depending on HPA axis integrity and/or on the patient's recovery from an exacerbation.

Depending on the baseline OCS dose and on the possibility of experiencing AI symptoms, each patient will spend a different amount of time in the reduction phase and the number of visits will be adjusted accordingly.

Approximately 1-2 weeks prior to end of the OCS reduction phase, the patients who have Partial AI, will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the OCS Reduction phase.

4.2.3 Maintenance phase

A patient will enter the approximately 24- to 32-week maintenance phase when they reach an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control. This could be earlier if OCS dose reduction fails due to clinical deterioration or if the patient experiences an asthma exacerbation. The duration of the maintenance phase will depend on when the patient enters the maintenance phase relative to the dosing cycle of benralizumab. During this phase, patients will continue benralizumab Q8W for 3 doses and then the EOT visit will be scheduled 8 weeks (± 7 days) after the last dose of benralizumab (assessments performed as per Table 1). However, if during this period, the patient experiences asthma deterioration or an exacerbation, the length of the maintenance phase will not be extended and the patient will continue on 3 doses of benralizumab Q8W. Additionally increases in the maintenance OCS dose due to an asthma exacerbation is permitted per investigator discretion. Patients who experience an asthma exacerbation that requires evaluation in an urgent care center or emergency department, hospitalization, or temporary increase of systemic steroids (bolus/burst dosing) will be managed as per details in Section 5.2.3.

Patients who have Complete AI or Partial AI at the end of the OCS Reduction phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to end of the OCS Maintenance phase (prior to EOT visit).

Patients will return the ePRO at the EOT visit. Completion of the treatment will be registered in IWRS/IVRS at the EOT visit for each patient. After stopping study drug, the patient will be adjusted to a post-study asthma maintenance regimen (which may include a respiratory biologic, if needed), per Investigator discretion.

Patients who prematurely discontinue study drug (see Section 3.6) should return to the study site and complete procedures described for the IPD visit and follow-up visit within 4 weeks (± 7 days) and 12 weeks (± 7 days) after the last dose of study drug, respectively. Study assessments and procedures to be performed at the IPD and follow-up visits are outlined in Table 1. Reasons for premature discontinuation of study drug should be recorded in the eCRF.

4.3 Follow-up period

All patients who complete the maintenance phase or who prematurely discontinue study drug will have a follow-up contact after 12 weeks of the last dose of benralizumab. The follow-up contact can be done either on-site or via telephone contact. During this visit, patients will be assessed for any ongoing safety issues, and AEs and concomitant medications will be collected. Patients who have Partial AI or Complete AI at the end of the Maintenance phase, should be followed-up by an endocrinologist or other appropriate specialist, if deemed necessary by the Investigator.

4.4 PONENTE Long Term Follow Up Substudy: Study Plan and Timing of Procedures

At the end of the PONENTE EOT visit, patients will be invited to participate in a long term follow up visit 12- to 18-months after completion of the main PONENTE study. This substudy is intended to further assess changes in asthma maintenance therapy in a real-world setting, i.e., according to the treatment prescribed by their healthcare provider. Additionally, there will be assessment of recovery from AI as well as assessment of glucocorticoid toxicity by means of GTI.

Between the EOT visit of the main PONENTE study and the long term follow up visit, patients will be treated according to standard practice; for example, any changes to maintenance asthma regimens are allowed, including further reductions of OCS as recommended in the GINA 2020 report. There will be one on-site visit 12-18 months after the EOT visit of the main PONENTE study. Patients who enrol in the long term follow up visit substudy will still complete the follow-up visit at the end of the main PONENTE study. See Appendix K for further details.

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

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

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

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

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).

- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).

- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, if possible. Additional information related to the visit can be obtained via telemedicine.

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

5. STUDY ASSESSMENTS

The Rave Web-Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the Clinical Study Protocol 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. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Please refer to Appendix K for details on study assessments conducted during the PONENTE Long Term Follow Up substudy.

5.1 Efficacy assessments

5.1.1 Assessment of OCS dose

All patients who meet eligibility criteria and enter the study will receive open-label benralizumab and reduce their OCS dose until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) as per the details provided in Section 4.2.2 and the schedule provided in Table 2 and Section 5.1.2

No further reductions will be made to OCS dose after completion of the reduction phase, and the patient will enter an approximately 24- to 32-week maintenance phase. In case of exacerbations, patients will be managed as per details provided in Section 5.2.3. Additionally, in case the patient experiences asthma deterioration or an exacerbation, increase in the maintenance OCS dose is permitted per investigator discretion.

All OCS dose changes will be documented in the source documentation and recorded in the appropriate eCRF form. Moreover, in case of OCS reduction being temporarily interrupted (in case of an exacerbation or asthma deterioration) or permanently interrupted (exacerbation, asthma deterioration, AI based on cortisol tests, or occurrence of an adrenal crisis), the reason should be documented in the appropriate eCRF, and reduction will be done slowly as per Table 3.

5.1.2 OCS dose titration

At Visit 1, patients will continue with or be switched to prednisone/prednisolone. For patients not previously receiving prednisone/prednisolone as OCS, the conversion table shown in Appendix F will be used to calculate the equivalent prednisone/prednisolone dose for dose titration.

The OCS dose titration in the reduction phase will be followed as per Table 2 depending on the initial OCS dose and HPA axis evaluation. If Table 2 instructs to reduce dose by 5mg increments, but the initial OCS dose is <5 mg to the nearest dosing level: The 1st reduction would be smaller, rounding down to the nearest 5 mg, then continue on with 5 mg Q2W reductions (examples below):

- e.g. 12.5 →10 mg →etc.
- e.g 23→20→15→10 mg →etc.
- e.g. 19→15→10 mg →etc.

If Table 2 instructs to reduce the initial dose by 2.5mg increments, but the initial dose is <2.5mg to the next dosing level: The 1st reduction would be smaller, rounding down to the nearest 2.5mg, then continue on with 2.5 Q4W reductions (examples below):

- e.g. 8→7.5→5→etc.
- e.g. 6.25→5→etc.

For all patients, HPA axis integrity will be evaluated after 4-weeks on 5 mg/day and prior to tapering down the OCS dose (for patients with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase)

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the patient has:

- Normal cortisol levels
- Complete adrenal insufficiency (AI)

Cortisol levels from the morning cortisol test that are below normal range and above the Complete AI range are considered “Indeterminate,” and require additional testing described below.

Secondly, the ACTH stimulation test (ie, Synacthen®, Cortrosyn™) is done within approximately 1 week in the subset of patients with indeterminate results from the morning cortisol test [see also Section 5.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the patient has:

- Normal cortisol levels
- Complete AI
- Partial AI.

Investigators may also choose to slow the down-titration to 1 mg Q4W once the patient reaches a OCS dose of 5 mg/day based on patient symptoms alone regardless of cortisol levels. Once there is evidence of recovery, OCS reduction will continue until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) without losing asthma control.

Table 2 OCS down-titration approaches

Initial OCS dose/day	OCS down-titration to reach an OCS dose of:				
	20 mg	**10 mg**	**7.5 mg**	**5 mg**	**0 mg**
>20 mg	Reduction of 5 mg weekly until reaching dose of 20 mg/day	Reduction of 5 mg Q2W until reaching dose of 10 mg/day	2.5 mg Q2W until reaching dose of 7.5 mg/day	2.5 mg Q4W until reaching dose of 5 mg/day	No AI: reductions of 2.5 mg Q4W until reaching dose of 0 mg/day Risk AI: reductions of 1 mg Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
>10 mg to ≤20 mg		Reduction of 5 mg Q2W until reaching dose of 10 mg/day	2.5 mg Q2W until reaching dose of 7.5 mg/day	2.5 mg Q4W until reaching dose of 5 mg/day	No AI: reductions of 2.5 mg Q4W until reaching dose of 0 mg/day Risk AI: reductions of 1 mg Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
>7.5 mg to ≤10 mg			2.5 mg Q2W until reaching dose of 7.5 mg/day	2.5 mg Q4W until reaching dose of 5 mg/day	No AI: reductions of 2.5 mg Q4W until reaching dose of 0 mg/day Risk AI: reductions of 1 mg Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
>5 mg to ≤7.5 mg				2.5 mg Q4W until reaching dose of 5 mg/day	No AI: reductions of 2.5 mg Q4W until reaching dose of 0 mg/day Risk AI: reductions of 1 mg Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
5 mg					No AI: reductions of 2.5 mg Q4W until reaching dose of 0 mg/day Risk AI: reductions of 1 mg Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]

[a] Risk AI means "partial AI" cortisol testing confirmed with ACTH stimulation testing. After repetition of the test 2 months later, the decision to further reduce OCS dose will be based on the morning cortisol test results. If test results are normal, the OCS dose may be reduced directly to 0 mg/day (if patient is receiving ≤3 mg); the patient will continue receiving 1 mg Q4W if still at risk. If complete AI is indicated, OCS dose will not be modified.

[b] If morning cortisol test results again indicate complete AI at 3 months, the OCS dose will not be modified as this is the final attempt. If morning cortisol test results indicate risk AI, then reductions will be 1 mg Q4W and, if normal, then reductions will be 2.5 mg Q4W.

Table 3 "Rescue" OCS down-titration after recovery from an asthma exacerbation or deterioration

Initial OCS dose/day	"Rescue" OCS down-titration after recovery from an asthma exacerbation or deterioration to reach an OCS dose of:		
	10 mg	**5 mg**	**0 mg**
>20 mg	Reduction of 5 mg Q4W until reaching a dose of 10 mg/day	Reduction of 2.5 mg Q4W until reaching a dose of 5 mg/day	No AI: Reduction of 2.5 mg Q4W Risk AI: 1 mg/day Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
>10 mg to ≤20 mg	Reduction of 5 mg Q4W until reaching a dose of 10 mg/day	Reduction of 2.5 mg Q4W until reaching a dose of 5 mg/day	No AI: Reduction of 2.5 mg Q4W Risk AI: 1 mg/day Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
>5 mg to ≤10 mg		Reduction of 2.5 mg Q4W until reaching a dose of 5 mg/day	No AI: Reduction of 2.5 mg Q4W Risk AI: 1 mg/day Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]
5 mg			No AI: Reduction of 2.5 mg Q4W Risk AI: 1 mg/day Q4W and repeat test 2 months later[a] Complete AI: No OCS dose reduction and repeat test 3 months later[b]

[a] After repetition of the test 2 months later, the decision to further reduce OCS dose will be based on the morning cortisol test results. If test results are normal the OCS dose may be reduced directly to 0 mg/day (if patient was receiving ≤3 mg); the patient will continue receiving 1 mg Q4W if still at risk.

[b] If morning cortisol test results again indicate complete AI at 3 months, the OCS dose will not be modified as this is the last attempt. If morning cortisol test results indicate risk AI, then reductions will be 1 mg Q4W and, if normal, then reductions will be 2.5mg Q4W.

For prednisone doses below 5 mg, if the exact dose strength is not available in the country, the daily dose to be administered could be achieved by dosing every other day. Daily dose will be the average of 2 days. See Appendix G for help dosing <5 mg in relation to tablet strength.

5.1.2.1 Asthma worsening or asthma exacerbation preventing OCS down-titration

The OCS dose titration will be interrupted in case of one of the following circumstances related to the asthma condition:

- Asthma deterioration will be assessed by the investigators when there is an increase in ACQ-6 scores of ≥0.5 from the value at Visit 2. If the ACQ-6 score at Visit 2 is missing, the 1st score recorded post-Visit 2 and pre-OCS reduction may be used as baseline value for the 0.5-point increase (note, however, that it will not be used to impute the baseline for ACQ-6 analysis). The Investigator will decide whether the worsening of asthma should lead to an interruption in tapering of OCS dose until asthma control improves.
- In case of an asthma exacerbation that requires treatment with systemic corticosteroids for at least 3 consecutive days, hospitalization, or emergency room admission, the OCS dose titration will be interrupted, and appropriate treatment will be administered as described in Section 5.2.3.

After recovery from the first asthma deterioration or exacerbation, patients will be offered to continue OCS tapering down at a slower speed (ie, Q4W); however, in the case of a second event of asthma deterioration or exacerbation, the OCS reduction will be stopped.

The lower OCS dose (0 mg or above, if required to control asthma disease) that is not changed during a period of 4 weeks and that ensures a patient does not suffer from an asthma exacerbation or that avoids the occurrence of an asthma deterioration/worsening requiring an increase in OCS dose, based on investigator criteria, will be considered the final OCS dose of the OCS reduction phase, and, thereafter, the patient will initiate the OCS maintenance phase on that OCS dose.

5.2 Safety assessments

5.2.1 HPA axis evaluation

For all patients, HPA axis integrity will be evaluated after 4-weeks on 5 mg/day and prior to tapering down the OCS dose (for patients with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase)

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the patient has:

- Normal cortisol levels
- Complete adrenal insufficiency (AI)

Cortisol levels from the morning cortisol test that are below normal range and above the Complete AI range are considered "Indeterminate," and require additional testing described below.

Secondly, the ACTH stimulation test (ie, Synacthen®, Cortrosyn™) is done within approximately 1 week in the subset of patients with indeterminate results from the morning cortisol test [see also Section 5.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the patient has:

- Normal cortisol levels
- Complete AI
- Partial AI.

The process will be as described in Figure 2.

For females using oral estrogen-containing contraceptives or oral estrogen-containing hormone replacement therapy, the threshold for normal values will be 2 times the normal morning cortisol levels and 1.5 times the normal ACTH stimulation test cortisol levels. Details related to values for normal, partial AI, and complete AI for these patients are provided in the laboratory manual.

For the morning cortisol test, the last OCS dose should be taken ≥ 24 hours prior to testing. Additionally, patients must not take ICS (or ICS/LABA if in single inhaler) treatment on the morning of the cortisol testing (for patients taking a once-daily ICS/LABA formulation, e.g. fluticasone furoate/vilanterol patients must not take the treatment ≤ 24 hours prior to the morning of the cortisol testing). If a patient requires a short course of macrolides, antivirals, or azoles, there must be a window of ≥1 week prior to the testing of cortisol levels (see Section 7.8).

Figure 2 HPA axis evaluation

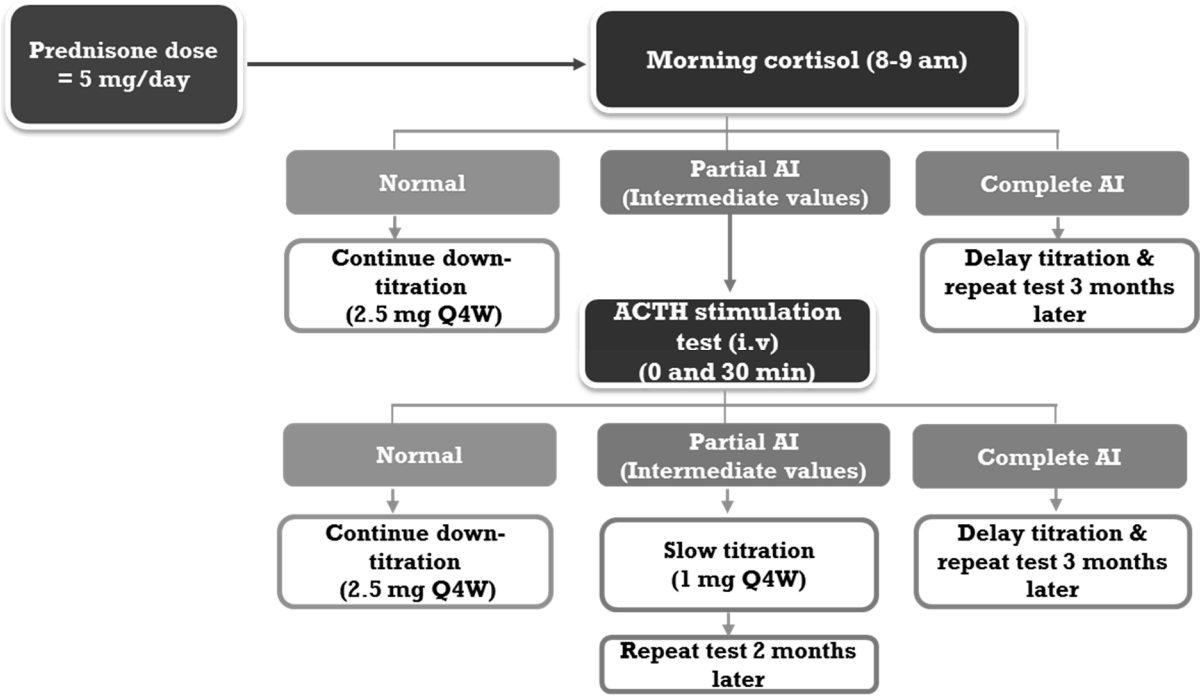


Figure 2: For normal cortisol levels with concurrent signs/symptoms of AI, OCS down-titration should continue at a slower pace (1 mg Q4W). For complete AI identified via morning cortisol testing, refer to section 5.2.1.1 for instructions on 3-month repeat testing. For partial AI or complete AI identified via ACTH stimulation test see Section 5.2.1.2 for instructions on 2-month or 3-month repeat testing respectively. Patients who have Partial AI will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the OCS Reduction phase. Patients who have Complete AI or Partial AI at the end of the OCS Reduction Phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the Maintenance phase (prior to EOT).
Note: Central lab reports list reference ranges that are different than this study-reference ranges. To interpret laboratory results for each morning cortisol or ACTH stimulation test, please look for the study-specific lab alerts indicating normal, partial AI, and complete AI on the lab reports provided by central labs. The study-specific reference ranges for normal, partial AI, and complete AI are provided in the laboratory manual.

5.2.1.1 Morning cortisol test (done at "OCS ≤ 5mg/day [morning cortisol]" visit)

For the morning cortisol test, hold OCS dose and other concomitant medications that could interfere with cortisol results per Section 5.2.1. Serum samples for cortisol will be collected between 8 and 9 am and will be sent to a central laboratory for evaluation. Once the results are available, the site will inform the patient of the results via telephone. Depending on the result, the actions that will be implemented are as follows:

- If cortisol levels are within normal range and the patient does not exhibit any signs and/or symptoms of AI, the patient will continue OCS down-titration by 2.5 mg Q4W

- If cortisol levels are within normal range but the patient exhibits signs and/or symptoms of AI, then OCS down-titration should continue at a slower pace (1 mg Q4W).
- If cortisol levels are below the normal range and above the complete AI range (indeterminate result), then the patient will be instructed to maintain the current OCS dose and come back to the site within 1 week for an ACTH stimulation test (Section 5.2.1.2)
- If complete AI is confirmed, sites will inform patients that the OCS dose will remain the same without further reduction until there is evidence of recovery from the complete AI without worsening of asthma control. The morning cortisol test will be repeated 3 months later, and patients will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards. During this repeat test 3 months later, the patient would also repeat all clinical assessments that were done with the initial morning cortisol test (see Table 1). After the repeat morning cortisol test, the site will inform the patient based on the results as follows:
  - If morning cortisol results at 3 months indicate normal cortisol values, then reductions will be 2.5 mg Q4W, and the patient would subsequently move to maintenance phase at OCS 0mg (or lowest possible dose)
  - If morning cortisol tests at 3 months are indeterminate, then reductions will be delayed further, and the patient would return approximately 1-week later for an ACTH stimulation test:
    - If normal result after ACTH stimulation: Reduce by 2.5mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)
    - If the result is Partial AI after ACTH stimulation: Reduce by 1mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)
    - If complete AI result after ACTH stimulation: OCS dose will not be reduced further, move to maintenance phase at current OCS dose
  - If morning cortisol tests again indicate complete AI at 3 months, the OCS dose will not be modified as this is the final attempt. The patient would move to maintenance phase at OCS 5mg (or lowest possible dose).

Patients who have Partial AI will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the OCS Reduction phase. Patients who have Complete AI or Partial AI at the end of the OCS Reduction Phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the Maintenance phase (prior to EOT). In the absence of evidence of HPA axis recovery, corticosteroid supplementation is recommended during situations of stress (ie, fractures, surgery, trauma, labor, invasive dental procedures, severe systemic infections, major burns, and fever >38.5ºC). Additionally, patients with Partial AI or Complete AI at the end of the Maintenance phase should be referred to an endocrinologist or other appropriate specialist, per Investigator discretion.

Details related to values for normal, partial AI and complete AI are provided in the laboratory manual.

5.2.1.2 ACTH stimulation test

The ACTH stimulation test (e.g., Synacthen®, Cortrosyn™, etc.) test will be performed when morning cortisol levels are below the normal range (but above complete AI levels). Please refer to the package insert of the product used locally for further guidance on preparation and administration. The sites will inform the patients of the morning cortisol results via phone call, and a visit will be scheduled within 1 week for the ACTH stimulation test. In the event of any issues with availability of the product used for the ACTH stimulation test, please consult with AZ study physician for further guidance.

For the ACTH stimulation test, hold OCS dose and other concomitant medications that could interfere with cortisol results per Section 5.2.1. An injection of the fast-acting ACTH stimulant will be given intravenously. Serum samples for cortisol will be collected between 8 and 9 am and will be sent to a central laboratory for evaluation as follows: a blood sample for serum cortisol will be collected at 0 minutes (before injection) and 30 minutes after the injection. Peak cortisol response at 30 minutes will be selected to assess AI, and the OCS taper will follow the applicable scenario below:

- If a normal peak cortisol level is demonstrated at 30 minutes, the site will inform the patient via phone call, and the patient will continue OCS dose titration by 2.5 mg Q4W, and subsequently would move to the maintenance phase at OCS dose of 0mg (or lowest possible dose).
- If the peak cortisol level at 30 minutes is below the normal range yet above the level of complete AI ("partial AI"), or there are some signs/symptoms of AI or corticosteroid withdrawal syndrome, the site will inform the patient to continue OCS down-titration at a slower speed (1 mg Q4W). The morning cortisol test will be repeated 2 months later, as per the process described in Figure 2. During this repeat test 2 months later, the patient would also repeat all clinical assessments that were done with the initial morning cortisol test (see Table 1).
    - If morning cortisol test results indicate normal cortisol values, then reductions will be up to 2.5 mg Q4W (based on patient's current OCS dose), and the patient would subsequently move to maintenance phase at OCS 0mg (or lowest possible dose)
    - If morning cortisol test results at 2 months are indeterminate, then reductions will be delayed, and the patient would return approximately 1-week later for an ACTH stimulation test.
        - If normal result after ACTH stimulation: Reduce by 2.5mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)
        - If the result is Partial AI after ACTH stimulation: Reduce by 1mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)

        - If complete AI result after ACTH stimulation: OCS dose will not be reduced further, move to maintenance phase at current OCS dose

    - If morning cortisol test results at 2 months indicate complete AI, the OCS dose will not be modified as this is the final attempt. The patient would move to maintenance phase at OCS 5mg (or lowest possible dose).

- If peak cortisol level at 30 minutes indicates complete AI, sites will inform patients that the OCS dose will remain the same without further reduction until there is evidence of recovery from the complete AI without worsening of asthma control. The morning cortisol test will be repeated 3 months later and patients will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards. During this repeat test 3 months later, the patient would also repeat all clinical assessments that were done with the initial morning cortisol test (see Table 1). After the repeat morning cortisol, the site will inform the patient based on the results as follows:

    - If results indicate normal cortisol values, then reductions will be 2.5 mg Q4W, and the patient would subsequently move to maintenance phase at OCS 0mg (or lowest possible dose)

    - If morning cortisol tests at 3 months indicate indeterminate results, then reductions will be delayed further, and the patient would return approximately 1-week later for an ACTH stimulation test.

        - If normal result after ACTH stimulation: Reduce by 2.5mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)

        - If the result is Partial AI after ACTH stimulation: Reduce by 1mg Q4W then move to maintenance phase at 0mg (or lowest possible dose)

        - If complete AI result after ACTH stimulation: OCS dose will not be reduced further, move to maintenance phase at current OCS dose

    - If morning cortisol tests again indicate complete AI at 3 months, the OCS dose will not be modified as this is the final attempt. The patient would move to maintenance phase at OCS 5mg (or lowest possible dose).

Patients who have Partial AI will undergo an additional morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the OCS Reduction phase. Patients who have Complete AI or Partial AI at the end of the OCS Reduction Phase, will undergo a final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) approximately 1-2 weeks prior to the end of the Maintenance phase (prior to EOT).

In the absence of evidence of HPA axis recovery, patients should be instructed to carry some type of identification (worn around the neck or wrist or carried as a card) warning of their clinical status of corticosteroid dependence along with a medical report detailing the treatment measures needed, including intramuscular hydrocortisone requirements. Corticosteroid supplementation is recommended during situations of stress (ie, fractures, surgery, trauma,

labor, invasive dental procedures, severe systemic infections, major burns, and fever >38.5ºC). Additionally, patients with Partial AI or Complete AI at the end of the study should be referred to an endocrinologist or other appropriate specialist, per Investigator discretion.

Details related to values for normal, partial AI and complete AI are provided in the laboratory manual.

5.2.2 Assessment of asthma exacerbations

During the study, an asthma exacerbation will be defined as a worsening of asthma symptoms that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (at a dose above one level higher than the current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids. Note: Per-protocol up-titration of the OCS dose to one level higher is not necessarily considered to be an exacerbation event
  - Patients who experience an exacerbation during the screening period (between Visits 1 and 2) can be granted an extension of the screening period to ensure that a patient recovers from an asthma exacerbation and the OCS dose is stabilized.
- An emergency room or 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 the above)
- Inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma

The Investigator must justify the decision for defining an event of worsening asthma as an exacerbation and record it in the source documents and eCRF. An asthma exacerbation that occurs within 7 days of the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event.

The patient may remain in the study after an exacerbation and continue to receive study drug if the Investigator judges that it is medically appropriate for the patient to do so and will be managed as per the details provided in Section 5.2.3.

Reasonable attempts should be made by the Investigator to bring the patient into the study site for patient-initiated asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled visit or as part of a routine center visit if the worsening happens to occur in line with a scheduled visit. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (eg, by the primary care provider or at an emergency department/hospital). Details should be entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medications due to exacerbations must be recorded in the appropriate module of the eCRF.

5.2.3 Management of asthma exacerbations during treatment period

Patients who experience an exacerbation during the treatment period may remain on the study drug at the Investigator's discretion. Asthma exacerbations will be treated with oral or other systemic corticosteroids according to standard clinical practice.

- **Induction phase:** If a patient experiences an exacerbation during the induction phase, the start of the OCS dose reductions may be delayed. After the OCS bolus/burst to treat an exacerbation is complete, the patient may be returned to a one-step higher dose level (or more if considered necessary by the Investigator) than what was prescribed when the exacerbation occurred. The Investigator may decide to maintain the same OCS dose. The patient's OCS dose should be stable for at least two weeks before entering the OCS reduction phase
- **Reduction phase:** If a patient experiences an exacerbation during the reduction phase, the Investigator may do one of the following for at least two weeks after completion of the OCS bolus/burst:
  - The patient may be returned to a one-step higher dose level (or more if considered necessary by the Investigator) than what was prescribed when the exacerbation occurred

    or
  - The same OCS dose may be maintained at a stable dosage and then OCS down-titration may be continued once the patient recovers from the exacerbation

  Further dose reductions during this phase will be considered as per the Investigator's opinion. After recovery from the first exacerbation, the patient will be allowed to proceed with another attempt to reduce their OCS dose; however, they would follow a lower speed of OCS down-titration (reductions every 4 weeks) (Table 3).

  In case of a second exacerbation, no further OCS dose reduction will be allowed, and the patient will continue the same dose or will return to a one-step higher dose level (or more as considered necessary by the Investigator) than what was prescribed when the exacerbation occurred. The patient will then enter the maintenance phase and continue the same dose through the end of study.
- **Maintenance phase:** If a patient experiences an exacerbation during the maintenance phase, the length of the maintenance phase will not be extended; and the patient will continue on 3 doses of benralizumab Q8W. After the OCS bolus/burst is complete, the patient may then be returned to a one-step higher dose level (or more if considered necessary by the Investigator) than the OCS dose they were on when the exacerbation occurred, or the Investigator may decide to maintain the same OCS dose throughout the maintenance phase.

5.2.4 Laboratory safety assessments

Laboratory safety assessments (listed in Table 4) will be performed in 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 according to the schedule provided in Table 1.

Laboratory results should be reviewed by the Investigator/authorized delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the Investigator/authorized delegate's judgement should be reported as AEs, as described in Section 6.

The copy of the laboratory results report should be signed and dated by the Investigator/authorized delegate and retained at the study site.

Table 4 Laboratory safety variables

Hematology/Hemostasis (whole blood)	**Serum chemistry**
Hematocrit	Alanine aminotransferase
Hemoglobin	Alkaline phosphatase
Platelet count	Aspartate aminotransferase
Red blood cell count	Creatinine
Absolute Leukocyte count (White blood cell count) and differential	Low-density lipoprotein
Glycated hemoglobin (HbA1c)	Gammaglutamyl transpeptidase
	Potassium
	Sodium
	Total bilirubin
	Glucose

5.2.4.1 Pregnancy test

The following tests are applicable to female patients only and will be conducted according to the schedule provided in Table 1.

- Serum beta-HCG (beta-human chorionic gonadotropin): To be done at screening visit (Visit 1) and EOT only for WOCBP (analyzed at central laboratory).
- Follicle-stimulating hormone: To be done at screening visit (Visit 1) only for female patients <50 years who have been amenorrhoeic for ≥12months to confirm postmenopausal status
- Urine HCG: To be performed at the study site for WOCBP at each treatment visit using a dipstick before any invasive study procedures (eg, blood sampling) are performed and before study drug administration. Positive urine test result must be confirmed with serum beta-HCG.

5.2.5 Physical examination

Physical examination will be done according to the schedule provided in Table 1.

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 AEs as described in Section 6.1.

5.2.5.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

5.2.5.2 Brief physical examination

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

5.2.6 Vital signs

Predose vital signs (pulse, blood pressure [BP], respiration rate and body temperature), will be recorded according to the schedule provided in Table 1.

The vital signs will be recorded prior to blood draw, administration of study drug, and, if possible, administration of usual asthma controller medication.

Pulse rate and BP should be measured after the patient has been resting for at least 5 minutes. The measurement will be taken in sitting position. Pulse rate will be obtained before BP.

Body temperature will be measured in Celsius before administration of study drug and in accordance with local standards.

5.2.7 Glucocorticoid toxicity index

Glucocorticoid toxicity index will be assessed as described by Miloslavsky et al 2017 (see Appendix H for details). The composite GTI captures common GC toxicities that are sensitive to differing cumulative GC doses over the period of a typical clinical trial (6 months to 3 years). The individual items within the GTI are weighted relative to each other for severity, and the instrument has the capability of measuring not only worsening of GC toxicity from baseline, but also improvement.

The composite GTI measures change in GC toxicity rather than absolute GC toxicity in order to account for the effects of prior GC therapy. Scoring should be performed as per the schedule of assessments, using entry assessment as the baseline. The GTI items were ranked in order of severity within each domain. The relative weights for each toxicity item were derived using multicriteria decision analysis. Multicriteria decision analysis has been used for

the creation of multiple classification criteria sets in a variety of inflammatory diseases, including rheumatoid arthritis (Neogi et al 2010), systemic sclerosis (Johnson et al 2014), and systemic lupus erythematosus (Tedeschi et al 2018).

The composite GTI will be assessed at the time points given in Table 1. Only a subset of items from the composite GTI will be assessed in PONENTE: body mass index, glucose tolerance (glycosylated hemoglobin), BP, low-density lipoprotein, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection (items from the Specific List will not be assessed).

5.3 Other assessments

5.3.1 Weight and height

Weight and height will be measured according to the schedule provided in Table 1. Height will be taken at screening Visit 1 only. The patient's weight will be recorded in kilograms, and height in centimeters. Weight and height measurements will be performed in light clothing and with shoes off.

5.3.2 Prednisone/Prednisolone levels

For patients who switch to prednisone/prednisolone only, a prednisone/prednisolone test will be done with V1 laboratory work. For these patients, the site should delay the laboratory test (for all parameters, not just prednisone/prednisolone levels) by 3 to 7 days after the patient has switched their OCS. Importantly, prednisone/prednisolone levels should be measured 1 to 2 hours after prednisone/prednisolone intake on that day to ensure levels are detectable. This test is not required for patients entering the study on prednisone/prednisolone.

5.3.3 Total IgE and Phadiatop

The tests will be performed at screening according to Table 1 and will be used to characterize patients at baseline. Analysis will be performed by the central laboratory. Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the centers.

5.3.4 Clinical outcome assessments

5.3.4.1 Patient-reported outcomes

Patient-reported outcomes data will be captured electronically using a handheld device (ePRO). Site personnel will be trained on using the ePRO. Detailed procedures for using the ePRO and training the patients will be described in a separate instruction manual. Patients will be trained on at-home use of the ePRO at Visit 2. Training will include explanation of device functionality and its proper use. Patients will also be asked to verify completion of training on the ePRO. Patients will be asked to bring the device back at each study visit. On-site PRO questionnaires should be completed prior to any other assessments. Data for all PROs will be collected in accordance with Table 1. Patients should be informed that the recording made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window. Patients will also be provided with information about when and where to request help if problems occur. The Investigator/authorized delegate

will check the patient's adherence to completing the ePRO as described in Table 1. There will be triggers in the PROs to alert investigators to signs of worsening of asthma and advising them to contact the patient for evaluation. These alerts will be described in a separate guide.

Asthma Control Questionnaire 6

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and use of short-acting β_2 agonists), omitting the forced expiratory volume in 1 second measurement from the original ACQ score.

Patients will be asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 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 scores >1.5 indicate not well-controlled asthma (Juniper et al 2006). Individual changes of ≥0.5 are considered to be clinically meaningful.

From Visit 2 onwards, the patient will complete the ACQ-6 at home every 1 week (± 2 days) until the EOT visit. The ePRO device will be set up with functionality to collect unscheduled ACQ-6 assessments on site if required by investigators at a visit.

At each clinic/phone call visit, in addition to the information provided by the patient on his/her asthma disease, investigators will have access to the patient's ACQ-6 scores (completed by means of an ePRO) to evaluate whether the patient's condition has not significantly deteriorated (ie, increase in score of ≥0.5 from baseline [baseline defined as value at Visit 2 before benralizumab administration]) and take the final decision to further reduce the OCS dose until the patient reaches an OCS dose of 0 mg/day (or lowest OCS dose possible in case no further OCS down-titration is allowed because of the presence of AI as measured by cortisol levels or in case of inadequate asthma control) while not losing asthma control.

St. George's Respiratory Questionnaire

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

as the criterion for minimal meaningful improvement (Jones 2005). SGRQ responders will be those with ≥4-unit decreases in SGRQ total score.
The SGRQ will be completed on site at the beginning of Visit 2 and EOT/IPD Visit using the ePRO.

Maintenance medication adherence assessment

Adherence with maintenance medication over the past week will be captured using a single question that asks the respondent to report the number of days they took their maintenance medication per their physician's instructions. Patients will respond to the maintenance medication query on a weekly (± 2 days) basis using the ePRO beginning at Visit 2 and ending at EOT/IPD Visit.

Patient Global Impression of Change assessment

The PGIC instrument is used for an overall evaluation of response to treatment. The patient will be asked to rate the degree of change in the overall asthma status compared to the first dosing using the following 7-point scale: Much Better (+3), Moderately Better (+2), A Little Better (+1), About the Same (0), A Little Worse (-1), Moderately Worse (-2), and Much Worse (-3).

The PGIC will be captured at Visit 2 as well as weekly (± 2 days) until the end of the Induction phase (day prior to Visit 3) by using the ePRO.

5.4 Pharmacokinetics

Pharmacokinetic samples will not be taken during the study.

5.5 Pharmacodynamics

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). Refer to Section 5.2.4.

5.6 Genomics

Approximately 10 mL blood samples for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the main study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient.

The genomic sample will be used to explore how genomic variation may be associated with study outcomes. In addition, the genomic sample may be used for further genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and response to medications. Genetic research may lead to better understanding of diseases,

better diagnosis of diseases, or other improvements in health care and to the discovery of new diagnostics, treatments, or medications.

Additional information regarding the genetics research component of the study is provided in Appendix C.

5.7 Biomarker collections and analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples will be collected for exploratory analyses to investigate the effect of benralizumab on biomarkers of inflammation, asthma disease, pharmacology of benralizumab, and potential predictors of response.

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

The results of the exploratory biomarker analyses will be reported separately from the Clinical Study Report (CSR) in a scientific report or publication.

5.7.1 Serum for biomarkers

Whole blood for the preparation of serum for analysis of proteins and inflammatory markers will be collected at the screening visit (Visit 1) and at the visit to assess morning cortisol levels, according to Table 1.

5.7.2 Plasma for eosinophil-derived neurotoxin

Plasma samples will be collected according to the schedule in Table 1 to evaluate EDN, a biomarker of eosinophil level and activation.

5.7.3 Sputum collection and biomarkers

Not applicable due to protocol amendment.

5.7.4 Storage, reuse, and destruction of biomarker samples

AstraZeneca or a designee will retain biomarker samples for investigation of asthma, the pharmacology of benralizumab, and potential predictors of response for a maximum of 15 years following the last patient's last visit, after which they will be destroyed.

The results of this biomarker research may be pooled with biomarker data from other studies with the study treatment to generate hypotheses to be tested in future research. Any residual samples may be used for future biomarker research. If a patient does not allow samples to be used for future biomarker research, they may continue with their samples being used for the main study.

The results of any investigation will not be reported in the CSR but separately in a scientific report or publication.

5.7.5 Labelling and shipment of biological samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the laboratory manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria). See Appendix B.

Any samples identified as Infectious Category A materials are not shipped, and no further samples will be taken from the patient unless agreed upon with AstraZeneca, and appropriate labelling, shipment, and containment provisions are approved.

5.7.6 Chain of custody of biological samples

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

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

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.

5.7.7 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.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator 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 (for example, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a preexisting 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 events

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- 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 an SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (12 weeks after the last dose of study drug).

Please refer to Appendix K for details regarding safety reporting in the PONENTE Long Term Follow Up substudy.

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

All AEs will be recorded in the eCRF. 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 study drug (yes or no)
- Action taken with regard to study drug
- 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 an 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 an SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess the causal relationship between the study drug 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 study drug?'

For SAEs, the 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 to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient, reported in response to the open question from the study site staff, '*Have you had any health problems since the previous visit/you were last asked?*', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol–mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and 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 study drug.

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 nonmandated parameters should be reported as AEs.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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.

The signs and symptoms of AI will not be considered as AEs except under certain circumstances (eg, adrenal crisis Appendix J).

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT levels ≥3 × ULN together with total bilirubin (TBL) levels ≥2 × ULN may need to be reported as SAEs.

Any potential Hy's Law case should be handled as a serious unexpected adverse event associated with the use of the drug and reported promptly (i.e., even before all other possible causes of liver injury have been excluded). It should be promptly reported to the appropriate regulatory/ethics authority before fully working up the patient to rule out other etiologies. Reporting should include all available information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up

until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Please refer to Appendix D for further instruction regarding cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

6.3.8 Disease under study

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 preexisting asthma history (defined as within 1 year prior to Visit 1) as judged by the Investigator

Asthma exacerbations occurring during the treatment period should be recorded in the eCRF. An asthma exacerbation should be recorded as an AE or SAE only if it fulfills any of the above criteria.

6.4 Reporting of serious adverse events

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

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

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

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC 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 reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

4.3.1 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

6.5 Overdose

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an 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 study, study drug should be discontinued immediately.

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

If any pregnancy occurs during the study, then the Investigator or other site personnel will 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 will work 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 eCRF will be used to report the pregnancy, and the pregnancy outcome (PREGOUT) form will be used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

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 study drug until 16 weeks (approximately 5 half-lives) after the last administration of study drug.

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

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

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

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

If a medication error occurs during the study, then the Investigator or other site personnel will 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 will work 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.

7. STUDY DRUG AND OTHER TREATMENTS

7.1 Identity of study drug(s)

Study drug will be manufactured in accordance with Good Manufacturing Practice (GMP).

Benralizumab administered in the study will be a clear to opalescent, colorless to yellow solution.

Study drug	Dosage form and strength	Manufacturer
Benralizumab	30 mg/mL solution for injection in prefilled syringe, 1 mL fill volume	MedImmune

7.2 Dose and treatment regimens

Benralizumab 30 mg/mL solution for injection in an APFS will be administered SC at the study site Q4W for the first 3 doses and then Q8W thereafter (8 weeks between the 3rd and 4th benralizumab doses). See Table 1 for more details.

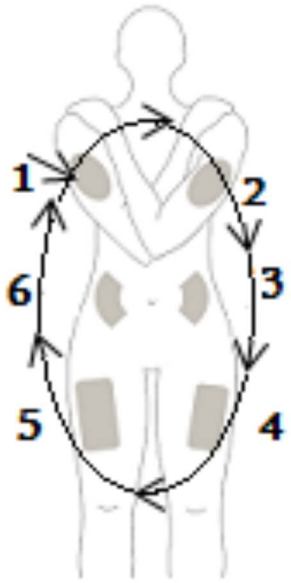
Before study drug administration

The Investigator or authorized delegate will assess the injection site as per standards of medical care. For WOCBP, a urine pregnancy test will be performed, and study drug will be administered when the result of the test is negative (Section 5.2.4.1).

Study drug administration

The study drug will be administered by the Investigator and/or authorized delegate. It is advised that the site of injection of the study drug be rotated such that the patient receives study drug at a different anatomical site at each treatment visit. A suggested injection site rotation sequence is presented below (see Figure 3).

Figure 3 Injection sites and rotation scheme



In cases where rotation of the injection site is not favorable for the patient and/or the Investigator, the reason should be recorded in the source documents. Further details on study drug administration can be found in applicable guidance outside of this Clinical Study Protocol. Study drug administration must be carried out in line with this guidance.

After study drug administration

After study drug administration, the patient should be observed for a minimum of 2 hours in case of any acute drug reactions for the first 3 doses of study drug. For the fourth dose and onwards, the patient should be observed for 1 hour.

Conditions that will require rescheduling of study drug administration

The Investigator should reschedule the visit and the study drug should not be administered until the rescheduled visit if either of the following occur:

- 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 is febrile (≥38°C; ≥100.4°F) within 72 hours prior to administration of the study drug

Every possible effort should be made to bring the patient in within the allowed visit window and study drug should be administered at that visit. If this is not possible, the AZ study physician should be contacted to discuss further.

7.3 Management of study drug–related reactions

Appropriate drugs such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available. Study personnel must be trained to recognize and treat anaphylaxis. Details on anaphylaxis management are provided in Appendix I.

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

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

Patients will have had a pre-assessment (ie, vital signs) prior to study drug administration and should be observed after study drug administration for a minimum of 2 hours for the appearance of any acute drug reactions for the first 3 doses of study drug. For the fourth dose onwards, patients should be observed for 1 hour after study drug administration.

7.4 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language where applicable. The label will include the following information:

- Study code
- Study drug dosage form, route of administration, and quantity of dosage units
- Kit identification
- P lot identification
- Expiry date
- Investigator name (if applicable locally; to be written on label)
- E-code (to be written on label)
- Sponsor name and contact details
- Directions for use
- Storage condition
- Standard statements required by regulatory authorities

- Storage

7.5 Storage

All study drugs should be kept in a secure place with limited access and under appropriate temperature-controlled storage conditions. The temperature should be monitored daily, and monitoring should be documented in a temperature monitoring log. The study drug must be kept in the original outer container and under conditions specified on the label (between 2°C and 8°C [36°F and 46°F] and protected from light).

The site should not use affected study drug and should immediately contact an AstraZeneca representative for further guidance in the following cases:

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

The center staff should not use affected study drug and should immediately contact an AstraZeneca representative for further guidance. Damaged study drug should be documented via IWRS/IVRS (please refer to the IWRS/IVRS manual for further details).

7.6 Compliance

The administration of all study drugs (including study drugs) should be recorded in the appropriate sections of the eCRF. Study drug will be administered at the study site during treatment visits as outlined in Table 1.

7.7 Accountability

The study drug provided for this study will be used only as directed in the Clinical Study Protocol. The study site staff will account for all study drugs dispensed to the patient. The monitor will account for all study drugs received at the site, for unused study drugs, and for appropriate destruction according to local procedures. Certificates of delivery, destruction, and/or return should be signed.

In case of malfunctioning APFS, the site should contact the study monitor to initiate return of the APFS according to the procedures described in the separate pharmacy manual.

7.8 Concomitant and other treatments

Information about any treatments received in the 3 months prior to the date of informed consent and all the concomitant treatments given during the study (through follow-up period) with reason for the treatment will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1) and recorded in the eCRF.

Use of ICS/LABA as a reliever (eg, Symbicort Maintenance and Reliever Treatment) that was part of the patient's usual asthma controller regimen at baseline is allowed. Any maintenance

therapy (in addition to ICS/LABA) such as long-acting muscarinic antagonists used prior to study entry should not be changed during the study. The 'as-needed' use of short-acting bronchodilators for relief of acute asthma symptoms is permitted throughout the study.

Please refer to Appendix K for details on concomitant medications and other treatments in the PONENTE Long Term Follow Up substudy.

Table 5 Medication Restrictions

Allowed medication/Class of drug	Usage
Inactive/killed vaccinations	Allowed provided they are not administered within 5 days before or after dosing with benralizumab
Allergen immunotherapy	Allowed if patient has been receiving stable therapy for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study drug
Prednisone/prednisolone	Allowed provided it is not administered 24 hours prior to morning cortisol level/ACTH stimulation test
High-dose ICS	Allowed; however, ICS (or ICS/LABA if in single inhaler) treatment should not be administered on the same day as morning cortisol/ACTH stimulation test (for patients taking a once-daily ICS/LABA formulation, e.g. fluticasone furoate/vilanterol; patients must not take the treatment the night prior or the morning of the cortisol testing).
Immunosuppressive medication	Topical or nasal administration may be allowed at the discretion of the Investigator

Table 6 Prohibited Medications

Prohibited medication/Class of drug	Usage
Macrolides, antivirals, and azole therapies	Chronic treatment with macrolides, antivirals, or azole therapies are not allowed during the study. If a patient has been receiving long-term treatment of these therapies, all such medications need to be stopped 30 days or 5 half-lives, whichever is the longer, prior to the date informed consent is obtained. If a patient requires short courses of these medications (short course defined as ≤ 2 weeks), they should be stopped at least 1 week prior to testing of cortisol levels

Prohibited medication/Class of drug	Usage
Benralizumab and other marketed respiratory biologics.	Any marketed respiratory biologic treatment (eg, omalizumab, mepolizumab, reslizumab, benralizumab) is not allowed 4 months or 5 half-lives (whichever is longer) prior to the date informed consent is obtained and throughout the entire treatment period. - For patients who have previously not tolerated or have not responded to marketed mepolizumab, omalizumab or reslizumab (as assessed by the treating physician), a shorter washout period of ≥ 30 days between the last dose of mepolizumab, omalizumab or reslizumab and the first dose of open label benralizumab (Visit 2), is allowed. - Patients who have previously received benralizumab still require a complete washout prior to date of informed consent; those who have not tolerated or have not responded to benralizumab would not be a candidate for this study.
Non-respiratory marketed biologics or any investigational biologics	Any marketed (non-respiratory) or investigational biologic treatment is not allowed 4 months or 5 half-lives (whichever is longer) prior to the date informed consent is obtained and throughout the entire treatment period
Immunosuppressive medications	Use of immunosuppressive medications (including, but not limited to, methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, any experimental anti-inflammatory therapy, or oral/parenteral/intra-articular corticosteroids for reasons other than asthma) is not allowed except maintenance use of OCS for asthma if present at baseline and rescue use of systemic corticosteroids (oral, intravenous, or intramuscular) to treat an asthma exacerbation. Immunosuppressive medications must be discontinued 3 months or 5 half-lives (whichever is longer) prior to Visit 1; during the treatment period; and 3 months or 5 half-lives (whichever is longer) after the last dose. For flare-ups of non-asthma related indications (e.g. arthritis, crohn's disease, atopic dermatitis) or AE/SAE requiring temporary OCS use (or temporary increase in maintenance OCS), a short course of OCS (≤ 2 weeks) use is allowed anytime during the study. Use of OCS for nasal polyposis, allergic rhinitis, or related eosinophilic conditions is not allowed.
Blood products or immunoglobulin therapy	Receipt of immunoglobulin or blood products is not allowed within 30 days prior to the date informed consent is obtained and throughout the entire treatment period

Prohibited medication/Class of drug	Usage
Live attenuated vaccines	Not allowed within 30 days of Visit 1 or during treatment period
Lipoxygenase inhibitors	Five-lipoxygenase inhibitors (eg, zileuton) are prohibited and are not allowed within 30 days of Visit 1 or during the treatment period

7.8.1 Other concomitant treatment

Medications other than those described in Section 3.5, which are 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 eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

The statistical analyses will be fully described in a Statistical Analysis Plan (SAP), as appropriate. Data from the main PONENTE study will be summarized for the population overall and by prespecified subgroups: baseline OCS dose, baseline blood eosinophil count, and duration of chronic OCS. Additional subgroups of interest will be further defined in more detail in the SAP.

Due to the single-arm study design, external data sources may be used to contextualize any change seen in asthma control, asthma exacerbation rate, or other safety endpoints in patients treated with benralizumab following reduction of OCS. Any data sources identified, together with planned analyses, will be described in a separate analysis plan.

Statistical analyses for this study will be conducted using SAS (Cary, NC) version 9.3 or higher and will be performed by AstraZeneca or a designated representative. The data cutoff for the primary analysis will occur when the last patient completes the follow up visit of the PONENTE main study. A separate document (SAP) to address detailed statistical analysis issues for the PONENTE main study will be developed and approved by the time the first patient is enrolled to the study. A second and separate SAP detailing the analyses for the PONENTE Long Term Follow Up substudy will be developed and approved prior to the final database lock (DBL) of the main study.

8.2 Sample size estimate

There is no predefined study hypothesis to test in this study. The sample size for this study is based on the ability to provide sufficient precision in point estimates, both in the FAS and in subgroups for statistical analysis.

The primary outcome, the observed proportion of patients down-titrated and maintained for at least 4 weeks, is expected to be equal to or greater than 50%. For the sample size estimation,

a success rate of 50% is assumed. Estimate precision is expressed in a two-sided 95% confidence interval (CI) distance from the point estimate of a 50% success rate for a total of approximately 600 patients. CI calculations were conducted using the exact Clopper-Pearson CI formula for a single proportion in SAS version 9.4M5.

A total sample size of approximately 600 patients is expected to provide a 95% CI extending approximately 4.1% from the point estimate of a 50% success rate. Estimates of the 95% CI for a >50% success rate are incrementally smaller, as is shown in the following table:

Table 7 Expected distance between observed proportion and confidence limit (Clopper-Pearson 95% CI width)

Proportion of Patients with Total OCS Reduction	Sample Size			
	100	**150**	**300**	**600**
50	±10.2	±8.3	±5.8	±4.1
60	-10.3, +9.7	-8.3, +7.9	-5.8, +5.6	-4.0, +4.0
70	-10.0, +8.8	-8.0, +7.2	-5.5, +5.1	-3.8, +3.6
80	-9.2, +7.3	-7.3, +6.1	-5.0, +4.4	-3.4, +3.1

The table also shows that the 95% Cis for subpopulation analyses as small as 100 are ≤10% from the point estimate for proportions between 70% and 80% and 10.2% for a proportion of 50%.

A sample size of 300 patients is expected to provide 95% Cis for a single proportion extending approximately 5.8% from the point estimate of a 50% success rate.

8.3 Definitions of analysis sets

The following statistical analysis sets will be defined to support data analyses of the study.

8.3.1 All patients analysis set

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

8.3.2 Full analysis set

All enrolled patients who received at least one dose of benralizumab will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Patients who withdraw from the study will be included up to the date of their study termination.

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

8.3.3 Safety analysis set

The FAS will be used for all safety analyses.

Analysis sets for the PONENTE Long Term Follow Up substudy will be detailed in Appendix K.

8.4 Outcome measures for analyses

The following study outcome measures are designed to support primary, secondary, and exploratory objectives of the study.

For a response outcome, if a patient withdraws from the study before reaching the defined endpoint, the patient will be considered as non-successful.

For a time-to-event outcome, if a patient withdraws from the study before reaching the defined endpoint or does not reach the endpoint by the end of the predefined study phase, the patient will be censored at the withdrawal date or at the end date of the corresponding study phase, whichever is earlier.

For outcomes measured in continuous data such as cumulative dose, ACQ-6 score, and SGRQ score, no imputation will be performed for missing outcomes.

Primary efficacy outcome variables

- Patients who achieve 100% reduction in daily OCS dose that is sustained over at least 4 weeks without worsening of asthma (as defined in Section 5.1.2.1 of the protocol)
- Patients who achieve 100% reduction or daily OCS doses of ≤5 mg, if reason for no further OCS reduction is AI, that are sustained over at least 4 weeks without worsening of asthma

Key supportive outcome variables

- Patients who achieve a daily OCS dose of ≤5 mg that is sustained over at least 4 weeks without worsening of asthma
- Patients who achieve a ≥90%, ≥75%, and ≥50% reduction in daily OCS dose, sustained over at least 4 weeks without worsening of asthma
- Change from baseline in daily OCS dose (mg) from start of OCS reduction to end of the OCS reduction phase

Secondary efficacy outcome variables

- Change in daily OCS dose from the end of OCS reduction phase to the end of the maintenance phase (at EOT visit)
- Time to first increase in OCS dose during the maintenance phase, after achieving the minimum OCS dose during the OCS reduction phase

- ACQ-6 scores at baseline (Visit 2), Visit 3, initial morning cortisol test, end of OCS reduction phase, and monthly from end of OCS reduction phase to end of maintenance phase (EOT visit)
- Change from baseline in ACQ-6 score to Visit 3, end of OCS reduction phase, and end of maintenance phase (EOT visit)
- Responder analysis of ACQ-6 scores from Visit 2 through end of maintenance phase
- Change from baseline (Visit 2) in SGRQ total scores to the end of maintenance phase (EOT visit)
- Responder analysis of SGRQ total scores at the end of maintenance phase

Safety outcome variables

- Patients with complete AI
- Annualized asthma exacerbation rate
- Annualized asthma exacerbation rate leading to hospitalization or emergency room visit
- AEs
- SAEs
- GTI

Exploratory outcome variables

- Change from baseline (Visit 1) blood eosinophils
- PGIC at Weeks 1, 2, 3, and 4

Outcome variables for the PONENTE Long Term Follow Up substudy will be detailed in Appendix K.

8.5 Methods for statistical analyses

Statistical tabulation will be presented for overall patients and by baseline OCS dose level, category of baseline eosinophil count, and category of duration of chronic OCS use. Continuous variables will be summarized using the mean, two-sided 95% CI of the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method. Time to event data will be summarized using median and 25^{th} and 75^{th} percentiles with 95% Cis. Data will be listed in patient-level data listings.

No formal hypothesis will be tested in this study, and no multiplicity adjustment will be applied in the statistical analysis. No imputation will be performed beyond the approach defined for outcome measures in Section 8.4. Imputation for partial date will be detailed in the SAP document.

Analysis methods for the PONENTE Long Term Follow Up substudy will be detailed in Appendix K.

8.5.1 Analysis of the primary variables

The count and proportion (with 95% CI) of patients who achieve 100% reduction in their OCS dose, sustained for at least 4 weeks without worsening of asthma or resumed OCS treatment, and the count and proportion of patients who achieve 100% reduction or a daily OCS dose of ≤5 mg, if reason for no further OCS reduction is AI, sustained over at least 4 weeks without worsening of asthma, will be tabulated.

The same analysis will be carried out for the supporting endpoints: patients who reduce to a daily OCS dose of ≤5 mg sustained over at least 4 weeks without worsening of asthma; and patients who achieve a ≥90%, ≥75% and ≥50% reduction in their daily OCS dose without worsening of asthma.

All 95% Cis for proportions will be calculated using the Clopper-Pearson exact method.

For patients who do not achieve 100% reduction in their daily OCS dose, the reason for no further reduction will be listed.

Change from baseline in OCS dose variables will be summarized using descriptive statistics in tables and graphs (supporting primary and secondary endpoints).

8.5.2 Analysis of the secondary variables

8.5.2.1 Time to 1st OCS increase

Time to first OCS increase in the maintenance phase will be summarized using median, 25th and 75th percentiles (with 95% Cis) and Kaplan Meier plots. The start time for the analysis will be the time, in the OCS reduction phase, at which the patient first reaches the minimum stable dose that is continued into the start of the maintenance phase.

Cox-regression model analysis will also be used to summarize and analyze time to first OCS increase; covariates will include at least baseline OCS daily dose and baseline eosinophil count (categorized). If a patient withdraws from the study before reaching the defined endpoint or does not reach the endpoint by the end of the study, whichever is earlier, the patient will be censored at that time point.

8.5.2.2 ACQ-6

Change from baseline ACQ-6 score will be summarized by study visit using descriptive statistics and analyzed using a mixed model for repeated measures, with change from baseline in ACQ-6 score as the response variable, and baseline ACQ-6 score, baseline OCS dose, and baseline categories of serum eosinophil count as covariates. Results of the mixed model

analyses will be presented in terms of least square mean with 95% CI of change from Visit 2 in ACQ-6 score.

Asthma control responders will be evaluated as a supportive analysis outcome measure. Patients will be categorized according to the following limits (Juniper et al 2005), where observed study time points include, but are not limited to, Visit 3, initial morning cortisol test (time point at which OCS dose equals 5mg for 4 weeks), end of OCS reduction phase, and end of maintenance phase (EOT visit) from Visit 2:

- Improvement: Change from baseline in ACQ-6 score of ≤ -0.5
- No change: Change from baseline in ACQ-6 score of > -0.5 and < +0.5
- Deterioration: Change from baseline in ACQ-6 score of ≥ +0.5

Asthma control responders will be defined as patients who had improvements based on changes from baseline in their ACQ-6 scores. Patients with no change or deterioration according to ACQ-6 score evaluation will be defined as nonresponders. Patients with missing or nonevaluable ACQ-6 scores at a postbaseline assessment time point will be considered nonresponders at the time point.

Furthermore, patients will be categorized according to their ACQ-6 score–defined asthma control status at post Visit 2 assessments using the following score thresholds (Juniper et al 2006):

- Well controlled: ACQ-6 score of ≤0.75
- Partially controlled: ACQ-6 score of >0.75 and <1.5
- Not well controlled: ACQ-6 score of ≥1.5

Asthma control responders will be summarized in count and proportion with 95% Cis estimated using the Clopper-Pearson method. Patients with missing or nonevaluable ACQ-6 scores will be considered nonresponders.

In the event that there is a differential proportion of patients with missing ACQ-6 score results at postbaseline study visits, based on review of an ACQ-6 reporting compliance summary, a sensitivity analysis will be performed using a hybrid last-observation-carried-forward approach. For this analysis, patients who complete the study visit and have missing ACQ-6 scores at the visit will have their last non-missing score carried forward. Patients who terminate early prior to the study visit will be treated as nonresponders.

The number and percentage of patients who achieve improvements, no change, or deterioration, and the number and percentage of patients who achieve ACQ-6 scores of ≤0.75 (well controlled), >0.75 to <1.5 (partially controlled), or ≥1.5 (not well controlled) will be summarized in a table. Clopper-Pearson 95% Cis will be presented, Patient with missing or nonevaluable ACQ-6 scores will be classified as “Not well controlled”.

8.5.2.3 SGRQ

Potential changes in health status will be evaluated by assessing the change from baseline to EOT visit in SGRQ total scores.

Summary statistics for SGRQ total score and domain scores (symptoms, activity, and impacts) at Visit 2 (baseline) and EOT visit along with change from baseline to EOT visit will be produced. Change from baseline in SGRQ total score and the three domain scores will also be analyzed separately using an analysis of covariance (ANCOVA) with change from baseline in SGRQ score as response variable and baseline SGRQ score and baseline OCS dose and baseline categories of serum eosinophil count as covariates. Results will be presented in terms of least square mean with 95% CI of change from baseline in SGRQ total score.

A 4-point threshold will be used to define the response. If there is a ≥4-point decrease from baseline in SGRQ total score, it will be defined as 'improvement'; if there is a ≥4-point increase at EOT from baseline, it will be defined as 'worsening'; if the change is not more than 4 points at EOT, it will be defined as 'no change'.

Missing SGRQ total score change at end of the study or assessment time points will be considered as 'not evaluable'.

For the responder analysis of SGRQ, a responder will be defined as a patient who had 'improvement' (ie, ≥4-point decrease in SGRQ total score). Patients who had SGRQ total score changes defined as 'no change' or 'worsening' will be considered nonresponders. If SGRQ total score change is not evaluable due to missing data, then the patient will also be treated as a nonresponder.

8.5.2.4 PGIC

PGIC will be presented descriptively by week during the induction phase. Calculation of percentages will be based on the number of patients in the full analysis set with a completed assessment. There will be no imputation for missing values.

Patients will also be categorized according to the following three responses starting at Visit 2 and through the induction phase:

- Much Better (+3), Moderately Better (+2), A Little Better (+1) → Improved
- Much Better (+3), Moderately Better (+2) → Moderately improved
- Much Better (+3) → Much improved.

These three categorized variables will be presented descriptively by week.

8.5.3 Analysis of safety outcomes

The number and percentage of patients diagnosed with AI will be tabulated as follows:

- Patients with complete AI

In addition, the number and percentage of patients diagnosed with AI will be tabulated according to the way of diagnosis. The association between AI diagnosis and OCS down-titration will be explored.

Spaghetti plots may be produced for patients with Partial AI throughout the OCS reduction phase, showing cortisol levels over time.

The incidence of AEs and SAEs will be summarized overall and stratified by relationship to study intervention and severity grade.

The annualized rate of asthma exacerbations will be summarized using mean, 95% CI, and dispersion based on the negative binomial distribution.

Glucocorticoid toxicity index will be summarized over time. Statistical correlation between GTI and daily OCS dose will be explored.

The number and percentage of patients diagnosed with AI will be tabulated overall and by baseline OCS dose according to the way of diagnosis: morning cortisol or ACTH stimulation test, morning cortisol test, intermediate morning cortisol and ACTH stimulation test, and intermediate morning cortisol and intermediate ACTH stimulation test.

In addition, the number and percentage of patients diagnosed with AI will be tabulated by subgroup according to duration of chronic OCS treatment.

8.5.4 Subgroup analysis

Prespecified subpopulations will include the following:

- Patients with baseline OCS dose >10 mg/day, >5 mg/day to ≤10 mg/day, and 5 mg/day
- Patients with baseline blood eosinophil count:
  - <150/μL and ≥150/μL;
  - <300/μL and ≥300/μL; and
  - <150, ≥150 to <300, and ≥300 cells/μL
- Patients with duration of chronic OCS use <1 year and ≥1 year

Additional subgroups may be described in the SAP.

8.5.5 Interim review and Analysis

One interim review may be performed after approximately 90-100 patients have completed (or have had the opportunity to complete) their OCS down-titration; further details will be described in a separate interim review plan.

An additional database lock and analysis of all relevant data collected through the end of the OCS reduction phase, may be performed after the final patient has had the opportunity to complete the OCS reduction phase. The purpose of this analysis is to generate a sub-set of the pre-planned analysis outputs of all relevant data for all patients up to the end of the OCS reduction phase. Further details will be provided in the SAP.

8.5.6 Sensitivity analysis

The primary efficacy outcome based on data as observed with exclusion of the early withdrawn patients will be analyzed using the same method used for the primary analysis of the FAS.

Further sensitivity analyses and missing data strategies will be specified in the SAP.

8.5.7 Exploratory analysis

Statistical analysis of the following exploratory outcomes will be detailed in the SAP for this study:

- Change from baseline in blood eosinophils
  - Baseline blood eosinophil counts may be further investigated by summarizing vs. baseline OCS dose and/or by region/country.
- Serum samples at baseline for protein biomarkers
- Plasma for EDN
- Association of common and rare genomic variants with patient responses

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 Clinical Study Protocol and related documents with the investigational staff and also train them on any study-specific procedures and the WBDC, IxRS, ePRO, and other systems to be utilized.

The Principal Investigator 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 Principal Investigator 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 AstraZeneca representative will have regular contact with the study site, including visits to:

- Provide information and support to the investigators
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRFs, 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 eCRFs 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, that the biological samples are identified and disposed of/destroyed accordingly, and that the action is documented and reported to the patient

The AstraZeneca representative will be available between visits if the investigators or other staff at the center needs information and advice about the study conduct.

9.2.1 Source data

Please refer to the Clinical Study Agreement for the location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of the Clinical Study Protocol 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 Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures take place or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator will follow the principles outlined in the Clinical Study Agreement.

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'. A patient is considered to have completed the study when he/she has completed his/her last

scheduled contact.

The study may be terminated at individual sites 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

Data management will be performed by AstraZeneca Data Management Center staff, 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 of the Medical Dictionary for Regulatory Activities. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The WBDC system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

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 Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived by the Investigator.

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.

When all activities have been performed to ensure data are complete and accurate, a clean file will be declared.

Serious Adverse Event Reconciliation

The SAE reconciliation will be performed by comparing the safety database standard reports with relevant AE/SAE listings from the clinical study database.

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 Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient 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 Ethics Committee (EC) should approve the final Clinical Study Protocol, 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 and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC 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 Clinical Study Protocol should be reapproved by the EC annually.

Before enrollment of any patient into the study, the final Clinical Study Protocol, 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, Ecs, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(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 (before any procedures are performed) as per local requirements.
- 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 ICFs are stored in the Investigator's Study File and kept for a period that is compliant with GCP/local regulatory requirements, whichever is longer
- 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 EC
- The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study, the patient must provide their signed and dated consent for both the main study and the genetic component of the study. A copy of the signed and dated consent form(s) must be given to the patient with the original filed at the study center. The Principal Investigator is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time

10.5 Changes to the Clinical Study Protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant EC and, if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for new versions of clinical study protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator for distribution to Ecs (see Section 10.3).

If a change to a Clinical Study Protocol requires a change to a site's ICF, AstraZeneca and the site's EC 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 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 and to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency or other body about an inspection or an audit at the study site.

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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 intravenous 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) 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 judgment. 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 : International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt – all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650–compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA-compliant courier and packaging materials should be used for packing and transportation, and packing should be done by an IATA-certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations, which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used

Appendix C: Genetic Research

Rationale and Objectives

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases, or other improvements in health care and to the discovery of new diagnostics, treatments, or medications.

In addition, collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses

Exclusion criteria

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

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

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are as follows:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.6.1 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 1 it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

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

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

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

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Informed consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study, the patient must provide their signed and dated consent for both the main study and the genetic component of the study. A copy of the signed and dated consent form(s) must be given to the patient with the original filed at the study center. The Principal Investigators is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

Patient data protection

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

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

Data management

Any genotype data generated during this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

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

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

Statistical Methods and Determination of Sample Size

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

Appendix D: 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. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver abnormalities can be found in Section 6.3.7 of the Clinical Study Protocol.

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.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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 Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) 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) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study drug irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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 PHL 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 without delay
- Complete the appropriate unscheduled laboratory eCRF 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 within this appendix for definitions) 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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

4.2. Potential Hy's Law criteria met

If the patient does meet PHL criteria, the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting. This should be reported promptly to the appropriate regulatory/ethics authority (i.e., even before all other possible causes of liver injury have been excluded) before fully working up the patient to rule out other etiologies. Reporting should include all available information, especially that needed for evaluating the severity and likelihood that the drug caused the reaction, and should initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the Investigator will:

    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
    - Complete the three Liver CRF Modules as information becomes available

A 'significant' change in the subject'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.

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.

As soon as possible 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 IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. 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.

Where 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: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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 IMP:

- Send updated 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 15 calendar days 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:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

No later than 3 weeks after the biochemistry abnormality is initially detected, the Study Physician will contact the Investigator to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the investigational medicinal product. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient 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 upon alternative explanation for the elevations in ALT or AST and TBL levels, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would explain the elevations in ALT or AST and TBL levels other than the investigational medicinal product:

- 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 follow-up 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

Not applicable in PONENTE

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease?

If **No**: follow the process described in Appendix D, Section 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Appendix D, Section 4.2 for reporting PHL as an SAE

A 'significant' change in the subject'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.

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Appendix E: Estimated Daily Doses for Inhaled Corticosteroids

Asthma therapy (adults and adolescents 12 years and older)	Total daily dose (µg/day)[b]	
Inhaled corticosteroid[a]	**Medium**	**High**
Beclomethasone dipropionate CFC[c]	> 500 -1000	>1000
Beclomethasone dipropionate HFA	>200 – 400	>400
Budesonide DPI	> 400 – 800	>800
Ciclesonide HFA	> 160 – 320	>320
Flunisolide[d]	2000	>2000
Fluticasone furoate DPI (eg, Arnuity® Ellipta®)[d]	n.a.	200
Fluticasone propionate DPI	> 250 – 500	>500
Fluticasone propionate HFA	> 250-500	>500
Mometasone furoate	>220 – 440	>440
Triamcinolone acetonide	> 1000 – 2000	>2000
Inhaled corticosteroid in ICS/LABA combination[d]	**Medium**	**High**
Beclomethasone dipropionate (eg, Fostair®)	400	>400
Fluticasone furoate (eg, Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184,200
Fluticasone propionate HFA (eg, Seretide®, Advair®)	>320 – 460	>460
Fluticasone propionate DPI (eg, Seretide® Diskus®, Advair® Diskus®)	> 250 – 500	>500
Budesonide HFA (eg, Symbicort®)	320 to <640	640
Budesonide DPI (eg, Symbicort® Turbuhaler®)	400 to <800	800
Mometasone furoate HFA (eg, Dulera®)	400	800
Mometasone DPI (eg Asmanex® Twisthaler®)	330 – 440	>440

CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; n.a. = not applicable

a Modified from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018. Available from: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention.

b. This protocol also allows any product with clinically comparable doses, including newer products and authorized generics. High-dose ICS via nebulized solution for inhalation is also allowed. For products not listed in this table, the highest approved maintenance ICS or ICS/LABA dose in the local country label will meet the protocol-defined criterion for "high-dose ICS." See Section 3.1). Additionally, in countries where the high-dose ICS or ICS/LABA is not available (e.g. only the medium-dose ICS or ICS/LABA is available in that country), the highest approved maintenance dose in the local label will also meet this ICS criterion

c. Beclomethasone dipropionate CFC is included for comparison with older literature

d. See local label.

Note: Data provided from GINA 2018 is not a table of equivalence, but of estimated clinical comparability. Categories of "low," "medium," and "high" doses are based on published information and available studies (at the time of GINA 2018 publication), including direct comparisons where available. Doses may be country-specific depending on labelling requirements. Most of the clinical benefit from ICS is seen at low doses, and clear evidence of dose-response relationships is seldom available within the dose ranges evaluated for regulatory purposes. "High" doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects. For new preparations, manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinical equivalent (GINA 2018).

Appendix F: Estimated OCS Dose Therapy Equivalence

Oral corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg
For conversions of other OCS doses or other OCS products, please see local label of OCS product or online conversion calculators (e.g. https://clincalc.com/corticosteroids/)	

Appendix G: Prednisone/Prednisolone Doses <5 mg in Relation to Available Tablet Strengths

Desirable daily dose	Available tablet strength	Administered number of tablets and frequency
0.5 mg	1 mg	½ tablet each day, or 1 tablet every other day
1.5 mg	1 mg	If divisible – 1½ tablets each day If non-divisible – Dose over 2 days as follows: 1 tablet on day 1 and 2 tablets on day 2.
2 mg	1 mg	2 tablets each day
2.5 mg	1 mg	If divisible – 2½ tablets each day If non-divisible – dose over 2 days as follows: 2 tablets on day 1 and 3 tablets on day 2.
2.5 mg	5 mg	½ tablet each day, or 1 tablet every other day
3 mg	1 mg	3 tablets each day
4 mg	1 mg	4 tablets each day

Appendix H: Glucocorticoid Toxicity Index

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Clinical and epidemiological research

Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis

Table 1
The Glucocorticoid Toxicity Index

Composite GTI	Item weight	Specific List
BMI		
Improvement in BMI	−8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	38	
Glucose tolerance		
Improvement in glucose tolerance	−8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	−10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	−9	
No change in lipids	0	
Worsening hyperlipidaemia	10	
Worsening hyperlipidaemia despite treatment	30	
Bone density		
Improvement in bone density	−1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	
Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GC-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade IV infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection
Grade III infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		Perforation
		Peptic ulcer disease
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	−36 to 439	

BMI, body mass index; GC, glucocorticoid; GTI, Glucocorticoid Toxicity Index.

Appendix H (continued)

Appendix III - Composite Glucocorticoid Toxicity Index

1. Body Mass Index (BMI) (compared to baseline)
a. Improvement in the direction of the normal range by more than 2 BMI units [normal range = 18.5-24.9 kg/m²]
b. No significant change (BMI remains within +/- 2 BMI units compared with baseline)
OR BMI remains within the normal range
c. Moderate increase in BMI (increase by more than 2 but less that 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m²])
d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m²])

2. Glucose Tolerance (compared to baseline)
a. Improvement in glucose tolerance:
- HbA1c declined >10% from baseline without medication increase
OR
- Decrease in diabetic medication without an increase in HbA1c of >10% or HbA1c < 5.7%

b. No significant change in glucose tolerance:
- HbA1c within 10% of baseline or HbA1c < 5.7% AND no change in medication
OR
- HbA1c increased to > 10% of baseline with a decrease in medication
OR
- HbA1c decreased by > 10% of baseline with an increase in medication

c. Worsening of glucose tolerance or medication status:
- HbA1c > 5.7% and increased to >10% of baseline without a change in medication
OR
- Increase in diabetic medication with < 10% increase in HbA1c

d. Worsening of glucose tolerance despite increased treatment:
- HbA1c > 5.7% AND increased to >10% of baseline AND an increase in diabetic medication

3. Blood Pressure (BP) (compared to baseline)
a. Improvement in BP:
- Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85
OR
- Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

b. No significant change in BP:
- BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication
OR
- Increase in either systolic or diastolic BP >10% with a decrease in medication
OR
- Improvement in systolic or diastolic BP of > 10% with an increase in medication

c. Worsening of hypertension:
- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication
OR
- An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP

d. Worsening of hypertension despite treatment:
- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication

4. Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)
a. Improvement in lipids:
- Decrease in LDL concentration >10% of baseline toward the target range without medication increase
OR
- Decrease in medication without an increase in LDL of >10% or LDL remains within target range

b. No significant change in LDL:
- LDL within 10% of baseline or within the target range for patient AND no change in medication
OR
- Increase in LDL > 10% with a decrease in medication
OR
- Improvement in LDL of > 10% with an increase in medication

c. Worsening of LDL or medication status:
- Increase in LDL of >10% to above target range without a change in medication
OR
- Increase in medication with <10% change in LDL

d. Worsening of LDL despite treatment:
- Increase in LDL of >10% AND an increase in medication

5. Bone Mineral Density (compared to baseline)
a. Improvement – increase in BMD by >3%
b. No significant change (BMD between -3% and +3%
c. Deterioration - decrease in BMD (BMD decrease by ->3%)
% refers to total BMD in gms/cm²

6. Glucocorticoid-induced myopathy
a. No steroid myopathy
b. Mild steroid myopathy (weakness WITHOUT functional limitation)
c. Moderate steroid myopathy (weakness WITH functional limitation)
See Steroid Myopathy definitions, below

7. Skin
a. No skin toxicity
b. Mild skin toxicity
c. Moderate skin toxicity

Appendix H (continued)

See Skin definitions, below
8. Neuropsychiatric toxicity a. No neuropsychiatric symptoms b. Mild neuropsychiatric symptoms c. Moderate neuropsychiatric symptoms See Neuropsychiatry definitions, below
9. Infection (since last assessment) a. No significant infection b. Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster) c. Grade 3 or complicated herpes zoster See Infection definitions, below

Glucocorticoid-induced Myopathy Definitions

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

Mild and moderate severity of myopathy are defined by a muscle strength of 4 on the standard Medical Research Council rating scale.

A 4 means weaker than normal but greater than antigravity strength against resistance.

"Mild" is mild weakness (Grade 4) that does NOT functionally limit the patient.

"Moderate" is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severe glucocorticoid-induced myopathy (defined as weakness of Grade 3 or less, which means no more than antigravity strength and unable to overcome any resistance or any degree weaker) is included in the Specific List. People who are severely weak may have difficulty rising from a chair without assistance or other major functional limitations but the formal categorization for severe should be based the degree of weakness on strength testing.

Severity of Glucocorticoid Toxicity in the Skin

Manifestations to be considered:

- Acneiform rash
- Easy Bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

Skin 6b. Mild	Skin 6c. Moderate	Severe (Specific Domain)
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)	Atrophy/Striae (Grade 3)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)	Erosions/Tears/Ulcerations (Grade 3)

Skin Definitions (from National Cancer Institute Common Terminology Criteria for Adverse Events):

Acneiform rash
- Grade 1 - Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2 – Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental ADL
- Grade 3 - Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self care ADL; OR associated with local superinfection with oral antibiotics indicated
- Grade 4 - Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; OR life- threatening consequences

Easy bruising
- Grade 1 – Localized or in a dependent area
- Grade 2 - Generalized

Hirsutism - In women, increase in length, thickness or density of hair in a male distribution
- Grade 1 - Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2 - Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact

Atrophy / Striae
- Grade 1 - Covering <10% BSA; OR associated with telangiectasias or changes in skin color
- Grade 2 – Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss
- Grade 3 - Covering >30% BSA; OR associated with ulceration

Erosions / Tears / Ulcerations
- Grade 1 – Combined area of ulcers <1 cm; OR nonblanchable erythema of intact skin associated with warmth or erythema
- Grade 2 – Combined area of ulcers 1 - 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat
- Grade 3 – Combined area of ulcers >2 cm; OR full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

Appendix H (continued)

Severity of Neuropsychiatric Glucocorticoid Toxicity

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive Impairment
- Depression

7b. Mild	7c. Moderate	Severe (Specific Domain)
Insomnia – (Grade 1)	Insomnia – (Grade 2)	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

Definitions of severity within the Neuropsychiatric Domain

Insomnia - Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening
- Grade 1: not associated with functional impairment
- Grade 2: associated with functional impairment

Mania
- Grade 1: Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 2: Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 3: Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

Cognitive impairment
- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids
- Grade 3: Frank delirium

Depression
- Grade 1: Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 2: Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 3: Severe constant feeling of being down or depression and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts.

Infection Definitions

No significant infection = No specific infections or serious infections, grade 3 or greater

Specific Infections – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement

Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

Grade 4 or 5 - Life-threatening consequences; urgent intervention indicated OR death from infection (included in the Specific List)

References

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Appendix H (continued)

Appendix IV - Specific List

	At Baseline or Before	New Since Baseline
Body Mass Index - An absolute increase in BMI of more than 8 units (and >24.9 kg/m^2)		
Blood Pressure - Hypertensive emergency (see definition, below) - PRES (Posterior reversible encephalopathy syndrome) (see definition, below)		
Endocrine - Symptomatic adrenal insufficiency		
Bone Health - Osteonecrosis of one joint - Osteonecrosis of more than one joint - Bone mineral density decrease > 6% - Insufficiency fracture - Insufficiency fracture in more than one bone		
Muscle & Tendon - Severe glucocorticoid myopathy (see definition) - Tendon rupture - More than one tendon rupture		
Eye - Central serous retinopathy - New-onset or worsened elevation of intra-ocular pressure requiring treatment or change in treatment - Posterior subcapsular cataracts (or history of same)		
Infection - Grade 4 infection (see definition, below) - Grade 5 infection (death from infection)		
Glucose Tolerance - Diabetic nephropathy - Diabetic neuropathy - Diabetic retinopathy		
Gastrointestinal Tract - Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use) - Peptic ulcer disease confirmed by endoscopy (excluding *H. pylori*)		
Skin - Severe skin toxicity (see definition, below)		
Neuropsychiatric - Psychosis, defined as hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression) - Glucocorticoid-induced violence toward self or others		
Other glucocorticoid toxicities Please specify: _____ _____ _____		

Appendix H (continued)

DEFINITIONS:

Hypertensive emergency: The blood pressure has reached levels that are damaging organs. Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mmHg systolic OR 120 mmHg diastolic, but can occur at even lower levels in patients whose blood pressure have not been elevated before. Complications can include: stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, pulmonary edema.

Posterior reversible leukoencephalopathy syndrome (PRES): A clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss, depending on the affected neuroanatomy. Characteristic Magnetic Resonance Imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of other potential causes (including hypertensive emergency).

Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy.

Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue. Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

Grade 4 infection: Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis).

Diabetic nephropathy: Macroalbuminuria; i.e., a urinary albumin excretion > 300 mg in a 24-hour collection or a urinary protein: creatinine ratio > 300mg/g.

Diabetic neuropathy: Any of four types of peripheral neuropathy occurring in the setting of diabetes mellitus, namely: 1) a distal sensory polyneuropathy; 2) autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues); 3) diabetic amyotrophy (muscle infarction); or 4) mononeuritis (e.g., foot drop attributed to diabetic neuropathy).

Diabetic retinopathy: Any form of retinopathy associated with diabetes mellitus, including both non-proliferative and proliferative forms of diabetic retinopathy as well as diabetic macular edema. These complications must be confirmed by an ophthalmologist.

Severe skin toxicity: Any of the three following manifestations:
Grade 4 acneiform lesions - Papules and/or pustules covering any % body suraface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated or life- threatening consequences
Grade 3 striae - Covering >30% BSA or associated with ulceration
Grade 3 ulcers - Combined area of ulcers >2 cm or full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

References

National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978.

American Heart Association. Hypertensive Crisis. Accessed http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Hypertensive-Crisis_UCM_301782_Article.jsp#.V0NnSzv2ZaQ. 5/1/2015.

Appendix I: Anaphylaxis: Signs, Symptoms, and Management

1. Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (eg, IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). 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.

If an anaphylactic reaction occurs, a blood sample will be drawn from the patient as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

2. Clinical Criteria for Defining Anaphylaxis

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

- 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 ONE OF THE FOLLOWING

(a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

(b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

- Two or more of the following 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 peak expiratory flow, hypoxemia)

(c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

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

- Reduced BP after exposure to known allergen for that patient (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that patient's baseline value

3. Signs, Symptoms, and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include the following:

- 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

- Assessment of airway, breathing, circulation, and adequacy of mentation
- Administer epinephrine intramuscularly every 5-15 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

(e) Place patient in recumbent position and elevate lower extremities

(f) Establish and maintain airway

(g) Administer oxygen

(h) Establish venous access.

(i) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(j) Consider epinephrine infusion.

(k) Consider H1 and H2 antihistamines

(l) Consider nebulized β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine

(m) Consider systemic corticosteroids

(n) Consider vasopressor (eg, dopamine)

(o) Consider glucagon for patient taking a β -blocker

(p) Consider atropine for symptomatic bradycardia

(q) Consider transportation to an emergency department or an intensive care facility

(r) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 2008;63(8):1061-70.

Appendix J: Adrenal Crisis Guidelines

Management of Acute Adrenal Insufficiency Secondary to Glucocorticoid Withdrawal

National or local guidelines for the management of acute adrenal insufficiency (adrenal crisis), where they exist, should be followed. The following guidelines have been adapted from the guidelines of the Society for Endocrinology. They are intended for guidance subject to clinical judgement only.

The possibility of acute adrenal insufficiency should be considered in any acutely unwell patient undergoing withdrawal of chronic systemic corticosteroid treatment.

Recognition

- Clinical signs and symptoms
  - Fatigue, lack of energy, weight loss
  - Low blood pressure, postural dizziness and hypotension (≥20 mmHg drop in systolic BP from supine to standing position), dizziness, collapse, and in severe cases hypovolaemic shock
  - Abdominal pain, tenderness and guarding, nausea, vomiting
  - Fever
  - Confusion, somnolence, in severe cases delirium or coma
  - Back and leg cramps/spasms may be reported
- Lab findings:
  - Hyponatraemia
  - Pre-renal failure (increased serum creatinine due to hypovolaemia)
  - Normochromic anaemia, sometimes also lymphocytosis and eosinophilia
  - Hypoglycaemia

Management

- **Hydrocortisone** (immediate bolus injection of 100 mg hydrocortisone i.v. or i.m. followed by continuous intravenous infusion of 200 mg of hydrocortisone per 24 hours (alternatively 50 mg of hydrocortisone per intravenous or intramuscular injection every 6 hours)
- **Rehydrate** with intravenous 0.9% sodium chloride in hypotensive patients. The rate and total volume of infusate must be decided on an individual patient basis with continuous monitoring for fluid overload. Correction of hyponatremia must be according to relevant local guidelines

- Consider any other potential precipitating factors (in addition to corticosteroid withdrawal), eg, infection; investigate and treat as appropriate

Contact an endocrinologist at an early stage to advise on ongoing management.

Reference

Arlt W; Society for Endocrinology Clinical Committee. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect 2016;(5):G1-G3.

Appendix K: PONENTE Long Term Follow Up Substudy

1. PONENTE Long Term Follow Up Substudy Background and Rationale

The PONENTE study assesses an algorithm for OCS reduction that also defines when OCS reduction should be interrupted (i.e. after 2 exacerbations, or after two laboratory tests showing complete AI within a 3-month period). Once the OCS dose has been completely reduced or the lowest OCS dose achieved based on the OCS reduction treatment algorithm, patients enter a maintenance phase where no further reductions in OCS dose are allowed. After completing the 6-month OCS maintenance phase, patients who couldn't completely reduce OCS may have been well-controlled on the lowest OCS dose achieved during the OCS reduction phase or may have recovered from AI, and, therefore, healthcare providers may decide to further reduce OCS or other background asthma medication, which is in line with the GINA report on severe asthma management (i.e. first reducing OCS and then, reducing ICS dose as tolerated according to clinical assessment) (GINA 2020).

According to the GINA report, asthma therapy should be periodically reviewed to assess patient's response to therapy. For patients who have had a good response to biologic therapy, the treating physician should consider not only the reduction or elimination of maintenance OCS, but also reducing the ICS dose from high to medium dose (GINA 2020). GINA describes this guidance as "consensus advice" recognizing that no data are available to guide this clinical decision.

However, it is anticipated that in the future healthcare providers are likely to reduce the ICS dose significantly or completely at the behest of patients whose asthma becomes well-controlled after the addition of biologic therapy.

This long term follow up substudy aims to observe changes in the OCS dose and other background asthma therapy, and to assess the amount of recovery from AI, in a real-world setting as well as assessment of glucocorticoid toxicity by means of GTI.

2. PONENTE Long Term Follow Up Substudy Design

After completion of the EOT visit procedures, eligible patients (See Appendix K – Section 4 and 5) may consent to a long term follow up visit 12 to 18 months after completion of the main PONENTE study. Accordingly, the long term follow up visit can occur in a range of 12 to 18 months after an eligible patient completes the EOT visit such that the last visit of the PONENTE Long Term Follow Up will take place 1-year after the last patient completes the EOT of the main PONENTE study.

Patients will be treated according to healthcare provider discretion and therefore no IP (i.e. Benralizumab) will be provided by the sponsor. Between the EOT visit of the main PONENTE study and the Long Term Follow Up visit, any changes in the maintenance asthma regimen are allowed, including further reductions of OCS as recommended in the GINA report (GINA 2020).

2.1 Consent:

Written consent must be obtained at any time from the EOT visit to prior to the Long Term Follow Up visit. Patients will complete the 4-week follow-up visit after EOT, regardless of whether they enrol in the long term follow up substudy, as this is the last visit of the PONENTE study.

Patients who have already completed the EOT visit or the follow-up visit before the start of the PONENTE Long Term Follow Up may be contacted after EOT for participation. In this case, all assessments previously captured during the EOT visit will be included in the analysis of the PONENTE Long Term Follow Up.

Enrolment into the long term follow up substudy will remain open until the last PONENTE patient has completed the EOT visit.

2.2 Long Term Follow Up Visit:

At the Long Term Follow Up visit, the patient will undergo an on-site visit for assessment of daily OCS dose, concomitant medications (including changes in background asthma regimen), asthma exacerbations, laboratory assessments, vital signs, and items for the GTI assessments. Additionally, patients who had Complete or Partial AI at the end of the OCS maintenance phase (EOT visit) of the primary PONENTE study, will undergo morning cortisol testing. Patients with indeterminate results from the morning cortisol test at the Long Term Follow Up visit will return on-site to conduct ACTH stimulation test within a week after the Long Term Follow Up visit.

2.3 Assessment and collection of asthma exacerbations:

Asthma exacerbations will be defined per Section 5.2.2. The Investigator will assess exacerbations at the PONENTE Long Term Follow Up, and if applicable, at any other time when made aware by the patient (Table 8). The Investigator must justify the decision for defining an event of worsening asthma as an exacerbation, and document this justification, including symptoms, in the source documents and the eCRF.

2.4 Safety reporting:

Any event that occurs from the time period between the main PONENTE study follow up visit and the patient signing the ICF will be captured as part of the medical history for the PONENTE Long Term Follow Up. After PONENTE Long Term Follow Up informed consent up until the Long Term Follow Up visit, any events will be captured as AEs/SAEs. Any AE/SAE that are unresolved at the Long Term Follow Up visit will be followed-up by the Investigator as long as medically necessary but will not be captured in the eCRF. Causality will be confirmed by the investigator per Section 6.3.4. Adverse events based on signs and symptoms, or based on examinations and tests, will be reported per Sections 6.3.5 and 6.3.6, respectively.

Any spontaneous reports of AE/SAE related to any drug products other than benralizumab will not be captured in the eCRF but will be reported as spontaneous reports to the drug

manufacturer (e.g. to AstraZeneca or other manufacturer) and/or local regulatory agencies as required by local regulations.

3. PONENTE Long Term Follow Up Substudy objectives

The main objective of the PONENTE Long Term Follow Up Substudy is to retrospectively collect changes of OCS and other background asthma maintenance medications, in a real-world setting 12 to 18 months after completion of the main PONENTE study. Additionally, the substudy aims to further observe shifts in the AI status in patients who had Complete or Partial AI at the end of the PONENTE study and to further evaluate the GTI over time.

Observational Objectives:	**Outcome Measures:**
To observe real-world clinical management of OCS dose 12 to 18 months after completion of the main PONENTE study	• Patients who achieve 100% reduction in daily OCS dose from baseline* OCS dose to the end of the long term follow up substudy • Patients who achieve a daily OCS dose of ≤5 mg at the end of the long term follow up substudy • Patients who achieve ≥90%, ≥75%, ≥50% or >0% OCS reduction from baseline* OCS dose to the end of the long term follow up substudy. • Change in daily OCS dose from baseline* to the end of the long term follow up substudy
To observe real-world clinical management of background maintenance asthma regimen	• Change in background asthma maintenance medication from EOT of PONENTE main study* to the end of the long term follow up substudy

Safety Objectives:	**Outcome Measures:**
To observe shift in AI status in patients who had Complete AI or Partial AI at the end of the PONENTE study	• Shifts in AI status and further OCS dose changes from the main PONENTE study to the long term follow up visit
To observe asthma exacerbations in adult patients from the main PONENTE study to the long term follow up visit	• Annualized asthma exacerbation rate • Percentage of patients without exacerbation
To assess the safety and tolerability from the main PONENTE study to the long term follow up visit	• Adverse events / Serious adverse events • Laboratory parameters and vital signs

To evaluate corticosteroid toxicity from the main PONENTE study to the long term follow up visit	• Glucocorticoid toxicity index

*the PONENTE main study baseline

4. Inclusion criteria

For inclusion in the PONENTE Long Term Follow Up substudy, patients should fulfil the following criteria:

a. Patients must have completed the PONENTE EOT visit.

b. Written informed consent to participate in the observational PONENTE Long Term Follow Up

5. Exclusion criteria

Patients should not enter the PONENTE Long Term Follow Up if any of the following exclusion criteria are fulfilled:

a. Concurrent enrolment in another interventional clinical trial
b. AstraZeneca staff involved in the planning and/or conduct of the study
c. Employees of the study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals

6. Study Plan and timing of procedures

Table 8 PONENTE Long Term Follow Up Substudy – Study plan: Enrolment to End of Study

Assessment/Activity	Protocol section	Enrollment	Long Term Follow Up Period	Withdrawal	Unscheduled Visit
		PONENTE Long Term Follow Up Enrolment (after EOT procedures)[a]	PONENTE Long Term Follow Up Visit		
Written Informed consent for long term follow up substudy[b]	Appendix K: 2.1	X			
Medical History		X			
Review EOT Visit Assessments	Table 1	X			
Brief physical examination	5.2.5.2	N/A		X	X
Vital signs	5.2.6	N/A	X	X	X
Weight	5.3.1	N/A	X	X	
Serum chemistry	5.2.4	N/A	X	X	
Hematology	5.2.4	N/A	X	X	
Morning Cortisol testing[c]	5.2.4	N/A	X	X	
Glucocorticoid toxicity index	5.2.1.1	N/A	X	X	
Assessment of asthma exacerbations	5.2.2/5.2.3	N/A	X	X	X
Adverse events	6.1	N/A	X	X	X
Concomitant medication	7.8 / Appendix K: 7	N/A	X	X	X
OCS and asthma medications	Appendix K: 7	N/A	X	X	X

a. Enrolment for the PONENTE Long Term Follow Up substudy can occur any time after all PONENTE EOT procedures are completed. Patients who have already completed EOT prior to the start of the PONENTE Long Term Follow Up substudy may be contacted for participation at any time up to 18 months after the EOT visit. Assessments labeled N/A are not applicable because they will be collected as a part of the PONENTE EOT visit.
b. ICF for the PONENTE Long Term Follow Up substudy must be obtained any time from EOT of the main PONENTE study and prior to any activities of the PONENTE Long Term Follow Up visit
c. Patients who have Complete AI or Partial AI at the end of the primary PONENTE study will undergo a morning cortisol test at the Long Term Follow Up visit. Patients with indeterminate results will return to the site within a week after the Long Term Follow Up visit to conduct an ACTH stimulation test.

7. Concomitant medication and other treatments

The PONENTE Long Term Follow Up is observational only. There are no sponsor-provided investigational products, restrictions related to concomitant medications other than those detailed in Section 3.5, or restrictions on concurrent disease. Restrictions described in Section 7.8 do not apply in the PONENTE Long Term Follow Up.

Additionally, from the EOT visit of the main PONENTE study to the Long Term Follow Up visit, any changes in the maintenance asthma regimen are allowed, including reductions of maintenance OCS therapy as recommended in the GINA report.

Due to potential interactions with morning cortisol and ACTH stimulation testing, the restrictions on concomitant medications detailed in Section 3.5 remain in place for the PONENTE Long Term Follow Up substudy.

8. Statistical Analyses by AstraZeneca

8.1 Statistical Analysis Plan

The PONENTE Long Term Follow Up will be managed under a separate SAP from the PONENTE main study and reported by way of an addendum to the PONENTE CSR.

8.2 Sample Size Estimate for PONENTE Long Term Follow Up substudy

The PONENTE Long Term Follow Up is not formally powered; all patients from the PONENTE main study meeting all inclusion criteria and no exclusion criteria of this long term follow up substudy will be eligible to enrol.

8.3 Definition of analysis sets for PONENTE Long Term Follow Up substudy

Observational and safety analyses will use a common analysis set – the Long Term Follow Up Analysis Set - which will include all patients who sign informed consent to continue into the PONENTE Long Term Follow Up . Two further analysis sets are defined as follows:

The "Biologic" Analysis Set will include all patients in the Long Term Follow Up Analysis set with >=50% exposure to any biologic treatment for asthma during the PONENTE Long Term Follow Up ; and

The "Benralizumab" Analysis Set will include all patients in the Long Term Follow Up Analysis set with >=50% exposure to commercial Benralizumab during the PONENTE Long Term Follow Up.

Additional analysis sets may be defined in the SAP.

8.4 Outcome measures for the PONENTE Long Term Follow Up substudy

Definition of baseline

Baseline definitions will be as per definitions for the PONENTE main study (see the main PONENTE SAP for full definitions).

Outcome variables

- Patients who achieve 100% reduction in daily OCS dose from PONENTE baseline dose to the Long Term Follow Up visit
- Patients who achieve a daily OCS dose of ≤5mg (prednisone equivalent dose) at the Long Term Follow Up visit
- Patients who achieve ≥90%, ≥75%, ≥50% and >0% reduction in daily OCS dose from PONENTE baseline dose to the Long Term Follow Up visit
- Change in daily OCS dose (mg prednisone equivalent dose) from the baseline dose of the PONENTE main study to the Long Term Follow Up visit
- Change in background asthma maintenance medication from baseline of the PONENTE main study to the Long Term Follow Up visit

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. Full details will be defined in the PONENTE Long Term Follow Up substudy SAP.

Safety outcome variables

- Patients with complete AI and changes in AI status
- Annualized asthma exacerbation rate
- AEs, SAEs
- Laboratory parameters and vital signs
- GTI

8.5 Methods for statistical analyses for the PONENTE Long Term Follow Up substudy

Statistical tabulation will be presented for all patients in the long term follow up analysis set, biologic analysis set and Benralizumab analysis set. Continuous variables will be summarized using the mean, two-sided 95% CI of the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method. Data will be listed in patient-level data listings.

No formal hypothesis will be tested and no multiplicity adjustment will be applied in the statistical analysis. No imputation of observational or safety data will be performed. Imputation for partial dates will be detailed in the SAP.

Analysis of the observational variables

Changes in OCS dose over time will be summarized using descriptive statistics in tables and presented graphically for the long term follow up analysis set, biologic analysis set and Benralizumab analysis set. Percentages achieving 100% reduction in OCS daily dose, a ≤5mg daily dose, other pre-specified percentage reductions in OCS daily dose and reductions in background asthma medications will be reported with nominal 95% CIs derived using the exact Clopper-Pearson method.

Additional analyses will be detailed in the PONENTE Long Term Follow Up substudy SAP.

Analysis of safety outcomes

The number and percentage of patients with complete AI at the Long Term Follow Up visit will be presented for the long term follow up analysis set, biologic analysis set and Benralizumab analysis set. A logistic regression model will be developed to identify factors potentially predictive of long-term adrenal insufficiency. Complete AI status at the Long Term Follow Up visit will be the dichotomous response variable with demographic, respiratory and metabolic baseline characteristics as explanatory variables. Full details will be provided in the SAP.

Spaghetti plots will be produced for patients in the long term follow up analysis set, biologic analysis set and Benralizumab analysis set with partial AI throughout the OCS reduction phase of the main PONENTE study, showing cortisol levels over time until the Long Term Follow Up visit.

The incidence of AEs and SAEs will be summarized over the PONENTE Long Term Follow Up substudy for comparison with incidence rates during the PONENTE main study. Summaries of laboratory parameters and vital signs may be provided, including absolute values and changes over time. Full details will be provided in the SAP.

The annualized rate of asthma exacerbations during the PONENTE Long Term Follow Up substudy will be summarized using mean, 95% CI and dispersion based on the negative binomial distribution, for the long term follow up analysis set, biologic analysis set and Benralizumab analysis set. This will be repeated for exacerbations resulting in hospitalization or an ER visit. Rates will be compared with those recorded during the PONENTE main study. The number and percentage of patients remaining exacerbation-free during the PONENTE Long Term Follow Up substudy will be presented.

Glucocorticoid toxicity index will be summarized over time from the start of the PONENTE main study to the end of the PONENTE Long Term Follow Up substudy, for the long term follow up analysis set, biologic analysis set and Benralizumab analysis set. Statistical correlation between GTI and daily OCS dose will be explored.

Subgroup analysis

Any subgroup analyses will be defined in the PONENTE Long Term Follow Up SAP.

9. Study timetable and end-of-study

Enrolment for the PONENTE Long Term Follow Up substudy will be closed once the final PONENTE patient completes the EOT visit. For patients who participate in the PONENTE Long Term Follow Up substudy, the final study visit will be the Long Term Follow Up visit except for patients with indeterminate morning cortisol results at this visit who will return within 1 week after Long Term Follow Up visit to conduct the ACTH stimulation test.

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

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

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

1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section 2 to Section 5. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

2 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patients home / or other remote location as per local Standard Operating Procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP). If applicable, assessments will be performed according a the revised Schedule of Assessments (SoA) in the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

3 Telemedicine Visit to Replace On-site Visit (where applicable)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, exacerbations, OCS dose (including reasons for no OCS reduction in an otherwise controlled patient), GTI data, blood sample collection for central lab analysis, etc to be reported and documented. If applicable, safety procedures and blood sample collection will be performed according to the revised SoA in the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

4 At-home or Remote Location IP Administration Instructions

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

4.1 - At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

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

5 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patient themselves if applicable.

Refer to the Study Instruction Manual for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis for step by step guidance.

6 Changes to Statistical Analyses

Additional sensitivity and supportive analyses to assess the impact of study disruption (e.g. effects of the COVID-19 pandemic) on the primary, secondary and key supportive efficacy endpoints may be defined. Full details will be included in the Statistical Analysis Plan.

SIGNATURE PAGE

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