Statistical Analysis Plan	
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PONENTE: A Multicentre, 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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire-6
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AI	Adrenal insufficiency
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRS	Chronic rhinosinusitis (without nasal polyps)
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSP	Clinical study protocol

Abbreviation or special term	Explanation
CSR	Clinical study report
DAE	AEs causing discontinuation of investigational product
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic case report form
ePRO	Electronic patient reported outcome
EDN	Eosinophil-derived neurotoxin
EOT	End-of-treatment
FAS	Full analysis set
FeNO	Fractional exhaled Nitric Oxide
GGT	Gamma-glutamyl transferase
GTI	Glucocorticoid toxicity index
HPA	Hypothalamic pituitary adrenal
ICF	Informed consent form
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IP	Investigational product
IPD	Premature IP Discontinuation
LABA	Long-acting β_2 agonist
LDL	Low-density lipoprotein
LRTI	Lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
PGIC	Patient Global Impression of Change
PI	Principal investigator
PRO	Patient reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or special term	Explanation
SAS	Statistical Analysis System (SAS Institute Inc., Cary, NC)
SBP	Systolic blood pressure
SC	Subcutaneous
SCS	Systemic corticosteroids
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SI	International System of Units
SOC	System organ class
TBL	Total bilirubin
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WBDC	Web Based Data Capture
WHODD	World Health Organisation Drug Dictionary
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

Date	Description of change
30 July 2018	Initial version (v1.0).
24 May 2019	Changes in line with Clinical Study Protocol amendments (to v2.0): 1. "Average daily OCS dose" has been amended to "daily OCS dose" in definitions of the key supportive outcome measures (sections 1.1.1 and 3.1). 2. The timepoint "time point at which the last OCS dose equals to 5 mg" in the analysis of ACQ-6 has been removed (sections 1.1.2, 3.2.3 and 4.2.6.3). 3. Baseline for SGRQ data specified as Visit 2 for clarity (sections 1.1.1, 3.2.4). 4. References to "severe" asthma exacerbations have been removed throughout. Exacerbations resulting in hospitalisation / emergency room visits are reported and analysed separately (sections 1.1.3, 3.1, 3.3, 3.3.2 and 4.2.7.4). 5. Updated text in section 1.2 (Study Design) in accordance with amendments made to the CSP (version 2.0). In particular: added clarification on the duration of each study period; added clarification that serum prednisone/prednisolone testing is only for patients who were not already on prednisone/prednisolone prior to Visit 1; added clarification around when the screening period may be extended; added clarification around benralizumab and OCS dosing during the induction phase and how to proceed if an exacerbation occurs during this phase; added clarification around timing of HPA axis integrity testing in the OCS reduction phase; and 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 in the maintenance phase. It is reiterated that patients should be maintained on their background asthma therapy (ICS/LABA) without change until EOT. 6. Figure 1 (including footnotes) has been updated for consistency with changes to section 1.2 and the CSP (version 2.0). 7. The Clopper-Pearson 95% confidence intervals for estimated success rates have been updated in the calculations for number of subjects (section 1.3). Calculations were carried out using SAS. 8. Important timepoints (in terms of visit window definitions) have been amended to reflect that not all patients may achieve a minimum OCS daily dose of 0 / 5mg (section 2.2.2). 9. Similarly, the definition of the final OCS dose achieved in the OCS reduction phase has been amended within the description of the primary outcome variables (section 3.1). 10. Clarification has been added that for prednisone doses below 5 mg, if the exact dose strength is not available in the country, the daily dose could be

Date	Description of change
	achieved by dosing every other day. The daily dose will then be calculated as the average over 2 days (section 3.1).
	11. The time to 1st increase in OCS dose in the maintenance phase will be measured from the time of achieving the final (minimum) OCS dose during the reduction phase (rather than end of OCS phase / start of maintenance phase) (sections 3.2.2, 4.2.6.2).
	12. Clarification has been added regarding missing baseline ACQ-6 scores. 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 in ACQ-6 to indicate deterioration. However, it will not be used to impute the baseline for ACQ-6 analysis (section 3.2.3).
	13. 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 3.2.3.
	14. Response categories for the Patient Global Impression of Change (PGIC) have been amended to "Improved", "Moderately improved" and "Much improved" (section 3.4.2)
	15. Updated sub-populations to be based on **blood** eosinophil count (rather than serum) & changed the equality/inequality so that the population is split as ≥300/µL and <300/µL (section 4.1).
	16. Reference to a synthetic control arm has been removed and replaced with "external data sources" which may be used to contextualise any changes seen in asthma control, asthma exacerbation rates or other safety endpoints in patients treated with benralizumab who follow OCS down-titration (section 4.1).
	17. Analysis methods for the absolute and percentage change from baseline in OCS dose during the OCS reduction phase have been specified (section 4.2.5.1).
	18. A second sensitivity analysis (excluding early withdrawn patients as per the CSP) has been included (section 4.2.5.2).
	19. Covariates included in the modelling of secondary endpoints include baseline categories of blood (rather than serum) eosinophil counts (sections 4.2.6.1, 4.2.6.3 and 4.2.6.4).
	20. Interim Analysis has been re-termed "Interim Review" and is now planned to be performed after 90-100 (amended from 300) patients have completed OCS reduction (section 5).
	21. Changes of analysis from the protocol have been removed following updates to the protocol (section 6).
	<u>Other changes:</u>
	22. Change to AstraZeneca Study Statistician.

Date	Description of change
	23. Change of third signatory, from AstraZeneca Global Product Statistician to GMA Statistical Lead. 24. List of Abbreviations: ALP, DBP, GGT, ICS, LRTI, PRO, Q2W, SBP, SCS, SGRQ and URTI added; Post BD removed (not used in SAP); some re-ordering to put into alphabetical order. 25. The abbreviation of Important Protocol Deviation as [IPD] has been removed (section 2.1) to avoid confusion with the use of IPD throughout this document as an abbreviation for Premature IP Discontinuation. 26. A definition for the sputum sub-study analysis set has been added (section 2.1.3). 27. An important protocol deviation category has been added – "Incorrect process or monitoring of OCS down-titration" (section 2.2.1). 28. Specific important protocol deviations from the Non-Compliance Handling Plan have been listed and NCHP referenced (section 2.2.1). 29. The definition of the final OCS dose in the OCS reduction phase has been expanded for clarification (section 3.1). 30. Clarification has been added to the definition of change in OCS dose during maintenance phase to specify that change is to EOT/IPD visit (in case of patient withdrawal) (section 3.2.1). 31. ACQ-6, change from baseline in ACQ-6 scores and SGRQ response will also be assessed following any premature IP discontinuation (IPD) (section 3.2.3 and section 3.2.4). 32. Clarification has been added regarding the timings of ACQ-6 summaries at Visit 3, end of OCS reduction phase and EOT (as ACQ-6 scores are recorded weekly and may not coincide exactly with the above timepoints (section 3.2.3). 33. Sub-populations have been amended. The inequality has been changed for the sub-populations based on baseline OCS dose (to ≥10 mg/day and <10 mg/day) and the sub-populations based on baseline blood eosinophil count amended to patients with baseline blood eosinophil count <150 /µL, ≥150 /µL and ≥300 /µL (section 4.1). 34. Patient disposition categories have been updated and the denominator for percentage calculations specified as the number of patients receiving treatment with benralizumab (section 4.2.1). 35. Change from baseline in ACQ-6 score will be analysed using an ANCOVA rather than mixed model (section 4.2.6.3). 36. For the analysis of time to 1st increase in OCS dose using a Cox Proportional Hazard model, it is specified that the assumption of proportional hazards will be tested for covariates and appropriate action

Date	Description of change
	taken if the assumption is not met; and the adjusted median time to 1st OCS dose increase, with 95% CI, will be reported (section 4.2.6.2). 37. Minor amendments to wording and grammar have been made throughout for improved clarity.
15 Jan 2020	Changes in line with Clinical Study Protocol amendments (to v3.0): 1. All sputum-related content (section 1.1.4, section 1.2, original section 2.1.3, original section 3.4.6, section 4.2.8.3) has been removed throughout. 2. Updated text in section 1.2 (Study Design) in accordance with amendments made to the CSP (version 3.0) on the OCS Reduction phase. In particular, clarifications on the differences between the morning cortisol test and ACTH stimulation test, both used to evaluate HPA integrity. Clarification 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. 3. 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 has been added (section 1.2). 4. A final morning cortisol test (and if required, ACTH stimulation test for indeterminate result) at the end of the Maintenance phase, for patients who have Complete AI or Partial AI at the end of the OCS Reduction phase has been added (section 1.2). 5. Updated text in section 1.2 (Study Design) in accordance with amendments made to the CSP (version 3.0) on the Follow-up period. In particular, 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. 6. The terminology “partial AI” has been replaced with “indeterminate AI” (or “indeterminate result”) where applicable throughout. 7. Initial morning cortisol test has been added as an additional timepoint for reporting ACQ-6 scores (section 3.2.3, 4.2.7.1). 8. Clarification has been made to the timepoint at which OCS dose equals 5mg of the initial morning cortisol test (section 3.2.3). 9. Sub-populations have been amended. The inequality and categories have been changed for the sub-populations based on baseline OCS dose (to >10 mg/day, >5 mg/day to ≤10 mg/day, and 5 mg/day) and the sub-populations based on baseline blood eosinophil count amended to 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 4.1, 4.2.2).

Date	Description of change
	10. The reason for no further reduction for patients who do not achieve 100% reduction in their daily OCS dose will be listed (section 4.2.5.1). 11. Spaghetti plots will be produced for patients with indeterminate AI throughout the OCS reduction phase (section 4.2.7.1). 12. Baseline blood eosinophil counts versus baseline OCS dose will be presented in scatter plots, and baseline blood eosinophil categories by region and by duration of chronic OCS use will be presented in bar graphs (section 4.2.8.2). 13. Details on the additional database lock which may occur after all patients have completed the OCS reduction phase (section 5). Other changes: 14. Clarification has been made to the difference in analysis methods for duplicate observations at the same visit between laboratory assessments and other assessments (section 2.2.3). 15. "For those patients who had a baseline OCS dose equals to 5mg, final OCS dose should be less than 5mg." has been deleted (section 3.1). 16. Clarification on the definition of AEs in the on-study period (section 3.3.3) to specify the Disposition Event date of End of Study will be used when a follow-up visit is not available. 17. Safety outcomes such as asthma exacerbations and AEs will not be assigned to on-treatment period or post-treatment period; only on-study period is needed. (section 3.3.2, section 3.3.3). 18. Change has been made to the unit of eosinophils counts which will be reported and presented (section 3.3.4, 3.4.3). 19. The further subgroups based on baseline OCS dose for patient disposition has been removed. Furthermore, absolute and percent change from baseline of daily OCS dose reduction from baseline to end of OCS reduction phase will be summarised by patients with/without complete AI at the end of OCS reduction phase (section 4.1). 20. In addition, BMI and BMI group will be summarised by age group and by region (section 4.2.2). 21. The sensitivity analysis to the first key supportive analysis has been added (section 4.2.5.2). 22. The method used to calculate 95% CIs of quantiles for time from achieving the final OCS dose during the reduction phase to first OCS increase during the maintenance phase is specified as complementary log-log transformation. (section 4.2.6.2). 23. Specified to use observed margin approach in the ANCOVA model analysing change from baseline in ACQ-6 score (section 4.2.6.3).

Date	Description of change
	24. Changed the definition of "most common AEs" from frequency >5% to frequency >=3% (section 4.2.7.2). 25. A shift table of HbA1c at baseline versus post-baseline will be produced to display normal (<5.7%), pre-diabetes (≥5.7%-<6.5%), and diabetes (≥6.5%) (section 4.2.7.3). 26. Each of the 8 items in GTI will be summarised (section 4.2.7.5). 27. Analysis methods to impute date of prior/concomitant medications if the start date of a therapy is null and the end date is not a complete date has been expanded for clarity in appendix 8.1. 28. Minor amendments to wording and grammar have been made throughout for improved clarity.
1 September 2020	1. Safety analysis set is removed from section 2.1. 2. Comprehensive important protocol deviation criteria are included based on Non-Compliance Handing Plan v3.0 (section 2.2.1). 3. The programming logic for baseline OCS dose calculation is added. >0% reduction from baseline OCS dose is added as a supportive variable to the primary outcome variables (section 3.1). 4. Assessment timepoints of the ACQ-6 asthma control status categories are clarified (section 3.2.3). 5. Safety variable "patients with complete AI" is renamed to "Disposition of adrenal function by morning cortisol and/or ACTH test" (section 3.3). 6. PGIC response category is renamed to PGIC improvement category (section 3.4.2). 7. Subgroups based on patient's AI status at the end of the OCS reduction phase are defined (section 4.1). 8. Patient disposition summary for DBL1 is clarified (section 4.2.1). 9. For the summary of concomitant medications, the original two groups (allowed and disallowed) are categorised to 4 groups: allowed starting prior to first IP dose, allowed starting after first IP dose, disallowed starting prior to first IP dose, disallowed starting after first IP dose (section 4.2.3). 10. Baseline characteristics are summarized for patients who fail to reduce to 0 mg OCS dose due to complete AI and those due to asthma exacerbation. Characteristics are listed. Also tabulation subgroups are defined (section 4.2.5.1). 11. A shift table of patients' AI status from initial morning cortisol test to end of OCS reduction phase is added (section 4.2.7.1). 12. The spaghetti plot is updated to include patients with partial AI (as determined by ACTH stimulation test) following the initial and repeat morning cortisol tests, showing all available cortisol levels over time. Morning cortisol test and ACTH stimulation test results will be plotted side

Date	Description of change
	by side. Plots will be repeated for patients with partial AI following the initial morning cortisol test and complete AI at the repeat. Patients taking oral estrogen containing contraceptive will be plotted on separate pages (section 4.2.7.1). 13. The threshold of LDL worsening for GTI calculation is defined (section 4.2.7.5). 14. The graphical analysis of statistical correlation between GTI and daily OCS dose is updated to be between GTI and change in cumulative OCS dose (section 4.2.7.5). 15. Appendix 8.2 is added to describe the analyses of COVID-19 impact. 16. Minor amendments to wording and grammar have been made throughout for improved clarity.
26 April, 2021	Changes in line with Clinical Study Protocol amendments (to v4.0): 1. Included the content of the PONENTE Long Term Follow Up Visit substudy and consequently, the following sections include a reference to the Addendum for the substudy: • *Section 1.2 – Study design* • *Section 2 – Analysis Sets* • *Section 3 – Primary and Secondary Variables* • *Section 4 – Analysis Methods* 2. *List of Abbreviations:* Added the abbreviation for coronavirus disease 2019 (COVID-19). 3. 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. *4. Section 1.2- Study Design:* • Added new paragraph to describe the addition of a long term follow up period to the PONENTE study, high-level objectives, and to refer to an Addendum for details. An additional database lock for the substudy is also described. 5. *Section 7 – 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. 6. Added new appendix 8.3 - *Additional reporting to assess the impact of the COVID-19 pandemic on data to the end of the study (DBL2).* This section details the analyses of data impacted by COVID-19 pandemic at DBL2. Other changes: 7. Section 2.2.1: To align with the updated Non-Compliance Handling Plan, the important protocol deviation of "failure to regularly record weekly

Date	Description of change
	ACQ-6 scores in ePRO throughout treatment period" is limited to "to end of OCS reduction phase". Added summary statistics of ACQ-6 compliance to the end of OCS reduction phase and to end of study will be presented plus the number and percentage of patients who missed >2, >3, >4, and >5 sequential diaries in OCS reduction phase. Indicated the effect of windowing around visits for ACQ-6 records will also be investigated. 8. Section 3.2.1: Emphasized IPD visit must be in the maintenance phase to ensure the calculations for the absolute change of daily OCS dose in maintenance phase are correct. Added definition of the final dose in the maintenance phase to clarify OCS dose associated with asthma exacerbations should not be counted for the analysis in this section. Removed definition of percentage change in OCS dose from end of OCS reduction phase as will not be calculable for many patients which would introduce a bias. 9. Section 3.2.2: Clarified there are two types of increase in OCS dose: increase in any asthma-related OCS dose and increase in maintenance OCS dose. Clarified ICS or SCS use to treat asthma exacerbations would also be counted as an event of asthma-related OCS dose increase. 10. Section 3.2.3: Added two variables for ACQ-6: change from end of OCS reduction phase to end of maintenance phase and asthma control improvement status from the end of OCS reduction phase to end of maintenance phase. 11. Section 3.2.4: Replaced the word "domain" with "component". 12. Section 3.3: Clarified the two variables: number of patients with 0, 1, 2, etc asthma exacerbations and number of patients with 0, 1, 2, etc asthma exacerbations leading to hospital or emergency room visit are also safety variables. 13. Section 3.3.2: Clarified asthma exacerbations will be summarised for the three study periods: on-study period to end of OCS reduction phase, on-study period during maintenance phase, and the overall on-study period. 14. Section 3.3.3: Clarified AEs will be summarised for on-study period up to end of OCS reduction phase at DBL1 and the overall on-study period at DBL2. 15. Section 4.1: Defined new subgroups: patient's AI status at the end of maintenance phase. 16. Section 4.2.1: Clarified the variables that will be summarised for DBL2. Indicated patient disposition will not be summarised by the subgroups of patient's AI status at the end of maintenance phase. 17. Section 4.2.2: Indicated demographics and disease related baseline characteristics will not be summarised by the subgroups of patient's AI status at the end of maintenance phase.

Date	Description of change
	18. Section 4.2.4: Defined exposure and compliance for study period to end of OCS reduction phase, and during maintenance phase. Clarified the original definition is for the overall study period. Indicated duration of IP administration will not be summarised by the subgroups of patient's AI status at the end of maintenance phase. 19. Section 4.2.5: Indicated primary outcome variables will not be summarised by the subgroups of patient's AI status at the end of maintenance phase. 20. Section 4.2.6.1: Indicated OCS reduction will not be summarised by the subgroups of patient's AI status at the end of maintenance phase. Summary statistics for OCS dose at end of maintenance phase to be repeated excluding withdrawals prior to EOT. 21. Section 4.2.6.3: Added sensitivity analyses for asthma control improvement status at the end of maintenance phase relative to the end of OCS reduction phase. Added shift from end of OCS reduction phase to end of maintenance phase for asthma control status. 22. Section 4.2.7.1: Clarified the additional morning cortisol tests and ACTH stimulation tests at the end of OCS reduction phase and end of maintenance phase if applicable will be summarised at DBL2. Clarified shift table of AI status from initial morning cortisol test to final AI pathway status will be provided at DBL2, plus 2 additional shift tables using all available data (at or after the protocol-defined initial morning cortisol test) regardless of AI pathway compliance. Also clarified spaghetti plots of individual patient's morning cortisol test and ACTH test will include data from the end of maintenance phase at DBL2. 23. Section 4.2.7.3: Clarified lab data is summarised to end of OCS reduction phase at DBL1 and will be summarised for the overall study period at DBL2. 24. Section 4.2.7.4: Clarified vital signs data is summarised to end of OCS reduction phase at DBL1 and will be summarised for the overall study period at DBL2. 25. Section 4.2.8.2: Described the analyses of blood eosinophil counts at EOT/IPD visit.

1. STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR). Additional analyses required for regional submissions (if applicable) will be pre-specified in a separate analysis plan and will be submitted to the appropriate authorities.

1.1 Study objectives

1.1.1 Primary Objective

Primary Objective	Outcome measure
To assess the ability to reduce oral corticosteroid (OCS) dose in adult patients with severe eosinophilic asthma treated with benralizumab 30 mg subcutaneously (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 adrenal insufficiency (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

1.1.2 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

1.1.3 Safety Objective

Safety objectives	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)

1.1.4 Exploratory Objective

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

1.2 Study design

This is an open-label, multicentre study designed to evaluate the efficacy and safety of reducing OCS use after initiation of a 30-mg dose of SC benralizumab administered every 4 weeks (Q4W) up until the third dose of benralizumab (Visits 2 to 4) and then every 8 weeks (Q8W) thereafter in approximately 600 adult patients with severe eosinophilic asthma who are receiving high dose inhaled corticosteroids (ICS)/long-acting β2 agonists (LABAs) 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.

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 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. 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. Additionally, if a 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). 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. 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. 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 hypothalamic pituitary adrenal (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 OCS reduction phase, and will end after 3 doses in the maintenance phase.

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 for each baseline OCS dose until they reach 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 carried out (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.

In the subset of patients with indeterminate results from the screening morning serum cortisol test, the adrenocorticotropic hormone (ACTH) stimulation test (i.e., Synacthen®, Cortrosyn™) is carried out within approximately 1 week from the morning cortisol test (see also Section 5.2.1.2 in CSP 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 (below normal but above complete AI).

If the results show Partial AI (250-450 nmol/L), a repeat morning cortisol test will be conducted.

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.

Maintenance phase: This phase will last approximately 24 to 32 weeks 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 depend on when the patient enters the maintenance phase relative to the dosing cycle of benralizumab (i.e. when the patient receives his/her last dose of benralizumab in the OCS reduction 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. If a patient experiences an exacerbation during the maintenance phase, the maintenance phase will not be extended.

Patients should be maintained on their currently prescribed ICS plus LABAs with or without other asthma controller therapy, without change, until the EOT visit.

All patients who prematurely discontinue study drug/investigational product or who discontinue from the study should return to the study centre and complete the procedures described for the Premature Investigational Product Discontinuation (IPD) visit within 4 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 the end of the OCS Maintenance phase.

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.

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

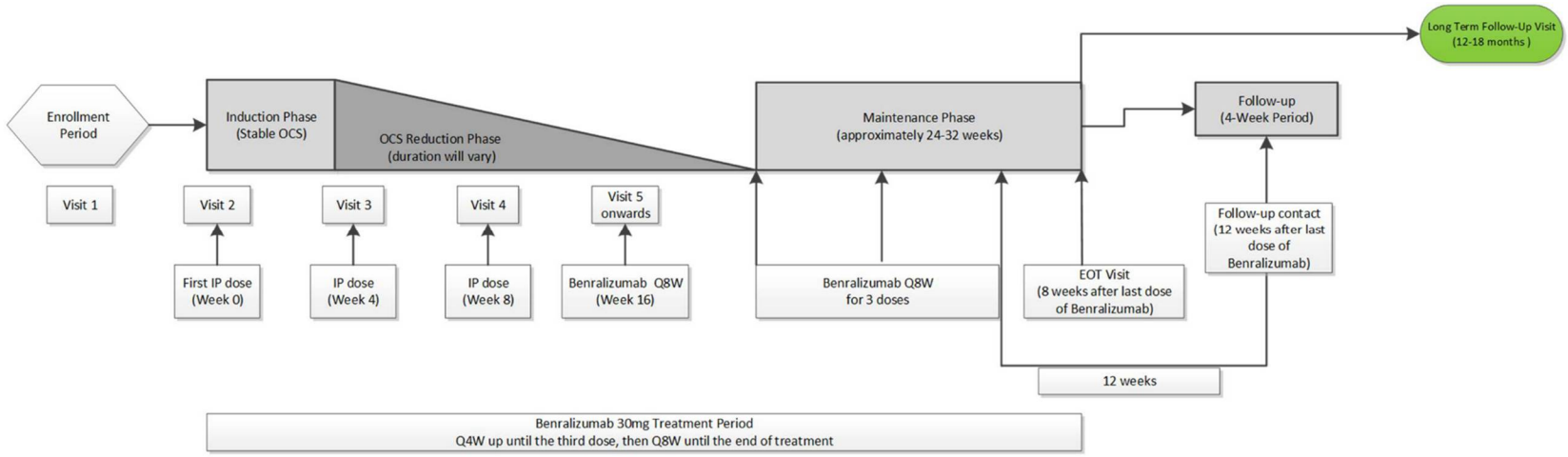
At the end of the PONENTE EOT visit, patients will be invited to participate in a long term follow up visit 12- to 18-months after completion of the main PONENTE study. This substudy is intended to further assess changes in OCS dose and other asthma maintenance therapy in a real-world setting, i.e., 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 their healthcare provider discretion; 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. Further details will be described in an Addendum.

Three database locks will be planned. The initial database lock (DBL1) will be performed after the final patient has had the opportunity to complete the OCS reduction phase (see section 5). The second database lock (DBL2) will be performed when the final patient completes the follow-up visit at the end of the main study. The final database lock (substudy DBL) will be performed when the final patient of the Long Term Follow Up Visit substudy completes the PONENTE Long Term Follow Up Visit.

For an overview of the study design see Figure 1.

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 an 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 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 will 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 centre 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 prior to any activities of the PONENTE Long Term Follow Up visit.

1.3 Number of subjects

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 full analysis set (FAS) and subsets 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) around 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 9.4.

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 Table 1:

Table 1 Expected distance between observed proportion and lower and upper confidence limit (Clopper-Pearson 95% CI width)

Percentage of Patients with Total OCS Reduction	Expected distance between observed proportion and lower and upper confidence limit for 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%.

2. ANALYSIS SETS

For analysis sets for the substudy, refer to the Addendum for the substudy.

2.1 Definition of analysis sets

Two patient populations are defined below:

- All patients analysis set
- Full analysis set (FAS)

Patients must have provided their informed consent. If no signed informed consent is collected (important protocol deviation), then the patient will be excluded from all analysis sets defined below.

2.1.1 All patients analysis set

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

2.1.2 Full analysis set

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

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still enrolled will be analysed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Important protocol deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Only important protocol deviations will be listed and tabulated in the CSR. Important protocol deviations will be reviewed and documented by the study physician and statistician prior to the study clean-file.

The following categories of protocol deviations will be reviewed by the study physician and statistician prior to database lock to determine those which are considered important deviations as outlined above.

- Patients who do not meet the inclusion criteria
- Patients who meet any of the exclusion criteria
- Concomitant use of disallowed medications (to be identified through programming)
- Patients who developed withdrawal criteria during the study but were not withdrawn

- Important deviation from OCS down-titration scheme or the monitoring of OCS down-titration.

More specifically, important protocol deviations (fully defined in section 4 of the study Non-Compliance Handling Plan (NCHP)) will include but are not limited to:

- Lack of 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

- Lack of documented chronic OCS therapy equivalent to a daily dose of 5mg of prednisone for at least 3 months directly preceding Visit 1

- Subject not on a stable dose of OCS for at least 4 weeks prior to Visit 1 or subject not switched to study-required prednisone/prednisolone as their oral corticosteroid for the duration of the study if on a different OCS medication

- Subjects who have a clinically important pulmonary disease other than asthma or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts

- Subject experiencing an asthma exacerbation requiring the use of systemic corticosteroids, increase in maintenance dose of OCS, or acute URTI/LRTI requiring antibiotics or antiviral medication within 30 days prior to Visit 2 (first dosing visit). (Note: An extension of the screening period up to 3 months is permitted to ensure full recovery of any exacerbation or acute infection)

- Subject who is concurrently enrolled in an interventional clinical trial

- Use of any concomitant medication not permitted as per protocol or failure to undergo the required washout period for a particular prohibited medication (see section 7.8 of the CSP)

- Subject experiencing coincident primary adrenal failure (Addison's disease) or irreversible secondary hypoadrenalism due to another independent cause

- Subject with co-existent inflammatory conditions for which chronic OCS doses are part of the maintenance treatment, such as, but not limited to, giant cell arteritis or polymyalgia rheumatic

- Lack of provision of informed consent prior to any study-specific procedures

- Failure to regularly record weekly ACQ-6 scores in ePRO throughout the treatment period to the end of OCS reduction phase (preventing safety monitoring of asthma worsening/deterioration). "Regularly" is defined as >2 missed sequential diaries or an overall compliance to the end of OCS reduction phase of <70%

- Failure to capture baseline (Visit 2) ACQ-6 data (preventing safety monitoring of asthma worsening/deterioration from baseline)

- Subject proceeded with down-titration of OCS below 5mg/day without AI testing or without conducting HPA axis testing (any issues that occur with OCS titration below 5mg/day will be classified as an IPD)

- OCS titration done faster than stipulated in the study protocol

- OCS dose adjusted during screening (prior to Visit 2) and appropriate period of stability was not followed prior to defining baseline Visit 2 OCS dose

- If after IP temperature excursion is noted the affected IP was administered to a subject without confirmation from Fisher SCSM regarding usability and 2 or more consecutive doses of affected IP were administered

- IP dosing error – 2 or more consecutive doses of IP are missed

The master list of important protocol deviations (along with descriptions) is available in section 4 of the study NCHP. Patients with an important protocol deviation recorded that impacts the interpretation of the study safety outcomes will have a footnote added to the applicable output to describe the deviation and its potential impact. Such patients will be identified as part of the protocol deviation review process, prior to database lock.

To investigate ACQ-6 ePRO compliance, summary statistics of compliance to the end of OCS reduction phase and to end of study will be presented plus the number and percentage of patients who missed >2, >3, >4 and >5 sequential diaries in OCS reduction phase. The effect of windowing around visits will also be investigated.

2.2.2 Visit window definitions

For all the assessments, the visit recorded in web-based data capture (WBDC) will be used. Visit windows are not relevant for most of the study. There are only 3 defined visits: Visit 1 (Week -2), Visit 2 (Week 0) and Visit 3 (Week 4). Once a patient enters the dose reduction phase, the visit programme is individual to the patient, depending on their dosing and down-titration schedule; and so data are not summarised by further visit numbers. After the start of dose reduction, the important time points include: date of morning cortisol test (4 weeks after achieving an OCS dose ≤5mg); date at which a patient reaches their final OCS dose in the OCS reduction phase; end of OCS reduction / start of maintenance phase; EOT; and follow-up. These will occur at different visits for different patients.

All data will be organized and analysed according to the visits specified in Table 1 of the CSP and as detailed in section 3 of this SAP.

2.2.3 Duplicate observations at the same visit

For all visits except baseline, if duplicate observations are collected at the same visit, the earliest record will be used for analysis. In case of retest in laboratory assessments, the retest record will be used for analysis. If duplicate observations are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit. Any repeat or additional assessments performed will be included in the individual patient data listings.

2.3 Baseline and change from baseline

In general, the last non-missing observation prior to the first dose of study treatment will serve as the baseline measurement. If there is no value prior to the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

Unless indicated otherwise, Visit 2 (Week 0) is the planned baseline visit, for all assessments carried out at the centre.

The absolute change from baseline is computed as (*visit value – baseline value*). Percent change from baseline is computed as ((*visit value – baseline value*)*/baseline value*) × 100%. If either a visit value or the baseline visit value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing. If baseline value is zero, the percent change will be set to missing.

2.4 Handling of dropouts and missing data

Unless otherwise specified, missing data will not be imputed. All missing data will be reported to data management to be queried.

3. PRIMARY AND SECONDARY VARIABLES

The primary and supportive endpoints, the secondary endpoint ACQ-6, the exploratory endpoint PGIC, all safety data and blood eosinophil counts to the end of the OCS reduction phase will be analysed at the initial database lock, when the final patient has had the opportunity to complete the OCS reduction phase. All secondary efficacy, safety and exploratory endpoints not fully analysed at the initial database lock will be analysed through to end of the study at the second database lock, when the final patient has completed the follow-up visit at the end of the main study. The primary and supportive endpoints will not be analysed again at the second database lock unless necessitated by changes to the raw or reporting datasets. For the details of primary, secondary, safety and exploratory endpoints for the substudy, refer to the Addendum for the substudy.

3.1 Primary outcome variables

Two primary endpoints will be evaluated in this study.

The first is the proportion of patients who achieve 100% reduction in daily OCS dose that is sustained over at least 4 weeks without worsening of asthma. The second is the proportion of patients who achieve 100% reduction or a daily OCS dose $\leq$ 5mg, if the reason for no further OCS reduction is AI, that is sustained as noted above.

The OCS dose reduction schedule during the reduction phase (Week 4 onwards) is presented in Table 2.

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.

The **baseline OCS dose** is defined as the dose upon which the patient is stabilised prior to Visit 2 (Week 0). It is calculated as the total OCS dose taken at the first IP dose day.

The **final OCS dose of the OCS reduction phase** will be used to calculate the percentage reduction from baseline. It will be determined by the Investigator and recorded as the final OCS dose of the OCS reduction phase in RAVE ("Asthma Stable Dose"). The final OCS dose will be 0 mg/day 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 patient will maintain this dose for at least 4 weeks without worsening of asthma and will initiate the OCS maintenance phase on this OCS dose. If the OCS dose recorded as the final OCS dose in RAVE is not maintained for at least 4 weeks without worsening of asthma, the final OCS dose will be defined as the last stable dose prior. This dose may be the dose at a previous OCS reduction step (e.g. one step higher) or the dose recorded after recovery from an exacerbation, but it will not be a dose recorded during treatment of an exacerbation or AE. The time at which the final OCS dose was reached will be unchanged and time to first increase will be the time from this point until the OCS dose exceeds the defined final dose. The time recorded as the end of the OCS reduction phase will also be unchanged. Similarly, if a patient withdraws during the OCS reduction phase, the final OCS dose will be defined as the last stable dose prior to withdrawal. If no such dose exists, the final dose will be the baseline dose.

The **percentage reduction from baseline** in OCS dose is defined as:

*{(Baseline OCS dose–final OCS dose)/baseline OCS dose} *100%*

For an individual patient, if the final OCS dose (as defined above) results in a **percentage reduction from baseline** of 100% (i.e. the final dose is 0mg), that patient will be classified as having a 100% reduction in OCS dose. The proportion of such patients will be calculated as a primary outcome.

The second primary outcome is the proportion of patients who achieve 100% reduction or final daily OCS doses of ≤5 mg, if (and only if) the reason for no further OCS reduction is AI, sustained over at least 4 weeks without worsening of asthma.

In addition, the following key supportive outcomes will be calculated:

- The proportion of patients who achieve a **final OCS dose** of ≤5 mg, sustained over at least 4 weeks without worsening of asthma.
- The proportion of patients who achieve the following **percentage reductions from baseline** in OCS dose:
    - ≥90% reduction
    - ≥75% reduction
    - ≥50% reduction

- >0% reduction

Furthermore, absolute and percentage change from baseline in daily OCS dose (mg) from the start of OCS reduction to the end of the OCS reduction phase (final OCS dose) will also be supportive variables to the primary outcome variables.

The baseline OCS dose and the final OCS dose of the reduction phase will be defined in the same way as outlined above. The absolute and percentage change will be calculated as detailed in section 2.3.

Note that for prednisone doses below 5 mg, if the exact dose strength is not available in the country, the daily dose could be achieved by dosing every other day. The daily dose will be the average of the 2 consecutive days.

3.2 Secondary outcome variables

3.2.1 Change in daily OCS dose in maintenance phase

The final OCS dose in the maintenance phase should not be associated with an asthma exacerbation or adverse event. If the OCS dose recorded at the EOT/IPD visit is to treat an asthma exacerbation or AE (therapy reasons including but not limited to "Asthma exacerbation per protocol", "Non-asthma condition", "Adverse Event"), the final OCS dose will be defined as the last maintenance dose prior. If a patient shows asthma worsening at the EOT/IPD visit (therapy reasons "Worsening of asthma, without exacerbation", "ACQ-6"), the final OCS dose in the maintenance phase will be the OCS dose prescribed for the worsening. If a patient withdraws during the OCS reduction phase, the final OCS dose in maintenance phase will be missing.

In order to study whether benralizumab benefits are maintained after OCS down titration or withdrawal, the absolute change in daily OCS dose from the end of the OCS reduction phase to the end of the maintenance phase (at EOT visit or IPD visit in maintenance phase) will be a secondary outcome variable calculated as follows:

Absolute change at EOT/IPD = final OCS dose at EOT/IPD visit in maintenance phase - final dose of the OCS reduction phase

3.2.2 Time to first increase in OCS dose

There are two types of increase in OCS dose: asthma-related increase and maintenance OCS dose increase. Asthma-related OCS dose increase includes any increase associated with asthma (asthma maintenance or treatment of asthma exacerbations or asthma-related AEs or signs/symptoms of AI). An increase to treat non-asthma-related AEs will be excluded. For maintenance OCS dose increase, only those which result in an increase in maintenance dose will be counted as an event. If patients have an OCS burst to treat an exacerbation but then return to the original maintenance dose, this will not count as an event. If patients have an exacerbation resulting in an increase in maintenance dose, the time of the event is the end of the exacerbation ; otherwise the time of the event is the first day of the maintenance dose

increase. Cases where patients have an ICS burst or a systemic corticosteroid burst (via intravenous / intramuscular route) to treat an asthma exacerbation will also be counted as an event of asthma-related OCS dose increase, and the start date of the exacerbation will be the time of the event.

Time to first asthma-related increase in OCS dose and time to first maintenance OCS dose increase during the maintenance phase from achieving the final OCS dose during the reduction phase will be secondary outcome variables, and are calculated as follows:

Start date of first increase in OCS dose during the maintenance phase – Date 1st achieved the final OCS dose in the reduction phase + 1.

The date that the final OCS dose of the OCS reduction phase is 1st achieved is defined as the date of the last initiation of that dose during the OCS reduction phase. The final OCS dose of the OCS reduction phase is defined in section 3.1.

If a patient withdraws from the study before reaching the first increase in OCS dose or does not increase their OCS dose by the end of the maintenance phase, the patient will be censored at the withdrawal date or at the end date of the maintenance phase, whichever is earlier.

The proportion of patients whose OCS dose is not increased due to asthma exacerbation or worsening within 6 months will be a supportive outcome variable for this endpoint. The proportion of patients whose maintenance OCS dose is not increased within 6 months will be another supportive outcome variable.

3.2.3 Asthma Control Questionnaire-6

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and use of short acting β2 agonists), omitting the forced expiratory volume in 1 second measurement from the original ACQ score.

Patients are 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. The mean score will be missing if any symptom score is missing.

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

The weekly ACQ-6 score will be monitored by Investigators, with an increase in ACQ-6 score of at least 0.5 from the value at Visit 2 indicating a potential **asthma deterioration**. If the ACQ-6 score at Visit 2 is missing, the first 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.

The outcome variables for ACQ-6 will be ACQ-6 scores at baseline (Visit 2), Visit 3, initial morning cortisol test, end of OCS reduction phase, and every 4 weeks from end of OCS reduction phase to end of maintenance phase (EOT visit); change from baseline in ACQ-6 score to Visit 3, initial morning cortisol test, end of OCS reduction phase, and end of maintenance phase (EOT visit); and change from the end of OCS reduction phase in ACQ-6 score to end of maintenance phase. ACQ-6, change from baseline, and change from the end of OCS reduction phase in ACQ-6 scores will also be assessed following any IPD visit. As the ACQ-6 is recorded weekly from Visit 2 to EOT, recorded scores may not coincide exactly with Visit 3 date, initial morning cortisol test, end of OCS reduction phase or EOT. For each of these timepoints, the ACQ-6 score recorded during the week (± 2 days) prior to the timepoint will be used for the outcome variable. The timing for the 4-weekly outcome variables (from the end of OCS reduction score to EOT) will be relative to the end of OCS reduction measurement, as per each patient's individual schedule. There will be no imputation for missing values.

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorized according to the following limits (Juniper et al 2005), where observed study time points include Visit 3, initial morning cortisol test (time point at which OCS dose equals 5 mg for 4 weeks), end of OCS reduction phase and end of maintenance phase (EOT visit):

- 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 the change from baseline in their ACQ-6 scores. Patients with no change or deterioration according to ACQ-6 score evaluation will be defined as non-responders. Patients with missing or non-evaluable ACQ-6 scores at a post-baseline assessment time point will be considered non-responders at the time point. (Note that baseline will be as defined in section 2.3 and will not be imputed (if missing) as for safety monitoring.)

Asthma control improvement status from the end of OCS reduction phase to end of maintenance phase will be evaluated as another supportive analysis. Patients will be categorized according to the following limits (Juniper et al 2005) at the end of maintenance phase:

- Improvement relative to end of OCS reduction phase: Change from the end of OCS reduction phase in ACQ-6 score of ≤-0.5
- No change relative to end of OCS reduction phase: Change from the end of OCS reduction phase in ACQ-6 score of >-0.5 and <+0.5
- Deterioration relative to end of OCS reduction phase: Change from the end of OCS reduction phase in ACQ-6 score of ≥+0.5

Additionally, patients will be categorized according to their ACQ-6 defined asthma control status at baseline and post-baseline (Visit 3, initial morning cortisol test, end of OCS reduction phase, end of maintenance phase (EOT visit)) 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

3.2.4 St. George's Respiratory Questionnaire (SGRQ)

The change from baseline (Visit 2) in SGRQ total scores to the end of maintenance phase (EOT) is a secondary endpoint of this study. The SGRQ will be completed on site at the beginning of Visit 2 and EOT/IPD visit using the ePRO device.

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;
- Part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition.

The SGRQ yields a total score and 3 component scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the component scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

A 4-point threshold will be used to define a response in SGRQ. 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 absolute change is less than 4 points at EOT, it will be defined as 'no change'. Response will also be assessed following any IPD.

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

To avoid incorrectly setting component and/or total scores to missing when items are logically skipped, the following items should **not** be considered as missing if logically skipped in the context of the subject's prior responses:

Question 6 (Length of worst attack of chest trouble):

If no severe or very bad, unpleasant attacks of chest trouble are reported in Q5, the length of the worst attack (Q6) will be logically skipped and should be imputed as zero, with the weight for Q6 remaining in the denominator.

Question 8 (Wheeze worse in the morning):

If the frequency of wheezing attacks is reported as 'None' in Q4, Q8 ('Wheezing worse in the morning') will be logically skipped and should be imputed as zero, with the weight for Q8 remaining in the denominator.

Question 14 (Medication does not help very much, Embarrassed using medication in public, Having side effects from medication, Medication interferes with life a lot):

If a patient is not taking any relevant medication, Q14 will be logically skipped. Therefore, if **all 4** responses are missing, all should be imputed as zero and the denominator for the component / total score(s) unchanged.

A missing SGRQ total score change at post-baseline 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' (i.e. ≥4-point decrease in SGRQ total score). Patients who had SGRQ total score changes defined as 'no change' or 'worsening' will be considered non-responders. If SGRQ total score change is not evaluable due to missing data, then the patient will also be treated as a non-responder.

3.3 Safety variables

Safety variables include:

- Disposition of adrenal function by morning cortisol and/or ACTH test
- Annualised asthma exacerbation rate and number (and percent) of patients with 0, 1, 2, etc exacerbations.
- Annualised asthma exacerbation rate leading to hospitalization or emergency room visit and number (and percent) of patients with 0,1, 2, etc exacerbations leading to hospitalization or emergency room visit
- AEs and SAEs
- Laboratory parameters
- Vital signs

- GTI

Safety analyses will use all available data, including data from unscheduled visits and repeated measurements.

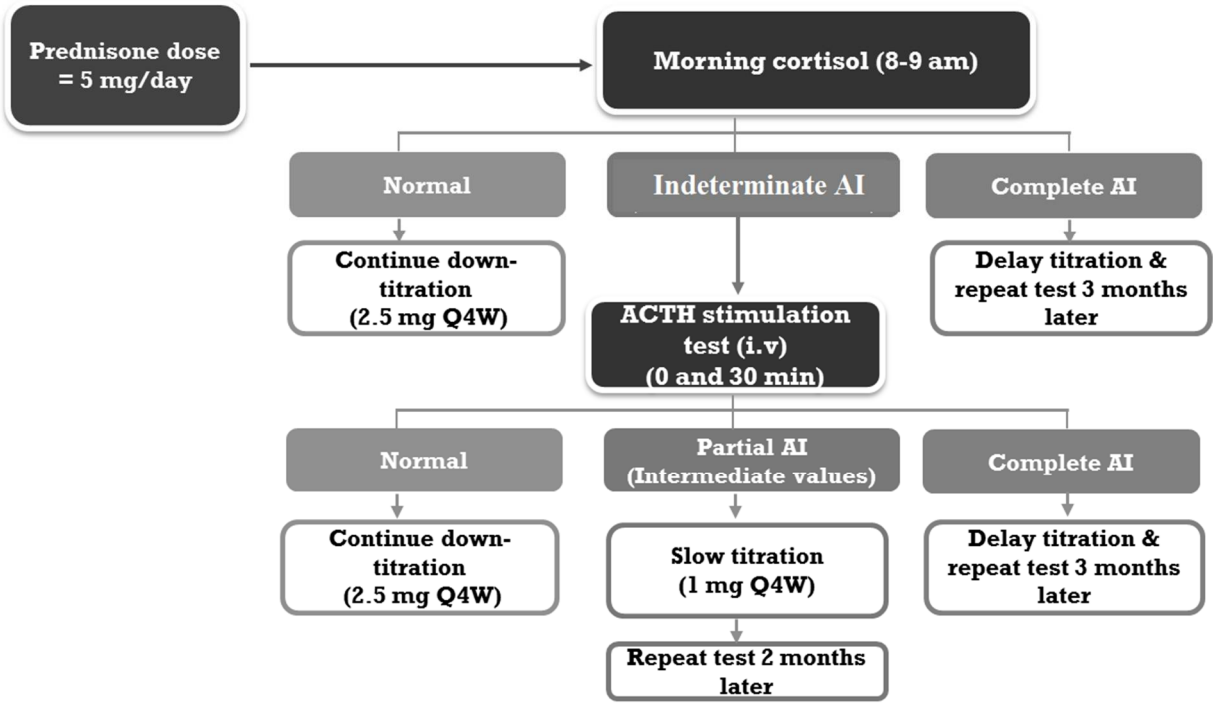
Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. Adverse events will be summarised by means of descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates is detailed in Appendix 8.1.

3.3.1 Adrenal insufficiency (AI) status

Adrenal insufficiency will be diagnosed by the following method: 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 by evaluating the morning cortisol levels (8-9 am). For those patients who had baseline OCS doses equal to 5 mg/day, HPA axis integrity will be assessed 4 weeks after the first dose of benralizumab administration and before initiation of the OCS reduction phase. The process will be as described in Figure 2.

Figure 2 HPA axis evaluation



Details related to values for normal, indeterminate/partial AI, and complete AI are provided in the laboratory manual and copied here for ease of reference:

Morning Cortisol Test:

Normal: >350 nmol/L; Indeterminate AI: 100-350 nmol/L; Complete AI: <100 nmol/L

ACTH Stimulation Test:

Normal: >450 nmol/L; Partial AI: 250-450 nmol/L; Complete AI: <250 nmol/L

For patients taking oral oestrogen containing contraceptives, morning cortisol test ranges will be 2X the above ranges, and ACTH stimulation test ranges will be 1.5X the above ranges.

3.3.2 Annualised asthma exacerbation rate

The number of asthma exacerbations and the annualised asthma exacerbation rate will be derived and summarized for the on-study period to end of OCS reduction phase at DBL1, on-study period during maintenance phase, and the overall on-study period at DBL2. On-study period to end of OCS reduction phase is defined as from the day of the first dose of study treatment to the end of OCS reduction phase; on-study period during maintenance phase is defined as from the start of the maintenance phase to the scheduled follow-up visit of the main study; and the overall on-study period is defined as from the day of the first dose of study treatment to the scheduled follow-up visit of the main study. A patient will be considered as having an asthma exacerbation if he/she starts a course of SCS (oral, parenteral) due to asthma, or has an emergency room/urgent care visit or a hospitalisation due to asthma.

The annualised asthma exacerbation rate will be calculated using the time-based approach. Annual asthma exacerbation rate=365.25×total number of exacerbations/total duration of follow-up (days).

The number and annualised rate of exacerbations requiring hospitalisation or an emergency room visit will also be derived and summarised for the on-study period to end of OCS reduction phase at DBL1, on-study period during maintenance phase, and the overall on-study period at DBL2.

As a sensitivity analysis, annualised exacerbation rates will also be calculated using total duration of follow-up less days with exacerbations (+ 7 days per exacerbation) as the denominator.

3.3.3 Adverse events

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

Adverse events will be summarised for on-study period to end of OCS reduction phase at DBL1 and the overall on-study period at DBL2. AEs in the on-study period to end of OCS reduction phase are defined as those with onset between day of the first dose of study treatment and the end of OCS reduction phase, inclusive. AEs in the overall on-study period are defined as those with onset between day of the first dose of study treatment and the

follow-up visit of the main study, inclusive. If follow-up is not available, then use the date of Disposition event of End of Study.

3.3.4 Laboratory variables

Laboratory safety assessments will be performed in a central laboratory at the times detailed in the CSP. The parameters outlined in Section 5.2.4, Table 4 of the CSP will be collected. Laboratory data are to be reported in SI units, except for the blood eosinophils counts which will be reported in conventional units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent assessment will be calculated. For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

For the purposes of haematology and clinical chemistry shift tables, baseline will be defined as the latest non-missing assessment prior to first IP dose date, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the unscheduled assessments.

For the liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin (TBL), the multiple of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point.

$$\text{Multiple} = \text{Value}/\text{ULN}$$

For example, if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

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

- AST ≥3xULN
- ALT ≥3xULN
- TBL ≥2xULN

3.3.5 Vital signs

Pre-dose vital signs (pulse, blood pressure (BP), respiration rate, and body temperature) will be obtained in accordance with schedule provided in the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Absolute values will be compared to the relevant reference ranges and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges (see Table 3) will be flagged.

Table 3 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38
Weight	kg	40	200

Body mass index (BMI) will be calculated from the height and weight as follows:

$$BMI\ (kg/m^2) = weight\ (kg)/(height\ (m))^2$$

3.3.6 Glucocorticoid toxicity index

Glucocorticoid toxicity index will be assessed as described by Miloslavsky et al 2017 at the times detailed in the CSP. Only a subset of items from the composite GTI will be assessed in this study: BMI, glucose tolerance (glycosylated haemoglobin), BP, low density lipoprotein, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection (items from the Specific List will not be assessed). Full details on GTI composite scoring are given in Appendix H to the CSP.

3.3.7 Physical examination

Complete and brief physical examinations will be performed at timepoints specified in Table 1 of the CSP.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 6 of the CSP.

3.4 Exploratory variables

3.4.1 Genomics variants

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.

3.4.2 Patient Global Impression of Change (PGIC) assessment

The PGIC will be captured weekly (± 2 days) from Week 1 to Week 4 (Visit 3) using the ePRO device.

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 (Week 0) using a 7-point scale, where 1 = much better; 2 = moderately better; 3 = a little better; 4 = about the same; 5 = a little worse; 6 = moderately worse; and 7 = much worse.

Patients will also be categorised according to the following three improvement categories at Week 1 to 4:

- Much better (1), moderately better (2), a little better (3) → A little better
- Much better (1), moderately better (2) → Moderately better
- Much better (1) → Much better

3.4.3 Eosinophil counts

Blood samples for determination of eosinophil count levels (haematology) will be taken at the time points detailed in the CSP and will be assessed in a central laboratory. Eosinophils will be presented in conventional units (cells/μL) in summaries.

3.4.4 Protein 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 of the CSP.

3.4.5 Eosinophil-derived neurotoxin

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

4. ANALYSIS METHODS

For analysis methods for the substudy, refer to the Addendum for the substudy.

4.1 General principles

The data analyses will be conducted using the SAS® System version 9.3 or above (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards.

For safety analyses, the statistical tabulation will be presented for all patients in the full analysis set (FAS). For demographics and patient characteristics and efficacy analyses, the

statistical tabulation will be presented for all patients in the FAS and for the following subpopulations:

- 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;
    - <150, ≥150 to <300, and ≥300 cells/µL
- Patients with duration of chronic OCS use <1 year and ≥1 year.

For summary statistics for absolute and percentage OCS dose reduction from baseline to the end of the OCS reduction phase, the statistical tabulation will also be presented for the following subgroups:

- Patient's AI status at the end of the OCS reduction phase*:
    - Normal;
    - Partial AI;
    - Complete AI.

* Note that AI status at the end of the OCS reduction phase will determined by the status at the repeat morning cortisol test (± ACTH stimulation test) for those with partial or complete AI at the initial morning cortisol test (± ACTH stimulation test) and by the status at the initial morning cortisol test (± ACTH stimulation test) for those with normal cortisol levels at the initial morning cortisol test (± ACTH stimulation test). Results from additional testing at the end of the OCS reduction phase for those with partial AI (see section 1.2) will not be included.

For summary statistics for absolute change in OCS dose from the end of the OCS reduction phase to the end of the maintenance phase, the statistical tabulation will also be presented for the following subgroups:

- Patient's AI status at the end of the maintenance phase:
    - Normal;
    - Partial AI;
    - Complete AI.

Continuous variables will be summarised using the mean, two-sided 95% CI of the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using the exact Clopper-Pearson method. All patients in the corresponding analysis set will be considered the denominator. Time to event data will be summarised using median and 25th and 75th 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 4.2.6.3.

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.

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarised using the all patients analysis set. The total number of patients will be summarised for the following groups: those who enrolled; and those who did not receive treatment after they have been enrolled (with reasons). The number and percentage of patients will be presented by the following categories: received treatment with study drug, entered OCS reduction phase, completed OCS reduction phase, entered maintenance phase, completed maintenance phase (defined as having attended EOT visit), completed maintenance phase and attended 3 dosing visits (not necessarily receiving IP) during maintenance phase, completed treatment with study drug, discontinued treatment (and reason), completed study and withdrawn from study (and reason). For DBL1, patients completed maintenance phase, completed maintenance phase and attended 3 dosing visits (not necessarily receiving IP) during maintenance phase, completed treatment with study drug, discontinued treatment, completed study and withdrawn from study will not be summarised. Instead, patients who discontinued treatment prior to the end of the OCS reduction phase and patients who withdrew from the study prior to the end of the OCS reduction phase will be summarised. Percentages will be based on the number of patients receiving treatment with the study drug. The same summary will also be presented for each subgroup defined in section 4.1 except the subgroups by patient's AI status at the end of the OCS reduction phase or at the end of maintenance phase.

The number of patients enrolled by region and by country and centre will be summarised for the FAS.

4.2.2 Demographics and patient characteristics

Demography data such as age, sex, race, and ethnicity will be summarised for all patients in the FAS and for each subgroup defined in section 4.1 except the subgroups by patient's AI

status at the end of OCS reduction phase or at the end of maintenance phase. Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For patients in countries where date of birth is not recorded the age as recorded in the eCRF will be used.

Descriptive statistics will be presented for the following demographic data (as per local regulations):

- Age
- Age group (≥18-<50 years, ≥50-<65 years or ≥65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, native Hawaiian or other Pacific islander, American Indian or Alaska native, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Descriptive statistics will be presented for the following baseline characteristics:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI group (Normal: ≤25, Overweight: >25 – 30, Obese: >30-35, Morbidly obese: >35)

In addition, BMI and BMI group will be summarized by age group and by region.

Various disease related baseline characteristics will also be summarised for all patients in the FAS and for each subgroup defined in section 4.1 except the subgroups by patient's AI status at the end of OCS reduction phase or at the end of maintenance phase. These include respiratory disease characteristics such as asthma duration, the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalizations in the previous 12 months.

The number and percentage of patients taking maintenance asthma medications at baseline will be summarized. Summary statistics will also be provided for ICS doses and OCS doses at baseline; ICS doses will be converted to their Fluticasone Propionate equivalent in micrograms and OCS doses will be converted to their Prednisolone equivalent in milligrams. The number and percentage of patients receiving OCS doses of >10 mg/day, >5 mg/day to ≤10 mg/day, and 5 mg/day will be presented. Duration of OCS treatment prior to study entry will be categorized as < 1 year and ≥1 year.

Medical and surgical histories will be summarised by MedDRA PT within MedDRA SOC in the full analysis set.

4.2.3 Prior and concomitant medications

A medication will be regarded as prior if it was stopped on or before the first IP dose date (i.e. medication stop date ≤first IP dose date).

A medication will be regarded as concomitant if the start date is after the first IP dose date, but prior to the end of treatment period, or if it started prior to the first IP dose date and was ongoing after the first IP dose date.

The number and percentage of patients who take prior medications, those who take allowed concomitant medications starting prior to first IP dose, those who take allowed concomitant medications starting after first IP dose, those who take disallowed concomitant medications starting prior to first IP dose, and those who take disallowed concomitant medications starting after first IP dose, will be presented for the FAS. Prior and concomitant medications will be classified according to the WHO Drug Dictionary (WHODD). The summary tables will present data by anatomical therapeutic chemical (ATC) classification category and preferred term (PT).

All prior and concomitant medications will be listed.

4.2.4 Study treatment administration

Study treatment exposure and compliance will be calculated for the period to end of OCS reduction phase at DBL1, during maintenance phase, and the overall study period at DBL2.

Exposure to end of OCS reduction phase is calculated in days as (last dose of IP date - first dose of IP date + 1) if patient's last dose is prior to end of OCS reduction phase; or as (end of OCS reduction phase date - first dose of IP date + 1) otherwise.

Exposure during maintenance phase is calculated in days as (last dose of IP date – start date of maintenance phase + 1) if patient's last dose is after the end of OCS reduction phase; or 0 otherwise.

Duration of investigational product administration for the overall study period will be calculated in days as:

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

and will be summarised for all patients in FAS and for each subgroup defined in section 4.1 except the subgroups by patient's AI status at the end of OCS reduction phase or at the end of maintenance phase.

Study treatment compliance will be summarised for the full analysis set and calculated as:

Study treatment compliance = (total doses administered/total doses expected) x 100.

Total number of doses expected will be calculated for the three study periods as defined for exposure. It includes all visits with protocol scheduled IP administration on or before a subject's IP discontinuation to end of OCS reduction phase or during maintenance phase, or treatment complete date (for the overall study period).

4.2.5 Primary outcome variables

All efficacy analyses will be conducted for all patients in the FAS and repeated by the subgroups defined in section 4.1 except the subgroups by patient's AI status at the end of OCS reduction phase or at the end of maintenance phase.

4.2.5.1 Primary analyses

For each of the primary endpoints and key supportive endpoints in Section 3.1, the data will be summarised using frequency counts and proportions. Proportions will be reported along with their two-sided 95% confidence interval, calculated using the Clopper-Pearson exact method.

The absolute and percent changes in OCS dose defined in section 3.1 will be summarised using descriptive statistics and displayed graphically.

For patients who do not achieve 100% reduction in their daily OCS dose, the starting OCS dose, the end OCS dose, the % reduction, and the reason for no further reduction will be listed. Baseline characteristics listed below will be summarized for patients who fail to reduce to 0 mg at the end of OCS reduction phase due to complete AI and those due to asthma exacerbation.

- Demographics: age, sex, race, height, weight, BMI, region
- Baseline and historical eosinophil count (category (<150, 150-<300, >=300) and summary statistics)
- Diagnosis of chronic rhinosinusitis without nasal polyps (CRS), or CRS with nasal polyps (CRSwNP)
- Past polypectomy (Y/N)
- Past sinus surgery (Y/N)
- Age at onset of Asthma (early vs. late onset (defined as <18 years / >=18 years) plus summary statistics for age)
- FeNO (historical)
- IgE and phadiatop (at screening)
- Baseline OCS dose per protocol cut-offs (<=5mg / >5-<=10mg / >10mg) and summary statistics
- Duration of chronic OCS use < or ≥ 1 year
- Number of prior exacerbations (categorised as 0, 1, 2, 3, 4+) and summary statistics
- Aspirin-triggered asthma (Y/N)
- GTI components at baseline

  - HbA1c, LDL, SBP and DBP – summary statistics and categories as per GTI
  - Steroid myopathy, skin toxicity, neuropsychiatric toxicity and infection – categories as per GTI
- Initial morning cortisol test result (as normal/partial/complete).

The statistical tabulation subgroups for the former summary will be normal/partial AI/complete AI by patient's AI status at the end of OCS dose reduction phase (see section 4.1). The statistical tabulation subgroups for the latter summary will be patients stopped down-titration due to 2+ asthma exacerbations and patients reached 0 mg OCS dose.

4.2.5.2 Sensitivity analysis

As a sensitivity analysis to the primary endpoint analysis, the primary efficacy outcome based on data as observed but excluding patients with any important protocol deviations related to efficacy (see section 2.2.1) may be analysed using the same method used for the primary analysis of the FAS.

As a second sensitivity analysis, the primary efficacy outcome based on data as observed but excluding patients who withdraw early from OCS reduction phase may be analysed using the same method used for the primary analysis of the FAS.

A sensitivity analysis to the first key supportive analysis will require patients with a baseline daily OCS dose of 5mg to achieve a final daily OCS dose of < 5mg unless the reason for no further reduction is complete AI.

4.2.6 Secondary outcome variables

4.2.6.1 OCS reduction

Absolute and percent change (where applicable) in OCS dose defined in section 3.2.1 will be summarised using descriptive statistics and displayed graphically. Absolute and percent changes will also be summarised by patient's AI status at the end of OCS reduction and at the end of maintenance phase (absolute changes only) (see section 4.1). Summary statistics for the OCS dose and absolute change in OCS dose at the end of the maintenance phase will be repeated excluding patients who withdraw from the study prior to the EOT visit, as a sensitivity analysis to address the objective of "sustained" reduction.

4.2.6.2 Time to first increase in OCS dose

Time from achieving the final OCS dose during the reduction phase to first asthma-related OCS increase and to first maintenance OCS dose increase during the maintenance phase will be summarised, if calculable, using median, 25th and 75th percentiles with 95% CIs calculated using complementary log-log transformation and displayed graphically using a Kaplan-Meier plot. All patients who enter the OCS reduction phase (and so have a final dose in the OCS reduction phase) will be included. Besides these cumulative statistics, the number of patients with an event and the number of patients censored will be summarised at 8 week

intervals along with the probability (and 95% CI) of no increase (Kaplan-Meier statistics) at each 8 week timepoint. This analysis will be repeated for patients who achieve 0 mg final OCS dose in reduction phase, and patients who achieve >0%, >=50%, >=75%, and >=90% OCS dose reduction in the reduction phase. For both types of time to first OCS dose increase, the number and percentage of patients with events will be summarised by the reason for the increase.

A Cox proportional hazard model will also be used to analyse time from achieving the final OCS dose during the reduction phase to the two types of first OCS increase during the maintenance phase defined in section 3.2.2; covariates will include baseline OCS daily dose and baseline categories of blood eosinophil count. If a patient withdraws from the study before increasing OCS dose or does not increase their OCS dose before the end of the maintenance phase, the time will be censored at the time of withdrawal / end of maintenance phase as applicable. The assumption of proportional hazards will be tested for covariates and appropriate action taken if the assumption is not met. The adjusted median time to the two types of 1st OCS dose increase, with 95% CI, will be reported, if calculable.

The number of patients whose OCS dose is not increased and the number of patients whose OCS dose is increased due to asthma exacerbation or worsening within 6 months during the maintenance phase will be presented. Proportions will be reported along with their estimates, and two-sided 95% confidence interval, calculated using the Kaplan-Meier time to event analysis (with 95% CI based on Greenwood's method). The number of patients with and without maintenance OCS dose increase within 6 months will be analysed in the same way. For both summaries, patients censored at the 6 month point will be summarised as still on study / in follow-up; completed study prior to 6 months; or withdrawn from study prior to 6 months.

4.2.6.3 ACQ-6

ACQ-6 scores and change from baseline ACQ-6 score will be summarised using descriptive statistics at baseline (Visit 2) (for absolute ACQ-6 scores only), Visit 3, initial morning cortisol test (time point at which OCS dose equals 5mg for 4 weeks), end of OCS reduction phase, and every 4 weeks from end of OCS reduction phase to end of maintenance phase (EOT visit) (See section 3.2.3 for windowing at these time points). Change in ACQ-6 scores at the end of maintenance phase from the end of OCS reduction phase will be summarised in the same way.

Change from baseline in ACQ-6 score at Visit 3, initial morning cortisol test, end of OCS reduction phase and end of maintenance phase will be analysed separately using an analysis of covariance (ANCOVA) with change from baseline in ACQ-6 score as the response variable, and baseline ACQ-6 score, baseline OCS dose, and baseline categories of blood eosinophil count as covariates. Adjusted means will be calculated from the ANCOVA using the observed margins approach, in which the contribution of model factors to the estimate is

weighted proportionally to the presence of these factors in the data. Results will be presented in terms of least square mean with 95% CI of change from Visit 2 in ACQ-6 score.

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 summarised. Patients with missing or non-evaluable ACQ-6 scores will be classified as "Missing". Clopper-Pearson 95% CIs will be presented. The number and percentage of patients who achieve improvements, no change, or deterioration at the end of maintenance phase timepoint relative to the end of OCS reduction phase will also be summarised. 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 (end of OCS reduction phase or end of maintenance phase) will have their last non-missing score carried forward. For the end of OCS reduction phase visit, this non-missing score must be on or after the date at which the patient reaches their final OCS dose of the reduction phase; for the end of maintenance phase visit, it must be during the maintenance phase. If a patient terminates early prior to the visit (end of OCS reduction phase or end of maintenance phase), the ACQ-6 score will not be imputed for that visit. Three imputation methods will be used: imputation of end of OCS reduction phase only, imputation of end of maintenance phase only, and imputation of both visits.

Shift from baseline to each of the post-baseline timepoints analysed above (i.e. Visit 3, initial morning cortisol test, end of OCS reduction phase and end of maintenance phase) and shift from end of OCS reduction phase to end of maintenance phase in asthma control status will be summarised. It will also be summarised by baseline OCS dose group defined in section 4.1.

Additionally, asthma control responders defined in section 3.2.3 will be summarised in count and proportion with 95% CIs estimated using the Clopper-Pearson method.

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 non-responders.

4.2.6.4 SGRQ

Summary statistics for SGRQ total score and component 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 component scores will also be analysed separately using an ANCOVA with change from baseline in SGRQ score as response variable and baseline SGRQ score and baseline OCS dose and baseline categories of blood eosinophil count as covariates. Adjusted means will be calculated from the ANCOVA using the observed margins approach, in which the contribution of model factors to the estimate is weighted proportionally to the presence of these factors in the data. Results will be presented in terms of least square mean with 95% CI of change from baseline in SGRQ total

score. Subgroup analyses (see section 4.2.5) will only include the SGRQ total score (not component scores).

In addition, SGRQ responders defined in section 3.2.4 will be summarised in count and proportion with 95% CIs estimated using the Clopper-Pearson method. No subgroup analyses will be carried out.

4.2.7 Safety outcome variables

All safety variables will be summarised using the full analysis set (FAS) and data presented as a single group.

4.2.7.1 AI status

The number and percentage of patients with complete or indeterminate AI at the morning cortisol test will be tabulated along with the number and percentage with a result in the normal range. For those showing complete or partial/indeterminate AI, results of the subsequent ACTH stimulation tests and/or further morning cortisol tests will be tabulated so that pathways through the AI testing schematic can be evaluated. At DBL1, morning cortisol test and ACTH stimulation test results are presented for the initial morning cortisol test and repeat morning cortisol test; at DBL2, the additional tests at the end of OCS reduction phase and end of maintenance phase if applicable will also be summarised. Patients AI status (normal/partial AI/complete AI) at each stage will also be tabulated. Results will be repeated by baseline OCS dose and baseline duration of chronic OCS use.

A shift table will be presented for patients from their initial morning cortisol test to final AI status at the end of OCS reduction phase. A similar shift table will be presented for patients from their initial morning cortisol test to their final AI pathway status, including test results up to the end of the maintenance phase. Two additional shift tables will be presented which will include all available data at or after the protocol-defined initial morning cortisol test regardless of AI pathway compliance: the first showing AI status at the initial morning cortisol test vs. AI status at the additional test at the end of the maintenance phase; and the second showing AI status at the initial morning cortisol test vs. final AI status recorded ever in the study.

In addition, spaghetti plots will be produced for patients with partial AI (as determined by the ACTH stimulation test) following both the initial and repeat morning cortisol tests. The plots will show all available cortisol levels from the initial morning cortisol test, the repeat morning cortisol test and the end of the OCS reduction phase (if applicable). Morning cortisol test results and ACTH stimulation test results will be plotted side by side. Patients receiving oral oestrogen containing contraceptives will be plotted on separate pages. Similar plots for patients with partial AI at the initial morning cortisol test (ACTH stimulation test) and complete AI at the repeat morning cortisol test (± ACTH stimulation test) will also be produced. At DBL2, these graphic presentations will be repeated including all available cortisol data from the initial morning cortisol test, the repeat morning cortisol test, the end of the OCS reduction phase and the end of maintenance phase.

4.2.7.2 Adverse events

Adverse events will be summarised for the on-study period to end of OCS reduction phase at DBL1 and the overall on-study period at DBL2, as defined in Section 3.3.3. All AEs will be listed.

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories: AEs, deaths due to AE, serious AEs (SAEs), and AEs causing discontinuation of IP (DAEs). The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e. accounting for multiple occurrences of the same event in a patient).

Adverse events, DAEs and SAEs will be summarised by SOC and PT assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least 1 occurrence will be presented, i.e. a patient with multiple occurrences of an AE will only be counted once. Serious AEs causing discontinuation of the study treatment and SAEs causing discontinuation from the study will also be summarised.

Adverse events and SAEs (by PT) will be summarised by Investigator's causality and maximum intensity. If a patient reports multiple occurrences of the same AE within the same reported period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). Deaths will also be summarised in separate tables.

A summary of the most common (i.e. frequency of ≥3%) AEs will also be presented.

Adverse events of injection site reactions (high level term of injection site reactions) will be summarised by PT for the on-study period. In addition, if there is a sufficient number of hypersensitivity events (standardised MedDRA query of hypersensitivity [narrow]), it will also be summarised by PT for the on-study period.

Separate listings of patients with AEs, SAEs, death due to AE, or discontinuations due to AEs will be presented.

4.2.7.3 Laboratory data

Laboratory parameters will be summarised as below for the on-study period to end of OCS reduction phase at DBL1 and the overall on-study period at DBL2, as defined in Section 3.3.3.

All continuous laboratory parameters will be summarised descriptively by absolute value at each visit, together with the corresponding changes from baseline. All parameters will be summarised in SI units, with the exception of cortisol results and blood eosinophil counts which will be summarised in both SI and conventional units. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and

missing values. The shift tables will present baseline and maximum/minimum post-baseline value, as applicable for each parameter.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced.

Data for patients who have treatment-emergent changes outside central laboratory reference ranges will be presented. This data presentation will include all visits for this subset of patients.

Maximum post-baseline total bilirubin (TBL) elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. Bilirubin will be presented in multiples of the following ULN ≤1.5, >1.5-2, >2, and AST and ALT will be presented in multiples of the following ULN ≤1, >1-3, >3-5, >5-10, >10.

Maximum post-baseline TBL will be presented (<2 and ≥2 x ULN) and plotted against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 x ULN), expressed as multiples of ULN. This will be repeated to show maximum post-baseline TBL against maximum post-baseline AST.

Data for patients with ALT or AST ≥3 x ULN, and bilirubin ≥2 x ULN will be presented, which will include all visits for this subset of patients. A line plot of liver biochemistry test results (including ALP, ALT, AST, TBL and GGT) over time will also be presented for this subset of patients.

A shift table of HbA1c at baseline versus post-baseline will be produced to display normal (<5.7%), pre-diabetes (≥5.7%-<6.5%), and diabetes (≥6.5%).

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

4.2.7.4 Asthma exacerbations

The number of asthma exacerbations, number of patients with at least one exacerbation, number of exacerbations per patient, duration of exacerbation, number of exacerbations requiring hospitalization, number of exacerbations requiring emergency room visits, and number of exacerbations requiring OCS/Systemic Corticosteroid use will be summarised for the three study periods as defined in section 3.3.2. All asthma exacerbations will be listed by patient.

4.2.7.5 Glucocorticoid toxicity index

Glucocorticoid toxicity index and each of the 8 items will be summarised over time. Low density lipoprotein (LDL) > 3 mmol/L will be considered worsening. All recorded GTI data will be listed.

Statistical correlation between GTI and change in cumulative OCS dose at scheduled timepoints will be analysed graphically. The change in cumulative OCS dose would be calculated as:

(Total OCS dose from baseline to the visit) – (Total OCS had the patient remained on their baseline dose from baseline to the visit*)

* i.e. baseline daily OCS dose multiplied by the number of days from baseline to the visit

4.2.7.6 Vital signs

Vital signs data will be summarised as below for the on-study period to end of OCS reduction phase at DBL1 and the overall on-study period at DBL2, as defined in section 3.3.3.

Descriptive statistics and change from baseline for vital signs data will be presented by visit. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable for each parameter and will include patients with both baseline and post-baseline data. All recorded vital signs data will be listed.

4.2.8 Exploratory variables

4.2.8.1 PGIC

PGIC will be presented descriptively by week (Weeks 1-4). Calculation of percentages will be based on the number of patients in the FAS with a completed assessment. There will be no imputation for missing values.

The number and percentage of patients defined as responders based on categorized responses detailed in section 3.4.2 will also be presented at Week 1 to 4.

4.2.8.2 Blood eosinophil levels

Blood eosinophil counts and change from baseline will be summarised using standard summary statistics at each visit. A scatter plot will be produced for baseline blood eosinophil counts versus baseline OCS dose. Bar graphs will be provided for baseline blood eosinophil category (<150, ≥150 to <300, and ≥300 cells/μL) by region and by duration of chronic OCS use.

4.2.8.3 Other exploratory variables

Statistical analysis of the following exploratory outcomes will be detailed in a separate exploratory analysis plan (EAP) and will be reported outside the clinical study report.

- Serum samples at baseline for protein biomarkers
- Plasma for EDN
- Association of common and rare genomic variants with patient responses

5. INTERIM REVIEW AND ANALYSIS

One interim review may be performed after approximately 90-100 patients have completed or had the opportunity to complete their OCS reduction as described in the primary objective of the study. This includes patients who have had the opportunity to achieve 100% reduction or a daily OCS dose ≤5 mg if the reason for no further OCS reduction is adrenal insufficiency (AI), sustained over at least 4 weeks without worsening of asthma; and also patients who discontinue their study drug prematurely. The analysis details will be prepared in a separate interim review plan.

An additional database lock and analysis of all relevant data collected through to the end of the OCS reduction phase, will 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 using data up to the end of the OCS reduction phase for all patients. Data of interest will include: patient disposition, patient recruitment, analysis sets, demographics and baseline characteristics, disease and medical history, prior and concomitant medications, treatment compliance, OCS reduction, ACQ-6 score, ACQ-6 asthma control responder status, ACQ-6 asthma control status, PGIC, blood eosinophil counts, duration of exposure, AEs, cortisol test results, lab results, vital signs, asthma exacerbations and GTI.

6. CHANGES OF ANALYSIS FROM PROTOCOL

1) A sensitivity analysis of the primary outcome has been included in section 4.2.5.2 which excludes any patients with an Important Protocol Deviation related to efficacy. This sensitivity analysis is not specified in the protocol.

2) A sensitivity analysis of the first key supportive analysis has been included in section 4.2.5.2 which will require patients with a baseline daily OCS dose of 5mg to achieve a final daily OCS dose of < 5mg, unless the reason for no further reduction is complete AI. This sensitivity analysis was not included in the protocol.

3) In protocol Section 8.5.2.2, a mixed model for repeated measures was planned to analyse the change from baseline in ACQ-6 score. Because phase and study duration will be different between patients, an ANCOVA model will be used to analyse the change from baseline at visit 3, initial morning cortisol test, end of OCS reduction phase and end of maintenance phase, only.

7. REFERENCES

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8. APPENDIX

8.1 Partial dates for adverse events and prior/concomitant medication

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

Adverse Events

- The missing day of onset of an AE will be set to:
  - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
  - The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
  - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.
- The missing day of resolution of an AE will be set to:
  - The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.

- If the onset date of an AE is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment
  - The date of the first treatment, if the onset year is the same as the year of the first study treatment
  - The date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an AE or end date of an IP is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

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

- If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the study end date.

- If the end date of a therapy is null and the start date is a complete date

  – and the start date is prior to the study end date then the end date will be set to the study end date.

otherwise, the end date will be set to the start date of the therapy.

8.2 Additional reporting to assess the impact of the COVID-19 pandemic on data to the end of the OCS reduction phase (DBL1)

Additional summaries will be produced, and analyses carried out, to assess the impact of the COVID-19 pandemic on study results. This appendix covers summaries and analyses at the initial database lock, when all patients will have completed or had the opportunity to complete the OCS reduction phase. The summaries and analyses are detailed below, with rationale (*in italics*), and referencing the section of the SAP to which they relate. A further appendix will be added prior to the second database lock (DBL2) detailing summaries and analyses required for data through to the end of the study.

COVID-19 phases (pre / during / post)

The start of the COVID-19 pandemic will be defined at a patient level as the earliest of:

- 11th March 2020 (the date the WHO declared COVID-19 to be a pandemic); and
- The date of the first COVID-19-related study disruption recorded by the patient.

Data recorded before that date will be *pre-pandemic*; data recorded on or after that date will be *during-pandemic*. As there is expected to be very little data *post-pandemic* prior to the end of the OCS reduction phase, this period will not be defined for analyses at DBL1.

Violations and deviations (SAP Section 2.2)

All COVID-related IPDs will be summarized and listed together with all non-COVID-related IPDs. A separate listing will be produced of all COVID-19-related protocol deviations (important and non-important). These will contribute to the definition of COVID-19-related study disruptions at a patient level at DBL1.

COVID-19-related study disruptions

A COVID-19 related study disruption is *any* change in the study conduct or the data collected due to the COVID-19 pandemic. Examples of COVID-19 related study disruptions include:

- Changes to visit schedules, missed visits, changes to study procedures;

- Changes to the protocol-defined down-titration schedule due to COVID-19;
- Discontinuation of IP or changes to the IP supply;
- The introduction of alternative monitoring approaches.

An additional table – COVID-19-related study disruptions - will summarise all disruptions. At DBL1, study disruptions will be based on protocol deviations (PDs) and monitoring logs and the scope of this table will be limited. A more detailed table will be produced at DBL2 when data from the COVID-19 eCRF modules are available. At DBL1, the number of patients with at least one COVID-19-related study disruption and the total duration of disruption will be reported for the FAS. The duration of a disruption (for DBL1) will be defined as the time from the start of the disruption until the end of the OCS reduction phase. Follow-up time is defined as the time from Week 0 to the end of the OCS reduction phase for a patient. The total duration as a proportion of the total follow-up time (to the end of the OCS reduction phase) will be reported. Total pre-pandemic and total during-pandemic times will also be summarised for the FAS, and the proportions of total follow-up time (to the end of the OCS reduction phase) presented, *as an indication of the proportion of study time potentially affected by COVID-19*.

The number and percentage of patients who missed at least one IP dose, the number and percentage missing 1, 2 and 3+ doses and the number and percentage of patients with 2+ consecutive missed doses due to COVID-19 during the OCS reduction phase will be presented.

The number and percentage of patients with on-site visits (IP dosing visits and other on-site visits (e.g. for HPA axis testing)) impacted by COVID-19 during the OCS reduction phase will be presented, along with the number and percentage of patients with missed / delayed cortisol tests.

The number and percentage of patients who deviated from the protocol-defined OCS down-titration schedule due to COVID-19 and patients with data affected by changes to the monitoring process due to COVID-19 will be reported.

A listing of all patients impacted by COVID-19 during the OCS reduction phase will be produced with details of changes to monitoring process, changed or missed visits, changes to or missed IP administration during the OCS reduction phase and changes to their OCS down-titration schedule due to COVID-19. This listing will include all patients who are ongoing in the OCS reduction phase on 11th March 2020 or recorded a COVID-19 related disruption prior to 11th March 2020 whilst in the OCS reduction phase.

Patient disposition (SAP Section 4.2.1)

The number of patients discontinuing IP or withdrawing from the study prior to the end of the OCS reduction phase for reasons related to COVID-19 will be added to the disposition table. This will be in addition to the existing summaries and include reasons (e.g. subject decision, adverse event).

Analysis of primary outcome variables (SAP Section 4.2.5)

Three additional sensitivity analyses of the 2 primary endpoints will be carried out, excluding:

- Patients with COVID-19-related IPDs during the OCS reduction phase; and
- Patients with any study disruption due to COVID-19 occurring before the end of the OCS reduction phase;
- Patients with any study disruption due to COVID-19 occurring before the end of the OCS reduction phase excluding those related to changes in monitoring procedures.

These sensitivity analyses will assess the effect of study disruptions on the primary endpoints.

Adverse Events (SAP Section 4.2.7.2)

The number and percentage of patients reporting COVID-19 adverse events (as defined based on MedDRA version 23.0 (April 2020) terms) during the OCS reduction phase will be summarised by system organ class (SOC) and preferred term (PT) for the on-study period.

8.3 Additional reporting to assess the impact of the COVID-19 pandemic on data to the end of the study (DBL2)

Additional summaries will be produced, and analyses carried out, to assess the impact of the COVID-19 pandemic on study results. This appendix covers summaries and analyses at the second database lock, when all patients will have completed or had the opportunity to complete the follow-up visit. The summaries and analyses are detailed below, with rationale (*in italics*), and referencing the section of the SAP to which they relate.

COVID-19 phases (pre / during / post)

The end of the COVID-19 pandemic may be defined at a site / country / study level and will be defined ahead of DBL2, if applicable.

Pre-pandemic is defined as at DBL1; data recorded on or after the start of the pandemic and prior to the end of pandemic (if defined) will be *during-pandemic*; data record after the end of pandemic (if defined) will be *post-pandemic*.

Violations and deviations (SAP Section 2.2)

All COVID-related IPDs will be summarized and listed together with all non-COVID-related IPDs. A separate listing will be produced of all COVID-19-related protocol deviations (important and non-important).

COVID-19-related study disruptions

COVID-19-related study disruptions at DBL2 will be summarised based on the data from the COVID-19 eCRF modules. The number of visits impacted by pandemic (and reasons), exposure impacted by pandemic, concomitant medications not started due to pandemic (and reasons), and the number of patients with at least one COVID-19-related study disruption will be reported for the FAS. Follow-up time is defined as the time from Week 0 to the end of the study for a patient. Total pre-pandemic, total during-pandemic and total post-pandemic (if applicable) times will also be summarised for the FAS, and the proportions of total follow-up time (to the end of the main study) presented, *as an indication of the proportion of study time potentially affected by COVID-19*.

The number and percentage of patients who missed at least one IP dose, the number and percentage missing 1, 2 and 3+ doses and the number and percentage of patients with 2+ consecutive missed doses due to COVID-19 during the whole study will be presented.

The number and percentage of patients with on-site visits (IP dosing visits and other on-site visits (e.g. for HPA axis testing)) impacted by COVID-19 during the study will be presented, along with the number and percentage of patients with missed / delayed cortisol tests.

The number and percentage of patients with data affected by changes to the monitoring process due to COVID-19 will be reported.

A listing of all patients impacted by COVID-19 during the study will be produced with details of changes to monitoring process, visits impacted by pandemic, and changes to or missed IP administration during the study due to COVID-19. This listing will include all patients who are ongoing in the study on 11th March 2020 or recorded a COVID-19 related disruption prior to 11th March 2020 whilst in the study.

Patient disposition (SAP Section 4.2.1)

The number of patients discontinuing IP or withdrawing from the study for reasons related to COVID-19 will be added to the disposition table. This will be in addition to the existing summaries and include reasons (e.g. subject decision, adverse event).

Adverse Events (SAP Section 4.2.7.2)

The number and percentage of patients reporting COVID-19 adverse events (as defined based on MedDRA version 23.0 (April 2020) terms) will be summarised by system organ class

(SOC) and preferred term (PT) for the on-study period. All COVID-19 adverse events will be listed.

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