Statistical Analysis Plan	
Study Code	D3250C00036
Edition Number	3.0
Date	31 January 2023

A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients with Uncontrolled Asthma (MIRACLE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation expressed in percentage
DAE	AEs leading to discontinuation of investigational product
DBP	Diastolic blood pressure
DL	Direct likelihood
DRMI	Dropout reason-based multiple imputation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of treatment
ePRO	Electronic patient reported outcome
ER	Emergency room
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
GGT	Gamma-glutamyltransferase
HRU	Healthcare resource utilisation
ICS	Inhaled corticosteroids
IP	Investigational product
IPD	Investigational product discontinuation
ITT	Intent-to-Treat

Abbreviation or special term	Explanation
LABA	Long-acting β_2 agonists
LSMEANS	Least squares means
LOESS	Locally estimated scatterplot smoothing
LOCF	Last observation carried forward
MACE	Major adverse cardiac events
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MNAR	Missing not at random
N/A	Not applicable
ND	Not Determined
nAb	Neutralizing antibodies
OCS	Oral corticosteroid
PD	Protocol deviations
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PN	Predicted normal
PRO	Patient reported outcome
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SGRQ	St. George's Respiratory Questionnaire
SI	Standard International
SOC	System organ class
TBL	Total bilirubin
UC	Urgent care
ULN	Upper limit of normal
WBDC	Web-based Data capture

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	03/Oct/2017	Initial Approved SAP Edition 1.0		
Secondary endpoint	20/Mar/2020	Replace “PK parameters” with “PK serum trough concentrations”.	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP to clarify only concentration data will be analysed, and the PK parameters will not be calculated.
Statistical analysis method	20/Mar/2020	Replace “at least 1 quantifiable serum PK” with “at least 1 measurable serum PK” in the PK analysis set.	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP in the definition of PK analysis set.
Statistical analysis method	20/Mar/2020	Remove Partial Dropout Reason-based Multiple Imputation (DRMI) method.	N/A	Based on studies under similar population/study design, results from partial DRMI and DRMI methods are very close. Thus it is unnecessary to conduct both MI methods.
Statistical analysis method	20/Mar/2020	Update the reasons for withdrawal used in DRMI.	N/A	To be consistent with the latest categories in eCRF DS form.
Statistical analysis method	20/Mar/2020	Add the analysis visit window for endpoint SGRQ.	N/A	To incorporate window algorithm in selection of SGRQ assessments by visit as SGRQ has different protocol schedule from other endpoints.
Statistical analysis method	20/Mar/2020	Add more details to clarify definition of baseline eosinophil counts for various analyses.	N/A	Further clarifications of baseline definitions of eosinophils to be used as stratification covariates, subgroup

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				factors, as well as for change from baseline evaluations of eosinophil counts.
Statistical analysis method	20/Mar/2020	Revise ACQ-6 responder and SGRQ responder definition.	N/A	Addition of conservative approach for missing evaluations at end of treatment to be non-responders as primary analysis. The hybrid last observation carried forward approach serve as sensitivity analysis.
Statistical analysis method	20/Mar/2020	Revise definition of on-treatment period.	N/A	To be consistent with CSP study design of IPD visit change.
Statistical analysis method	20/Mar/2020	Add a sub-section of physical examination in safety section.	N/A	To clarify that no separate summary of physical examination results as it is reported as adverse event.
Statistical analysis method	20/Mar/2020	For subgroup analysis of primary exacerbation endpoint, add subgroup factors of "number of exacerbations during ICS/LABA in the previous year", "region (China, Non-China)", "nasal polyps", "IgE" and remove "race" for patients with eosinophil ≥300/μL.	N/A	Add additional subgroup factors that are meaningful for MIRACLE and that are explored in other studies. Remove race considering all participated countries are in Asia.
Statistical analysis method	20/Mar/2020	Add one sub-section for China subpopulation analyses.	N/A	Add brief explanation of analyses to be repeated for patients from China only.

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Statistical analysis method	20/Mar/2020	Replace endpoint "SGRQ" with "total asthma symptom score" in the Appendix 8.1 and 8.3.	N/A	The analyses specified in Appendix is for key secondary endpoints.
Statistical analysis method	20/Mar/2020	Remove "overall post-baseline mean" for endpoint asthma symptom score.	N/A	Remove considering not a meaningful summary variable by averaging all visits across post-baseline period.
Statistical analysis method	20/Mar/2020	Remove "The number of patients remaining on treatment, patients discontinued IP but still in study follow-up and patients who withdraw from the study will be presented by treatment group and scheduled visit. The number of patients who performed follow-up visits will also be provided".	N/A	The by-visit descriptive summary of patient discontinuation is removed considering it is not a meaningful summary.
Statistical analysis method	20/Mar/2020	Replace "The model-based annual exacerbation rate estimates in the individual treatment groups will be estimated via marginal standardisation methods to further characterise the primary analysis results" by "The model-estimated annual exacerbation rate in each treatment group will be estimated via marginal standardisation method".	N/A	To clarify that only marginal rate will be presented.
Statistical analysis method	20/Mar/2020	Add additional ADA responses and relevant analyses: treatment induced ADA positive, treatment boosted ADA positive, ADA persistently positive, ADA transient positive. Remove analyses of patients with >75% reduction in titre.	N/A	To further characterise immunogenicity profile.
Statistical analysis method	20/Mar/2020	Add total OCS dose summary for patients with baseline eosinophil count <300/μL.	N/A	As a complement for patients with baseline eosinophil count ≥300/μL.

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Statistical analysis method	20/Mar/2020	Modify the subgroup analysis of pre-bronchodilator FEV_1 "A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect, the treatment by subgroup interaction, and visit by treatment by subgroup interaction model statement" to "A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect, and the treatment by subgroup interaction."	N/A	To be consistent with all other subgroup analysis method.
Other: sample size	20/Mar/2020	Replace "Approximately 834 patients will be randomised, of which at least 534 will be randomised from China" with "Approximately 666 patients will be randomised, of which approximately 80% will be randomised from China".	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP for patient sample size change and operational flexibility in patient management and randomisation.
Other: IPD visit schedule	20/Mar/2020	Replace "complete IPD visit within 4 weeks (+7 days) after the last dose of IP" by "complete IPD visit within 4 weeks (+7 days, for the last dose being the protocol scheduled first or second dose) or 8 weeks (+7 days, for the last dose being the protocol scheduled third or the following dose) after the last dose of IP".	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP to clarify the IPD visit timeframe and various scenarios for patients that prematurely discontinue IP.
Other: Covariate	20/Mar/2020	Replace the covariate "country" by "region (china/non-china)" in the statistical model for primary and secondary analyses.	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP due to the small number of patients in non-China countries.
Other: Covariate	20/Mar/2020	Replace the covariate "number of exacerbations associated with an ER visit or a hospitalisation in the year before the study" with "category variable (yes/no) of exacerbations associated with an ER visit or a hospitalisation in the year before the study" in statistical model.	N/A	Sparse values for number of previous ER/hospitalisation are expected. Thus categorical covariate is more appropriate.

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Other: Terminology	20/Mar/2020	Remove the term "estimand" in main body and rephrase the context accordingly; "estimand" is used only in Appendix 8.1 "Accounting for missing data".	N/A	Simplify the wording in main body as estimand is the terminology mainly for missing data assessment.
Other: Important Protocol deviation	20/Mar/2020	Rephrase the definition of important protocol deviation to include important deviations that may affect safety of the IP and replace specific important protocol deviation with general categories.	Yes (CSP version 4.0, 19/Dec/2019)	To incorporate wider range of important protocol deviations.
Other: add HRU	20/Mar/2020	Add variables to be analysed for health resource utilisation	Yes (CSP version 4.0, 19/Dec/2019)	To be consistent with CSP for collections of HRU.
	20/Mar/2020	Approved SAP Edition 2.0		
Primary or secondary endpoints	31/Jan/2023	Section 1.1.2: Added the incidence of nAb and ADA titre for characterizing the immunogenicity endpoint	Yes (CSP version 5.0, 18/Dec/2020)	In line with CSP for the immunogenicity endpoint clarification.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.1: Clarified the derivation of "last 14 days" in the baseline for daily assessments.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.1: Removed the text regarding the baseline definition for ACQ-6, SGRQ and safety laboratory.	N/A	Removed redundant text for simplification. The general definition of baseline applies to ACQ-6, SGRQ and safety laboratory.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.1: Added text to clarify that safety data collected on the day of first IP dosing without assessment time will be treated as pre-dose in baseline derivation.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.1: Removed text regarding the baseline derivation for categorical (yes/no) respiratory disease characteristics.	N/A	Removed as not applicable. Respiratory disease characteristics are

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				only collated at enrolment.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.1: Updated that the blood eosinophil count used for randomisation stratification will be used for baseline in analysis, except for the analyses of change from baseline and percent change from baseline.	N/A	Provided clarification for the definition of baseline blood eosinophil counts for various analyses.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.2: Addition of Section 3.1.2 for the definition of change from baseline.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Removed local ECG from visit window definitions.	N/A	Removed as not applicable. No by-visit summary for local ECG.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Clarified that the data will be allocated to a specific visit window based on the actual assessment date.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Clarified the definition of the analysis window “Week 0 Day 1” and “Week 0 Day 1” will be only used in listings.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: For the visit window table header, replaced “Adjusted Defined Windows Visit” by “Scheduled Visit”, replaced “Scheduled Study Day” by “Study Day”, replaced “Maximum Windows” to “Adjusted Analysis-defined Visit Windows”.	N/A	Updated the table for text consistency and error correction.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: For the table header of bi-weekly window for daily assessment, removed “Scheduled Study Day”, replaced “Adjusted Defined Windows Visit” by “Timepoint”, and replaced “Maximum Windows” by “Adjusted Analysis-defined Windows”.	N/A	Updated the table for text consistency and error correction.

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Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Corrected the schedule of study visits to be in line with CSP.	Yes (CSP version 5.0, 18/Dec/2020)	Updated for error correction.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Added definition of the adjusted analysis-defined visit window for PK and immunogenicity data.	N/A	The general definition of visit window is not applicable for PK and immunogenicity assessment due to sparse collection timepoints.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.1.3: Added text regarding the data collection for morning and evening PEF.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.2: Added text regarding the definition of the follow-up time in the primary analysis for the primary endpoint.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.2: Clarified the difference in the on-treatment period definition between efficacy analysis and safety analysis.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.3.2: Clarified that the time to first asthma exacerbation for patient without any event will be censored at the end of follow-up for exacerbation.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.3.3: Clarified that only those spirometry tracings determined to be acceptable or borderline will be included in the analysis.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.4.5: Added text noting that the ACQ-6 score will be missing if response to any of the 6 questions is missing.	N/A	Provided additional clarification. No change to analysis.
Derivation of primary or secondary	31/Jan/2023	Section 3.4.5: Clarified the definition of end of treatment and baseline for the asthma control responder status.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.

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endpoints				
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.4.6: Added the definition of SGRQ total score.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.6.1: Updated the rule of categorising AE to the on-treatment period in the event of EOT or IPD visit beyond the protocol visit window and in the event of EOT or IPD visit is missing.	Yes (CSP version 5.0, 18/Dec/2020)	Updated to be in line with the new schedule of IPD visit in CSP.
Derivation of primary or secondary endpoints	31/Jan/2023	Section 3.6.3: Removed text regarding weight and body mass index from the vital signs section.	Yes (CSP version 5.0, 18/Dec/2020)	Removed as weight and body mass index are not included in the vital signs summaries.
Derivation of primary or secondary endpoints	31/Jan/2023	Sections 3.6.4, 4.2.10.4: Added borderline to the categories of ECG overall evaluation.	N/A	Updated to be in line with the data collected in CRF.
Statistical analysis method	31/Jan/2023	Section 2.1: Added the “randomised patients analysis set”.	No (CSP version 5.0, 18/Dec/2020)	Defined an analysis set instead of using “All randomised patients” for outputs. No change to analysis.
Statistical analysis method	31/Jan/2023	Section 2.1: Rephrased the definition of PK analysis set.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Section 4.1, Appendix 8.4: Addition of analyses to assess the impact of the COVID-19 pandemic.	Yes (CSP version 5.0, 18/Dec/2020)	Required output for CSR.
Statistical analysis method	31/Jan/2023	Section 4.1.1: Added text regarding the testing hypotheses for key secondary endpoints.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Section 4.2.1: Added text regarding the Kaplan-Meier plots for time to study treatment discontinuation and time to premature study withdrawal.	N/A	Provided clarity for the censoring for patients who do not have the event.

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Statistical analysis method	31/Jan/2023	Section 4.2.4.2: Added text regarding the derivation of study treatment compliance for IP discontinuations.	N/A	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Sections 4.2.5.1, 4.2.6.3, 4.2.7.1, Appendix 8.6: Addition of Appendix 8.6 for details regarding estimand for primary and key secondary endpoints.	N/A	Added text regarding estimand per latest authority guidance.
Statistical analysis method	31/Jan/2023	Section 4.2.5.2: Added sensitivity analysis regarding time at risk, i.e., follow-up time subtracting exacerbation duration and the subsequent 7 days, as offset in the negative binomial model for exacerbation.	N/A	Required output for CSR.
Statistical analysis method	31/Jan/2023	Section 4.2.5.3: Updated subgroup analyses for primary endpoint: removed subgroup of IgE; added subgroup of prior treatment with Xolair; changed subgroup categories for age, baseline body mass index and prior exacerbations during ICS/LABA treatment.	No (CSP version 5.0, 18/Dec/2020)	Removed IgE as no IgE data collected. Added new subgroup of clinical interest. Changed subgroup categories due to small patient number expected.
Statistical analysis method	31/Jan/2023	Section 4.2.5.3: Added text regarding the standardised effect plot.	N/A	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Sections 4.2.5.3, 4.2.6.3, 4.2.7.1: Updated that the LOESS plot will be based on baseline eosinophil count and prior exacerbations for the primary and key secondary endpoints.	N/A	Provided clarity for the LOESS analysis.
Statistical analysis method	31/Jan/2023	Sections 4.2.6.3, 4.2.7.1: Added subgroup analyses by prior exacerbations and baseline ICS dose for the key secondary endpoints.	N/A	Added subgroups of clinical interest for key secondary endpoints.
Statistical analysis method	31/Jan/2023	Section 4.2.6.1: Replaced the covariate “number of exacerbations in previous year” by “number of exacerbations in the previous year (2, ≥3 exacerbations)” in the Cochran-Mantel-Haenszel test for proportion of patients with ≥1 exacerbation.	No (CSP version 5.0, 18/Dec/2020)	Update the analysis to pool strata with sparse data.

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Statistical analysis method	31/Jan/2023	Section 4.2.6.4: Added text regarding the analysis of asthma exacerbation associated with a hospitalisation only or an ER/UC only.	N/A	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Sections 4.2.6.4, 4.2.6.5: Updated that the model will be re-run after dropping the covariate(s) until convergence, in the event of model convergence issues.	N/A	Clarified the analysis in the event of convergence issues that possibly due to small number of events.
Statistical analysis method	31/Jan/2023	Section 4.2.7: Added text noting that in the model specification for daily assessment, bi-weekly period will used as covariate instead of visit.	Yes (CSP version 5.0, 18/Dec/2020)	Visit is not applicable for daily assessment.
Statistical analysis method	31/Jan/2023	Sections 4.2.7.5, 4.2.7.6: In the logistic regression model for the ACQ-6 and SGRQ responder variables, removed the covariate "number of exacerbations in previous year".	Yes (CSP version 5.0, 18/Dec/2020)	Updated the responder model covariates to be consistent with the MMRM models for ACQ-6 and SGRQ change from baseline.
Statistical analysis method	31/Jan/2023	Section 4.2.9: Added text regarding the separate modelling by baseline blood eosinophil count, prior exacerbation and baseline ICS dose for primary and key secondary endpoints.	N/A	Provided additional clarification and updated MMRM analysis for same variance-covariance matrix across subgroup categories.
Statistical analysis method	31/Jan/2023	Section 4.2.11: Added text regarding the handling of PK concentrations below LLOQ in the analysis.	N/A	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Appendix 8.1: Additional specification provided for the imputation algorithm of missing data.	N/A	Provided additional clarification. No change to analysis.
Statistical analysis method	31/Jan/2023	Appendix 8.1: Modified the non-treatment related reason for IP discontinuation and study withdrawal to less clear reason that need review to determine the imputation rule in DRMI.	N/A	Updated for a more conservative approach for the sensitivity analysis of missing data.

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Statistical analysis method	31/Jan/2023	Appendix 8.1.2: Removed text regarding the plots of change from baseline in key secondary endpoints by dropout pattern.	N/A	Removed as of little value for the interpretation.
Statistical analysis method	31/Jan/2023	Appendix 8.3: Added text regarding the definition of ADA prevalence and ADA incidence.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Section 2.3.1: Updated that COVID-19-related non-important protocol deviations will also be listed.	N/A	Required output for CSR.
Data presentations	31/Jan/2023	Section 3.1.4: Updated that the maintenance asthma medications at baseline will be identified following a physician review prior to database lock.	N/A	Clarified the determination of maintenance asthma medications at baseline.
Data presentations	31/Jan/2023	Sections 3.1.4, 4.2.3: Added text noting that the concomitant medication will be further classified as on-treatment or post-treatment, on-treatment medications will be summarised and post-treatment medications will be only listed.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Section 3.3.4: Removed the analyses of time to first exacerbation associated with a hospitalisation only and time to fist exacerbation associated with an ER/UC visit only.	N/A	Removed the supportive analyses with small number of events expected.
Data presentations	31/Jan/2023	Sections 3.6.2, 4.2.10.2: Updated that laboratory parameters AST, ALT, ALP and GGT will be presented in both SI and conventional units.	N/A	Provided additional data for interpretation.
Data presentations	31/Jan/2023	Section 3.6.2: Updated that shift table for white blood cell will only be baseline to maximum CTCAE grade post-baseline.	N/A	Maximum CTCAE grade is of clinical interest.
Data presentations	31/Jan/2023	Section 3.6.2: For the urinalysis data category, replaced “negative” by “negative (or normal)”, and replaced “>+++” by “++++”.	N/A	Updated to be in line with the actual lab reporting.

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Data presentations	31/Jan/2023	Section 3.7: Added text noting that only serum trough concentration data will be present for patients receiving benralizumab for PK summary.	Yes (CSP version 5.0, 18/Dec/2020)	Provided clarity for PK summary and to be in line with the latest lab analyses process.
Data presentations	31/Jan/2023	Section 4.2.1: Updated the categories of patient disposition, including category removal/addition/renaming.	N/A	Provided clarity for patient disposition summary.
Data presentations	31/Jan/2023	Section 4.2.2: Addition of imputation rule for date of birth.	N/A	Required imputation for patients with partial date of birth.
Data presentations	31/Jan/2023	Section 4.2.2: Removed text regarding the post-bronchodilator lung function data.	Yes (CSP version 5.0, 18/Dec/2020)	Removed as not applicable. No post-bronchodilator data collected post-randomisation.
Data presentations	31/Jan/2023	Section 4.2.3: Updated the number of patients taking other maintenance asthma medication(s) in addition to ICS/LABA and the number of patients taking medium or high ICS dose will be summarised.	N/A	Provided additional data for interpretation.
Data presentations	31/Jan/2023	Section 4.2.3: Added text noting that the disallowed medications will be identified following a physician review according to CSP prior to database lock.	N/A	Clarified the determination of disallowed medications.
Data presentations	31/Jan/2023	Section 4.2.3: Added text noting that total number of OCS treatment days associated with exacerbations will also be summarised together with total OCS dose.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Section 4.2.4.2: Updated that the study treatment compliance will also be summarised by baseline blood eosinophil count group.	N/A	Provided additional data for interpretation.
Data presentations	31/Jan/2023	Sections 4.2.5.2, 4.2.6.3, 4.2.6.6, 4.2.7.1, 4.2.7.5: Replaced “150/µL-299/µL” by “≥150/µL-<300/µL”, replaced “300/µL-449/µL” by	Yes (CSP version 5.0, 18/Dec/2020)	Updated the categories for additional clarification. No change to analysis as blood eosinophil

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		"≥300/µL-<450/µL" for the baseline blood eosinophil count categories.		counts are measured in integer.
Data presentations	31/Jan/2023	Sections 4.2.5.2, 4.2.6.3, 4.2.7.1, 4.2.7.5: Added summaries of primary and secondary endpoints for patients with baseline eosinophils count <150/µL, <200/µL, <250/µL, <300/µL, <350/µL, <400/µL, <450/µL respectively.	N/A	Required output for CSR.
Data presentations	31/Jan/2023	Section 4.2.6.5: Clarified that time to first asthma exacerbation associated with hospitalisation or ER/UC visit will be analysed for patients with baseline blood eosinophil count ≥300/µL only.	N/A	Provided clarity that the analyses will not repeat on patients with baseline blood eosinophil count <300/µL.
Data presentations	31/Jan/2023	Section 4.2.7.6: Added texts regarding the MMRM analyses of SGRQ score by cumulative baseline blood eosinophil count category and by baseline blood eosinophil count category.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Section 4.2.8: Addition of summary of asthma specific resource utilisation over the previous year.	N/A	Provided baseline summary in addition to post-randomisation summary.
Data presentations	31/Jan/2023	Section 4.2.10.1: Removed the summary of SAE leading to IP discontinuation and SAE leading to study withdrawal.	N/A	Removed due to little clinical interest and AE leading to discontinuation summary is sufficient.
Data presentations	31/Jan/2023	Section 4.2.10.1: Clarified the definition of total period with patients at risk of AE.	N/A	Provided clarity for the calculation of AE rate per patient-years at risk.
Data presentations	31/Jan/2023	Section 4.2.10.1: Clarified that the summary by PT and maximum intensity will only be done using all AEs.	N/A	Provided clarity that no subset of AEs will be summarized by PT and maximum intensity.

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Data presentations	31/Jan/2023	Section 4.2.10.1: Updated that the AE summary by the Investigator's causality assessment (yes/no) will be replaced by the summary of causally related AE only.	N/A	AEs not causally related to IP as assessed by the Investigator is of little clinical interest.
Data presentations	31/Jan/2023	Section 4.2.10.4: Updated that borderline ECG will be grouped with normal for the reporting.	N/A	Provided clarification for the ECG shift table presentation.
Data presentations	31/Jan/2023	Section 4.2.13: Clarified the types of analyses that will be repeated for China subpopulation and clarified no region covariate in the China subpopulation analyses.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Appendix 8.2: Added text regarding the imputation rule for the partial dates of asthma first diagnosed and first appearance of asthma symptoms.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Appendix 8.3: Removed the summary of demographics and patient characteristics by ADA subgroup, the summary of first post-baseline positive ADA, the nAb summary for ADA persistently positive patients, the summary of SAE by ADA and causality, the listing of patients with >4-fold increase in titre from time of first post-baseline ADA positive result.	N/A	Removed as little clinical interest based on the results from previous benralizumab studies.
Data presentations	31/Jan/2023	Appendix 8.3: Added text regarding the summary of ADA positive patients with maximum titre ≤ and > the median of maximum titres.	N/A	Provided additional clarification. No change to analysis.
Data presentations	31/Jan/2023	Appendix 8.3: For the listing of ADA positive patients, replaced "days from previous/first dose and first positive result" by "days from previous dose", added "number of active doses received".	N/A	Updated the key patient information that will list for ADA positive patients.
Data presentations	31/Jan/2023	Appendix 8.3: Updated the ADA subgroups to be consistent across the	N/A	To have consistent evaluation of the

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		summary of eosinophil, efficacy, safety and PK by ADA subgroup.		impact of ADA on eosinophil, efficacy, safety and PK.
Other	31/Jan/2023	Updated the specification for "In line with the CSP" of amendment history: replaced "Y" by "Yes", replaced " " by "N/A", added CSP version date.	N/A	In line with the latest SAP template.
Other	31/Jan/2023	Section 1: Replaced "the global clinical study report" by "the clinical study report".	N/A	Provided clarification of the single clinical study report.
Other	31/Jan/2023	Sections 1.2, 1.3: Changed the percentage of China patients from approximately 80% to at least 70%.	Yes (CSP version 5.0, 18/Dec/2020)	In line with CSP for the China patient number change.
Other	31/Jan/2023	Section 1.2: Updated that the maintenance therapy should be stable "from visit 1 until the end of the study" instead of "enrolment throughout the run-in and treatment period" and added "other asthma controllers" to maintenance therapy.	Yes (CSP version 5.0, 18/Dec/2020)	In line with CSP for the clarification of stable use of maintenance therapy.
Other	31/Jan/2023	Section 1.2: Clarified that China subpopulation consists of patients from mainland of China and Taiwan.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Other	31/Jan/2023	Section 1.2: Updated the schedule of IPD visit to be "8 weeks + 7 days after the last dose of IP" and last visit for study withdrawal to be "16 weeks ±7 days after the last dose of IP".	Yes (CSP version 5.0, 18/Dec/2020)	In line with CSP for the change of visit schedule.
Other	31/Jan/2023	Section 1.3: Clarified that the study is powered for the primary analysis of primary endpoint.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification for the study power calculation.
Other	31/Jan/2023	Moved sub-sections of "Visit window definitions", "The definition of baseline" and "Prior and concomitant medications" from Section 2.3 "Violations and deviations" to Section 3 "Primary and secondary variables".	N/A	In line with the latest SAP template.

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	31/Jan/2023	Section 3.1.4, Appendix 8.5: Added the OCS dose therapy equivalence table. Clarified the ICS dose conversion will be according to CSP.	Yes (CSP version 5.0, 18/Dec/2020)	Provided clarity for the OCS and ICS dose conversion.
Other	31/Jan/2023	Section 3.2: Clarified that the definitions of exacerbation, the start and end date of exacerbation are from CSP.	Yes (CSP version 5.0, 18/Dec/2020)	Provided additional clarification. No change to analysis.
Other	31/Jan/2023	Sections 3.7, 4.2.11: Updated that PK samples will be only analysed for patients receiving benralizumab by a central laboratory.	Yes (CSP version 5.0, 18/Dec/2020)	Updated to be in line with latest AZ standard process.
Other	31/Jan/2023	Section 4.1.1: Replaced “the family wise error rate” by “the overall type 1 error rate” in the description of multiple testing strategy.	No (CSP version 5.0, 18/Dec/2020)	Updated terminology to be line with latest practice.
Other	31/Jan/2023	Sections 4.2.5.1, 4.2.5.2: Moved text regarding supportive and sensitivity analysis from Section 4.2.5.1 to a new sub-section 4.2.5.2.	N/A	No change to content. Moved irrelevant text as Section 4.2.5.1 is the primary analysis.
Other	31/Jan/2023	Section 4.2.10.1: Updated the high level term used to define AE of injection site reactions: replaced “administration and injection site” by “injection site reaction”.	N/A	Corrected the definition of AE of injection site reactions.
Other	31/Jan/2023	Section 6: Addition of changes from latest CSP version 5.0.	N/A	Mandatory section update.
Other	31/Jan/2023	Appendix 8.1: Removed text regarding estimand from this appendix and rephrased the text accordingly.	N/A	A new appendix is added to provide the details of estimand. The removed text is also not aligned with latest estimand guidance.
Other	31/Jan/2023	Administrative update for abbreviations.	N/A	Consistency of abbreviations throughout document.

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	31/Jan/2023	Administrative update for text consistency, duplicate text removal and text cross-reference.	N/A	No change to content. Adjusted text for consistency and simplification.
Other	31/Jan/2023	Formatting and links fixed.	N/A	No change to content. Adjusted formatting to reflect house style and errors in links resolved.

1. STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the clinical study report (CSR) of study D3250C00036.

1.1 Study objectives

1.1.1 Primary objective

Objective	Endpoint
To evaluate the effect of benralizumab on asthma exacerbations in patients on medium to high-dose inhaled corticosteroid plus long-acting β2-agonist (ICS/LABA) with uncontrolled asthma.	Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening[a] of asthma requiring: • Use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid (OCS) background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An emergency room (ER)/urgent care (UC) visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids for at least 3 days (as per above) • An inpatient hospitalisation due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours)

[a] For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs (examination or lung function) that can be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The electronic patient reported outcome (ePRO) device will be programmed to alert both the patient and study centre when certain pre-specified worsening thresholds are crossed including: decrease in morning peak flow ≥30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or 1 new or additional nebulised β2 agonist on at least 2 of 3 successive days compared with the average use for the previous week, and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or an increase in total asthma symptom score (the sum of daytime [evening assessment] and night-time [morning assessment]) of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

1.1.2 Secondary objectives

Objective	Endpoint
To assess the effect of benralizumab on pulmonary function	Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) [b]
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total[b], daytime, and night-time) • Rescue medication use • Home lung function (morning and evening peak expiratory flow [PEF]) • Nights with awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6)
To assess the effect of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥1 asthma exacerbation
To assess the effect of benralizumab on health-related quality of life	St. George's Respiratory Questionnaire (SGRQ)
To assess the effect of benralizumab on ER/UC visits and hospitalisations due to asthma	Annual rate of asthma exacerbations that are associated with an ER/UC visit or a hospitalisation
To evaluate the effect of benralizumab on health care resource utilisation	Asthma specific resource utilisation (e.g., unscheduled physician visits, use of other asthma medications)
To characterize the pharmacokinetics (PK) and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity: Incidence of anti-drug antibodies (ADA) and neutralizing antibodies (nAb), ADA titre
To assess the impact of benralizumab on blood eosinophil levels	• Blood eosinophils

[b] Key secondary efficacy endpoints

1.1.3 Safety objective

Objective	Endpoint

To assess the safety and tolerability of benralizumab	• Adverse event (AE)/Serious adverse event (SAE) • Laboratory variables • Electrocardiogram (ECG) • Vital Signs

1.2 Study design

This is a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously for patients with a history of asthma exacerbations and uncontrolled asthma receiving medium to high-dose ICS/LABA with or without OCS and additional asthma controllers.

Approximately 666 patients will be randomised, of which at least 70% patients will be from China (including the mainland of China and Taiwan). The randomisation will be stratified by country/region (the mainland of China, Taiwan, South Korea or Philippine), age group (adult or adolescent), and peripheral blood eosinophil count at time of Visit 1 (<300 or ≥300 cells/μL).

All the patients will be randomised to either placebo or benralizumab in a 1:1 ratio, every 4 weeks for the first 3 doses and then every 8 weeks thereafter. Study recruitment will be closed when recruitment is closed for all strata, based on the following strata closure process:

1. The eosinophil <300/μL stratum will be closed to the patients from China when the total number of Chinese patients in the eosinophil <300/μL stratum reaches approximately 166.

2. The eosinophil <300/μL stratum will be closed to the patients from all countries when the total number of patients in the eosinophil <300/μL stratum reaches approximately 222.

3. The whole study will be closed for recruitment when the total number of patients in the eosinophil ≥300/μL stratum reaches approximately 444, with at least 70% Chinese patients in the stratum.

After initial enrolment and confirmation of entry criteria, patients will proceed to the run-in period of a minimum 4 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Patients who meet eligibility criteria will be randomised to a 48-week treatment period. Patients will be maintained on their currently prescribed medium to high-dose ICS/LABA therapy and other asthma controllers, without change, from visit 1 until the end of the study.

A follow-up visit will be conducted at Week 56.

All patients who prematurely discontinue investigational product (IP) should return to the study centre and complete the procedures described for the premature IP discontinuation (IPD) visit within 8 weeks + 7 days after the last dose of IP. At that visit, patient should be encouraged to remain in the study to complete all subsequent study visits, procedures and assessments, or alternatively agree to be contacted by phone calls at monthly intervals in order to collect AEs/SAEs, changes in concomitant medication, health care utilisation, and asthma exacerbation information. Patients not willing to continue to participate in the study should return to the study centre one last time within 16 weeks ±7 days after the last dose of IP for final study related assessments. See clinical study protocol (CSP) Section 3.9.1 for procedures for discontinuation of a patient from IP.

See CSP Section 4, Tables 1 and 2 for a detailed list of visits and assessments.

1.3 Number of subjects

The study will stratify patients with baseline blood eosinophil counts ≥300/μL and <300/μL at a ratio of approximately 2:1. The 2:1 stratification ratio is intended as a means of enriching the population for patients most likely to respond to benralizumab (i.e., ≥300/μL), while still including patients below this threshold in order to help understand efficacy and safety in this group. The study is powered for the primary efficacy analysis of primary endpoint in patients with baseline blood eosinophils ≥300/μL.

The efficacy analyses will comprise both adult and adolescent patients.

For the primary endpoint, annual asthma exacerbation rate, approximately 222 adult and adolescent patients with baseline blood eosinophil counts ≥300/μL per treatment arm (approximately 444 in total) will need to be randomised to achieve approximately 90% power

As stated above, a ratio of approximately 2:1 will be used for patients with baseline blood eosinophil counts ≥300/μL and <300/μL. Therefore, the study will also randomise approximately 111 patients/arm (approximately 222 in total) with baseline blood eosinophil counts <300/μL. So a total of approximately 666 adult and adolescent patients are expected to be randomised in the study, of which at least 70% patients will be from China.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Five analysis sets are defined below: all patients analysis set, randomised patients analysis set, full analysis set (FAS), safety analysis set, and PK analysis set.

2.1.1 All patients analysis set

This analysis set comprises all patients who signed informed consent form for the study (including screen failures) and will be used for the reporting of patient disposition.

2.1.2 Randomised patients analysis set

This analysis set comprises all patients randomised to study treatment, irrespective of whether IP was subsequently taken. The number and percentage of patients in each of the FAS, safety and PK analysis sets will be summarized using this analysis set.

2.1.3 Full analysis set

All patients who were randomised and received any IP will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued IP, according to the intent-to-treat (ITT) principle. Patients who withdraw consent, and assent when applicable, to participate in the study will be included up to the date of their study termination.

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

2.1.4 Safety analysis set

All patients who received any IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on 1 or several occasions received active treatment will be classified as active. All safety and ADA analyses will be based on this analysis set.

2.1.5 Pharmacokinetic (PK) analysis set

All patients who received benralizumab and had at least 1 measurable serum PK observation post first dose from PK blood samples that are assumed not to be affected by factors such as protocol deviations (PDs) will be included in the PK analysis set. All PK summaries will be based on this analysis set.

2.2 China subpopulation

The China subpopulation is defined as all patients enrolled in the study centres in the mainland of China and Taiwan. The analysis sets used in the analyses for the China subpopulation are defined similarly as the analysis sets described in Section 2.1 and include only the patients from the China subpopulation.

2.3 Violations and deviations

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

2.3.1 Important protocol deviations

Important PDs are a subset of PDs that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. The final list of important PDs will be documented prior to unblinding the study data and will include but may not be limited to the following categories:

- Did not fulfil key eligibility criteria
- Developed discontinuation criteria but continued study treatment
- Received prohibited/restricted medication prior to and during the study
- Deviation from key study procedure/assessment
- Deviation from IP management

The study PD Instructions outline the management of PDs and include the proposed specific categories of PDs in this study. Any PDs which are not defined as important will not be reported and discussed in the CSR, with the exception of COVID-19-related PDs. The important PDs will be tabulated by treatment group and listed in the CSR, and only for randomised patients (not screening failures). The important PDs will be identified, reviewed and documented through a PD review process consisting of blinded review meeting involving the study physician and study statistician prior to unblinding.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 The definition of baseline

In general, the last non-missing measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints, and the last non-missing measurement prior to first dose of study treatment will serve as the baseline measurement for safety endpoints. If there is no value on or prior to the date of randomisation (or prior to first dose of study treatment, depending on the endpoint), then the baseline value will not be imputed and will be set to missing. No data known to be collected post first dose will be used in determining the baseline value, unless otherwise specified.

For re-screened patients, only the last screening data will be used for baseline evaluation.

For pre-bronchodilator FEV_1, the last non-missing value with acceptable quality (acceptable or borderline quality grade, accessed by a clinical specialist from ERT and aligned with the Investigator) on or prior to the date of randomisation will be used as baseline.

For daily assessments of asthma symptoms, night time awakenings, rescue medication usage and peak expiratory flow (PEF), baseline is defined as the mean of the available data over the

last 14 days prior to the date of randomisation. The “last 14 days” starts with the evening of Day -14 and ends with the morning of the date of randomisation (Day 1). The mean is calculated as the sum of all non-missing daily measures/scores over the 14 sequential days divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within the baseline period are missing, then baseline will be set to missing. For daily assessments which are made in both morning and evening, the whole day is defined by the assessments in the evening and the following morning, and the daily assessment will be considered missing if either evening or following morning is missing.

For safety variable, if the time is missing for an assessment and the assessment takes place on the date of first dose of study treatment, this will be assumed to be a pre-dose assessment and considered in the baseline derivation.

For the summaries and analyses related with blood eosinophil count, the following rules for baseline will be applied:

- For data summaries and analyses by baseline blood eosinophil count strata (<300/µL vs. ≥300/µL), by baseline blood eosinophil count category (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL), by cumulative baseline blood eosinophil count category (e.g., <150/µL, <200/µL) and by continuous baseline blood eosinophil count (locally estimated scatterplot smoothing (LOESS)), and for descriptive summaries of baseline blood eosinophil counts for patient characteristics, the blood eosinophil count value that was used to randomise the patient into strata will be used for the baseline.

- For data summaries and analyses for change from baseline and percent change from baseline in blood eosinophil counts, baseline value will be defined as the last non-missing value prior to the first dose of study treatment.

3.1.2 Absolute change from baseline

Absolute change from baseline is defined as *(post-baseline value - baseline value)*.

If either the post-baseline value or the baseline value is missing, then the absolute change from baseline will also be missing.

Unless otherwise specified, “change from baseline” is assumed to be the absolute change from baseline.

3.1.3 Visit window definitions

For the exacerbation-related analyses, no windows will be applied. For local laboratory (if any) and all vital signs variables, the visit recorded in web-based data capture (WBDC) will be used.

For endpoints that present visit-based data, the data will be summarised based on the scheduled visit with adjusted analysis-defined visit windows. The adjusted analysis-defined

windows will be based on the collection schedule listed in the protocol, and the data will be windowed to the closest scheduled visit based on the actual assessment date. Visit windows have been constructed so that every observation collected post-baseline can be allocated to a particular visit, with the exception of PK and immunogenicity assessments.

No visit windows will be defined for screening visits. "Week 0 Day 1" will contain the data collected on the date of randomisation which is not selected as baseline, and will only be used in the patient listings, if applicable.

The adjusted analysis-defined windows for assessments conducted at Weeks 0, 4, 8, and every 8 weeks to Week 48 are summarised in Table 1. This applies to ACQ-6 and pre-bronchodilator spirometry assessments.

Table 1 Visit windows for assessments conducted at Weeks 0, 4, 8, and every 8 weeks to Week 48

Scheduled Visit	Study Day	Adjusted analysis-defined visit windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤Study Day≤42
Week 8	57	43 ≤Study Day≤84
Week 16	113	85 ≤Study Day≤140
Week 24	169	141≤Study Day≤196
Week 32	225	197≤Study Day≤252
Week 40	281	253≤Study Day≤308
Week 48	337	309≤Study Day

Table 2 presents the adjusted analysis-defined windows for safety laboratory assessments (except for blood eosinophil counts) conducted at Weeks 4, 8, 24, 40, and 48.

Table 2 Visit windows for assessments conducted at Weeks 4, 8, 24, 40, and 48

Scheduled Visit	Study Day	Adjusted analysis-defined visit windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤Study Day≤42
Week 8	57	43 ≤Study Day≤112
Week 24	169	113≤Study Day≤224
Week 40	281	225≤Study Day≤308
Week 48	337	309≤Study Day

Table 3 presents the adjusted analysis-defined windows for assessments conducted at Weeks 4, 8, 24, 40, 48, and 56. This applies to blood eosinophil counts.

Table 3 Visit windows for assessments conducted at Weeks 4, 8, 24, 40, 48, and 56

Scheduled Visit	Study Day	Adjusted analysis-defined visit windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤Study Day≤42
Week 8	57	43 ≤Study Day≤112
Week 24	169	113≤Study Day≤224
Week 40	281	225≤Study Day≤308
Week 48	337	309≤Study Day≤364
Week 56 (Follow-up)	393	365≤Study Day

Table 4 presents the adjusted analysis-defined windows for SGRQ assessments conducted at Weeks 0, 8, and every 8 weeks until Week 48.

Table 4 Visit windows for assessments conducted every 8 weeks to Week 48

Scheduled Visit	Study Day	Adjusted analysis-defined visit windows
Week 0 Day 1	1	Study Day=1
Week 8	57	2 ≤Study Day≤84
Week 16	113	85 ≤Study Day≤140
Week 24	169	141≤Study Day≤196
Week 32	225	197≤Study Day≤252
Week 40	281	253≤Study Day≤308
Week 48	337	309≤Study Day

Serum samples for PK and immunogenicity are scheduled to be collected at Weeks 0, 24, 48 and at the IPD visit where applicable. PK data will be assigned to the adjusted analysis-defined visit windows based on the following rule:

- Week 0 (Baseline): Only pre-dose samples at Study Day 1. If no pre-dose sample was taken at Study Day 1, the last pre-dose sample prior to Study Day 1 will be used for baseline.

- Week 24: Only pre-dose samples within 2 weeks around the scheduled visit (155≤ Study Day ≤183) that were also taken between ≥42 and ≤70 days post the previous IP dose.

- Week 48: Only pre-dose samples within 2 weeks around the scheduled visit (323≤ Study Day ≤351) that were also taken between ≥42 and ≤70 days post the previous IP dose.

Immunogenicity data will be assigned to the adjusted analysis-defined visit windows based on the following rule:

- Week 0 (Baseline): Only pre-dose samples at Study Day 1. If no pre-dose sample was taken at Study Day 1, the last pre-dose sample prior to Study Day 1 will be used for baseline.

- Week 24: Only pre-dose samples within 4 weeks around the scheduled visit (141≤ Study Day ≤197).

- Week 48: Only pre-dose samples within 4 weeks around the scheduled visit (309≤ Study Day ≤365).

For assignment of data to the adjusted analysis-defined visit windows, Study Day will be defined as follows:

(Date of assessment – date of randomisation) +1

By this definition, the day of randomisation will be Study Day 1 and the planned date of Visit 6 (Week 4) will be study day 29 (=28+1), for example.

If multiple assessments are recorded within a single adjusted analysis-defined visit window, please refer to the rules below:

- If there are 2 or more observations within the same visit window, then the non-missing 1 closest to the date of scheduled visit will be used in the analysis.

- If 2 observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.

- If 2 observations are collected on the same day then the non-missing 1 with the earlier collection time will be included in the analysis.

- For patient reported outcomes (PROs) collected twice daily, if 2 observations are collected on the same day during the same period (i.e., a.m. or p.m.) then the non-missing observation with the earlier collection time during the period will be included in the analysis.

If a visit window does not contain any observations, then the data will remain missing for that visit. The data collected at IPD visits will be mapped to the nearest protocol scheduled visits.

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

For daily diary and home PEF assessments, bi-weekly means will be calculated using daily entries in the bi-weekly windows in Table 5. For daily diary assessments of rescue medication use and asthma symptom scores, the daytime measurement is captured in the evening and the night-time measurement is captured the following morning. Night-time awakenings are captured the following morning. Morning PEF is captured in the morning upon awakening and evening PEF is captured in the evening at bedtime. Any observation recorded after the morning of Study Day 337 will not be included in the analysis but will be listed.

Table 5 Bi-weekly windows for daily diary and home PEF assessments

Timepoint	Adjusted analysis-defined windows
Baseline	The last 14 days from evening of Study Day -14 to the morning of Study Day 1
Week 2	Evening of Study Day 1 to the morning of Study Day 15
Week 4	Evening of Study Day 15 to the morning of Study Day 29
Week 6	Evening of Study Day 29 to the morning of Study Day 43
Week 8	Evening of Study Day 43 to the morning of Study Day 57
Week 10	Evening of Study Day 57 to the morning of Study Day 71
Week 12	Evening of Study Day 71 to the morning of Study Day 85
Week 14	Evening of Study Day 85 to the morning of Study Day 99
Week 16	Evening of Study Day 99 to the morning of Study Day 113
Week 18	Evening of Study Day 113 to the morning of Study Day 127
Week 20	Evening of Study Day 127 to the morning of Study Day 141
Week 22	Evening of Study Day 141 to the morning of Study Day 155
Week 24	Evening of Study Day 155 to the morning of Study Day 169
Week 26	Evening of Study Day 169 to the morning of Study Day 183
Week 28	Evening of Study Day 183 to the morning of Study Day 197
Week 30	Evening of Study Day 197 to the morning of Study Day 211
Week 32	Evening of Study Day 211 to the morning of Study Day 225
Week 34	Evening of Study Day 225 to the morning of Study Day 239
Week 36	Evening of Study Day 239 to the morning of Study Day 253
Week 38	Evening of Study Day 253 to the morning of Study Day 267

Table 5 Bi-weekly windows for daily diary and home PEF assessments

Timepoint	Adjusted analysis-defined windows
Week 40	Evening of Study Day 267 to the morning of Study Day 281
Week 42	Evening of Study Day 281 to the morning of Study Day 295
Week 44	Evening of Study Day 295 to the morning of Study Day 309
Week 46	Evening of Study Day 309 to the morning of Study Day 323
Week 48	Evening of Study Day 323 to the morning of Study Day 337

For overall analyses not based on any particular study visit (e.g., AE summary, shift table), all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For safety endpoints, the post-baseline data will be included in the overall analysis up to and including the follow-up visit. For efficacy endpoints, the post-baseline data will be included up to and including the end of treatment (EOT) visit.

3.1.4 Prior and concomitant medications

A medication will be identified as a maintenance asthma medication at baseline following a physician review prior to database lock. A medication is defined as at baseline if it started on or prior to randomisation and was ongoing after randomisation. Inhaled corticosteroid (ICS) doses will be converted to their Fluticasone Propionate equivalent in micrograms according to Appendix E of the CSP and oral corticosteroid (OCS) doses will be converted to their Prednisolone equivalent in milligrams according to Appendix 8.5.

A medication will be regarded as prior if it was stopped on or before the date of randomisation (medication stop date ≤ date of randomisation). A medication will also be regarded as prior if the start and stop dates are both on the date of randomisation.

A medication will be regarded as concomitant if the start date is on or after the date of randomisation, or if it started prior to the date of randomisation and was ongoing after the date of randomisation. The concomitant medication will be further classified as on-treatment (the start date is before or during the on-treatment period) or post-treatment (the start date is after the end of on-treatment period), using the same definition of on-treatment period as for efficacy endpoint, see Section 3.2.

The total OCS dose associated with asthma exacerbations during the 48-week treatment period will be calculated using converted doses and is the total OCS dose summed over all exacerbations for each patient.

3.2 Primary outcome variable

The annual asthma exacerbation rate during the 48-week double-blind treatment period will be used as the primary efficacy variable. The primary analyses are based on the exacerbation data

(exacerbation is defined in Section 1.1.1 as in the CSP) reported by the Investigator in the exacerbation eCRF page.

In order to calculate the number of exacerbations experienced by a patient during the 48-week treatment period, the following rules will be applied.

The start of an exacerbation is defined in the CSP as the start date of systemic corticosteroids or the start date of a temporary increase in a stable oral corticosteroid background dose, or the start date of hospital admission, whichever occurs earlier. The end date is defined in the CSP as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital, whichever occurs later.

Additional systemic corticosteroid treatments, ER/UC visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation will not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

For the primary analysis, the follow-up time for exacerbation will be defined as follows, and the maximum follow-up time for calculation of the annual exacerbation rate is approximately 48 weeks.

- For patients who attended Visit 17 (EOT visit at Week 48), for example, those who completed study or those who discontinued IP but remained in the study, the follow-up time will be defined as the time from the date of randomisation up to and including the date of Visit 17:

  Follow-up time (days) = date of Visit 17 – date of randomisation + 1.

- For patients who did not attend Visit 17 (EOT visit at Week 48), for example, those who were lost to follow-up or withdrew consent/assent before Visit 17 or those who completed study but missed Visit 17, the follow-up time will be defined as the time from the date of randomisation to the time point after which an exacerbation could not be assessed:

  Follow-up time (days) = earliest [date of randomisation + 48 weeks, maximum (date of last visit, date of last assessment of exacerbation status from the EXACD eCRF page)] – date of randomisation + 1.

Exacerbations that start after Visit 17 will not be included in the efficacy analyses but will be listed. If a patient misses Visit 17, then any exacerbations that start after the scheduled Visit 17 date will be excluded from the efficacy analyses. If an exacerbation is ongoing at Visit 17, the exacerbation will be counted in the calculation of annual exacerbation rate, however the follow-up time will be truncated at the date of Visit 17, as will the duration of the exacerbation.

In the primary analysis, the number of asthma exacerbations experienced by a patient during the 48-week double-blind treatment period will be used as a response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur.

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

*Annual Exacerbation Crude Rate = 365.25*Total Number of Exacerbations / Total duration of follow-up within the treatment group (days).*

The on-treatment annual exacerbation rate will be calculated similarly, as a supportive analysis, using only exacerbations and follow-up time during the on-treatment period (using the same definition of on-treatment period as for adverse events, see Section 3.6.1, with the exception that the on-treatment period for efficacy endpoint starts on the date of randomisation and the on-treatment period for safety endpoint starts on the date of first dose of study treatment).

3.3 Secondary efficacy outcome variables

3.3.1 Proportion of patients with ≥ 1 asthma exacerbation during the 48-week double-blind treatment period

The proportion of patients with ≥ 1 asthma exacerbation during the 48-week double-blind treatment period will be a supportive variable to the primary outcome variable.

An exacerbation event will be defined in the same way as outlined in Section 3.2. In the statistical analysis, a binary variable taking on the value 1 if a patient has experienced 1 or more exacerbations during the 48-week double-blind treatment period and 0 otherwise, will be used as the response variable.

3.3.2 Time to first asthma exacerbation

Time from randomisation to the first asthma exacerbation during the 48-week treatment period will also be used as a supportive variable to the primary outcome variable, and is calculated as follows:

Start date of first asthma exacerbation - Date of randomisation + 1.

An exacerbation event will be defined in the same way as outlined in Section 3.2. The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at the end of the follow-up time for exacerbation, as defined in Section 3.2 (e.g., censored at Visit 17 for patients who completed Visit 17).

3.3.3 Pre-bronchodilator forced expiratory volume in 1 second (FEV_1)

Pre-bronchodilator FEV_1 is a key secondary efficacy endpoint of this study, and the change from baseline to Week 48 is included in the multiple testing strategy.

The change from baseline to each of the post-randomisation visits up to and including the end of 48-week double-blind treatment visit (Visit 17) will be used as outcome variables. The baseline FEV_1 is defined in Section 3.1.1.

Only those spirometry tracings determined to be acceptable or borderline will be included in the analysis.

3.3.4 Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalisation

The annual rate of asthma exacerbations that are associated with an ER/UC visit (requiring use of systemic corticosteroids) or a hospitalisation, as reported by the Investigator will be a secondary efficacy variable.

The number of asthma exacerbations associated with a hospitalisation or an ER/UC visit experienced by a patient during the 48-week double-blind treatment period and the follow-up time used in the calculation of this annual exacerbation rate will be derived according to the rules for the primary efficacy endpoint in Section 3.2.

Similarly, the annual rate of asthma exacerbations that are associated with an ER/UC visit only and the annual rate of asthma exacerbations that are associated with a hospitalisation only will also be derived.

In the statistical analysis, the number of asthma exacerbations that are associated with an ER/UC visit or a hospitalisation experienced by a patient during the 48-week double-blind treatment period will be used as a response variable, and the logarithm of the patient's corresponding follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times during which the events occur. The annual rate of asthma exacerbations that are associated with an ER/UC visit only and the annual rate of asthma exacerbation associated with a hospitalisation only will be treated similarly.

Time to first asthma exacerbation associated with a hospitalisation or an ER/UC visit will be derived following the approach outlined in Section 3.3.2.

3.4 Patient reported outcome variables

Patient reported outcomes (PROs) include asthma control questionnaire (ACQ-6), St. George's Respiratory Questionnaire (SGRQ), and daily diary metrics (asthma symptom scores, rescue medication use, night time awakenings due to asthma symptoms requiring rescue medication, and home PEF), and will be derived from the data collected through the ePRO device.

Daily diary metrics will be recorded in the asthma daily diary each day from the evening of Visit 2 to the morning of Visit 17. Baseline is defined as the mean value of the last 14 days before randomisation for the daily metrics, as defined in Section 3.1.1. Post-randomisation periods for the daily diary metrics will be defined for the calculation of bi-weekly means using the adjusted analysis-defined visit windows described in Section 3.1.3 and listed in Table 5. The post-randomisation bi-weekly means for daily diary metrics are calculated as the sum of

all non-missing daily measures/scores over the 14-day window divided by the number of non-missing daily measures/scores. If more than 7 daily measures/scores (>50%) within that window are missing, then the bi-weekly mean for that period will be set to missing. The change from baseline to each post-randomisation period will be used as outcome variables.

3.4.1 Asthma Symptom Score

The change from baseline in total asthma symptom score is a key secondary efficacy endpoint of this study, and the change from baseline to Week 48 is included in the multiple testing strategy.

Asthma symptoms during night-time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale of 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning of the next calendar day), and total score will be calculated and presented separately. The total score will be calculated by taking the sum of the daytime score recorded in the evening and the night-time score recorded the following morning. If a patient is missing a value for either the daytime or night-time asthma symptom score on a given day, then the total score for that day will be set to missing.

Bi-weekly mean scores and change from baseline in bi-weekly mean scores will be calculated for total asthma symptom score, daytime asthma symptom score and night-time asthma symptom score.

The number of asthma symptom-free days will be calculated for each patient as the total number of days in the 48-week treatment period for which the total asthma symptom score is 0. The proportion of asthma symptom-free days will be calculated using the total number of days with completed asthma symptom score diary during the 48-week treatment period as the denominator.

3.4.2 Rescue medication use

The number of rescue medication inhalations and nebuliser treatments taken will be recorded by the patient in the Asthma Daily Diary twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning of the next calendar day. Inhaler usage will be reported as the number of puffs in a given period, whereas nebuliser use will be reported as the number of times. Rescue medication usage will be summarised as the number of puffs, with 1 instance of nebuliser use converted to 2 puffs.

The number of rescue medication inhalations and nebuliser treatments captured in the Asthma Daily Diary each day will be calculated per patient. If a patient is missing a value for either daytime or night-time rescue medication use on a given day, then the total rescue medication use for that day will be set to missing.

Total rescue medication use (inhaler and/or nebuliser), defined as number of puffs per day will be calculated as follows:

Number of daytime inhaler puffs (recorded in the evening diary) + 2 x [number of daytime nebuliser times (recorded in the evening diary)] + number of night-time inhaler puffs (recorded in the morning diary of next calendar day)+ 2 x [number of night-time nebuliser times (recorded in the morning diary of next calendar day)].

Total reliever inhaler puffs per day will be calculated as:

Number of daytime inhaler puffs (recorded in the evening diary) + number of night-time inhaler puffs (recorded in the morning diary of next calendar day)

Total nebuliser use (number of times) per day will be calculated as:

Number of daytime nebuliser times (recorded in the evening diary) + number of night-time nebuliser times (recorded in the morning diary of next calendar day)

Bi-weekly mean total rescue medication use (number of puffs/day) and change from baseline in the bi-weekly mean total rescue medication use will be summarised.

3.4.3 Home lung function (morning and evening PEF)

Home PEF testing will be performed by the patient in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Patients should perform 3 successive peak flow maneuvers while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening maneuvers respectively.

Bi-weekly means and change from baseline in bi-weekly means will be calculated for morning PEF and evening PEF respectively.

3.4.4 Nights with awakening due to asthma

Night time awakenings due to asthma symptoms and requiring rescue medication use will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response, as well as the follow-up question whether he/she used rescue medication upon awakening during the night.

The bi-weekly proportion of nights with nocturnal awakenings due to asthma symptoms and requiring rescue medication use out of the nights with non-missing night time awakening data and the corresponding change from baseline for each post-randomisation period will be calculated.

3.4.5 Asthma Control Questionnaire (ACQ-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 short-acting β2 agonist use), omitting the FEV_1 measurement from the full version of ACQ.

Patients are asked to recall the status of their asthma during the previous week and respond to the symptom and bronchodilator use questions of the ACQ-6, on a 7-point scale. The ACQ-6 questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the mean of the responses from all the items in the questionnaire. If response to any of the 6 questions is missing, the ACQ-6 score will be missing.

The questionnaire will be completed by the patients using the ePRO device every 4 weeks until Week 8 and then every 8 weeks throughout the 48-week treatment period.

The outcome variable for ACQ-6 will be the change in mean score from baseline to each of the post-randomisation time points.

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorised according to the following thresholds (Juniper et al 2005), where end of treatment is the ACQ-6 score of Visit 17 (EOT visit at Week 48) and the baseline is defined in Section 3.1.1.

- ACQ-6 (End of treatment – baseline) ≤-0.5 → Improvement,
- -0.5 < ACQ-6 (End of treatment – baseline) <0.5 → No change,
- ACQ-6 (End of treatment – baseline) ≥0.5 → Deterioration.

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6 score, i.e., an ACQ-6 responder variable takes value 1 (for responder) if change from baseline to end of treatment in ACQ-6 ≤-0.5 and 0 (for non-responder) otherwise. A patient missing ACQ-6 score at EOT will be considered as a non-responder.

A sensitivity analysis for ACQ-6 responder will be conducted using hybrid last observation carried forward (LOCF) approach. That is, for patients who did not discontinue study treatment but had a missing EOT result, their last observation will be carried forward to determine their responder status. Patients who discontinued study treatment and had a missing EOT result will still be treated as the non-responder.

Furthermore, patients will be categorised according to their ACQ-6 score at the end of treatment using the following thresholds (Juniper et al 2006):

- ACQ-6 (End of treatment) ≤0.75 → Well controlled,
- 0.75< ACQ-6 (End of treatment) <1.5 → Partly controlled,
- ACQ-6 (End of treatment) ≥1.5 → Not well controlled.

3.4.6 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health-related quality of life of patients with airway diseases. The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment.

The change from baseline to each post-randomisation period will be used as outcome variable. Change in the 3 domain scores from baseline to each of post-randomisation periods will be calculated separately.

A decrease of 4 units in the SGRQ total score compared to baseline has been established as the criterion for minimal meaningful improvement. SGRQ responders will be those with a SGRQ total score ≥4 unit decrease compared to baseline, i.e., SGRQ (End of treatment - baseline) ≤ -4.

The SGRQ responder status will be evaluated in the same manner as for ACQ-6 responder status. A patient missing total score at EOT will be considered as a non-responder. A sensitivity analysis will also be conducted using hybrid LOCF approach.

3.5 Healthcare resource utilisation (HRU)

Broad-based health care utilisation asthma related event information will be collected by the Investigator/authorised delegate at each visit (as shown in Tables 1 and 2 in CSP) and recorded in the appropriate eCRF pages.

At Visit 1 HRU information will be collected with a 1 year recall period. Subsequent visits will collect HRU information with a recall period of 'since last visit'.

Note: Cases of hospitalisation also must be reported as SAEs (see CSP Section 6.2 and 6.4).

Following are the resource categories utilised for each patient. The number and percentage of patients who had the following HRU will be presented by categories of healthcare utilised.

- Ambulance transport
- Hospitalisation, intensive care (days in intensive care)
- Hospitalisation, general care (days in general care)
- Emergency room visit
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician

- Home visit, other health care
- Telephone call to physician
- Telephone call to nurse
- Telephone contact with other physician/health care provider
- Advanced pulmonary function test

3.6 Safety outcome variables

The following safety data will be collected: reported AEs (including SAEs), haematology, clinical chemistry, urinalysis, 12-lead ECG and vital signs.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements. For lab assessment summary by visit, the data will be mapped to scheduled visits as described in Section 3.1.3.

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

No safety data will be imputed. The handling rule of partial/missing dates for AEs, prior/concomitant medications and respiratory disease history is detailed in Appendix 8.2.

3.6.1 Adverse events (AEs)

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.

For analysis, AEs will be categorised according to their onset date into the following study periods:

- AEs in the on-study period are defined as those with onset date between the date of first dose of study treatment and the date of study completion or withdrawal from study, inclusive.

- AEs in the on-treatment period are defined as those with onset date between the date of first dose of study treatment and the date of scheduled EOT visit or IPD visit (for those patients who prematurely discontinue study treatment), inclusive. In the event that the EOT or IPD visit is completed beyond the protocol-defined visit window, AE with onset date after the date of last dose of study treatment + 8 weeks + 7 days will be excluded from the on-treatment period and instead assigned to the post-treatment period.

- AEs in the post-treatment period are defined as those with onset date in the on-study period but after the on-treatment period defined above.

For instances where a patient attends the follow-up visit without an earlier IPD visit or EOT visit, AEs occurring on or before the date of last dose of study treatment +8 weeks will be assigned to the on-treatment period, while AEs with onset date after this time will be assigned to the post-treatment period.

If an AE has a completely missing onset date then unless the stop date of the AE indicates otherwise, this AE will be considered an on-treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE.

3.6.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the timepoints detailed in the CSP, and will be assessed in a central laboratory. The laboratory parameters outlined in Section 5.2.4, Table 3 of the CSP will be collected.

In table summaries, listings and figures, laboratory results and normal ranges will be presented in the International System (SI) unit. Blood eosinophil counts, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and Gamma glutamyl transferase (GGT) will be presented in both SI and conventional units in summaries and listings.

Changes in haematology and clinical chemistry variables between baseline and each post-baseline timepoint assessment will be calculated. The change from baseline is defined as in Section 3.1.2. There will be no imputation for missing values. For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged. Shift table summaries of white blood cell by common terminology criteria for adverse events (CTCAE) grade for baseline to maximum grade post-baseline will also be considered.

Urinalysis data will be categorised as negative (or normal), trace, positive (+), or strongly positive (++, +++, or ++++) at each time point.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the last non-missing value prior to first dose of study treatment, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the post-treatment period.

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

Multiple = Value / ULN

That is, if the ALT value was 1.13356 ukat/L (ULN 0.56678) then the multiple would be 2.

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

- AST ≥ 3x ULN
- ALT ≥ 3x ULN
- TBL ≥ 2x ULN

3.6.3 Vital signs

Pre-dose vital signs (pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, and body temperature) will be obtained in accordance with schedule provided in the protocol.

Changes in vital signs variables between baseline and each post-baseline timepoint assessment will be calculated. Baseline is defined as the last non-missing value prior to the first dose of study treatment. The change from baseline is defined as in Section 3.1.2. There will be no imputation for missing values.

Absolute values will be compared to the company reference ranges in Table 6 and classified as low (below range), normal (within range or on limits) or high (above range). Absolute values falling outside the reference ranges will be flagged.

Table 6 Vital signs reference ranges

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

3.6.4 Local electrocardiograms (ECGs)

In all patients, the printouts of the ECG will be collected and signed, dated and stored at the study centre along with a signed and dated copy (if the printouts are not on archive-quality

paper). A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes.

The outcome of the overall evaluation is to be recorded as normal, borderline or abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.6.5 Physical examination

Physical examination results judged as a new clinically meaningful finding or a clinically meaningful aggravation of an existing finding by the Investigator is recorded in the eCRF. These are reported as AEs, and thus will not be separately summarised.

3.7 Pharmacokinetic (PK) variables

Blood samples (processed to serum) for PK assessments will be collected from all patients at baseline prior to first dose of IP administration, and at scheduled time points before IP administrations during the treatment period, according to the CSP schedule of assessments.

Samples for determination of benralizumab concentration in serum will be analysed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Following AZ standard process, bioanalytical lab will analyse PK samples only for patients receiving benralizumab.

Due to the limited sampling schedule, only serum trough concentration data will be available (for the benralizumab group only); no other PK parameters will be derived for any analysis within the scope of this SAP.

3.8 Immunogenicity variables

The ADA variables, such as ADA responses, will be generated and analysed as per the details in Appendix 8.3.

4. ANALYSIS METHODS

4.1 General principles

In general, the analysis of the primary and secondary efficacy endpoints will include all data captured during the 48-week double-blind treatment period, defined as the period from randomisation at visit 4 and the conclusion of visit 17 (Week 48), inclusive. This includes data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent/assent to study participation. In general, the analysis of safety endpoints will include all data captured during the on-study period, defined as the period from first dose of IP administration and the conclusion of the follow up visit (Week 56), inclusive.

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

Summary data will be presented in tabular format by treatment group. Categorical variables will be summarised by the number and percentage of patients in each category. Continuous variables will be summarised by descriptive statistics including number of observations (n), mean, standard deviation (SD), median, and range. All data will be listed.

All hypothesis testing will be reported using 2-sided tests. All reported p-values will be nominal (i.e., not multiplicity adjusted) and will be rounded to 4 decimal places. Statistical models will use stratification factors of region (China or non-China) and baseline blood eosinophil count (<300/µL or ≥300/µL), see Section 3.1.1 for details.

The absolute change from baseline is defined as in Section 3.1.2. Percent change from baseline is computed as [(*post-baseline value – baseline value*)*/baseline value*] × 100%. If either a post-baseline value or the baseline value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing. Additional details regarding the definition of baseline are provided in Section 3.1.1.

Demography and baseline characteristics will be summarised by treatment group for the FAS. In the event that there are major differences between the FAS and safety analysis set, these summaries will also be repeated for the safety analysis set.

Additional analyses and summaries to assess the impact of the COVID-19 pandemic on the study results are presented in Appendix 8.4.

4.1.1 Testing strategy to account for multiplicity considerations

A hierarchy testing strategy will be applied to the following two-sided hypotheses testing for the primary (annual asthma exacerbation rate) and 2 key secondary endpoints (the change in pre-bronchodilator FEV_1 and total asthma symptom score from baseline to Week 48, respectively) for patients with baseline blood eosinophil counts ≥300/µL.

Primary endpoint:

H01: annual asthma exacerbation rate ratio over 48 weeks (benralizumab/placebo) = 1

versus

H11: annual asthma exacerbation rate ratio over 48 weeks (benralizumab/placebo) ≠ 1

The direction of superiority of benralizumab is indicated by a rate ratio less than 1.

Key secondary endpoints:

H02: Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 48 (benralizumab minus placebo) = 0

Versus

H12: Difference in mean change from baseline in pre-bronchodilator FEV_1 at Week 48 (benralizumab minus placebo) ≠ 0

The direction of superiority of benralizumab is indicated by a difference in means greater than 0.

H03: Difference in mean change from baseline in bi-weekly mean total asthma symptom score at Week 48 (benralizumab minus placebo) = 0

versus

H13: Difference in mean change from baseline in bi-weekly mean total asthma symptom score at Week 48 (benralizumab minus placebo) ≠ 0

The direction of superiority of benralizumab is indicated by a difference in means less than 0.

The overall type 1 error rate, will be strongly controlled at the 2-sided 5% significance level across the primary and key secondary endpoints. This testing strategy will be according to the following gatekeeping procedure:

Step 1: Perform the test of annual asthma exacerbation rate (H01 vs. H11) at the 2-sided 5% significance level. If the p-value is less than 0.05, then proceed to Step 2; otherwise, null hypothesis H01 is not rejected.

Step 2: Test the 2 key secondary endpoints simultaneously at the overall 2-sided 5% significance level using a Holm Procedure (Holm 1979). Let smaller p-value and larger p-value denote the ordered unadjusted p-values from these 2 endpoints.

Step 2a: If the smaller p-value is less than 0.025, then reject the corresponding null hypothesis and continue to *Step 2b*; otherwise stop and both null hypotheses of the 2 key secondary endpoints (H02 and H03) are not rejected.

Step 2b: If the larger p-value is less than 0.05, then reject the corresponding null hypothesis (i.e., both null hypotheses H02 and H03 are rejected); otherwise, the corresponding null hypothesis is not rejected (i.e., only the null hypothesis corresponding to the smaller p-value is rejected).

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 categories: those who were enrolled, and those who were not randomised (and reason). The number and percentage of patients within each treatment group will be presented by the following categories: randomised, received study treatment, did not receive study treatment (and reason), completed study treatment, discontinued study treatment (and reason), completed study treatment but withdrawn from study, discontinued study treatment but completed study, discontinued study treatment and withdrawn from study, completed study, and withdrawn from study (and reason).

The number of patients randomised by country/region and centre will be summarised by treatment group using the FAS.

Kaplan-Meier plots will be produced summarising separately the time (in weeks) to study treatment discontinuation and to premature study withdrawal.

- Time to study treatment discontinuation = [date of last dose of study treatment - date of first dose of study treatment] + 1. Patients who did not prematurely discontinue study treatment will be censored at the date of last dose of study treatment.

- Time to premature study withdrawal = [date of study withdrawal – date of randomisation] + 1. Patients who did not prematurely withdraw from study will be censored at the date of study completion.

4.2.2 Demography data and patient characteristics

Demography data such as age, gender, race, and ethnicity will be summarised by treatment group for all patients in the FAS and for patients in the FAS with baseline blood eosinophil count <300/μL and baseline blood eosinophil count ≥300/μL.

Age will be derived from (date of informed consent - date of birth + 1), rounded down to the nearest integer (in years). For patients in countries where partial date of birth is recorded, the date of birth will be imputed following the below rule and then used in the age derivation.

- For the date of birth missing the day, the missing day will be set to the first day of the month of birth.

- For the date of birth missing both the day and month, the date will be set to July 1st of the year of birth.

Various baseline characteristics will also be summarised by treatment group using the FAS. These include smoking status, medical and surgical histories, FEV_1 at baseline, and respiratory disease characteristics (including asthma duration, age at asthma diagnosis, the number of exacerbations in the previous 12 months, the number of exacerbations during

background ICS/LABA treatment in the previous 12 months, and the number of exacerbations resulting in hospitalisation in the previous 12 months).

The following baseline data will be summarised for all patients in the FAS and repeated for patients in the FAS with baseline blood eosinophil count <300/μL and baseline blood eosinophil count ≥300/μL:

- Patient characteristics (weight, height, body mass index (BMI), and blood eosinophil count). Note: BMI will be calculated as: BMI (kg/m^2) = Weight (kg) / [Height (m)] ^{2}.
- Pre-bronchodilator lung function data (FEV_1 [L], FEV_1 [% predicted normal (PN)], FVC [L], FVC [% PN], FEV_1/FVC [%], FEF 25-75% [L/S]).
- Reversibility.
- Home lung function (morning and evening PEF)
- ACQ-6 score and total asthma symptom score
- Respiratory disease characteristics

Medical and surgical histories will be summarised by MedDRA Preferred Term (PT) within System Organ Class (SOC).

4.2.3 Prior and concomitant medications

The number and percentage of patients taking maintenance asthma medications at baseline, including ICS/LABA fixed dose combinations, will be summarised. For those patients taking ICS with or without OCS at baseline, the converted dose will be summarised for ICS and OCS. The number and percentage of patients taking at least one maintenance asthma medication at baseline in addition to ICS/LABA will be displayed. The total daily ICS dose (converted) at baseline will be further classified as medium dose or high dose according to Appendix E of the CSP. The number of patients taking maintenance ICS at baseline will be summarised in a separate table by ATC classification code and preferred term, with total daily dose (non-converted) at baseline summarised for each preferred term. A similar table will be produced to summarise total daily dose of maintenance OCS at baseline.

The number and percentage of patients who take prior medications, those who take allowed concomitant medications during the on-treatment period and those who take disallowed concomitant medications during the on-treatment period, will be separately presented by treatment group. Concomitant medication during the post-treatment period will only be listed. Disallowed medications are defined as prohibited/restricted medications according to Appendix F of the CSP, which will be identified following a physician review prior to database lock. Prior and concomitant medications will be classified according to WHO Drug Dictionary. The summary tables will present data by preferred term within ATC code.

Total OCS dose (converted) and total number of OCS treatment days associated with asthma exacerbations during the 48-week treatment period will be summarised descriptively by treatment group for patients with baseline blood eosinophil count ≥300/μL as well as for patients with baseline blood eosinophil count <300/μL, from the FAS.

4.2.4 Study Treatments

4.2.4.1 Exposure

Exposure to IP will be calculated in days as:

Date of last dose of IP – date of first dose of IP + 1;

and will be summarised descriptively by treatment group using the safety analysis set.

4.2.4.2 Compliance

Study treatment compliance will be summarised descriptively for all patients, patients with baseline blood eosinophil count <300/μL and ≥300/μL in the FAS respectively and will be calculated as:

(Total number of IP doses administered / total number of IP doses expected) x 100%.

For patients who discontinue IP early, the number of expected dosing occasions will be calculated as the number of dosing visits up to and including the last available dosing visit for that patient.

4.2.5 Primary outcome variable

4.2.5.1 Primary analysis

The primary efficacy variable is the annual asthma exacerbation rate, and the primary analysis is to compare the annual asthma exacerbation rate of benralizumab group with placebo group in patients in the FAS with baseline blood eosinophil counts ≥300/μL.

The primary analysis will include all data captured during the 48-week treatment period regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence. The details regarding the estimand for the primary endpoint are specified in Appendix 8.6.

Annual exacerbation rate in the benralizumab group will be compared to annual exacerbation rate in the placebo group using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by a patient over the 48-week treatment period. The model will include covariates of treatment group, region (China/Non-China), number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no). The logarithm of the follow-up time (as defined in Section 3.2) will be used as an offset variable in the model to adjust for patients having different exposure times during which the events occur.

This negative binomial model will be used to perform the hypothesis testing as specified in Section 4.1.1. The estimated treatment effect (i.e., the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the annual exacerbation rate (both crude and model-estimated rates) and the corresponding 95% CI (for model-estimated rates only) within each treatment group and the absolute difference between treatment groups with the corresponding 95% CI will be presented. The model-estimated annual exacerbation rate in each treatment group will be estimated via marginal standardisation method (Bartlett, 2018).

4.2.5.2 Supportive and sensitivity analysis

The annual exacerbation rate will also be summarised and analysed in patients with baseline blood eosinophil count <300/µL, and also by baseline blood eosinophil count category (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL), and by cumulative baseline blood eosinophil count category (≥150/µL, ≥200/µL, ≥250/µL, ≥300/µL, ≥350/µL, ≥400/µL, ≥450/µL, <150/µL, <200/µL, <250/µL, <300/µL, <350/µL, <400/µL, <450/µL). Baseline blood eosinophil count used for classification is derived per Section 3.1.1.

The individual exacerbation criteria (ER/UC visit due to asthma that required systemic corticosteroids, hospitalisation due to asthma, or use of systemic corticosteroids) will also be summarised descriptively as supportive analysis.

Asthma exacerbation summary statistics will be presented based on the FAS by treatment group for patients with baseline blood eosinophil counts ≥300/µL and <300/µL.

On-treatment annual exacerbation rates (using only exacerbations occurring during the on-treatment period) will be calculated similarly as the primary analysis for patients with baseline blood eosinophil counts ≥300/µL as a supportive analysis. The on-treatment period is defined in Section 3.2.

A sensitivity analysis will be conducted using a similar model as for the primary analysis, in which the logarithm of the time at risk will be used as the offset instead of the follow-up time, to adjust for patients having different times at risk for exacerbation. To calculate the time at risk, days during the exacerbations and the subsequent 7 days following an exacerbation in which a new exacerbation cannot occur, will be subtracted from the follow-up time (as defined in Section 3.2). For example, if a patient has only two exacerbations which lasts 4 days and 5 days respectively, then the time at risk = the follow-up time – 23 days.

Additional subgroup analyses for the annual asthma exacerbation rate are outlined in Section 4.2.5.3. Additional sensitivity analyses to assess the robustness of the primary analysis results to missing data are outlined in Appendix 8.1.

4.2.5.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses will be performed in patients in FAS with baseline blood eosinophil count ≥300/µL for the following factors: maintenance OCS use at baseline (yes,

no), maintenance ICS dose at baseline (medium, high), gender (male, female), age group (≥18 - <65, ≥65 years), region (China, Non-China), country (China, South Korea, Philippines), baseline BMI (≤30, >30 kg/m^2), the number of exacerbations in the previous year (2, ≥3 exacerbations), the number of exacerbations during background medium-high ICS/LABA treatment in the previous year (≤2, ≥3 exacerbations), prior treatment with Xolair (yes, no), and nasal polyps (yes, no).

For each of the subgroup factors in turn, a separate negative binomial regression model will be fitted using the similar model as for the primary analysis (defined in Section 4.2.5.1), with additional covariates for the subgroup main effect and the treatment by subgroup interaction. Similar output will be presented for each subgroup as for the primary analysis.

It is important to note that the study has not been designed or powered to assess efficacy within any of these pre-defined subgroups, and as such these analyses are considered as exploratory (no multiplicity control).

The standardised effect plot will be produced for subgroups defined above, displaying the estimated effects for each subgroup category along with reference lines for what would be expected for the most extreme observations by chance.

A LOESS plot will be produced for baseline blood eosinophil count and the number of exacerbations in the previous year to assess the efficacy consistency across the continuum level.

4.2.6 Secondary efficacy outcome variables

All the secondary efficacy endpoints will be analysed in patients with baseline blood eosinophil counts ≥300/μL and <300/μL, with formal statistical analyses conducted in the baseline blood eosinophil count ≥300/μL group. For the multiplicity protected key secondary endpoints (pre-bronchodilator FEV_1 and total asthma symptom score), additional formal statistical analyses will be conducted in the baseline blood eosinophil count <300/μL group and by further baseline eosinophil count categories.

4.2.6.1 Proportion of patients with ≥1 asthma exacerbation

The proportion of patients with ≥1 asthma exacerbation during the 48-week treatment period will be addressed as a supportive variable to the primary objective for patients with baseline blood eosinophil count ≥300/μL. The proportion in benralizumab group will be compared with the proportion in the placebo group using a Cochran–Mantel–Haenszel test controlling for region (China/Non-China), number of exacerbations in the previous year (2, ≥3 exacerbations), and the use of maintenance oral corticosteroids (yes/no).

The results of the analyses will be presented using the odds ratio, together with associated 95% CI and 2-sided p-value for benralizumab versus placebo. The number and percentage of patients with ≥1 asthma exacerbation will also be summarised by treatment group.

4.2.6.2 Time to first asthma exacerbation

Time to first asthma exacerbation will be analysed as another supportive efficacy variable to the primary objective to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment group, region (China/Non-China), number of exacerbations in the previous year, and the use of maintenance oral corticosteroids (yes/no).

Results of these analyses will be summarised via the hazard ratio, with corresponding 95% CI and p-value for patients with baseline blood eosinophil count ≥300/μL.

Time to first asthma exacerbation will be displayed graphically using a Kaplan-Meier plot, separately for patients with baseline blood eosinophil count ≥300/μL and <300/μL.

4.2.6.3 Pre-bronchodilator FEV_1 measured at the study centre

Change from baseline in pre-bronchodilator FEV_1 at Week 48, in the baseline blood eosinophil count ≥300/μL group, is a multiplicity protected key secondary endpoint (Section 4.1.1). The details regarding the estimand for the key secondary endpoint are specified in Appendix 8.6.

Change from baseline in pre-bronchodilator FEV_1 at Week 48 will be compared between the benralizumab group and the placebo group using a mixed-effects model for repeated measures (MMRM) analysis on patients with a baseline pre-bronchodilator FEV_1 assessment and at least 1 post-baseline pre-bronchodilator FEV_1 assessment.

The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at each post-baseline protocol-specified visit (up to and including the EOT visit). Treatment group will be fitted as the explanatory variable, region (China/Non-China), the use of maintenance oral corticosteroids (yes/no), visit, and treatment*visit interaction as fixed effects factors and baseline pre-bronchodilator FEV_1 as a continuous covariate. The variance-covariance matrix will be assumed to be "unstructured". If the model does not converge then the "Toeplitz", "first-order autoregressive", "compound symmetric", "variance components" variance-covariance matrix will be used instead sequentially. The model is:

*Change from baseline in pre-bronchodilator FEV_1 = Treatment group + baseline pre-bronchodilator FEV_1 + region (China/Non-China) + use of maintenance oral corticosteroids (yes/no) + visit + treatment*visit*

Results will be presented in terms of least square means (LSMEANS), treatment group differences in LSMEANS, corresponding 95% CIs and p-values. The OBSMARGINS option in LSMEANS statement in SAS will be used to specify different weighting scheme for computing the LSMEANS.

The above analysis will be repeated for the following as supportive analysis:

- Baseline blood eosinophil count <300/μL

- Cumulative baseline blood eosinophil count categories (≥150/µL, ≥200/µL, ≥250/µL, ≥300/µL, ≥350/µL, ≥400/µL, ≥450/µL, <150/µL, <200/µL, <250/µL, <300/µL, <350/µL, <400/µL, <450/µL)

- On-treatment pre-bronchodilator FEV_1 in patients with baseline blood eosinophil count ≥300/µL (using the same definition of on-treatment period as described in Section 3.2).

Additional sensitivity analyses to assess the robustness of the repeated measures analysis to missing data are outlined in Appendix 8.1.

A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect, and the treatment by subgroup interaction will be conducted for the following factors based on the FAS:

- Baseline blood eosinophil count categories (<150/µL, ≥150/µL-<300/µL, ⩾ 300/µL-<450/µL, ≥450/µL),

- The number of exacerbations in the previous year (2, ≥3 exacerbations),

- Maintenance ICS dose at baseline (medium, high).

A LOESS plot will be produced for baseline blood eosinophil count and the number of exacerbations in the previous year to assess the efficacy consistency across the continuum level.

4.2.6.4 Annual rate of asthma exacerbations that are associated with an emergency room/urgent care visit or a hospitalisation

Annual rate of asthma exacerbations that are associated with an ER/UC visit or a hospitalisation will be analysed using a similar negative binomial model as outlined for the primary efficacy variable in Section 4.2.5.1. The response variable in the model will be the number of asthma exacerbations associated with an ER/UC visit or a hospitalisation over the 48-week treatment period. The model will include covariates of treatment group, region (China/Non-China), category variable (yes/no) of any exacerbations associated with an ER/UC visit or a hospitalisation in the year before the study, and the use of maintenance oral corticosteroids (yes/no). The logarithm of the follow-up time will be used as an offset variable in the model.

Annual rate of asthma exacerbations that are associated with a hospitalisation only or associated with an ER/UC visit only will be analysed separately using a similar negative binomial model as outlined above.

In the event of model convergence issues (possibly due to the small number of events), the negative binomial model will be re-run, after dropping the covariates sequentially in the following order, until convergence: region (China/Non-China), the use of maintenance oral corticosteroids (yes/no), category variable (yes/no) of events in the year before the study.

4.2.6.5 Time to first asthma exacerbation that is associated with an emergency room/urgent care visit or a hospitalisation

Time to first asthma exacerbation associated with an ER/UC visit or a hospitalisation will be analysed to explore the extent to which treatment with benralizumab delays the time to first exacerbation compared with placebo. A Cox proportional hazard model will be fitted to data with the covariates of treatment group, region (China/Non-China), category variable (yes/no) of any exacerbations associated with an ER/UC visit or a hospitalisation in the previous year, and the use of maintenance oral corticosteroids (yes/no). Results of these analyses will be summarised via the hazard ratio with corresponding 95% CI and p-value for patients with baseline blood eosinophil count ≥300/µL.

In the event of model convergence issues (possibly due to the small number of events), the Cox proportional hazard model will be re-run until convergence, by adjusting for the same covariates as the negative binomial model for exacerbations associated with an ER/UC visit or a hospitalisation (see Section 4.2.6.4)

Time to first asthma exacerbation associated with an ER/UC visit or a hospitalisation will be displayed graphically using a Kaplan-Meier plot for patients with baseline blood eosinophil count ≥300/µL.

4.2.6.6 Blood eosinophils

The baseline blood eosinophil count used to inform primary and secondary efficacy analysis is defined in Section 3.1.1.

An important marker of the biological activity of benralizumab is the depletion in eosinophils in the peripheral blood. Blood eosinophil count is included in the protocol as one of the secondary objectives to address the expected pharmacodynamic effect of benralizumab. Absolute blood eosinophil counts along with their absolute changes from baseline, and percentage changes from baseline will be summarised using descriptive statistics by treatment group and visit using conventional units (cells/µL). Baseline is defined as the last non-missing value prior to the first dose of study treatment. Percent change from baseline in blood eosinophil counts will be compared between the benralizumab group and the placebo group using a repeated measures analysis, as defined for analysis of pre-bronchodilator FEV_1 in Section 4.2.6.3. Results will be presented by baseline blood eosinophil count (<300/µL and ≥300/µL) as defined in Section 3.1.1.

A shift table will be produced for the placebo group to display change from baseline for blood eosinophil count categories (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL). The shift table will present the number and percent of patients at baseline and each post-baseline visit for each category, with baseline defined as the last non-missing value prior to the first dose of study treatment.

4.2.7 Patient reported outcome variables

4.2.7.1 Asthma Symptom Score

Change from baseline at Week 48 in total asthma symptom score in the baseline blood eosinophil count ≥300/μL group is a multiplicity protected key secondary endpoint. The details regarding the estimand for the key secondary endpoint are specified in Appendix 8.6.

Change from baseline in total asthma symptom score, daytime score, and night-time score will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, separately for patients with baseline blood eosinophil count ≥300/μL and <300/μL. Each bi-weekly period of the 48 weeks used for bi-weekly mean calculation will replace visit in the model specification as for pre-bronchodilator FEV_1.

This analysis will be repeated for total asthma symptom score for the following as supportive analysis:

- Cumulative baseline blood eosinophil count categories (≥150/μL, ≥200/μL, ≥250/μL, ≥300/μL, ≥350/μL, ≥400/μL, ≥450/μL, <150/μL, <200/μL, <250/μL, <300/μL, <350/μL, <400/μL, <450/μL),
- On-treatment total asthma symptom score in patients with baseline blood eosinophil count ≥300/μL (using the same definition of on-treatment period as described in Section 3.2).

Additional sensitivity analyses to assess the robustness of the repeated measures analysis to missing data are outlined in Appendix 8.1.

A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect and the treatment by subgroup interaction, will be conducted for total asthma symptom score for the following factors, based on the FAS:

- Baseline blood eosinophil count categories (<150/μL, ≥150/μL-<300/μL, ≥300/μL-<450/μL, ≥450/μL),
- The number of exacerbations in the previous year (2, ≥3 exacerbations),
- Maintenance ICS dose at baseline (medium, high).

A LOESS plot will be produced for baseline blood eosinophil count and the number of exacerbations in the previous year to assess the efficacy consistency across the continuum level.

The proportion and corresponding 95% CI of asthma symptom-free days up to and including Week 48 will also be summarised for patients with baseline blood eosinophil count ≥300/μL.

4.2.7.2 Rescue medication use

Change from baseline in bi-weekly mean total rescue medication use (number of puffs/day) will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, for patients with baseline blood eosinophil count ≥300/μL. Descriptive statistics will be provided separately for patients with baseline blood eosinophil count ≥300/μL and <300/μL.

4.2.7.3 Home lung function (morning and evening PEF)

Change from baseline in bi-weekly mean morning and evening PEF will each be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, for patients with baseline blood eosinophil count ≥300/μL. Descriptive statistics will be provided separately for patients with baseline blood eosinophil count ≥300/μL and <300/μL.

4.2.7.4 Nights with awakenings due to asthma

Change from baseline in the bi-weekly proportion of nights with nocturnal awakenings due to asthma symptoms and requiring rescue medication will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, for patients with baseline blood eosinophil count ≥300/μL. Descriptive statistics will be provided separately for patients with baseline blood eosinophil count ≥300/μL and <300/μL.

4.2.7.5 Asthma Control Questionnaire (ACQ-6 score)

Change from baseline in ACQ-6 score will be summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, for patients with baseline blood eosinophil count ≥300/μL.

This analysis will be repeated for the following as supportive analysis:

- Baseline blood eosinophil count <300/μL
- Cumulative baseline blood eosinophil count categories (≥150/μL, ≥200/μL, ≥250/μL, ≥300/μL, ≥350/μL, ≥400/μL, ≥450/μL, <150/μL, <200/μL, <250/μL, <300/μL, <350/μL, <400/μL, <450/μL)

A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect and the treatment by subgroup interaction, will be conducted for the following factors, based on the FAS:

- Baseline blood eosinophil count categories (<150/μL, ≥150/μL-<300/μL, ≥300/μL-<450/μL, ≥450/μL).

Asthma control responder status based on ACQ-6 at EOT (Week 48), as defined in Section 3.4.5, will be analysed using a logistic regression model with covariates of treatment group, region (China/Non-China), baseline ACQ-6 value, and the use of maintenance oral

corticosteroids (yes/no), for patients with baseline blood eosinophil count ≥300/µL. Patients with missing ACQ-6 score at Week 48 will be considered the non-responders. A sensitivity analysis will be conducted similarly, using hybrid LOCF approach as described in Section 3.4.5.

The number and percentage of patients achieving an improvement, no change, or deterioration, and the number and percentage of patients achieving ACQ-6 ≤0.75 (Well controlled), >0.75 - <1.5 (Partly controlled) and ≥1.5 (Not well controlled) at EOT (Week 48) as defined in Section 3.4.5 will be summarised by treatment group, separately for patients with baseline blood eosinophil count ≥300/µL and <300/µL. These summaries will also be repeated for patients in the FAS, by baseline blood eosinophil count categories (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/ µL) and by cumulative baseline blood eosinophil count categories (≥150/µL, ≥200/µL, ≥250/µL, ≥300/µL, ≥350/µL, ≥400/µL, ≥450/µL, <150/µL, <200/µL, <250/µL, <300/µL, <350/µL, <400/µL, <450/µL).

4.2.7.6 St. George's Respiratory Questionnaire (SGRQ)

Change from baseline in SGRQ total score and the 3 domain scores will be separately summarised and analysed using the same method, MMRM, as for pre-bronchodilator FEV_1 described in Section 4.2.6.3, for patients with baseline blood eosinophil count ≥300/µL.

This analysis will be repeated for the cumulative baseline blood eosinophil count categories (≥150/µL, ≥200/µL, ≥250/µL, ≥300/µL, ≥350/µL, ≥400/µL, ≥450/µL, <150/µL, <200/µL, <250/µL, <300/µL, <350/µL, <400/µL, <450/µL) as supportive analysis.

A subgroup analysis, using the same MMRM model defined above with additional terms for the subgroup main effect and the treatment by subgroup interaction, will be conducted for the baseline blood eosinophil count category (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL), based on the FAS.

SGRQ responder status, as defined in Section 3.4.6, will be analysed using a logistic regression model with covariates of treatment group, region (China/Non-China), baseline SGRQ value, and the use of maintenance oral corticosteroids (yes/no), for patients with baseline blood eosinophil count ≥300/µL. Patients with missing SGRQ total score at Week 48 will be considered the non-responders. A sensitivity analysis will be conducted similarly, using hybrid LOCF approach as described in Section 3.4.6.

4.2.8 Healthcare resource utilisation due to asthma

The number and percentage of patients with asthma specific resource utilisation (defined in Section 3.5) in the year before the study and over the 48-week treatment period will be presented by treatment group for patients with baseline blood eosinophil count ≥300/µL and <300/µL.

4.2.9 Additional analyses for primary and key secondary endpoints

Additional analyses for the primary and key secondary endpoints will be performed to assess the efficacy across the subgroup categories by baseline blood eosinophil count, the number of exacerbations in the previous year and maintenance ICS dose at baseline.

The following analyses will be conducted:

- Annual asthma exacerbation rate by baseline blood eosinophil count (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL).
- Annual asthma exacerbation rate by the number of exacerbations in the previous year (2, ≥3 exacerbations).
- Annual asthma exacerbation rate by maintenance ICS dose at baseline (medium, high).
- Change from baseline at Week 48 in pre-bronchodilator FEV_1 by baseline blood eosinophil count (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL).
- Change from baseline at Week 48 in pre-bronchodilator FEV_1 by the number of exacerbations in the previous year (2, ≥3 exacerbations).
- Change from baseline at Week 48 in pre-bronchodilator FEV_1 by maintenance ICS dose at baseline (medium, high).
- Change from baseline at Week 48 in total asthma symptom score by baseline blood eosinophil count (<150/µL, ≥150/µL-<300/µL, ≥300/µL-<450/µL, ≥450/µL).
- Change from baseline at Week 48 in total asthma symptom score by the number of exacerbations in the previous year (2, ≥3 exacerbations).
- Change from baseline at Week 48 in total asthma symptom score by maintenance ICS dose at baseline (medium, high).

It is important to note that the study has not been designed or powered to assess efficacy within any of these pre-defined subgroup categories, and as such these analyses are considered as exploratory (no multiplicity control).

Unlike the subgroup analysis as described in Sections 4.2.5.3, 4.2.6.3 and 4.2.7.1, a similar model as for the primary analysis (see details in Sections 4.2.5.1, 4.2.6.3 and 4.2.7.1) will be fitted for patients in each subgroup category separately. In order to ensure the MMRM model consistency across the subgroup categories for the same subgroup factor, the first variance-covariance matrix within the hierarchy which allow the MMRM to converge for all categories will be selected.

4.2.10 Safety outcome variables

All safety variables will be summarised using the safety analysis set and data presented according to actual treatment received.

4.2.10.1 Adverse events (AEs)

AEs will be summarised separately for the on-study, on-treatment, and post-treatment periods, as defined in Section 3.6.1. All AEs will be listed for each patient, regardless of treatment period. All summaries will be presented by treatment group.

An overall summary table will be produced showing the number and percentage of patients with at least one AE in each of the following categories: AEs, serious adverse events (SAEs), AEs with outcome of death, and AEs leading to discontinuation of IP (DAEs). This summary will also be repeated by baseline blood eosinophil count (<300/μL, ≥300/μL) for the on-study and on-treatment periods. 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).

AEs, AEs with outcome of death, SAEs and DAEs 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 one occurrence will be presented, i.e., for a patient multiple AE occurrences of the same PT will only be counted once. Presentations for AEs and SAEs by SOC and PT will also be repeated for baseline blood eosinophil count (<300/μL, ≥300/μL) for the on-study and on-treatment periods.

The rate of AEs per patient-years at risk, calculated as (number of patients reporting AE)/(total period with patients at risk of AE), will also be reported by treatment group for the on-study and on-treatment periods. The total period with patients at risk of AE for the on-study and on-treatment periods will be defined as the sum of the on-study and on-treatment period across all patients in the treatment group, respectively. Rates will be expressed in terms of events per 100 patient-years.

A summary of the most common (frequency of ≥3% in any treatment group) AEs will be presented by PT. AEs will be summarised by PT and maximum intensity. If a patient reports multiple AE occurrences of the same PT within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). AEs, SAEs and DAEs causally related to IP as assessed by the Investigator will be summarised by PT. The summary of related AEs and related SAEs will also be repeated for baseline blood eosinophil count (<300/μL, ≥300/μL) for the on-study and on-treatment periods.

AEs of injection site reactions (high level term of injection site reaction) and hypersensitivity (standardised MedDRA query of hypersensitivity based on the latest MedDRA version) will be summarised by PT. The summary of AEs of hypersensitivity will be repeated for baseline blood eosinophil count (<300/μL, ≥300/μL) for the on-study and on-treatment periods. The

hypersensitivity AEs causally related to IP as assessed by the Investigator will also be summarised by PT.

Separate listings of patients with AEs, AEs with outcome of death, SAEs, or DAEs will be presented.

Adjudicated events (major adverse cardiac events [MACE] and malignancies) will be summarised by treatment group and listed.

4.2.10.2 Laboratory data

All continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding change from baseline. All parameters will be summarised in SI units. Blood eosinophil counts, AST, ALT, ALP and GGT 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 and will include patients with both baseline and post-baseline data.

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 post-baseline values 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 elevations by maximum post-baseline ALT and AST will be presented. Total bilirubin will be presented in multiples of ULN (≤1.5, >1.5-2, >2 x ULN), and ALT and AST will be presented in multiples of ULN (≤1, >1-3, >3-5, >5-10, >10 x ULN).

Maximum post-baseline total bilirubin 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 total bilirubin against maximum post-baseline AST.

Data for patients with ALT or AST ≥3 x ULN, and total 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, total bilirubin, and GGT) over time will also be presented for this subset of patients.

For all patients who meet the biochemical criteria for confirmed Hy's law (see CSP Appendix C), a Patient Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these patients.

A summary of shifts from baseline to maximum post-baseline CTCAE grade will be produced using CTCAE version 4.03 (June 14, 2010) or above for White blood cell counts and its components. The summary of shifts from baseline to maximum grade post-baseline will be produced, with results categorised as no grade, grades 1 to 4. White blood cells tests included in these summaries are: neutrophils, lymphocytes, and leukocytes. These will be from the complete blood count reports and will be done by absolute count.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each parameter and will include patients with both baseline and post-baseline data.

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

4.2.10.3 Vital signs

Descriptive statistics for the absolute value at each visit and corresponding change from baseline for vital signs data will be presented for each treatment group. 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.

4.2.10.4 Local electrocardiograms (ECGs)

The Investigator's assessment of the 12-lead ECG (normal, borderline or abnormal) will be listed for all patients, detailing whether any abnormalities were clinically significant or not.

A shift table will be produced to display normal, abnormal – not clinically significant, abnormal – clinically significant and not done. For this purpose, borderline will be grouped with normal. The shift table will present baseline and last observation post-baseline.

4.2.11 Pharmacokinetic (PK) variables

Benralizumab serum concentrations will be summarised for the benralizumab group only using descriptive statistics by visit and will be listed.

Serum concentrations, that are below the LLOQ (<LLOQ) or if there are missing values, will be handled as follows:

- Where there are missing values, these will be set to missing in the analysis.
- At a time point where less than or equal to 50% of the values are <LLOQ, all values <LLOQ will be set to LLOQ/2, and all descriptive statistics will be calculated.

- At a time point where more than half of the values are <LLOQ, the mean, geometric mean, SD and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to <LLOQ.

- If all values are <LLOQ at a time point, no descriptive statistics will be calculated for that time point. Not Applicable (N/A) will be written in the field for SD and CV% and <LLOQ will be written in fields for the mean, geometric mean, minimum, median, and maximum.

The PK modelling is out of the scope of this SAP. Population PK model might be performed and described in a separate report.

4.2.12 Immunogenicity variables

ADA assessments will be conducted and analysed as per the details in Appendix 8.3.

4.2.13 China subpopulation analysis

China subpopulation analysis will be performed using the same methodology as for the overall study population. Region (China or non-China) will not be adjusted in the statistical models as for the overall study population, because all patients in the China subpopulation are from China (see Section 2.2 for the definition of China subpopulation).

The key efficacy analyses of the primary endpoint (annual asthma exacerbation rate), key secondary endpoints (pre-bronchodilator FEV_1, total asthma symptom score) and other selected secondary endpoints will be repeated for China subpopulation. In general, the sensitivity analyses will not be repeated for China subpopulation. All statistical analyses for China subpopulation will be considered exploratory. No adjustment for multiplicity will be made and so the multiple testing procedure as described in Section 4.1.1 will not be followed for China subpopulation analyses.

The patient disposition and selected baseline data will be summarised for China subpopulation. The key safety analyses as outlined in Section 4.2.10 will be repeated for China subpopulation. Selected PK and immunogenicity analyses will be repeated for China subpopulation as well.

5. INTERIM ANALYSES

No interim analysis planned for this study. The study will remain blinded until database lock.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The randomised patients analysis set has been defined in Section 2.1.2, but is not included as an analysis set in the protocol v5.0.

The protocol v5.0 specifies that "all efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomised IP at Visit 4 and the conclusion of End of Treatment visit". The double-blind treatment period definition is replaced in Section 4.1 by "the period from randomisation at visit 4 and the conclusion of visit 17 (Week 48), inclusive.".

The protocol v5.0 specifies that "ACQ-6 and SGRQ baseline will be the last observation prior to study drug administration". This is clarified in Section 3.1.1 that "the last non-missing measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints".

As specified in Section 8.5.2.1 of protocol v5.0, "number of exacerbations in the year before the study" is one of the covariates adjusted in the Cochran-Mantel-Haenszel test for the proportion of patients with ≥1 asthma exacerbation. This covariate is replaced by "number of exacerbations in the previous year (2, ≥3 exacerbations)" in Section 4.2.6.1.

The protocol v5.0 specifies that if the MMRM procedure does not converge with unstructured variance-covariance matrix, then a compound symmetric matrix will be used instead. This is clarified in Section 4.2.6.3 that if the model does not converge then the "Toeplitz", "first-order autoregressive", "compound symmetric", "variance components" variance-covariance matrix will be used instead sequentially.

The subgroup factors of "ICS dose at study enrolment (medium, high)", "age (<18, 18 - <65, and ≥65 years)", "BMI (<35, >35 kg/m^2)", and "the number of exacerbations during medium-high ICS/LABA treatment prior to study enrolment (2, >3 exacerbations)" are specified in the protocol v5.0, that are replaced in Section 4.2.5.3 by "maintenance ICS dose at baseline (medium, high)", "age group (≥18 - <65, ≥65 years)", "baseline BMI (≤30, >30 kg/m^2)" and "the number of exacerbations during background medium-high ICS/LABA treatment in the previous year (≤2, ≥3 exacerbations)". "Prior treatment with Xolair (yes, no)" has been included as a subgroup factor in Section 4.2.5.3, but is not included in protocol v5.0.

7. REFERENCES

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8. APPENDIX

8.1 Accounting for missing data

8.1.1 Accounting for missing data for primary endpoint (Annual asthma exacerbation rate)

In this study some patients dropping out of the study potentially leads to unobserved events. The amount of missing data is minimised as the patients are encouraged per the protocol to complete all subsequent study visits after they discontinue from randomised treatment.

This Appendix summarises how we will describe the pattern of and reasons for missing data from the study. It will also describe how we plan to account for missing data, including both the primary and sensitivity analyses to assess the robustness of the treatment effect under different underlying assumptions to account for missing data.

8.1.1.1 Missing data descriptions

Tabular summaries for the percentage of patients by the reason for discontinuation of randomised treatment as well as for withdrawal from the study will be presented by treatment to describe why patients discontinue from randomised treatment or withdraw from the study. The time to discontinuation of randomised treatment and withdrawal from the study will be presented using Kaplan Meier plots (overall and split by treatment related/not treatment related reason for discontinuation as defined in Table 7 and Table 8). Dependent on these outputs additional exploratory analyses may be produced as deemed necessary to further understand the pattern of missing data.

8.1.1.2 Primary analysis under the Missing at Random (MAR) assumption

The primary analysis allows for differences in outcomes over the entire study treatment period to reflect the effect of initially assigned randomised treatment as well as if subsequent treatments are taken. This primary analysis includes all data until patients withdraw from the study regardless of if they discontinue from randomised treatment. The primary analysis uses the negative binomial regression model with (logarithm of) the observation period as an offset term and assumes that missing data is missing at random (MAR) and is a direct likelihood approach (DL). No imputation will be conducted for the missing data.

8.1.1.3 Sensitivity analysis under the MAR and Dropout reason-based multiple imputation (DRMI) assumptions

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional sensitivity analyses will be performed using controlled multiple imputation method introduced in [1] and further developed at AstraZeneca [2, 3] which allows for different underlying assumptions to be used. As with the primary analysis, the sensitivity analyses includes all data until patients withdraw from the study regardless of if they discontinue from randomised treatment. Imputation will be conducted for the missing data.

For this method, an underlying negative binomial stochastic process for the rate of exacerbations is assumed and post study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal. This allows various assumptions about the missing data to be analysed by modifying the post-withdrawal model assumption.

The method involves first fitting the primary analysis, i.e., negative binomial regression model to the observed data and then imputing post-withdrawal counts by sampling from the below conditional negative binomial probability relating post-withdrawal counts and observed prior-withdrawal counts based on various assumptions:

$$\Pr\left(Y_{ij,2} = y_2 \middle| Y_{ij,1} = y_1\right) = \frac{\Gamma(\gamma+y_1+y_2)}{\Gamma(y_2+1)\Gamma(\gamma+y_1)} p_j^{y_2}\left(1-p_j\right)^{\gamma+y_1}. \qquad (1)$$

Here y_1 is number of counts before withdrawal from the study, y_2 is number of counts after withdrawal from the study, $1/\gamma$ is the dispersion parameter and which is assumed to be the same for different treatment arms, j denotes the treatment arm and i denotes the patient identifier. Furthermore

$$p_j = \frac{p_{j,2}-p_{j,1}p_{j,2}}{1-p_{j,1}p_{j,2}}, \qquad (2)$$

where $p_{j,1}$ is the negative binomial distribution rate parameter (i.e., probability of an event occurs) before withdrawal from the study, and $p_{j,2}$ is the rate parameter after withdrawal from the study as determined based on various assumptions. $p_{j,1}$, $p_{j,2}$ and γ will be generated based on the use of Markov Chain Monte Carlo (MCMC) method.

The imputed number of exacerbations that would have been seen is then combined with the observed exacerbations and data is analysed using the primary analysis methodology (DL). This analysis is repeated 100 times and the results combined using Rubin's formulae [6, 7].

The default assumptions that will be used to impute the missing data for who withdraw early from the study are as follows:

a) MAR: Missing counts in each arm are imputed assuming the expected event rate within that arm.

b) Dropout Reason-based Multiple Imputation (DRMI): Missing counts will be imputed differently depending on the reason for dropout; missing counts for patients in the benralizumab arms who dropped out for a treatment related reason are imputed based on the expected event rate in the placebo arm, whereas the remaining patients who have dropped out are imputed assuming MAR.

Some reasons for withdrawal are clearer to determine as treatment related ('*Adverse Event', 'Death', 'Development of study-specific withdrawal criteria', 'protocol deviation'*). Other reasons are less clear (*'Lost to follow up', 'Failure to meet randomisation criteria',*

'*Withdrawal by subject*' and '*Other*'); a review of each patient who withdraws from the study will therefore be carried out prior to unblinding the study. The review will include assessment of the reason for discontinuation of randomised treatment for those patients who discontinued randomised treatment and then withdrew from the study and the free text reason for when the reason of study withdrawal or discontinuation of randomised treatment is *'Failure to meet randomisation criteria', 'Withdrawal by subject' or 'Other'*. Based on this review, the assumptions for DRMI as described in b) and Table 7 will be determined. A list of these patients and the assumptions made under DRMI will be documented prior to unblinding of the study.

A summary of reasons for patients withdrawing from study and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI is given in Table 7.

Table 7 Summary of reasons for patients withdrawal from study used to calculate the imputation exacerbation rate in the benralizumab arm under MAR and DRMI

Reason for withdrawal[a]	MAR	DRMI
Adverse event	Benralizumab	Placebo
Development of study-specific withdrawal criteria	Benralizumab	Placebo
Death[b]	Benralizumab	Placebo
Protocol deviation	Benralizumab	Placebo
Failure to meet randomisation criteria	Benralizumab	Based on review prior to study unblinding
Lost to follow up	Benralizumab	Based on review prior to study unblinding
Withdrawal by subject	Benralizumab	Based on review prior to study unblinding
Other	Benralizumab	Based on review prior to study unblinding

Note all patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate.
[a] Reasons as recorded in eCRF DS form
[b] Although death is not the source of missing data, imputation will still be performed to assess the impact of no data after death (if any death occurs).

Together with the primary analysis, the sensitivity analyses are considered to cover the range from realistic to plausible worst case assumptions about missing data. The MAR multiple imputation approach is expected to correspond closely to the primary analysis, and is included to allow for comparisons with Missing Not At Random assumptions (specifically DRMI) using the same multiple imputation methodology.

The DRMI approach was selected as the most conservative approach based on the fact that placebo patients are receiving standard of care and are not expected to change to a substantially more effective treatment after withdrawing from study or study treatment. For

patients receiving benralizumab who withdraw from the study due to treatment related reasons, it is assumed that at worst they would be on the standard of care treatment, i.e., the placebo arm. For patients receiving benralizumab who withdraw from the study due to non-treatment related reasons (based on blinded review), it seems reasonable to assume they would be similar to those patients who complete treatment in the benralizumab arm.

8.1.1.4 On-Treatment Analyses

In addition to the primary and sensitivity analyses described previously, 2 alternative analyses will be conducted using only the initial randomised treatment data:

- On-treatment analyses without imputation (supportive analysis): This will be estimated using the primary analysis method (DL) but including only data from patients whilst being on the initial randomised treatment.

- On-treatment analyses with imputation (sensitivity analysis): This will be estimated using the controlled multiple imputation approaches (MAR and DRMI) including only data from patients whilst being on the initial randomised treatment.

Therefore the primary analyses and sensitivity analyses described previously in Appendix 8.1.1.2 and 8.1.1.3 will be repeated including only data from patients whilst being on the initial randomised treatment, i.e., excluding data once patients discontinue from randomised treatment.

A summary of reasons for patients discontinuing from randomised treatment and the corresponding treatment arm used to calculate the imputation exacerbation rate under MAR and DRMI are given in Table 8. Again, as for patients who discontinue from randomised treatment, a review of the reason for each patient discontinued randomised treatment will be carried out prior to unblinding the study. Based on this review, the assumptions for DRMI as described in Table 8 will be determined. A list of these patients and the assumptions made under DRMI will be documented prior to unblinding of the study.

Table 8 Summary of reasons for discontinuation of randomised treatment used to calculate the imputation exacerbation rate in the benralizumab arm under MAR and DRMI

Reason for discontinuation of randomised treatment[a]	MAR	DRMI
Adverse event	Benralizumab	Placebo
Development of study specific discontinuation criteria	Benralizumab	Placebo
Severe non-compliance to protocol	Benralizumab	Placebo
Subject lost to follow up	Benralizumab	Based on review prior to study unblinding
Subject decision	Benralizumab	Based on review prior to study unblinding

Table 8 Summary of reasons for discontinuation of randomised treatment used to calculate the imputation exacerbation rate in the benralizumab arm under MAR and DRMI

Reason for discontinuation of randomised treatment[a]	MAR	DRMI
Other	Benralizumab	Based on review prior to study unblinding

Note all patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate
[a] Reasons as recorded in eCRF DOSDISC form.

Using on-treatment data is easier to interpret as it is not impacted by any subsequent pattern of alternative treatments once patients discontinue from randomised treatment. The analyses under MAR assumption will estimate what would have been the outcome if all patients had stayed on the randomised treatment. The analyses under the DRMI allow for alternative assumptions to be made based on reasons for discontinuation.

8.1.1.5 Overall summary of analyses to account for missing data

A summary of the different analyses of the primary endpoint to be carried out under different assumptions are described in Table 9.

Table 9 Summary of the different analyses of the primary endpoint to be carried out under different assumptions

	Intent-To-Treat Analyses			On-Treatment Analyses		
	DL	**MI-MAR**	**MI-DRMI**	**DL**	**MI-MAR**	**MI-DRMI**
Data	**On-treatment + post-discontinuation of randomised treatment until study completion/withdrawal**			**On-treatment**		
Exacerbation rate for imputation in Benralizumab arm[b]	No imputation[a]	Benralizumab rate assumed for all reasons for study withdrawal	Placebo rate assumed for reasons of "Adverse event", "Death", "Development of study-specific withdrawal criteria" and "Protocol deviation", otherwise based on review prior to study unblinding	No imputation[a]	Benralizumab rate assumed for all reasons for discontinuation of randomised treatment	Placebo rate assumed for reasons of "Adverse event", "Development of study-specific discontinuation criteria" and "Severe non-compliance to protocol", otherwise based on review prior to study unblinding
Default definition for $\boldsymbol{p_{j,1}}$ and $\boldsymbol{p_{j,2}}$ based on formula (2)[c].		$p_{j,2} = p_{j,1}$ For all treatment arms j=B and P	$p_{\mathrm{B},2} = p_{\mathrm{P},1}$ $p_{\mathrm{P},2} = p_{\mathrm{P},1}$ for reasons above otherwise $p_{\mathrm{B},2} = p_{\mathrm{B},1}$		$p_{j,2} = p_{j,1}$ For all treatment arms j=B and P	$p_{\mathrm{B},2} = p_{\mathrm{P},1}$ $p_{\mathrm{P},2} = p_{\mathrm{P},1}$ for reasons above otherwise $p_{\mathrm{B},2} = p_{\mathrm{B},1}$

[a] Implicitly assumes unobserved rate the same as observed.

[b] All patients on exacerbation rate in the placebo arm are imputed using the placebo arm rate (i.e., $p_{\mathrm{P},2} = p_{\mathrm{P},1}$).

[c] Note can be changed by review prior to study unblinding.

B Benralizumab; P Placebo; DL Direct Likelihood; MI Multiple Imputation; MAR Missing At Random; DRMI Dropout Reason-based Multiple Imputation.

Forest plots will be used to show the primary analysis results along with the missing data sensitivity analysis results.

It is noted that if the primary analysis is statistically significant, it is not necessarily expected that all sensitivity analyses will also give statistically significant results. If the results of the sensitivity analyses provide reasonably similar estimates of the treatment effect to the primary analysis, this will be interpreted as providing assurance that neither the lost information nor the mechanisms which cause the data to be missing have an important impact on the primary analysis conclusions. Based on these outputs and the drug's mechanism of action, the plausibility of the assumptions we make about missing data in the different analyses will be considered and described in the CSR.

8.1.2 Accounting for missing data for key secondary endpoints (Pre-bronchodilator FEV_1 and Total asthma symptom score)

8.1.2.1 Primary analysis under the MAR assumption

As for the primary endpoint, the primary analysis of the pre-bronchodilator FEV_1 and total asthma symptom score includes all data captured during the entire treatment period to reflect the effect of initially assigned randomised treatment. This primary analysis includes all data until patients withdraw from the study regardless of if they discontinue from randomised treatment. The MMRM model used is a DL approach which is valid under the MAR assumption.

8.1.2.2 Sensitivity analysis under the MAR and DRMI assumptions

Sensitivity analyses of the repeated measures analyses will be performed for the Pre-bronchodilator FEV_1 and total asthma symptom score using controlled sequential multiple imputation methods based on pattern mixture models, as described in [4, 5].

The method is analogous to the multiple imputation of exacerbation events and the imputation process consists of a sequence of MI steps, where each step is intended to impute missing values at 1 time-point only. This method will assume that some pre-specified subset of patients who withdraw from the study have correlations with future (unobserved) visits similar to patients in the placebo arm. As for the exacerbation events, this allows us to assess various deviations from the MAR assumption.

The assumptions that will be used to impute the missing data of patients who withdraw from study early are as follows:

(a) MAR: Assumes that the trajectory for patients who dropped out in each arm is similar to those observed in their own treatment arm.

(b) DRMI: Assumes that the trajectory for patients in the benralizumab arms who dropped out for treatment related reasons (according to the same classification as for the DRMI analysis of the primary endpoint) is similar to that of the placebo

patients, whereas the remaining patients who has dropped out are imputed assuming MAR.

Approach b) can be considered more conservative than the approach for the primary analysis because the assumptions mean that as soon as patients withdraw from study for a treatment related reason, they begin to worsen immediately. As for the primary endpoint, the assumptions for DRMI as described in b) will be determined based on the review prior to study unblinding.

The on-treatment analyses without or with imputation (MAR and DRMI) will be conducted similarly as for the primary endpoint.

The sequential multiple imputation is achieved by only using appropriate data at each stage of the imputation. Imputation will be done in 2 steps: the non-monotone (intermediate) missing values will be imputed first (MCMC method is used to partially impute the data using SAS PROC MI) and then the remaining missing value at each visit will be imputed using a sequential regression method (using MONOTONE REG option of SAS PROC MI).

For example, to impute missing values at time t for patients in the benralizumab arms that dropped out due to an AE, the imputation will include the placebo observations up to and including time t, plus observations from patients in the benralizumab arms that dropped out due to an AE up to and including time t-1. This is done for each visit, 1 at a time using observed data, and missing values are just imputed. Placebo missing observations and benralizumab missing observations that are not treatment-related are imputed assuming MAR and follow the pattern of observed observations in each treatment arm respectively.

100 imputations will be carried out, and a random seed of 784088 will be used for the non-monotone imputation step and a random seed of 409345 will be used for the sequential regression imputation step. The analysis of each of the imputed dataset will be as described for the primary analysis in Sections 4.2.6.3 and 4.2.7.1 and these will be combined using SAS procedure PROC MIANALYZE.

References

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8.2 Handling rule for partial dates

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, to classify prior/concomitant medications and to derive the time since asthma diagnosis/symptoms started:

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 study 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 study 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 study treatment
- If the resolution date of an AE 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 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 date of the last study visit.

- 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 date of the last study visit then the end date will be set to the date of the last study visit.

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

Respiratory disease history

- For the date of asthma first diagnosed and the date of first appearance of asthma symptoms, if both the month and the year are available, the first of the recorded month will be imputed, unless the date of birth is within the same month and year. In the case of same month and year as the date of birth, the date of birth will be imputed instead.

- For the date of asthma first diagnosed and the date of first appearance of asthma symptoms, if only the year is available, 1st January will be imputed, unless the date of birth is within that same year. In the case of same year as the date of birth, the date of birth will be imputed instead.

8.3 Analysis plan for anti-drug antibodies (ADA) data

The purpose of this appendix is to provide a general reference for the analysis of ADA data in this study. The complete set of presentations described in this appendix will be conducted.

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

For each patient, the following responses variables will be evaluated:

- ADA positive at any visit (including baseline and/or post-baseline) (ADA prevalence)
- ADA positive at both post-baseline and baseline
- ADA positive at post-baseline only (treatment-induced ADA positive)
- Baseline ADA titre increased by >4-fold at ≥1 post-baseline timepoint (treatment-boosted ADA positive)
- ADA positive at baseline only
- ADA persistently positive, where persistently positive is defined as at least 2 post-baseline positive ADA measurements with at least 16 weeks (112 days) between the first and last positive measurement or a positive ADA result at the last available post-baseline assessment
- ADA transiently positive, defined as ADA negative at baseline and at least one post- baseline ADA positive measurement and not fulfilling the conditions for persistently positive
- Treatment-emergent ADA positive, defined as either treatment-induced ADA positive or treatment-boosted ADA positive (ADA incidence)
- nAb positive at any visit (applicable for ADA-positive patients only)

All analyses will be conducted on the safety analysis set and by treatment group unless otherwise specified. All ADA results will be listed.

8.3.1 ADA results during the study

The numbers and percentages of patients with ADA responses listed above during the study will be summarised by treatment group. The number and percentage of treatment-emergent ADA positive patients will be computed as the sum of treatment-induced and treatment-boosted ADA positive patients. No formal hypothesis testing will be conducted.

The maximum titre across the different visits (including both baseline and post-baseline measurements) will be summarised by descriptive statistics (n, minimum, quartiles [Q1, median and Q3] and maximum). The number and percentage of ADA positive patients with

maximum titre ≤ and > the median of maximum titres will be also summarised respectively. The median of maximum titre will be calculated based on the maximum titre of each ADA positive patient within each treatment group.

The key patient information will be listed for patients with positive ADA results only. This listing will include but not be limited to a patient's ADA result, sample collection date, days from previous dose, number of active doses received, titre result, nAb status, benralizumab concentration, and eosinophil counts. A listing of all collected ADA results (including ADA negative) will also be provided.

8.3.2 ADA results by visit

ADA response (positive or negative) and the titre values will be summarised at baseline and at all scheduled post-baseline visits by treatment group. In the event a patient has more than one titre result within a given visit window, the maximum ADA titre will be used in the by-visit summary. A line plot of proportion of patients who are ADA positive by visit will also be provided.

8.3.3 ADA and eosinophil levels

Blood eosinophil counts will be summarised by visit for ADA positive patients, ADA negative patients, treatment-emergent ADA positive patients, ADA positive with titre > median of maximum titre, ADA persistently positive patients, and nAb positive patients, using the following descriptive statistics: n, mean, standard deviation, median, Q1, Q3, minimum and maximum. A line plot of eosinophil counts by visit and ADA status will also be presented.

8.3.4 nAb response

nAb response (positive or negative) will be summarised by visit for ADA positive patients.

8.3.5 ADA and efficacy

The effect of ADA on the primary endpoint (annual asthma exacerbation rate) and 2 key secondary endpoints (change from baseline in pre-bronchodilator FEV_1 and change from baseline in total asthma symptom score) will be evaluated by treatment group and ADA subgroups (ADA positive, ADA negative, treatment-emergent ADA positive, ADA persistently positive, nAb-positive, and ADA positive with titre > median of maximum titre). Due to the expected small number of ADA positive patients in the placebo group, no formal statistical analysis on efficacy (benralizumab vs. placebo) by ADA status (positive/negative) is planned.

The following analyses will be performed:

- ADA and exacerbation rate: The descriptive summary statistics of the annualised exacerbation rate by ADA subgroups will be provided.

- ADA and pre-bronchodilator FEV_1: The descriptive summary statistics of the change from baseline in pre-bronchodilator FEV_1 by ADA subgroups will be provided.

- ADA and total asthma symptom score: The descriptive summary statistics of the change from baseline in total asthma symptom score by ADA subgroups will be provided.

For calculation of the annual exacerbation rate, the follow-up time for exacerbation will be defined as in Section 3.2. For pre-bronchodilator FEV_1 and total asthma symptom scores, the last valid non-missing observation by EOT visit or IPD visit will be included in the calculation.

8.3.6 ADA and safety

The effect of ADA on safety will be examined by descriptive summaries.

AE and SAEs during the study (separately for on-treatment and on-study periods) will be summarised. The on-treatment and on-study periods are defined Section 3.6.1. The AE will also be evaluated by causality. The potential impact of ADA on hypersensitivity will be assessed.

The summaries will be presented for ADA positive patients, ADA negative patients, ADA positive patients with titre > median of maximum titre, ADA persistently positive patients, nAb positive patients, and treatment-emergent ADA positive patients.

8.3.7 ADA and PK

Benralizumab serum concentrations will be summarised by visit for ADA positive patients, ADA negative patients, treatment-emergent ADA positive patients, ADA positive patients with titre > median of maximum titre, ADA persistently positive patients, and nAb positive patients.

8.4 Analyses to assess the impact of the COVID-19 pandemic

Additional analyses and summaries will be produced to assess the impact of the COVID-19 pandemic on the primary results. The analyses and summaries are detailed below, referencing the section of this SAP to which they relate to.

COVID-19 phases (pre- / during-)

The start date of COVID-19 pandemic will be defined at a country level: 29th January 2020 (the date China declared COVID-19 to be a national public health crisis, i.e., significant emergent public health grade one response started across China mainland provinces) for China mainland, and 11th March 2020 (the date WHO declared COVID-19 to be a pandemic) for non-China countries and Taiwan.

Data recorded before the start date will be *pre-pandemic*. Data recorded on or after the start date will be *during-pandemic*, as the end date of COVID-19 pandemic is not defined.

Violations and deviations

The important PDs will be summarised and listed together, including COVID-19-related and non-COVID-19-related important PDs (see Section 2.3.1). An additional summary will present COVID-19-related important PDs and non-COVID-19-related important PDs separately, by treatment group, for the FAS. A separate listing will be produced, including all COVID-19-related PDs (important and non-important) by treatment group.

COVID-19-related study disruptions

A COVID-19-related study disruption is any important change in the study conduct or data collection due to the COVID-19 pandemic. COVID-19-related study disruptions may include, but not necessarily be limited to:

- Changes to visit schedules, missed visits, changes to visit procedures;
- Discontinuation of IP, missed IP, changes to IP administration;
- Discontinuation of study.

An additional table will summarise all COVID-19-related study disruptions by treatment group for the FAS. The number and percentage of patients with at least one COVID-19-related study disruption will be reported. A listing of all COVID-19-related study disruptions will be produced with details.

The number and percentage of patients randomised pre-pandemic and during-pandemic will be reported, respectively. Total pre-pandemic and during-pandemic follow-up times will be presented in total patient-years, and also as proportions of total overall follow-up time, as an indication of the proportion of study time potentially affected by COVID-19. The overall follow-up time is the duration between the date of randomisation and the date of study completion or withdrawal from study, inclusive.

The number and percentage of patients who missed at least one IP dose due to COVID-19, the number and percentage of patients missing 1, 2, and ≥3 doses due to COVID-19, and the number and percentage of patients with consecutive missed doses due to COVID-19 will be presented. The number and percentage of patients who had at least one IP dose delayed due to COVID-19 will also be presented.

The number and percentage of patients with at least one scheduled visit impacted due to COVID-19 will be summarised by treatment group. Impacted visits will be classified as "missed scheduled visit", "delayed scheduled visit" or "changed format of scheduled visit". "Changed format of scheduled visit" will be further classified by as "On-site only, partially completed", "Remote visit (Audio or Video) only", and "Both remote and on-stie used".

The number of patients discontinuing IP or withdrawing from the study due to COVID-19 will also be summarised by treatment group.

Kaplan-Meier plots will be produced summarising separately the time (in weeks) to first visit impacted by COVID-19 and to first IP dose missing due to COVID-19.

- Time to first visit impacted by COVID-19 = [intended date of the first impacted visit – date of randomisation] + 1, where the intended date is based on the visit schedule listed in the protocol. Patients who did not have any visits impacted by COVID-19 will be censored at the date of study completion or study withdrawal.

- Time to first IP dose missing due to COVID-19 = [intended date of the first missed IP dose – date of randomisation] + 1, where the intended date is based on the visit schedule listed in the protocol. Patients who did not have any IP dose missing due to COVID-19 will be censored at the date of last dose of IP.

Analyses of the primary endpoint

Two additional sensitivity analyses of the primary endpoint will be carried out to compare annual asthma exacerbation rates in the benralizumab group with those in the placebo group during the pre-pandemic phase and the during-pandemic phase respectively. The first analysis will use the pre-pandemic data only, i.e., all observed data over the 48-week treatment period (see Section 3.2) up to and including the day prior to the start date of pandemic. The second analysis will use the during-pandemic data only, i.e., all observed data from the start date of pandemic until the end of 48-week treatment period. These analyses will use all observed data in the specific COVID-19 phase regardless of adherence to randomised treatment or the use of an alternative treatment**.**

All these sensitivity analyses will use the similar negative binomial model as specified for the primary analysis (see Section 4.2.5.1). The response variable will be the number of exacerbations experienced by a patient during the follow-up for exacerbation in the specific COVID-19 phase. The logarithm of the patient's corresponding follow-up time in the specific COVID-19 phase will be used as an offset variable in the model. The model will include

covariates of treatment group, region (China/Non-China), number of exacerbations in the year before the study, and the use of maintenance oral corticosteroids (yes/no).

Asthma exacerbation summary statistics as described in Section 4.2.5.2 will also be repeated by pandemic phase: pre-pandemic, during-pandemic.

AEs

All AE-related analyses described below will be based on the safety analysis set using the on-treatment period (see Section 3.6.1).

The overall AE summary table (AEs in any category reported) will be repeated by pandemic phase: pre-pandemic, during-pandemic. Categories will include: any AEs, SAEs, AEs with outcome of death, DAEs, COVID-19 AEs (as defined by standardised MedDRA query of COVID-19 based on the latest MedDRA version) and non-COVID-19 AEs.

Summaries of AEs and SAEs by SOC and PT along with the rates per patient-years at risk will be provided by pandemic phase: pre-pandemic, during-pandemic. Summaries of COVID-19 AEs and non-COVID-19 AEs by SOC and PT along with the rates per patient-years at risk will be provided for the during-pandemic phase.

If there are more than 10 patients reporting COVID-19 AEs, then the AE listing will be repeated including only these patients, with details of all AEs reported by these patients.

8.5 OCS conversion factors for prednisone equivalents

Total daily OCS dose will be converted to a prednisone equivalent using the following table:

Table 10 Estimated OCS dose therapy equivalence

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg

For example, to convert a cortisone total daily dose to a prednisone equivalent total daily dose, a multiplication factor of 0.2 = 10/50 should be used.

8.6 Efficacy estimand

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
Primary objective: To evaluate the effect of benralizumab on asthma exacerbations in patients on medium to high-dose ICS/LABA with uncontrolled asthma.				
<u>Primary estimand (primary objective):</u> Difference in exacerbation rate between benralizumab and placebo in patients with severe uncontrolled asthma, regardless of whether patients discontinue study treatment, initiate new treatment or change background treatment	Treatment with benralizumab versus placebo, as add-on to standard of care / Patients with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS with or without OCS	Annual asthma exacerbation rate / Annual asthma exacerbation rate ratio of benralizumab versus placebo over 48 weeks	• Use of alternative treatment (Treatment policy strategy) • Discontinuation of study treatment (Treatment policy strategy) • Change in background treatment (Treatment policy strategy) • Patient death (While on treatment strategy) • COVID-19 pandemic (Treatment policy strategy)	• Main estimation (Section 4.2.5.1): The primary analysis will compare annual asthma exacerbation rate between treatment groups using a negative binomial model, including all observed data during the 48-week treatment period. • Sensitivity analyses for missing data (Appendix 8.1.1): Controlled multiple imputation will be conducted to impute missing data post study withdrawal, under MAR and DRMI assumptions respectively. • Sensitivity analyses for pandemic impact (Appendix 8.4): Similar negative binomial models as for the primary analysis will be carried out separately for the pre-pandemic data and during-pandemic data.

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
Supplementary estimand (primary objective): Difference in exacerbation rate between benralizumab and placebo in patients with severe uncontrolled asthma, whilst being on the initial randomised study treatment	Treatment with benralizumab versus placebo, as add-on to standard of care / Patients with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS with or without OCS	Annual asthma exacerbation rate / Annual asthma exacerbation rate ratio of benralizumab versus placebo over 48 weeks	• Use of alternative treatment (Treatment policy strategy) • Discontinuation of study treatment (While on treatment strategy) • Change in background treatment (Treatment policy strategy) • Patient death (While on treatment strategy) • COVID-19 pandemic (Treatment policy strategy)	• Main estimation (Section 4.2.5.2, Appendix 8.1.1): The analysis will compare annual asthma exacerbation rate between treatment groups using a negative binomial model, including all observed data during the 48-week treatment period until patients discontinue from randomised study treatment. • Sensitivity analyses for missing data (Appendix 8.1.1): Controlled multiple imputation will be conducted to impute missing data post study treatment discontinuation, under MAR and DRMI assumptions respectively.
Two key secondary objectives: (1) To assess the effect of benralizumab on pulmonary function, (2) To assess the effect of benralizumab on asthma symptoms.				
Secondary estimand (key secondary objective):	Treatment with benralizumab versus placebo, as add-on to standard of care / Patients	(1) Change from baseline in Pre-bronchodilator FEV_1 / Difference in mean change from baseline	• Use of alternative treatment (Treatment policy strategy)	• Main estimation (Sections 4.2.6.3 and 4.2.7.1): The primary analysis will compare mean change from baseline at Week 48 between treatment groups using a

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
Difference in change from baseline between benralizumab and placebo in patients with severe uncontrolled asthma, regardless of whether patients discontinue study treatment, initiate new treatment or change background treatment	with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS with or without OCS	of benralizumab vs placebo at Week 48 (2) Change from baseline in bi-weekly mean total asthma symptom score / Difference in mean change from baseline of benralizumab vs placebo at Week 48	• Discontinuation of study treatment (Treatment policy strategy) • Change in background treatment (Treatment policy strategy) • Patient death (While on treatment strategy) • COVID-19 pandemic (Treatment policy strategy)	MMRM model, including all observed data during the 48-week treatment period. • Sensitivity analyses for missing data (Appendix 8.1.2): Controlled sequential multiple imputation methods based on the pattern mixture models will be conducted to impute missing data post study withdrawal, under MAR and DRMI assumptions respectively.
Supplementary estimand (key secondary objective): Difference in change from baseline between benralizumab and placebo in patients with severe uncontrolled asthma, whilst being on the	Treatment with benralizumab versus placebo, as add-on to standard of care / Patients with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS	(1) Change from baseline in Pre-bronchodilator FEV1 / Difference in mean change from baseline of benralizumab vs placebo at Week 48 (2) Change from baseline in bi-weekly mean total asthma symptom score / Difference in mean	• Use of alternative treatment (Treatment policy strategy) • Discontinuation of study treatment (While on treatment strategy) • Change in background treatment (Treatment policy strategy)	• Main estimation (Sections 4.2.6.3 and 4.2.7.1, Appendix 8.1.2): The analysis will compare mean change from baseline at week 48 between treatment groups using a MMRM model, including all observed data during the 48-week treatment period until patients discontinue from randomised study treatment. • Sensitivity analyses for missing data (Appendix 8.1.2): Controlled sequential multiple imputation methods based on the pattern mixture models will be conducted

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
initial randomised study treatment	with or without OCS	change from baseline of benralizumab vs placebo at Week 48	• Patient death (While on treatment strategy) • COVID-19 pandemic (Treatment policy strategy)	to impute missing data post study treatment discontinuation, under MAR and DRMI assumptions respectively.

FEV_1 = Forced Expiratory Volume in 1 second; MAR = Missing At Random; DRMI = Dropout Reason-based Multiple Imputation; MMRM = Mixed-effects model for repeated measures.

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