SHAMAL: A Multicentre, Randomised, Open-Label, Parallel-Group, Active-Controlled, Phase IV Study to Assess the Reduction of Daily Maintenance ICS/LABA Treatment Towards Anti-Inflammatory Reliever Treatment in Patients with Severe Eosinophilic Asthma Treated with Benralizumab

ClinicalTrials.gov Identifier: NCT04159519

Date of Protocol: 15 December 2022

Statistical Analysis Plan	
Study Code	D3250C00072
Edition Number	3.0
Date	15 December 2022

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-5	Asthma control questionnaire-5 item
AE	Adverse event
AER	Annual exacerbation rate
APS	All patients set
ATC	Anatomical therapeutic chemical
AQLQ(S)+12	Standardised asthma quality of life questionnaire for 12 years and older
AUC	Standardised area under the curve
AZ	AstraZeneca
BID	bis in die (twice per day)
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAEs	AEs causing the discontinuation of study treatment
eCRF	Electronic case report form
EOT	End of treatment
ePRO	Electronic patient-reported outcome
FAS	Full Analysis Set
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
ICF	Informed consent form
ICS	Inhaled corticosteroids
IP	Investigational product
LABA	Long-acting β_2-agonist
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measures
n	The number of non-missing observations or the number of patients providing data at the relevant timepoint
OCS	Oral corticosteroids

Abbreviation or special term	Explanation
ppb	parts per billion
PRN	pro re nata (as needed)
PRO	Patient-reported outcome
PT	Preferred term
PY	Pack-years
Q8W	Every 8 weeks
SABA	Short-acting β-agonist
SAF	Safety analysis set
SAE	Serious adverse event
SD	Standard deviation
SMART	Symbicort® maintenance and reliever therapy
SoA	Schedule of assessments
SOC	System organ class
WHODD	World Health Organisation Drug Dictionary

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	23 July 2020	1. Inclusion of Section 4.2.8. 2. Update of wording "subject" to "patient" in Section 2.2 and Section 3.4.3. 3. Moved sentence regarding missing ACQ 5 and AQLQ(S)+12 scores questionnaire data from Section 3.5.3 to Section 4.1.1. 4. References to numbered appendices in the CSP have been updated. 5. "Serum protein biomarkers (sub-study)." Added to exploratory objective endpoints. 6. "To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment (main and sub-study)" added as exploratory objective with "Change from baseline in airway oscillometry during the study period (sub-study)." as the corresponding variable. 7. "Nasal" replaced by "sputum" throughout the SAP. 8. Update to Visit numbering as per CSP. 9. Trial Design schema updated. 10. Partial date of diagnosis and date of birth imputation rules/references added in Section 4.1.1, Section 4.2.1.2 and Appendix 8.1.2. 11. Appendix 8.1 updated to Appendix 8.1.1 to account for new partial date imputation rules, references to Appendix 8.1.1 updated throughout. 12. Parexel Biostatistics Lead sign-off page removed.	Yes	1. Due to the COVID-19 pandemic, alternative means of data collection may be required, as outlined in the CSP Amendment/ protocol version 2.0. Additional data summaries/analyses may be required. 2. Minor updates to wording for consistency. 3. Previously located in the incorrect section. 4. Updated to reflect changes in the CSP. 5. Updated to reflect changes in the CSP. 6. Updated to reflect changes in the CSP. 7. Updated to reflect changes in the CSP. 8. Updated to align with new Schedule of Activities in the CSP. 9. Updated to reflect changes in the CSP. 10. Updated to account for partial date related derivations in countries where date of birth cannot be collected. 11. Updated to account for partial date related derivation rules and consistency throughout. 12. Updated in line with AZ SAP sign-off process.

		13. Updates to wording related to commercial Fasenra use in Section 4.2.1.3 to align with CRF updates. 14. MMRM readout wording changes from "average mean change" and "estimated treatment effect" to "Least Square mean change" throughout Section 4. 15. Confidence interval presentation rules added to Section 4.1.		13. Updated wording of exacerbation history items to align with CRF. 14. Updated for clarity. 15. Updated for consistency.
	11 November 2022	1. The outcome variable for the MMRM of ACQ-5 score has been changed from "Change from baseline ACQ-5" to "Change from baseline in mean ACQ-5 score over the previous 8 weeks" in Section 4.2.3.1. 2. Addition of sub-study analysis set in Section 2.1.3. 3. Updates to specify that all ICS dose analyses will be presented in microgram (mcg) throughout. 4. Updates to visit window for questionnaire data in Section 4.1.2. 5. Addition of safety analysis set in Section 2.1.4. 6. Addition of conversion of Symbicort dose level to microgram in Section 4.2.3.2. 7. Update to the formula of mean total daily ICS in Section 3.2.2. 8. Update to the definition of concomitant medication in Section 3.5.3. 9.Update to the definition of most common adverse events in Section 4.2.6. 10. Update to clarify definition of worst ACQ-5 score in Section 4.2.3.1. 11. Update of imputation rule for prior/concomitant medication and		1. Updated to align with summary of ACQ-5 score tables. 2. Added for additional summary tables required. 3. Updated for clarity. 4. Updated for clarity. 5. Updated to align with Protocol. 6. Added for clarity. 7. Updated for clarity. 8. Updated for clarity 9. Update based on request of safety team 10. Updated for clarity. 11. Updated to account for partial date related derivation rules and consistency throughout. 12. Updated to align with CSP. 13. Updated to align with CSP. 14. Summarised elsewhere in the TFLs and update based on request of safety team.

		addition of imputation rule for partial date of exacerbation history, and medical and surgical history in Section 8.1. 12. Addition of clinical remission as an endpoint in Section 1.1.2, Section 3.2 and Section 4.2.3. 13. Removal of reference to a primary read-out at Week 32 in Section 4.2.3.1. 14. Summary of injection site reactions updated to only if sufficient number of events reported and removal of SAEs causing discontinuation of the study treatment/study from Section 4.2.6. Summary of most common AEs changed to frequency of > 1%.		

* Pre-specified categories are:
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other.

1 STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Objective	Outcome measures
To assess the potential for Fasenra®-treated patients to reduce Symbicort® maintenance treatment while maintaining asthma symptom control [a]	Proportion of patients who reduced their Symbicort® maintenance dose at the end of the reduction period (Visit 6; Week 32) to: • Medium-dose Symbicort® maintenance and reliever therapy (SMART), or • Low-dose SMART, or • Symbicort® anti-inflammatory reliever only

[a] Asthma symptom control is defined as 1) no asthma exacerbations since the last visit, and 2) no increase in ACQ-5 ≥0.5 units in the last four weeks (compared to Visit 1) and no significant increase in Symbicort® use in the last four weeks (a weekly average of >8 inhalations of Symbicort®/day).

1.1.2 Secondary objectives

Objectives	Outcome measures
To assess changes in patient-reported outcomes for Fasenra®-treated patients while stepping down Symbicort® maintenance treatment	• Change from baseline in asthma control questionnaire-5 item (ACQ-5) score at the end of the reduction period • Change from baseline in standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12) at the end of the reduction period • Proportion of patients with no deterioration in AQLQ(S)+12 (deterioration defined as a decrease of at least 0.5 units compared to baseline) at the end of the reduction period • Proportion of patients with no deterioration in ACQ-5 (deterioration defined as an increase of at least 0.5 units compared to baseline) at the end of the reduction period

Objectives	Outcome measures
To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment	• Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV_1) during the study period
To assess asthma exacerbation rate	• Annualised asthma exacerbation rate during the study period
To assess the total inhaled corticosteroids (ICS) dose exposure	• Cumulative total daily ICS dose (maintenance + reliever) for: – The reduction period – The maintenance period – The study period • Total daily ICS dose (maintenance + reliever) at the end of the reduction period
To assess if reductions in Symbicort® maintenance achieved at the end of the reduction period are maintained until the end of the maintenance period	• Proportion of patients using the same Symbicort® daily dose at the end of the maintenance period (Visit 8b; Week 48) that they achieved at the end of the reduction period (Visit 6; Week 32) • Supportive outcomes: – Number of exacerbations occurring from end of the reduction period to end of the maintenance period – Total daily ICS dose from the end of the reduction period to the end of the maintenance period – Change in ACQ-5, AQLQ(S)+12, and FEV_1 from the end of the reduction period to the end of the maintenance period

Objectives	Outcome measures
To assess clinical remission in patients at end of the reduction and maintenance periods	• Number and proportion of patients that met each composite endpoint defining clinical remission (no exacerbations, <10% deterioration in FEV1, ACQ-5 < 1.5 or ACQ-5 ≤ 0.75) at Visit 6 (Week 32) and Visit 8b (Week 48). • Number and proportion of patients that met 0, 1, 2 and all 3 composite remission endpoints.

1.1.3 Safety objectives

Objectives	Outcome measures
To assess the safety and tolerability of Fasenra® in patients with severe asthma, while stepping down Symbicort® maintenance treatment and maintaining asthma symptom control	• Adverse Events (AEs)/Serious Adverse Events (SAEs)

1.1.4 Exploratory Objectives

Objectives	Outcome measures
To assess changes in inflammation markers during and following stepping down Symbicort® maintenance treatment	• Fractional exhaled nitric oxide (FeNO) • Blood eosinophil count • Serum protein biomarkers (sub-study).
To assess patient experience	• CCI [redacted]
To assess the potential for Fasenra®-treated patients to maintain lung function while	• Change from baseline in airway oscillometry during the study period (sub-study).

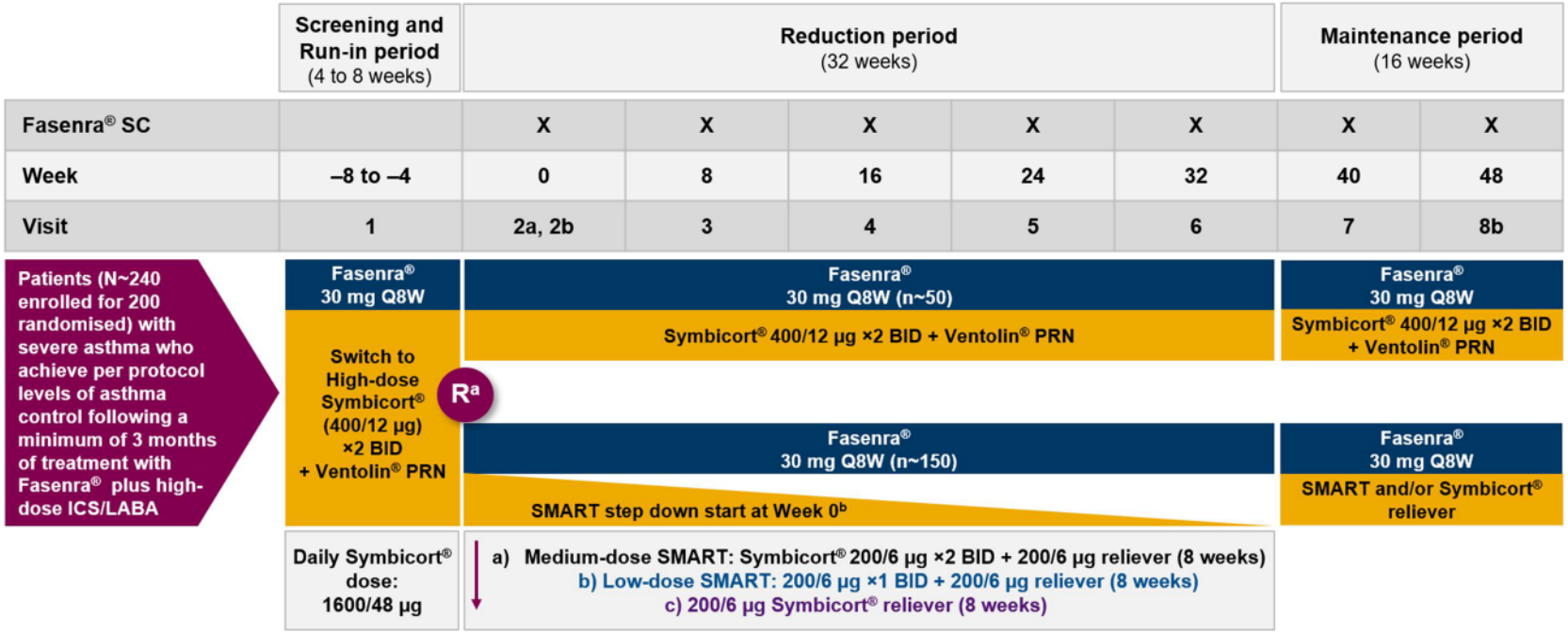
stepping down Symbicort® maintenance treatment (main and sub-study)	
To characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy (sub-study) [b]	• Patient inflammatory biomarkers profile including eosinophils, microbiome, and sputum biomarkers (cytokines)

[b] All sub-study specific objectives will be reported separately from the Clinical Study Report.

1.2 Study design

This is a multicentre, randomised, open-label, parallel-group, active-controlled, Phase IV study to assess the reduction of daily Symbicort® maintenance to anti-inflammatory reliever treatment only in patients with severe eosinophilic asthma on Fasenra® treatment, while maintaining asthma control. General study design is summarised in Figure 1.

Figure 1: Study design



BID=twice per day; ICS/LABA=Inhaled corticosteroids/long-acting β_2-agonist; PRN=as needed; Q8W=every 8 weeks; R=Randomisation; SC=subcutaneous; SMART=Symbicort® maintenance and reliever therapy.

[a] If the patient does not fulfil all randomisation criteria (Section 5.1.1 of the Clinical Study Protocol [CSP]) then the patient will be classed as a screen failure.

[b] SMART step down should follow the dosing regimen and algorithm shown in Section 1.2.2.2.

For the purpose of this study, maintained asthma symptom control is defined as:

- No asthma exacerbations since the last visit (as defined in Section 3.2.5), and
- No increase in ACQ-5 ≥0.5 units in the last four weeks (compared to Visit 1) and no significant increase in Symbicort® use in the last four weeks (a weekly average of >8 inhalations of Symbicort®/day).

In this study, the ICS/long-acting β_2-agonist (LABA) will be standardised for all patients who will switch from any ICS/LABA therapy to budesonide/formoterol (Symbicort®). At the Screening Visit (Visit 1), all patients will switch to high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment. Patients randomised to the Reference arm will remain on the high dose of Symbicort® for the duration of the study; patients randomised to reduce the daily Symbicort® maintenance treatment will follow the SMART approach.

This study will be conducted at approximately 25 study sites in approximately 3-5 countries. The study duration for each patient will be approximately 52-56 weeks. Approximately 240 patients with severe eosinophilic asthma taking high-dose ICS/LABA who have been treated for severe eosinophilic asthma with at least three consecutive doses of Fasenra® and have clinically responded since the start of Fasenra® treatment (defined for the purpose of this study as an ACQ-5 score <1.5 at Visit 1 and Visit 2b) will be enrolled into this open-label study. Use of other maintenance asthma therapy such as daily oral corticosteroids (OCS), leukotriene receptor antagonists, long-acting muscarinic antagonists or theophyllines is not allowed during the study period.

The study consists of a Screening Visit (Visit 1) and 4- to 8-week screening and run-in period (to align the randomisation study visit with the next Fasenra® injection), a reduction period of 32 weeks, and a 16-week maintenance period.

1.2.1 Screening and run-in period

During the screening and run-in period, patients will continue to receive Fasenra® 30 mg every eight weeks (Q8W). At Screening (Visit 1), all patients will switch from their previous ICS/LABA maintenance treatment and rescue medication to high-dose Symbicort® maintenance (budesonide/formoterol 400/12 µg) ×2 inhalations twice per day (BID) + Ventolin® (salbutamol 100 µg) reliever as needed (PRN).

Patients will continue on this medication for the duration of the 4- to 8-week screening and run-in period. The end of the run-in period will coincide with the next Fasenra® injection.

1.2.2 Reduction period

At the Randomisation visit (Visit 2b; Week 0), patients will undergo the ACQ-5 assessment and an assessment of exacerbation history to determine whether they are eligible for randomisation (see Section 5.1.1 of the CSP) or whether they are a screen failure (see Section 1.3). Eligible patients will be randomly assigned to the Treatment reduction arm or to the Reference arm in a 3:1 ratio:

- Treatment reduction arm
  - Fasenra® 30 mg Q8W + SMART or Symbicort® reliever only (starting with medium-dose Symbicort® 200/6 µg ×2 inhalations BID maintenance + Symbicort® 200/6 µg reliever PRN; tapering to Symbicort® 200/6 µg reliever only, as per tapering scheme and depending on degree of asthma control [see Section 1.2 for definition])
- Reference arm
  - Fasenra® 30 mg Q8W + high-dose Symbicort® maintenance ×2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN.

1.2.2.1 Reference arm

Eligible patients randomised to the Reference arm will continue high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment for 32 weeks.

1.2.2.2 Treatment reduction arm

At the Randomisation visit (Visit 2b; Week 0) eligible patients randomised to the Treatment reduction arm will automatically be stepped down to medium-dose SMART. Patients who demonstrate maintained asthma control will taper (step down) their SMART regimen until they achieve either Symbicort® as anti-inflammatory reliever treatment only, or until no further reductions of SMART are permitted due to loss of asthma control (see Section 1.2). In case of loss of asthma control, the patient in the reduction arm can move to the most recent previously assigned higher dose level. The reduction period in this arm will last 32 weeks. At each post-randomisation study visit (Visit 3 and Visit 4; Visit 5 if required), the Investigator will evaluate the occurrence of asthma exacerbations, worsening of asthma control (ACQ-5 ≥0.5 units compared to baseline), and overuse of Symbicort® 200/6 µg treatment (a weekly average of >8 inhalations of Symbicort®/day). The Investigator will then decide to reduce, maintain, or increase the Symbicort® dose based on a pre-specified algorithm (see Section 1.2.2.2, Figure 2).

Patients who are not on Symbicort® reliever only by Visit 4 will be given one additional opportunity to step down at Visit 5 if they demonstrate asthma control. Patients who step

down to Symbicort® reliever only at Visit 4 will attend Visit 5 but will not reduce their dose any further. All patients will begin the maintenance period after Visit 6 (Week 32).

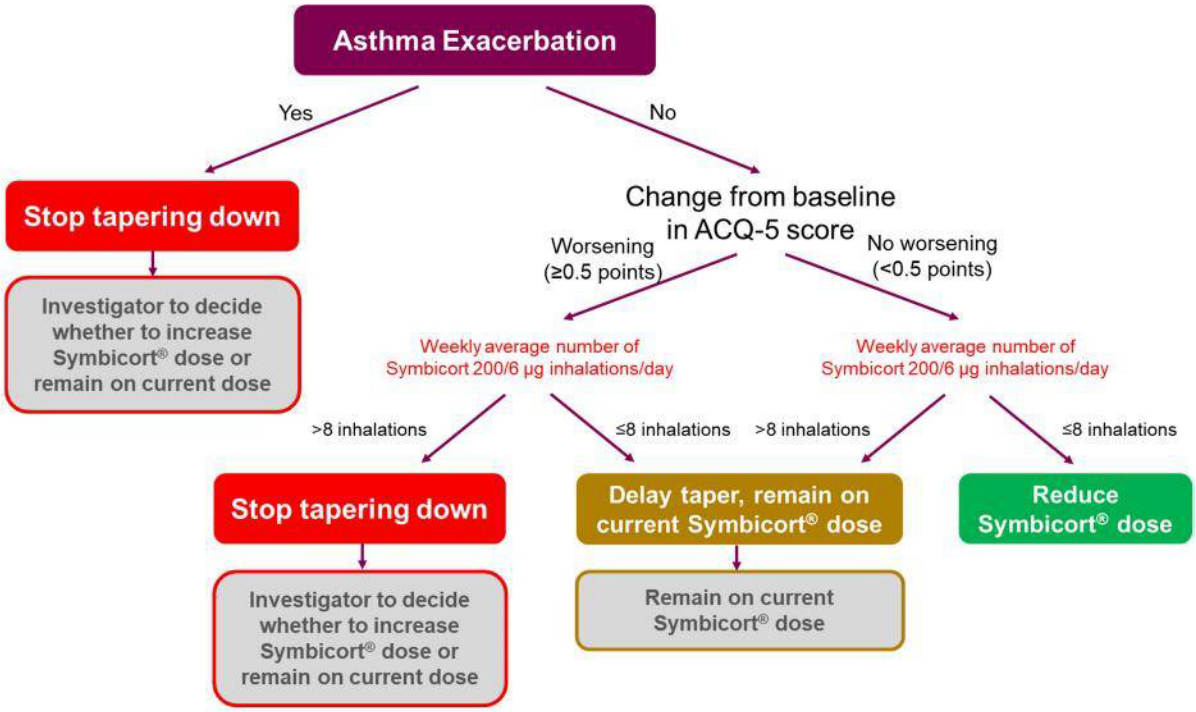
An example of how the daily high-dose Symbicort® maintenance treatment will be reduced to either medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever is shown in Table 1 with the algorithm for stepping down, or stepping up, Symbicort® treatment shown in Figure 2.

Table 1: Symbicort® dosing regimen for patients who maintain asthma control during the reduction period

Step	Maintenance Treatment	Reliever Treatment
Visit 1 and run-in period (4 to 8 weeks)	High-dose Symbicort® (400/12 µg ×2 inhalations BID)	Ventolin® 100 µg
Visit 2b (Week 0)	Medium-dose Symbicort® (200/6 µg ×2 inhalations BID)	Symbicort® 200/6 µg
1st Step down (Visit 3 onwards)	Low-dose Symbicort® (200/6 µg ×1 inhalation BID)	Symbicort® 200/6 µg
2nd Step down (Visit 4 onwards)	None	Symbicort® 200/6 µg

Asthma exacerbations will be assessed since the last study visit; the change from baseline in ACQ-5 and the weekly average of Symbicort® 200/6 µg inhalations/day will be assessed for the four weeks prior to the study visit.

Figure 2: Algorithm for stepping down/up treatment in the reduction period



A patient will stop stepping down for the duration of the reduction period if:

- The patient experiences an asthma exacerbation (see Section 3.2.5) since the last visit, OR
- During the last four weeks prior to each study visit the patient experiences an ACQ-5 worsening of ≥0.5 points compared to baseline and has a weekly average of >8 inhalations of Symbicort®/day.

A patient will delay taper if during the last four weeks prior to each study visit:

- The patient experiences an ACQ-5 worsening of ≥0.5 units compared to baseline and has a weekly average of ≤8 inhalations of Symbicort®/day, OR
- The patient experiences no ACQ-5 worsening (<0.5 units compared to baseline) and has a weekly average of >8 inhalations of Symbicort®/day.

1.2.3 Maintenance period

Patients in both arms will automatically enter the 16-week maintenance period during which patients in the Treatment reduction arm will continue on the Symbicort® treatment level they achieved at the end of the reduction period. In the event of asthma worsening during the maintenance period, the Investigator may decide to step up the Symbicort® dose. No reductions in Symbicort® doses are allowed during the maintenance period.

The final analysis will be performed after the last patient has completed their last visit (Visit 8b; Week 48/end of treatment [EOT]). The final analysis will include all study data from both the reduction and maintenance periods.

1.2.3.1 Sub-study

A subset of patients who consent to participation in the sub-study (approximately 32 patients are to be included, spread across the two treatment arms) will undergo additional sub-study specific tests at pre-defined timepoints (see Schedule of Assessments [SoA] in the CSP) for exploratory biomarker research. The results of the sub-study will be reported separately from the Clinical Study Report (CSR) with a separate exploratory analysis plan outlining the content of the sub-study report.

1.2.4 Study completion/end of treatment

Patients will be considered to have completed the study if they complete Visit 8b, ie, the last scheduled visit. Patients who discontinue treatment prematurely will attend an EOT visit, which includes all the assessments at Visits 8a and 8b, in order to exit the study.

1.3 Number of patients

A total of approximately 240 patients will be screened to achieve 200 randomised patients, assuming a screen failure rate of approximately 15%. A total of 200 randomised patients, according to a randomisation ratio of 3:1 (Treatment reduction arm: Reference arm), is considered sufficient to address the primary objective for the study assuming a drop-out rate of no more than 15% evaluable patients in both arms resulting in approximately 125 to 150 evaluable patients in the Treatment reduction arm and approximately 40 to 50 evaluable patients in the Reference arm. Table 2 provides the expected precision around the primary outcome, the proportion of patients successfully reducing to medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only.

The selected sample size is expected to provide a nominal 95% confidence interval (CI) around the observed proportions with a half-width of less than 10 percentage points in the Treatment reduction arm.

Screen failures are defined as patients who signed the Informed Consent Form (ICF) to participate in the clinical study but are not subsequently randomly assigned to a study treatment arm at Visit 2b (Week 0). Patients who do not fulfil the randomisation criteria (see Section 5.1.1 of the CSP) will be considered screen failed.

Table 2: Expected lower and upper half-width of exact 95% CIs (Clopper-Pearson) around observed proportion of patients successfully stepping down SMART

Observed proportion	N=50	N=100	N=125	N=150	N=200
25%	11.2% / 14.3%	8.1% / 9.7%	7.3% / 8.5%	6.7% / 7.7%	5.8% / 6.6%
35%	12.9% / 14.8%	9.3% / 10.2%	8.3% / 9.0%	7.6% / 8.2%	6.6% / 7.0%
50%	14.5% / 14.5%	10.2% / 10.2%	9.1% / 9.1%	8.3% / 8.3%	7.1% / 7.1%
65%	14.8% / 12.9%	10.2% / 9.3%	9.0% / 8.3%	8.2% / 7.6%	7.0% / 6.5%
75%	14.3% / 11.2%	9.7% / 8.1%	8.5% / 7.3%	7.7% / 6.7%	6.6% / 5.8%

2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All Patient Set

The All Patient Set (APS) will include all patients screened for the study and will be used for reporting of patient disposition and screen failure information.

Patient disposition will be summarised using the APS.

2.1.2 Full Analysis Set

The Full Analysis Set (FAS) will include all randomised patients, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed irrespective of whether they prematurely discontinue study treatment, according to the intent-to-treat principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

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

2.1.3 Sub-Study Analysis Set

The sub-study analysis set (SSAS) will include all patients from the site 2801 enrolled for the sub-study.

2.1.4 Safety Analysis Set

The safety analysis set (SAF) will include all patients from the FAS who receive any amount of study treatment and will be used for all safety analyses. Patients will be analysed according to the actual treatment received.

2.2 Violations and deviations

The final list of all protocol deviations (PDs) will be finalised and documented, and will be based on deviations defined in the study PD Specification, with all PDs, either programmable or observable, undergoing regular review as per the PD Specification document.

Patients who do not meet eligibility criteria but are still randomised will be analysed according to the analysis sets described in Section 2.1. This study does not include a Per-Protocol Set, thus no patients will be excluded from analyses.

Protocol deviations will be reviewed and may be classified as important, depending on the impact of the deviation to the analysis and/or the impact to patients. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Only important PDs will be listed and tabulated in the Clinical Study Report (CSR).

Protocol deviations confirmed to be due to Coronavirus Disease 2019 (COVID-19) may be summarised separately. See Section 4.2.8 for more information.

3 PRIMARY AND SECONDARY VARIABLES

The treatment period refers to the combination of run-in, reduction and maintenance periods spanning 52 to 56 weeks in total, depending on the duration of the run-in period.

The study period refers to the combination of reduction and maintenance periods only, spanning 48 weeks in total.

Unless otherwise specified, the last non-missing observation prior to randomisation (Visit 2b; Week 0) will serve as the baseline measurement for change from start of step down of SMART (Visit 2b; Week 0). If there is no value prior to randomisation, then the baseline value will not be imputed and will be set to missing.

For assessments of the maintenance period looking at the changes from end of the reduction period, the maintenance period baseline will be defined as the visit when the patient completed their reduction period (Visit 6; Week 32).

The absolute change from baseline:

$$Absolute\ change\ from\ baseline = visit\ value - baseline\ value$$

Depending on the period being investigated, baseline value will be either that of Visit 2b (Week 0) or the maintenance period baseline, as defined above.

Percentage (%) change from baseline:

$$\%\ change\ from\ baseline = \frac{visit\ value - baseline\ value}{baseline\ value} \times 100$$

Depending on the period being investigated, baseline value will be either that of Visit 2b (Week 0) or the maintenance period baseline, as defined above.

If either a visit value or the Visit 2b (baseline) value is missing, the absolute change from baseline value and the percentage change from baseline will also be set to missing. If baseline value is zero, the percentage change will be set to missing.

For the comparisons over the maintenance period, if either a visit value or the Visit 6 (maintenance period baseline) value is missing, the absolute change from maintenance period baseline value and the percentage change from maintenance period baseline will also be set to missing. If maintenance period baseline value is zero, the percentage change will be set to missing.

3.1 Primary Efficacy Variable

The primary aim of this study is to assess the potential to reduce Symbicort® maintenance treatment while maintaining comparable asthma symptom control to Fasenra®-treated patients on high-dose Symbicort® maintenance treatment.

The primary outcome measure is the proportion of patients who reduced their Symbicort® maintenance dose while maintaining asthma symptom control to either medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only at the end of the reduction period (Visit 6; Week 32).

A 2-sided 95% CI for proportions computed using the exact Clopper-Pearson method will be presented, as appropriate.

Symbicort® dose, as prescribed at the visit, will be recorded at each post-baseline visit up to Visit 8b (Week 48). The Symbicort® dose variable is an ordinal variable with the levels: high-dose Symbicort® maintenance treatment, medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only.

The primary outcome measure is only assessed in the treatment reduction arm as the high-dose reference arm is not tapered, by design.

The primary outcome measure related to the reduction period will be analysed once all patients have completed their Visit 6 (Week 32) assessments, and subsequently analysed when all patients have completed the study (Visit 8b; Week 48/EOT).

The proportion of patients who reduce their Symbicort® maintenance dose while maintaining asthma control to medium-dose SMART is calculated as:

$$Proportion\ of\ patients\ reducing\ Symbicort\ ®\ dose\ to\ medium\text{-}dose\ SMART = \frac{Number\ of\ patients\ on\ medium\text{-}dose\ SMART}{Number\ of\ patients\ in\ Treatment\ reduction\ arm}$$

The proportion of patients reducing Symbicort® dose to medium-dose SMART will be evaluated for the number of patients, as randomised at Day 1, as well as the number of patients with a valid measurement at Visit 6; Week 32.

The proportion of patients who reduce their Symbicort® maintenance dose while maintaining asthma control to low-dose SMART is calculated as:

$$Proportion\ of\ patients\ reducing\ Symbicort\ ®\ dose\ to\ low\text{-}dose\ SMART = \frac{Number\ of\ patients\ on\ low\text{-}dose\ SMART}{Number\ of\ patients\ in\ Treatment\ reduction\ arm}$$

The proportion of patients reducing Symbicort® dose to low-dose SMART will be evaluated for the number of patients, as randomised at Day 1, as well as the number of patients with a valid measurement at Visit 6; Week 32.

The proportion of patients who reduce their Symbicort® maintenance dose while maintaining asthma control to Symbicort® as anti-inflammatory reliever only is calculated as:

$$Proportion\ of\ patients\ reducing\ Symbicort\ ®\ dose\ to\ Symbicort®\ as\ anti\text{-}inflammatory\ reliever\ only = \frac{Number\ of\ patients\ on\ Symbicort®\ as\ anti\text{-}inflammatory\ reliever\ only}{Number\ of\ patients\ in\ Treatment\ reduction\ arm}$$

The proportion of patients reducing Symbicort® dose to anti-inflammatory reliever only will be evaluated for the number of patients, as randomised at Day 1, as well as the number of patients with a valid measurement at Visit 6; Week 32.

The number and percentage of patients who do not reduce their maintenance treatment will summarised.

3.2 Secondary Efficacy Variables

The secondary outcome measures related to the reduction period will be analysed once all patients have completed their Visit 6 (Week 32) assessments, and subsequently analysed when all patients have completed the study (Visit 8b; Week 48/EOT).

3.2.1 ACQ-5

The ACQ-5 is a shortened version of the full 7-item ACQ Patient-Reported Outcome (PRO) (Juniper et al 1999) that assesses asthma symptoms (night-time awakening, symptoms on awakening, activity limitation, shortness of breath, and wheezing) but omits the FEV_1 measurement and short-acting β-agonist (SABA) use from the original ACQ assessment (see Appendix F of the CSP for details).

Patients are asked to recall how their asthma has been during the previous week by responding to five symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled).

The ACQ-5 score is the un-weighted mean of the responses. If response to any of the questions is missing, the ACQ-5 score will be missing. Mean scores of ≤0.75 indicate well controlled asthma, scores between >0.75 and <1.5 indicate partially controlled asthma, and a score ≥1.5 indicates not well controlled asthma (Juniper et al 2006). Individual changes of ≥0.5 are considered to be clinically meaningful (Juniper et al 2005).

Patients will be categorised according to the following limits (Juniper et al 2006):

- Improvement: ACQ-5 score change from baseline ≤-0.5
- No Change: -0.5 < ACQ-5 score change from baseline <0.5
- Deterioration: ACQ-5 score change from baseline ≥0.5.

In addition, asthma control worsening responder variable is defined as an at least 0.5-unit worsening (increase) in ACQ-5 score from baseline; ie, an ACQ-5 worsening variable takes value 1, if change from baseline ACQ-5 ≥0.5, and 0 otherwise. Patients with missing or non-evaluable ACQ-5 score at a post-baseline assessment timepoint will be considered asthma worsening responders at the timepoint.

Change from maintenance period baseline (see Section 3 for definition) in ACQ-5 will be derived as Visit 8b (Week 48)/EOT score minus maintenance period baseline (Visit 6; Week 32) ACQ-5 score, with categorisation of ACQ-5 score analogous to that for the baseline. The changes in ACQ-5 will be summarised for the maintenance period separately.

Change from baseline in mean ACQ-5 score over the previous 8 weeks will also be calculated for Week 8, 16, 24, 32, 40 and 48. The mean ACQ-5 score over the previous 8 weeks will be derived as follows:

$$\frac{Total\ ACQ-5\ score\ at\ the\ visit\ and\ during\ the\ previous\ 8\ weeks}{Number\ of\ weeks\ with\ available\ ACQ-5\ at\ the\ visit\ and\ during\ previous\ 8\ weeks}$$

3.2.2 ICS Exposure

Cumulative ICS will be calculated as the sum of the doses administered each day. In order to assess the cumulative total daily ICS dose during the reduction and maintenance periods, the patient's daily dose will be collected each day and the following outcome variables will be derived:

- The patient's cumulative total daily ICS dose since the beginning of the reduction period until the end of reduction period
- The patient's cumulative total daily ICS dose throughout the duration of the study period
- The patient's cumulative total daily ICS dose since the beginning of the maintenance period to the end of maintenance period.

In addition, the patient's mean total daily ICS dose (maintenance + reliever) during the previous four/eight weeks, as required by individual patient duration of the run-in, will be derived during the study period at Week 0, 8, 16, 24, 32, 40, and 48 as the total recorded ICS dose (mcg) divided by the number of days with recorded ICS dose (including any days with 0 mcg ICS dose reported).

$$Mean\ total\ daily\ ICS\ dose\ (mcg) = \frac{Total\ recorded\ ICS\ dose\ (mcg)\ at\ the\ visit\ and\ during\ the\ previous\ 8\ weeks}{Number\ of\ days\ with\ recorded\ ICS\ dose\ (including\ 0\ mcg\ dose\ days)\ at\ the\ visit\ and\ during\ previous\ 8\ weeks}$$

The within-patient change from baseline in mean total ICS dose for the previous eight weeks will be derived as the patient's mean total daily ICS dose at each post-baseline visit minus the patient's mean total daily ICS dose at baseline (Visit 2b; Week 0).

The within-patient percentage change from baseline in mean total ICS dose for the previous eight weeks will also be derived as: 100 × (the patient's mean total daily ICS dose at each post-baseline visit minus the patient's mean total daily ICS dose at baseline [Visit 2b; Week 0])/(the total daily ICS dose at baseline value).

The total daily ICS dose for the maintenance period will be summarised from maintenance period baseline (Visit 6; Week 32) to Visit 8b (Week 48) separately.

The standardised area under the curve (AUC) of ICS dose up to Visit 6, up to Visit 8b, and from Visit 6 to Visit 8b, will be calculated as follows:

For each instance of a daily dose level, the duration of the given dose level will be calculated as end date – start date + 1. If the start date is before Visit 2b (date of randomisation), Visit 2b will be used instead for calculating the AUC up to Visit 6, and up to Visit 8b. If the start date is before the date of Visit 6, the date of Visit 6 will be used instead for calculating the AUC

from Visit 6 to Visit 8b. If the end date is after the date of Visit 6, or after the date of Visit 8b, the date of Visit 6 and Visit 8b respectively will be used instead for calculating the AUC up to Visit 6 and Visit 8b. The AUC for each dose level will be derived by the daily dose (mcg/day) multiplied by the duration (in days). The AUC is the sum of the AUCs of the individual dose levels. The AUC of ICS dose will only be calculated if all necessary data are available up to Visit 6, or Visit 8b, respectively. For patients who discontinued the study before Visit 6 or Visit 8b, respectively, the AUC will be calculated up to the date of study discontinuation.

Doses that are recorded by the inhaler sensor but confirmed by the patient to be knowingly not inhaled (eg, due to the patient priming the inhaler before use), and approved by the site and study team, will be removed from the database and hence not included in the analysis of ICS.

The standardised AUC will be derived as:

- For standardised AUC up to Visit 6: AUC divided by the available days (date of Visit 6/EOT– date of Visit 2 + 1) multiplied by 224 (ie, 32 weeks).
- For standardised AUC from Visit 6 to Visit 8b: AUC divided by the available days (date of Visit 8b/EOT – date of Visit 6 + 1) multiplied by 112 (ie, 16 weeks).
- For standardised AUC up to Visit 8b: AUC divided by the available days (date of Visit 8b/EOT – date of Visit 2 + 1) multiplied by 336 (ie, 48 weeks).

3.2.3 AQLQ(S)+12

The AQLQ(S)+12 (Juniper et al 1992, Juniper et al 2005) is a PRO that measures the health-related quality of life experienced by asthma patients (see Appendix E of the CSP for details).

The questionnaire comprises four separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous two weeks before each visit and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The four individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. Individual AQLQ(s)+12 total or domain score changes of ≥ 0.5 are considered clinically meaningful (Juniper et al 1994).

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12. The AQLQ(S)+12 responder variable will take the following values:

- 1 if change from baseline to end of treatment in AQLQ(S)+12 ≥0.5, and
- 0, otherwise.

Patients with missing or non-evaluable AQLQ(S)+12 score at a post-baseline assessment timepoint will be considered non-responders at the timepoint.

Patients will also be categorised according to the following limits in change from baseline, respectively:

- Improvement: AQLQ(S)+12 (post-baseline visit – baseline visit) ≥0.5
- No change: -0.5 < AQLQ(S)+12 (post-baseline visit – baseline visit) <0.5
- Deterioration: AQLQ(S)+12 (post-baseline visit – baseline visit) ≤-0.5.

Depending on the analysis, the baseline visit will be either Visit 2b (Week 0) for comparisons looking at data from start of the reduction period, or the maintenance period baseline (see Section 3 for definition) for analyses looking at data from start of the maintenance period.

3.2.4 Pre-bronchodilator FEV_1

Change from baseline pre-bronchodilator FEV_1 will be calculated as post-baseline pre-bronchodilator FEV_1 (L) minus baseline pre-bronchodilator FEV_1 (L) for all post-baseline measurement points.

Change from the end of the reduction period to the end of the maintenance period for pre-bronchodilator FEV_1 will be calculated as Visit 8b (Week 48)/EOT pre-bronchodilator FEV_1 (L) minus maintenance period baseline pre-bronchodilator FEV_1 (L).

3.2.5 Asthma Exacerbations

During the study, an asthma exacerbation will be defined as a worsening of asthma symptoms that leads to any of the following (this may lead to stepping up of the dosage in the Treatment reduction arm):

- A temporary bolus/burst of systemic corticosteroids for at least three consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids
- An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above)
- In-patient hospitalisation (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

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

To calculate the number of exacerbations experienced by a patient during the study period (total reduction and maintenance periods), the following rule will be applied.

The start of an exacerbation is defined as the start-date of systemic corticosteroids or start-date of a temporary increase in a stable OCS background dose, or start-date of a hospital admission, whichever occurs earlier. The end-date is defined as the last day of systemic corticosteroids, or the last day of a temporary increase in a stable OCS background dose, or the date of discharge from a hospital, whichever occurs later. The number of exacerbations observed for a patient during the 48-week study period (total of reduction and maintenance periods) will be used as the response variable.

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

An asthma exacerbation that occurs within seven days of the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event.

Maximum follow-up time for a patient is approximately 48 weeks; defined as the time from first dose of Fasenra® taken in the reduction period to the end of the study. For a patient lost to follow-up, this will be defined as the time from first dose of Fasenra® taken in the reduction period to the timepoint after which an exacerbation could not be assessed.

For the production of summary statistics, the annual exacerbation rate (AER) per patient is calculated and standardised using data from the study period (total of reduction and maintenance periods), the reduction period and the maintenance period separately, according to the formula described below:

$$AER = \frac{Number\ of\ Exacerbations\ in\ period}{Follow\text{-}Up\ Date - Date\ of\ first\ Fasenra^{®}\ dose\ in\ period + 1} \times 365.25$$

Follow-up date for the study and maintenance periods is Visit 8b (Week 48) and the follow-up date for the reduction period is the date of Visit 6 (Week 32).

The number of exacerbations during the maintenance period will be summarised from end of Visit 6 (Week 32) to Visit 8b (Week 48) separately.

3.2.6 Symbicort® dose at the end of the maintenance period

Similar to the primary efficacy variable in Section 3.1, the proportion of patients who were using the same Symbicort® daily dose at the end of the maintenance period (Visit 8b; Week 48), as they achieved at the end of the reduction period (Visit 6; Week 32), will be calculated.

3.2.7 Clinical Remission

The number and proportion of patients achieving composite endpoints defining clinical remission at the end of the reduction phase (Visit 6, Week 32) or at the end of the study period (Visit 8b, Week 48) will be presented. Clinical remission at Week 32 or Week 48 is defined as:

- Exacerbation free between randomisation (Visit 2b) and the relevant timepoint
- Less than 10% deterioration in FEV1 at the relevant timepoint compared to randomisation (Visit 2b)
- ACQ-5 < 1.5 at the relevant timepoint

Additionally, clinical remission with ACQ-5 $\leq$ 0.75 will be assessed and reported.

3.3 Safety variables

Safety and tolerability will be evaluated in terms of reported AEs (including SAEs [refer to CSP Appendix B for definition]).

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements, refer to Section 4.1.2 for Visit Windows. Adverse events presenting during the run-in period will be reported as by-patient listings only. All AE summaries will be presented for the study period.

Change from baseline to each post-treatment timepoint 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 of partial/missing dates for AEs and prior/concomitant medications is detailed in Section 4.1.1. Duration of AEs and prior/concomitant medications will not be calculated using imputed dates and will instead be set to missing.

3.3.1 Adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a

causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in period, even if no study treatment has been administered. All AEs and SAEs will be recorded from the time of signing the ICF.

Duration of an AE will be calculated as follows:

$$Duration\ of\ AE\ (days) = AE\ end\ date - AE\ onset\ date + 1$$

Adverse event data will be categorised according to their onset date into the following study periods:

- AEs in the run-in period are defined as those with onset on or after date of signing the ICF and prior to randomisation date.
- AEs in the study period are defined as those with onset on or after date of randomisation and on or prior to the Visit 8b/EOT visit.

If an AE has a missing onset date it will be considered a study period event unless the stop date of the AE indicates otherwise. Similarly, if an AE has a partial onset date it will be considered a study period AE unless the partial onset date or the stop date indicates otherwise.

Adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

3.4 Exploratory variables

3.4.1 Blood eosinophils count

Blood eosinophil samples will be collected from all patients at all study visits indicated in the SoA (refer to CSP for details). If there is an EOT visit, a blood sample for eosinophils will be taken. Analysis will be performed at a local laboratory.

The results will be summarised and reported descriptively within the CSR after all patients have completed Visit 8b (Week 48). Final results will be presented for all patients with an EOT visit as well.

3.4.2 CCI

The CCI designed to capture patient beliefs about the perceived importance of CCI

CCI [redacted]. Patients will be asked to complete the questionnaire at study visits indicated in the SoA (refer to CSP for details). The patient response to each statement is captured using a 3-point scale for Part 1 of the questionnaire and 5-point Likert Scale (strongly disagree to strongly agree) for Part 2 of the questionnaire.

3.4.3 Health economics

After the exacerbation assessment at each visit, per SoA in CSP, the Investigator or authorised delegate will assess whether the patient has had any CCI [redacted] If yes, CCI [redacted]

The number of days/times the following resources were utilized will be presented for each patient:

- CCI [redacted]

3.5 Assessment of study population

In this study, "enrolled" patients are defined as those who provide informed consent by signing the ICF at Visit 1. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number at Visit 2b.

3.5.1 Demographics

Demographic characteristics and baseline disease characteristics will be assessed.

3.5.2 Medical and surgical history

Medical and surgical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

3.5.3 Prior and concomitant medications

All medications will be classified into Anatomical Therapeutic Chemical (ATC) drug classes using the latest version of the World Health Organisation (WHO) Drug Dictionary (WHODD).

Any medications or vaccines received by the patient with an end date prior to 3 months before informed consent will be considered as prior medications.

Any medication or vaccines received by the patient in the 3 months prior to the date of informed consent and medications received at the time of enrolment or during the study will be considered as concomitant medication.

3.5.4 Exposure to Fasenra®

The duration of exposure to Fasenra® is defined as the number of days between first dose of Fasenra® following randomisation and the end dates of Fasenra® plus the dosing frequency time:

$$\begin{aligned} &Duration\ of\ exposure\ to\ Fasenra\ (days) \\ &\quad = (Last\ dosing\ date + 56\ days) \\ &\quad - First\ Fasenra\ dosing\ date\ after\ randomisation + 1 \end{aligned}$$

The total number of injections will be counted per patient. Furthermore, the number of patients with an injection will be assessed in 8-weekly categories (ie, 8 weeks, 16 weeks, …, 40 weeks).

4 ANALYSIS METHODS

4.1 General principles

Continuous data will be summarised in terms of the number of non-missing observations (n), mean, standard deviation (SD), 2-sided 95% confidence interval (CI) of the mean (except safety data), median, minimum, and maximum, unless stated otherwise.

The minimum and maximum will be reported to the same number of decimal places, as the raw data recorded in the database. The mean and median will be reported to one more decimal place, and SD will be reported to two more decimal places, than the raw data

recorded in the database. Any CIs will be presented to one more decimal place than the raw data.

A maximum of four decimal places will be used for all summary statistics.

Confidence intervals will be presented to one more decimal place than the point estimate.

Categorical data will be summarised in terms of the number of patients providing data at the relevant timepoint (n), with frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator, unless stated otherwise.

SAS® version 9.3, or higher, will be used for the data analysis.

Study Day 1 is defined as the date of randomisation.

For visits (or events) that occur on or after randomisation, study day:

$$Study\ day = Date\ of\ visit\ [event] - Date\ of\ randomisation\ +\ 1$$

For visits (or events) that occur prior to randomisation, study day:

$$Study\ day = Date\ of\ visit\ [event] - Date\ of\ randomisation$$

There is no Study Day 0.

No multiplicity adjustments are planned for this study.

4.1.1 Missing data

Prior and concomitant medication partial dates will be imputed as outlined in Appendix 8.1.1.

Adverse events with partial dates missing the day, or both day and month of the year will adhere to the conventions outlined in the Appendix 8.1.1.

For details of dealing with missing ACQ-5 and AQLQ(S)+12 scores, refer to Section 3.2.1 and Section 3.2.3, respectively.

Partial date of birth and date of first asthma diagnosis will be imputed, as described in Appendix 8.1.2.

4.1.2 Visit windows

All visit-based summaries will use analysis visits. All post-randomisation scheduled and unscheduled visits (excluding EOT), will be mapped to an appropriate analysis visit as follows:

Table 3 Analysis Visit Mapping

CRF visit	Target day	Actual assessment day	Analysis visit
Visit 1 (screening)	-D56/-D28	-D56/-D28 to -D1	Screening
Visit 2b (randomisation)	D1	D1	Randomisation
Visit 3	D57	D2 to D85	Week 8
Visit 4	D113	D86 to D141	Week 16
Visit 5	D169	D142 to D197	Week 24
Visit 6	D225	D198 to D253	Week 32
Visit 7	D281	D254 to D309	Week 40
Visit 8b	D337	D310 to D365	Week 48

If multiple readings are recorded within a single visit window, the following rules will be followed.

- If there are two or more observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis. If not possible, the earliest non-missing record collected within the visit window will be used in analysis.
- If two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If two observations are collected on the same day, then the non-missing one with the earlier collection time will be included in the analysis.

The following rules will be followed for questionnaire related data:

- If multiple records on the same day are collected but only one with time recorded, then the non-missing record with time recorded will be used in the analysis.
- If multiple records are collected on the same day, all with time recorded, then the earliest of the non-missing records will be used in the analysis.

A listing will be presented for all records, with flags identifying the source of the record and whether the score was used in analysis tables.

If a visit window does not contain any observations, then the data will remain missing.

4.2 Analysis methods

All efficacy analyses will be performed using the FAS. Safety analyses will be performed using the SAF.

The end of the reduction period is considered to be Visit 6 (Week 32). The end of the maintenance period is considered to be Visit 8b (Week 48) or EOT.

4.2.1 Assessment of study population

4.2.1.1 Patient disposition

Patient disposition will be summarised using the APS. The number and percentage of patients will be presented by the following categories: enrolled, randomised, completed reduction phase (ie, attended Visit 6), completed the study (ie, attended Visit 8b) and discontinued from the study (with reasons for discontinuation). A summary of patients who discontinued treatment (with reason for discontinuation) will also be provided.

4.2.1.2 Demographic characteristics

Demographic and baseline patient characteristics will be presented by descriptive statistics by treatment arm, as well as overall for the FAS.

Age will be derived from the date of informed consent minus date of birth, rounded down to the nearest integer. For patients in countries where date of birth is not recorded, the age as recorded in the eCRF will be used. Refer to Appendix 8.1.2, for rules on imputation of partial dates for date of birth and date of first asthma diagnosis.

The following standard descriptive statistics will be presented for data collected at Screening for patients in the FAS (as per local regulations):

- Age (years) (continuous)
- Age group (years):
  - ≥18 - <50
  - ≥50 - <65
  - ≥65.
- Sex:
  - Male
  - Female.
- Race:
  - White
  - Black or African American

  - Native Hawaiian or Other Pacific Islander
  - Asian
  - American Indian or Alaska Native
  - Other.
- Ethnic group:
  - Hispanic or Latino:
    - Yes
    - No.
- Country:
  - France
  - Italy
  - Germany
  - United Kingdom.
- Smoking status:
  - Current
  - Former
  - Never.

A by-patient line-listing of demographic and baseline characteristics will be presented.

4.2.1.3 Baseline characteristics

The following patient characteristics will be presented for data collected at baseline visit (Visit 2b; Week 0).

Following ePROs will be summarised at baseline:

- ACQ-5 score
- AQLQ(S)+12 score.

Following disease characteristics will be summarised at baseline:

- Age at first asthma diagnosis, calculated as:

$$\frac{Date\ at\ first\ asthma\ diagnosis - Date\ of\ birth}{365.25}$$

- Number of pack-years (PY)
- Asthma duration (years), calculated as:

$$\frac{(Date\ of\ randomisation - Date\ of\ first\ asthma\ diagnosis) + 1}{365.25}$$

- Number of exacerbations in the 12 month period prior to first commercial Fasenra
- Number of exacerbations requiring systemic corticosteroid treatment use in the 12 month period prior to first commercial Fasenra
- Number of exacerbations requiring emergency room treatment in the 12 month period prior to first commercial Fasenra
- Number of exacerbations requiring hospitalisation in the 12 month period prior to first commercial Fasenra
- Number of exacerbations from starting Fasenra® treatment to Visit 1
- Number of exacerbations requiring systemic corticosteroid treatment use from starting first commercial Fasenra® treatment to Visit 1
- Number of exacerbations requiring emergency room treatment from starting first commercial Fasenra® treatment to Visit 1
- Number of exacerbations requiring hospitalisation from starting first commercial Fasenra® treatment to Visit 1
- Most recent exacerbation type:
  - Required systemic corticosteroids treatment
  - Asthma-related hospitalisation
  - Required systemic corticosteroids treatment and asthma-related hospitalisation
- Time since last exacerbation (days), calculated as:

$$Date\ of\ randomisation - Date\ of\ most\ recent\ exacerbation$$

- Pre-bronchodilator Pulmonary Function Tests:
  - FEV_1 (L)
  - Predicted FEV_1
  - Forced vital capacity (FVC) (L)
  - Predicted FVC.
- FeNO
- Blood eosinophil count at baseline.

4.2.1.4 Medical and surgical history

Medical history will be summarised by SOC and PT for the FAS. Surgical history will be listed.

4.2.1.5 Prior and concomitant medications

The following summaries will be produced:

- Summary of prior medications by ATC level 3 code and PT, overall for the FAS.
- Summary of prior asthma medications by ATC level 3 code and PT, overall for the FAS.

- Summary of concomitant medication by ATC level 3 code and PT, overall and by treatment for the FAS.

Multiple records for a patient in the same ATC level 3 category and PT will be counted only once.

4.2.2 Primary Efficacy Analysis

The proportion of patients in the reduction arm who reduce their Symbicort® maintenance treatment to either medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only at Week 32 will be assessed using a table containing the number of patients and proportion of patients at each step down together with exact 2-sided 95% CI (Clopper-Pearson).

The primary analysis will evaluate the data for patients with non-missing Week 32 assessment values.

The number and percentage of patients recording each prescribed Symbicort® dose level will also be summarised by visit.

The proportion and percentage of patients who maintain the same Symbicort® daily dose at the end of the maintenance period as they achieved at the end of the reduction period will also be included.

Final analysis will evaluate the data for patients with non-missing Week 48 assessment values once all randomised patients have completed their treatment.

4.2.2.1 Sensitivity Analysis

A sensitivity analysis to assess the effect of missing data/drop-out on the primary outcome measure will be performed by including all patients with a missing Week 32 assessment, irrespective of whether a patient discontinued treatment, as a "Non-responder" (ie, unable to reduce their Symbicort® maintenance treatment to either medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only).

4.2.3 Secondary Efficacy Analyses

4.2.3.1 ACQ-5

Change from baseline ACQ-5 will be derived weekly up to end of the reduction period and up to the end of the maintenance period as post-baseline score minus baseline ACQ-5 score (Visit 2b; Week 0) for the reduction period analysis, and post-baseline score (Week 40, Week 48/EOT) minus maintenance period baseline (Visit 6; Week 32) score for maintenance period analysis.

The change from baseline in mean ACQ-5 score over the previous 8 weeks will also be summarised for Week 8, 16, 24, 32, 40 and 48. Baseline for the mean ACQ-5 score over the previous 8 weeks will be defined as the last non-missing ACQ-5 score prior to randomisation. Missing ACQ-5 score will not be imputed. Change from baseline in mean ACQ-5 over the previous 8 weeks will be evaluated using a mixed model repeated measures (MMRM) comparing the reduction arm with the reference arm, with treatment arm, visit, visit × treatment and baseline ACQ-5 score as covariates. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation. An unstructured correlation pattern will be used to estimate the variance-covariance of the within-patient repeated measures. In the case that the model does not converge using an unstructured covariance matrix, the heterogeneous Toeplitz covariance structure will be evaluated, followed by the heterogeneous autoregressive of first order, heterogeneous compound symmetry, and homogeneous compound symmetry covariance structures in the case of further non-convergence. The restricted maximum likelihood method will be used. The least-square mean and mean difference in ACQ-5 score change from baseline between the two treatment arms, standard errors and the 95% CI at each 8-weekly timepoint will be presented.

The proportion of patients achieving no deterioration in ACQ-5 (no deterioration means change from baseline <0.5) at the end of the reduction period will be presented for each treatment arm. Summary statistics for ACQ-5 and change from baseline will be presented by visit.

Deterioration is defined as an increase in ACQ-5 of ≥0.5 units compared to baseline, respective to the baseline of interest.

A summary table of worst ACQ-5, defined as the maximum ACQ-5 score within four weeks prior to the scheduled visit (including the visit) will be presented for each scheduled visit throughout the reduction period.

If the model assumptions of normality are violated for the efficacy outcome measure, appropriate alternative non-parametric analyses methods will be considered.

4.2.3.2 ICS Exposure

ICS exposure will be reported using the following variables and will be summarised by treatment arm for the FAS, separately for the reduction, maintenance and study periods:

- Cumulative daily ICS dose (maintenance + reliever)
- Mean total daily ICS dose (maintenance + reliever)
- Standardised AUC for the reduction, maintenance and study periods.

The change from baseline in the mean total daily ICS dose (maintenance + reliever) during the previous eight weeks will be evaluated using an MMRM approach including mean total daily ICS dose at baseline, visit, treatment arm, and visit × treatment as covariates. The Least Square mean change and corresponding 95% CIs will be presented.

If the model assumptions of normality are violated for the efficacy outcome measure, appropriate alternative non-parametric analyses methods will be considered.

Summary statistics for total daily ICS dose and change from baseline will be presented by visit.

The number and proportion of patients sustaining the same Symbicort® daily dose at the end of the maintenance period (Visit 8b; Week 48) as the dose they achieved at the end of the reduction period (Visit 6; Week 32) will be summarised.

All ICS dose analyses will be presented in micrograms (mcg). Symbicort 200/6 doses will be converted to 200 mcg and Symbicort 400/12 doses will be converted to 400 mcg for the purpose of ICS dose calculations.

4.2.3.3 AQLQ(S)+12

Change from baseline AQLQ(S)+12 will be derived up to Week 48 as post-baseline score minus baseline AQLQ(S)+12 score (Visit 2b; Week 0). The mean change from baseline AQLQ(S)+12 at the end of the reduction period is defined as at Week 32.

The mean change from baseline AQLQ(S)+12 will be analysed using an MMRM approach including baseline AQLQ(S)+12 score, visit and treatment arm, and visit × treatment as covariates. The estimated Least Square mean change from baseline AQLQ(S)+12 during the reduction and the study periods will be presented by treatment and visit together with 2-sided 95% CIs, respectively.

The proportion of patients achieving no deterioration in AQLQ(S)+12 at the end of the reduction period will be presented for each treatment arm. Summary statistics for AQLQ(S)+12 and change from baseline will be presented by visit.

Deterioration is defined as a decrease in AQLQ(S)+12 of $\geq$0.5 units compared to baseline.

If the model assumptions of normality are violated for the efficacy outcome measure, appropriate alternative non-parametric analyses methods may be considered.

The change in AQLQ(S)+12 from the maintenance period baseline to the end of maintenance period/EOT is defined as Visit 8b (Week 48)/EOT score minus maintenance period baseline (Visit 6; Week 32) score and will follow categorisation outlined in Section 3.2.3.

4.2.3.4 Change from baseline in FEV_1

Change from baseline (Visit 2b; Week 0) pre-bronchodilator FEV_1 will be assessed at Weeks 8, 16, 24, 32, 40, and 48. The mean change from baseline pre-bronchodilator FEV_1 at the end of the reduction period is defined as at Week 32. Summary statistics for FEV_1 and change from baseline will be presented by visit.

The mean change from baseline pre-bronchodilator FEV_1 will be analysed using an MMRM approach including baseline FEV_1 visit, treatment arm, and visit × treatment as covariates. The estimated Least Square mean change from baseline pre-bronchodilator FEV_1 during the reduction and the study periods will be presented by treatment and visit together with 2-sided 95% CIs, respectively.

If the model assumptions of normality are violated for the efficacy outcome measure, appropriate alternative non-parametric analyses methods may be considered.

Change from maintenance period baseline to the end of the maintenance period for pre-bronchodilator FEV_1 will be calculated as Visit 8b (Week 48)/EOT value minus maintenance period baseline (Visit 6; Week 32) value.

4.2.3.5 Asthma Exacerbations

The AER from Visit 2b (Week 0) up to Visit 8b (Week 48) of the reduction arm will be compared to the AER of the reference arm using a negative binomial model. The response variable in the model will be the number of asthma exacerbations experienced by the patient over the study period. The model will include the randomised treatment arm as a covariate, with the logarithm of the patient's corresponding follow-up used as an offset variable in the model.

The estimated treatment effect (ie, the rate ratio of reduction arm as compared to the reference arm) with corresponding 95% CI will be presented, along with model estimated rates for each treatment arm.

The number of exacerbations will be summarised for the reduction, maintenance and study periods similarly to the exacerbation count derivation, from Visit 2b (Week 0) to date of Visit 6 (Week 32), from Visit 6 (Week 32) to Visit 8b (Week 48), and from Visit 2 to Visit 8b, respectively.

Summary statistics for the AER will be presented for the study, reduction and maintenance periods separately. The cumulative number of exacerbations over time will be plotted standardised by the number of patients in the randomised treatment arms.

The proportion of patients with ≥1 asthma exacerbation during the 48-week study period will also be derived.

4.2.3.6 Clinical Remission

Descriptive summaries of the number and proportion of patients meeting each composite endpoint criteria defining clinical remission at Week 32 (Visit 6) or at Week 48 (Visit 8b) (i.e., no exacerbations between randomisation and relevant timepoints, less than 10% deterioration in FEV1 at relevant timepoint, and ACQ-5 ≤ 0.75 or ACQ-5 < 1.5 at relevant timepoints) will be presented for both treatment arms.
A remission score calculated for each patient still in the study at Week 32 or Week 48 and based on the number of remission components achieved will describe the number and proportion of patients achieving multiple combinations of the endpoints:

- 0, 1, 2 and 3 remission endpoints achieved (ACQ-5 < 1.5, < 10% FEV1 deterioration and zero exacerbations; ACQ-5 ≤ 0.75, < 10% FEV1 deterioration and zero exacerbations)
- Only exacerbation and ACQ-5 endpoints achieved, i.e., 0, 1 and 2 remission endpoints achieved (ACQ-5 < 1.5 and zero exacerbations; ACQ-5 ≤ 0.75 and zero exacerbations)

Patients will be included for any individual component for which they have data. Patients will be excluded from the remission summary (0, 1, 2, 3) if they are missing one of the relevant components.

4.2.4 Exploratory Analyses

4.2.4.1 Change from baseline FeNO

The change from baseline FeNO (parts per billion [ppb]) will be assessed descriptively and using a MMRM approach including, baseline FeNO measurement, treatment arm, visit, and visit × treatment as covariates. The estimated Least Square mean change from baseline FeNO during the reduction and the study periods will be presented by treatment and visit together with 2-sided 95% CIs, respectively.

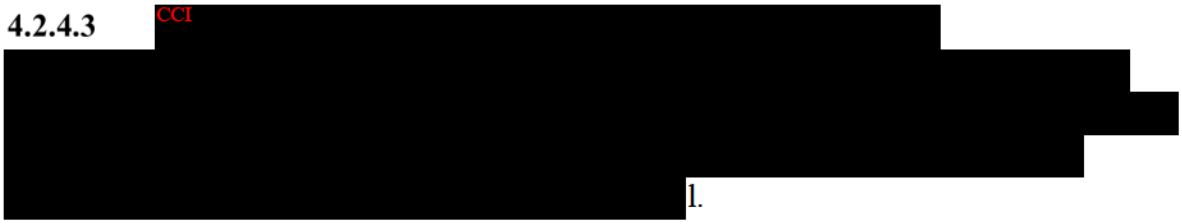
A shift table will be produced for FeNO categories to display <25, ≥25 - <50, ≥50, and missing values. The shift tables will present baseline and value at the end of the reduction period, as well as end of study period, as applicable, and will include patients with both baseline and post-baseline data throughout the study period.

Shift plots showing each individual patient's laboratory value at baseline and at the end of reduction period and at the end of the study period will be produced for continuous FeNO data.

4.2.4.2 Change from baseline in blood eosinophil count

The change from baseline blood eosinophil count will be assessed descriptively and using a MMRM approach including baseline blood eosinophil count, treatment arm, visit, and treatment × visit as covariates. The estimated Least Square mean change from baseline eosinophil count during the reduction and the study periods will be presented by treatment and visit together with 2-sided 95% CIs. These analyses will be performed using eosinophil values presented in conventional units.

4.2.4.3 CCI



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4.2.5 Exposure to Fasenra

Exposure will be summarised by treatment arm for the FAS.

Summary statistics will be provided for the cumulative duration of exposure. The number and percentage of patients treated ≥8 weeks, and up to 48 weeks in 8-weekly intervals will be provided.

The number and percentage of patients with injections will be presented by total number of injections (ie, 1, 2, …, 6) and in 8-weekly intervals (ie, 8 weeks, 16 weeks, …, 40 weeks).

4.2.6 Safety Analyses

All safety variables will be summarised for all patients in the SAF and presented by treatment arm.

AEs will be summarised for the study period (reduction and maintenance periods combined), when attributed to Symbicort®, Ventolin® or Fasenra®, as defined in Section 3.3.1. All AEs will be listed for each patient, regardless of the time period.

An overall summary table will be produced showing the number and percentage of patients with at least one AE in any of the following categories: AEs, deaths due to AE, SAEs, and AEs causing the discontinuation of study treatment (DAEs), for the study period. The total

number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a patient).

Adverse events, DAEs, and SAEs will be summarised by SOC and PT assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least one occurrence will be presented (ie, a patient with multiple occurrences of an AE will only be counted once).

AEs and SAEs (by PT) will be summarised by Investigator's causality (related vs not related) for Fasenra®, Ventolin® and for Symbicort®, and maximum intensity for each of the treatments. If a patient reports multiple occurrences of the same AE within the same reported period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). Similarly, the worst causality will be attributed and used in the by causality summaries. Deaths will also be summarised in separate tables.

A summary of the most common (ie, frequency of >1%) AEs will also be presented by PT.

If there is a sufficient number of hypersensitivity events (standardised MedDRA query of hypersensitivity) or AEs of injection site reactions (high level term of administration and injection site), it will be summarised by PT for the treatment period as well as the study period.

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

4.2.7 Health economics

The number and percentage of patients with asthma specific resource utilization (defined in Section 3.4.3) will be presented by randomised treatment arm.

4.2.8 Impact on analyses due to COVID-19 pandemic

Given the uncertainty surrounding the future impact of the COVID-19 worldwide pandemic on clinical trials, operational procedures are being implemented in this study to maintain the integrity of collected data. Efforts may be made to collect data via alternative means where possible, when on-site visits cannot be performed.

If there is a sufficient number of protocol deviations or study disruptions as a result of COVID-19, then sensitivity analyses may be conducted to evaluate their impact on the interpretation of results. Protocol deviations, including doses or visits missed due to COVID-19 related protocol deviations may be described separately in the CSR. Confirmed or suspected cases of COVID-19 will be listed and included as AEs as appropriate.

5 INTERIM ANALYSES

No interim analyses are planned for this study.

The final database lock will be performed after all patients have completed the maintenance period (Visit 8b/EOT) and will inform the pre-defined final analysis outputs, as well as cover the contents of the CSR.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Section 9.4.1 of the CSP (Asthma Exacerbations):

The calculation of the number of exacerbations experienced by a patient will be done for the study period (reduction and maintenance) instead of treatment period (run-in, reduction and maintenance period).

Section 9.4.1 of the CSP (Total ICS Dose Exposure):

Inhaled corticosteroid exposure section assessing cumulative total daily ICS dose variables has been updated as per team request:

- The patient's total daily ICS dose on each day - will not be derived
- The patient's cumulative total daily ICS dose each day since the beginning of the reduction period until the end of reduction period and until to the end of maintenance period – variables will be derived for the period but will not be split out for each day
- The patient's cumulative total daily ICS dose each day since the beginning of the maintenance period to the end of maintenance period - variable will be derived for the period but will not be split out for each day.
-

Section 9.4.2 of the CSP (AQLQ(S)+12, Change from Baseline FEV_1, Total Daily ICS Dose):

All secondary endpoint MMRM analyses will include baseline value as a covariate.

Section 9.4.3.1 of the CSP (Adverse events):

- All instances of summaries and listings related to adrenal insufficiency will not be produced as per erroneous inclusion of adrenal insufficiency in the CSP v1.0.
- SAEs causing discontinuation of the study treatment/study will not be summarised.
- A summary of the most common AEs will be presented for AEs with frequency > 1% and not > 5%
- AEs of injection site reactions (high level term of administration and injection site) will only be summarised by PT for the treatment period if a sufficient number of events are reported.

Section 9.4.4 (Change from baseline FeNO and Change from baseline in blood eosinophil count):

All exploratory endpoint MMRM analyses will include baseline value as a covariate.

7 REFERENCES

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Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994; 47(1): 81-87.

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Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes. 2005; 3: 58.

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8 APPENDIX

8.1 Imputation rules for partial dates

8.1.1 Adverse events, medical history and prior/concomitant medications

Dates missing the day, or both the day and month of the year will adhere to the following conventions to classify medical history, prior and concomitant medications, and adverse events:

Adverse Events

- The missing start day will be set to:
  - First day of the month of occurrence, if the start YYYY-MM is after the YYYY-MM of first study treatment
  - The day of the first study treatment, if the start 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 end day will be set to:
  - The last day of the month of the occurrence, if the end YYYY-MM is after the YYYY-MM of the first study treatment
  - Death date if the patient died in the same month
  - The day of last study treatment if the YYYY-MM of occurrence is the same as the last study treatment
- If the start date is missing both the day and month, the start date will be set to:
  - January 1 of the year of occurrence if the start year is after the year of first study treatment
  - The date of the first study treatment, if the start year is the same as the year of the first study treatment
- If the end date is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence
  - Date of death if the patient died in the same year

  - Last study treatment date if the year of occurrence is the same as the last study treatment date

- If the start date is null, the date will be set to:
  - The date of first study treatment
  - January 1 of the same year as the end date, if the end date suggests that the start date could be prior to the date of first study treatment
- If the end date is null and not recorded as ongoing, the date will be set to:
  - The date of the first study treatment, if the start date is prior to the date of first study treatment
  - The date of last visit, if the start date is on or after the date of first study treatment
- If the end date is null and recorded as ongoing, the end date will not be imputed.

Prior/Concomitant medication and Medical History

- The missing start day will be set to:
  - First day of the month of occurrence
- The missing end day will be set to:
  - The last day of the month of the occurrence
- If the start date is missing both the day and month, the start date will be set to:
  - January 1 of the year of occurrence
- If the end date 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 prior/concomitant medication is null and the end date is not a complete date, the start date will be set to the earlier of:
  - Imputed partial end date, and
  - Date of first study treatment
- If the start date of prior/concomitant medication is null and the end date is a complete date, the start date will be set to:

  - The date of the first study treatment, if the end date is after the date of first study treatment
  - The end date of the therapy otherwise

- If the end date is null and recorded as ongoing, the end date will not be imputed.
- If the start or end dates of medical history are null, they will not be imputed.

8.1.2 Partial dates for date of birth and date of first asthma diagnosis

If the first asthma diagnosis date or date of birth is a partial date, the following imputation rules will be implemented:

- If the year is present but the month and day are missing, then July 1 will be imputed as the start date.
- If the year and month are present but the day is missing, then 15 will be imputed as the start date.

8.1.3 Partial dates for most recent exacerbation date

If the most recent exacerbation date is a partial date, the following imputation rules will be implemented:

- If the year is present but the month and day are missing, then July 1 will be imputed as start date
- If the year and month are present but the day is missing, then 15 will be imputed as the start date

8.1.4 Partial dates for surgical history

If surgical history date is a partial date, the following rules will be applied:

- If start or end date of surgical history date is a partial date, then the following will be applied:
  - If the start date is not partial and the end date is partial, then the end date will be imputed as the start date.
  - If the end date is not partial and the start date is partial, then the start date will be imputed as the end date.
  - If the start date and end date is missing the month and day but year is present, then July 1 will be imputed as the start and end date

  - If the start date and end date is missing the month but day and year is present, then July will be imputed as the start and end month
  - If the start date and end date is missing the day but month and year is present, then 15 will be imputed as the start and end day

- If the end date is null or recorded as ongoing, then the end date will not be imputed.

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Document Title:	Statistical Analysis Plan Edition 3	
Document ID:	Doc ID-004223075	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
17-Jan-2023 13:17 UTC	PPD	Content Approval
11-Jan-2023 08:09 UTC	PPD CYTEL	Content Approval
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SHAMAL: A Multicentre, Randomised, Open-Label, Parallel-Group, Active-Controlled, Phase IV Study to Assess the Reduction of Daily Maintenance ICS/LABA Treatment Towards Anti-Inflammatory Reliever Treatment in Patients with Severe Eosinophilic Asthma Treated with Benralizumab

Statistical Analysis Plan Addendum

Parexel Project Number: 243961

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Approved by: PPD
Senior Biostatistician
AstraZeneca

Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan Addendum was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	Date of last signature	New document
2.0	Date of last signature	Addition of section 1.2 to state the updated definition of baseline ACQ-5. Addition of section 1.3 to update the outcome measure for the secondary endpoint of ICS dose exposure.
3.0	Date of last signature	Addition of section 1.4 and 1.5 to state that a "Missing" category will be added to distinguish the number and percentage of patients with missing score contributing to Non-Responders at each timepoint.

1 CHANGES TO THE STATISTICAL ANALYSIS PLAN

1.1 Secondary Efficacy Analyses – Asthma Exacerbations

Section 4.2.3.5 of the statistical analysis plan (SAP) version 3.0 stated that a negative binomial model will be used to model the Asthma Exacerbation Rate (AER) from visit 2b (Week 0) up to Visit 8b (Week 48) of the reduction arm compared to the reference arm.
This is being updated to a poisson model. The response variable, covariates and offset variable will remain the same as that mentioned in the SAP version 3.0. The change is being made as the negative binomial model does not converge when applied to the locked data.

1.2 Secondary Efficacy Analyses – ACQ-5

Section 4.2.3.1 of the SAP version 3.0 stated that baseline for the mean ACQ-5 score over the previous 8 weeks will be defined as the last non-missing ACQ-5 score prior to randomisation.
This has been updated to the following: Baseline for the mean ACQ-5 score over the previous 8 weeks is defined as the Visit 2b (Week 0) result. The change is being made as it was later noted that some subjects had Visit 2b (Week 0) prior to randomisation ACQ-5 scores recorded on paper CRF and entered in the EDC after randomisation.

1.3 Secondary Objectives – To assess the total inhaled corticosteroids (ICS) dose exposure

Section 1.1.2 of the SAP version 3.0 stated that one of the outcome measures for the secondary objectives to assess the total ICS dose exposure is defined as Total daily ICS dose (maintenance + reliever) at the end of the reduction period.
This outcome measure has been updated to the mean total daily ICS dose in the previous 8 weeks. The derivation of the Mean total daily ICS dose in the previous 8 weeks is given in Section 3.2.2 of the SAP version 3.0. This change is being made as mean total daily ICS dose in the previous 8 weeks measures more accurately the SMART step-down of subjects and to align Section 1.1.2 in the SAP with the analyses already approved and described in Section 3.2.2.

1.4 Secondary Efficacy Analyses – ACQ-5

Updated Section 3.2.1 of the SAP version 3.0 to specify that patients will be categorised as Responders and Non-responders. Patients with an improvement in their ACQ-5 score at the timepoint will be summarised under the Responder category. Patients with no change or deterioration in their ACQ-5 at the timepoint will be summarised under the Non-responder category.

Section 3.2.1 of the SAP version 3.0 stated that patients with missing or non-evaluable ACQ-5 score at a post-baseline assessment timepoint will be considered asthma worsening responders at the timepoint.
This has been updated to: patients with missing or non-evaluable ACQ-5 change score at a post-baseline assessment timepoint will be considered asthma non-responders at the timepoint, and presented as Missing category.

1.5 Secondary Efficacy Analyses – AQLQ(S)+12

Updated Section 3.2.3 of the SAP version 3.0 to specify that patients will be categorised as Responders and Non-responders. Patients with an improvement in their AQLQ(S)+12 score at the timepoint will be summarised under the Responder category. Patients with no-change or deterioration in their AQLQ(S)+12 at the timepoint will be summarised under the Non-responder category.
Section 3.2.3 of the SAP version 3.0 stated that patients with missing or non-evaluable AQLQ(S)+12 score at a post-baseline assessment timepoint will be considered non-responders at the timepoint.

This has been updated to: patients with missing or non-evaluable AQLQ(S)+12 change score at a post-baseline assessment timepoint will be considered non-responders at the timepoint, and presented as Missing category.

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Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
11-Jul-2023 06:51 UTC	PPD CYTEL	Content Approval
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