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

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Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2019-001924-37

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 4.0	15 November 2022
Version 3.0	17 September 2021
Version 2.0	10 July 2020
Version 1.0 (Original Protocol)	04 June 2019

Clinical Study Protocol, Version 4.0, 15 November 2022

This clinical study protocol (CSP) amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

- To add a secondary endpoint.
- To clarify blinding results of fractional exhaled nitric oxide (FeNO) measurement will be applicable to all 'study site staff' and patients.
- To add Ventolin to adverse event (AE) causality collection section.
- To remove reference to analysis after patients reach Visit 6 (32 weeks).
- To remove reference to the initial read-out of primary analysis of the reduction period.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.2, Synopsis; Section 3, Objectives and Endpoints; Section 9.4.1, Outcome measures for analyses calculation or derivation of efficacy variables	Updated to add a secondary endpoint ie, clinical remission	Clinical Remission composite score is a new endpoint, not available during previous Clinical Study Protocol (CSP) versions, so is added as it is becoming an important emerging endpoint in the severe asthma community	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.2.2, Fractional exhaled nitric oxide	Updated to add text 'study site' staff	To clarify blinding results of fractional exhaled nitric oxide (FeNO) measurement will be applicable to all 'study site staff' and patients.	Non-substantial
Section 8.3.5, Causality collection	Updated to add Ventolin	To clarify adverse event (AE) causality to Ventolin will be reported.	Non-substantial
Section 9.1.1, Estimation and testing strategy	Deleted reference to analysis after patients reach V6 (32 weeks)	The initial read-out of analysis at V6 (32 weeks) will no longer be performed for the study as analysis of V6 data will be included in the final read-out after V8 (48 weeks).	Substantial
Section 9.4.2.2, Secondary analysis	Deleted text related to primary read-out		
Section 9.4.6, Study read-out	Deleted text related to primary analysis		

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of assessments

	Screening	Run-in period	Reduction period						Maintenance period			Unscheduled visit	Details in CSP section or Appendix
Visit	**1**	-	**2a[a]**	**2b**	**3**	**4**	**5**	**6[b]**	**7**	**8a[a] or EOT[c]**	**8b or EOT[c]**		
Week	**-8 or -4**	**-8/-4 to 0**	**0**	**0**	**8**	**16**	**24**	**32**	**40**	**47 or EOT[c]**	**48 or EOT[c]**		
Day	**-56 or -28**	**-56/-28 to -1**	**-1**	**1**	**57**	**113**	**169**	**225**	**281**	**336 or EOT[c]**	**337 or EOT[c]**		
Window (days)	-		1 day prior to V2b	±7	±7	±7	±7	±7	±7	1 day prior to V8b	±7		
Informed consent	X												Section 5.1
Eligibility criteria	X		X	X									Section 5.1 and 5.2
Routine clinical procedures													
Demography	X												Section 5.1
Medical history and comorbid conditions	X												Section 5.1
Prior medication	X												Section 6.5
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	Section 6.5
Routine safety measurements													
Adverse events[d]	X		X	X	X	X	X	X	X	X	X	X	Section 8.3
SARS-CoV-2 test (sub-study)[e]			X							X			Section 8.2
Pregnancy test[f]	X												Section 5.1
Electronic patient-reported outcomes (ePROs)													
ePRO/device training[g]	X			X	X	X	X	X	X				Section 8.1.1
ACQ-5[h]	X	Weekly (±2 days, except for Visits 2b and 8b) including visit days											Section 8.1.1.1
AQLQ(S)+12[i]				X	X	X	X	X	X		X		Section 8.1.1.2
CCI [redacted][j]				X				X			X		Section 8.1.1.3
Physiological asthma assessments													
Pre-bronchodilator pulmonary function tests (FEV_1, FVC)[k]				X	X	X	X	X	X		X	X	Section 8.1.2.1
Airway oscillometry (sub-study)[l]				X	X	X	X	X	X		X		Section 8.1.2.3
FeNO[m]				X	X	X	X	X	X		X		Section 8.1.2.2
Assessment of asthma exacerbation history	X												Section 8.1.3
Collection of asthma exacerbation information				X	X	X	X	X	X		X	X	Section 8.1.3
Collection of asthma-related healthcare resource utilisation information				X	X	X	X	X	X		X	X	Section 8.9
Biomarker samples													

	Screening	Run-in period	Reduction period						Maintenance period			Unscheduled visit	Details in CSP section or Appendix
Visit	**1**	**-**	**2a[a]**	**2b**	**3**	**4**	**5**	**6[b]**	**7**	**8a[a] or EOT[c]**	**8b or EOT[c]**		
Week	**-8 or -4**	**-8/-4 to 0**	**0**	**0**	**8**	**16**	**24**	**32**	**40**	**47 or EOT[c]**	**48 or EOT[c]**		
Day	**-56 or -28**	**-56/-28 to -1**	**-1**	**1**	**57**	**113**	**169**	**225**	**281**	**336 or EOT[c]**	**337 or EOT[c]**		
Window (days)	-		1 day prior to V2b	±7	±7	±7	±7	±7	±7	1 day prior to V8b	±7		
Induced sputum (sub-study) [l]			X							X			Section 8.8.1.2
Bronchoscopy (sub-study) [l]				X							X		Section 8.8.1.1
Haemostatic sample (sub-study) [l,n]				X							X		Section 8.8.1.1
Serum samples for exploratory biomarkers (sub-study) [l]				X				X			X		Section 8.8.1.3
Blood sample for eosinophils [o]				X				X			X		Section 8.8.2
Study treatment administration													
Fasenra® SC injection				X	X	X	X	X	X				
Run-in treatment dispensed	X												
Run-in treatment collected				X									
Randomisation				X									
Randomised treatment dispensed				X	X	X	X	X	X				
Randomised treatment collected					X	X	X	X	X		X		
Treatment reduction arm tapering (step down of SMART) [p]				X	X	X	X						Section 4.1.1

ACQ-5=Asthma control questionnaire-5 item; AQLQ(S)+12=Standardised asthma quality of life questionnaire for 12 years and older; CSP=Clinical study protocol; EOT=End of treatment; FVC=Forced vital capacity; FeNO=Fractional exhaled nitric oxide; FEV_1=Forced expiratory volume in 1 second; SC=Subcutaneous; SMART=Symbicort® maintenance and reliever therapy.

[a] Visits 2a and 8a and the assessments scheduled for these visits apply only to patients in the sub-study.

[b] Visit 6 is listed under the reduction period; however, no further reduction of Symbicort® is permitted at this visit. For statistical analysis purposes, Visit 6 is the end of the reduction period and also the baseline visit for the maintenance period.

[c] The EOT Visit is comprised of the assessments at Visit 8a and Visit 8b.

[d] Adverse events (AEs) and serious adverse events (SAEs) will be collected from the time of signing the informed consent form (ICF).

[e] Test to be performed and results obtained prior to sputum induction and should be performed as per standard of care in the participating site.

[f] A serum pregnancy test will be done for women of childbearing potential (WOCBP) at screening. Analysis will be performed at a local laboratory. If serum test is positive, the patient should be excluded.

[g] Patient ePRO/device training will be performed at Visit 1 for all patients. From Visit 2b to Visit 7, additional training will be performed in the event of poor compliance.

[h] All patients will complete the ACQ-5 questionnaire at the study site for Visit 1 and weekly and at home thereafter. On study visit days (Visit 2b onwards), patients will complete the questionnaire prior to or during the study visit.

[i] Patients will complete the questionnaires at the study visit prior to any study-related procedure.

[j] All patients will complete the questionnaire at Visit 2b. Only patients in the treatment reduction arm will complete the questionnaire at Visit 6 and Visit 8b.

[k] Symbicort® should be withheld for 12 hours prior to the study visit. Ventolin® should be withheld for a minimum of 6 hours prior to the study visit. If either condition is not met, the visit should be conducted when these conditions are met, either by delaying the time of the lung function evaluation or by re-scheduling the study visit. Prior to pulmonary function tests at Visit 2b, the height of the patient will be measured. Exceptionally, consistent with Appendix G, spirometry can be omitted under circumstances where it is not recommended because of precautions for infection control around pandemic disease.

[l] For the sub-study, patients will be stratified separately from the main study with a 3:1 ratio by treatment arm (treatment reduction arm: reference arm).

[m] The FeNO assessment must be performed prior to pulmonary function tests. Patients must not eat or drink 1 hour prior to having the FeNO assessment.

[n] A haemostatic analysis will be performed for all patients undergoing a bronchoscopy assessment. Analysis will be performed at a local laboratory. Patients must fast for 6 hours prior to any bronchoscopy procedures.

[o] Blood samples will be collected from all patients in the study. Analysis will be performed at a local laboratory.

[p] Treatment reduction arm tapering occurs at Week 0, 8, 16, and 24. At Week 24 dose reduction occurs only in patients who are still receiving SMART and have not stepped down to Symbicort® as anti-inflammatory reliever only (provided the patient meets all criteria to step down).

1.2 Synopsis

International Coordinating Investigator:

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Protocol Title:

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

Rationale:

The rationale for this study is to explore a new precision-based approach to treat severe eosinophilic phenotype asthma patients based on benralizumab (Fasenra®) maintenance treatment plus budesonide/formoterol (Symbicort® 200/6 µg) anti-inflammatory reliever as needed. Therefore, this study aims to assess the potential for Fasenra®-treated severe eosinophilic asthma patients to safely and effectively reduce their Symbicort® maintenance asthma treatment burden while maintaining asthma symptom control.

Objectives and Endpoints

Primary Objective:	Endpoint/Variable:
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 (Week 32) to: o Medium-dose Symbicort® maintenance and reliever therapy (SMART), or o Low-dose SMART, or o Symbicort® anti-inflammatory reliever only.

Objectives and Endpoints

Secondary Objectives:	Endpoint/Variable:
To assess changes in patient-reported outcomes for Fasenra®-treated patients while stepping down Symbicort® maintenance treatment	• Change from baseline in ACQ-5 score at the end of the reduction period. • Change from baseline in 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.
To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment	• Change from baseline in pre-bronchodilator FEV_1 during the study period.
To assess asthma exacerbation rate	• Annualised asthma exacerbation rate during the study period.
To assess the total ICS dose exposure	• Cumulative total daily ICS dose (maintenance + reliever) for: o The reduction period. o The maintenance period. o 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 (Week 48) that they achieved at the end of the reduction period (Week 32). • Supportive outcomes: o Number of exacerbations occurring from end of the reduction period to end of the maintenance period. o Total daily ICS dose from the end of the reduction period to the end of the maintenance period. o Change in ACQ-5, AQLQ(S)+12, and FEV_1 from the end of the reduction period to the end of the maintenance period.
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, less than 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.

Objectives and Endpoints

Safety Objective:	Endpoint/Variable:
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/Serious Adverse Events.
Exploratory Objectives:	**Endpoint/Variable:**
To assess changes in inflammation markers during and following stepping down Symbicort® maintenance treatment	• FeNO. • Blood eosinophil count. • Serum protein biomarkers (sub-study).
To assess patient experience	• CCI .
To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment (sub-study)	Change from baseline in airway oscillometry during the study period (sub-study).
To characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy (sub-study)	• Patient inflammatory biomarkers profile including eosinophils, microbiome, and sputum biomarkers (cytokines).

ACQ-5=Asthma control questionnaire-5 item; AQLQ(S)+12=Standardised asthma quality of life questionnaire for 12 years and older; FEV_1=Forced expiratory volume in 1 second; ICS=Inhaled corticosteroids; FeNO=Fractional exhaled nitric oxide; SMART=Symbicort® maintenance and reliever therapy

[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 4 weeks (compared to baseline; Visit 1) and no significant increase in Symbicort® use in the last 4 weeks (a weekly average of >8 inhalations of Symbicort®/day).

Overall 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.

In this study, the inhaled corticosteroids (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 treatment 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 3 consecutive doses of Fasenra® and have clinically responded since the start of Fasenra® treatment (defined for the purpose of this study as an Asthma Control Questionnaire-5 item [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, leukotriene receptor antagonists (LTRAs), long-acting muscarinic antagonists (LAMAs) 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.

Patients will be randomised in a 3:1 ratio to either the treatment reduction arm or the reference arm.

Study Period:

Estimated date of first patient enrolled: Q3 2020

Estimated date of last patient completed: Q1 2023

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 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. 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.

Treatments and Treatment Duration:

Screening and run-in period: During the 4- to 8-week screening and run-in period, patients will receive Symbicort® as maintenance treatment and Ventolin® as reliever treatment at the following dose:

- High-dose Symbicort® maintenance (budesonide/formoterol 400/12 µg) ×2 inhalations twice per day (BID) + Ventolin® (salbutamol 100 µg) reliever as needed (PRN).

Reduction period: Patients will be randomised at the beginning of the reduction period (Visit 2b); 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 every 8 weeks (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).
- **Reference arm**: Fasenra® 30 mg Q8W + high-dose Symbicort® maintenance ×2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN.

The reduction period will last for 32 weeks. At the randomisation visit (Visit 2b) 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. If a patient is receiving medium-dose SMART and loses asthma control, they can be stepped up to high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment (ie, returning to the study treatment provided during the run-in period).

At each post-randomisation study visit, the Investigator will evaluate the occurrence of asthma exacerbations, worsening of asthma control (ACQ-5 $\geq$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 for patients in the treatment reduction arm based on a prespecified algorithm. A patient will stop stepping down for the duration of the reduction period if 1) the patient experiences an asthma exacerbation since the last visit or 2) if the patient experiences a worsening of asthma control AND overuse of Symbicort® 200/6 µg treatment during the 4 weeks prior to each study visit.

Maintenance period: At the end of the reduction 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.

Sub-study: A subset of patients who consent to participation in the sub-study (approximately 32 patients are to be included, spread across the 2 treatment arms) will undergo airway oscillometry to assess a measure of lung function and will undergo bronchoscopy and induced sputum sampling at specific timepoints for exploratory biomarker research. Patients will be

enrolled from 1 study site in the UK and will be stratified into the sub-study separately from the main study with a 3:1 ratio by treatment arm (treatment reduction arm: reference arm).

Scientific Committee:

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

Statistical Methods:

Populations for analysis include an All Patients Set (APS; all patients screened for the study), a Full Analysis Set (FAS; all randomised patients irrespective of protocol adherence and continued participation in the study), and a Safety Analysis Set (SAF; all randomised patients who have received at least one dose of the study treatment).

Patient disposition will be summarised using the APS. Demography, baseline, and patient characteristic data will be evaluated using the FAS. The efficacy endpoints will be evaluated using the FAS. All safety analyses will be performed using the SAF by actual treatment received.

The primary outcome 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 number and percentage of patients who do not reduce their maintenance treatment will also be included.

Changes from baseline to post-randomisation visits for ACQ-5, AQLQ(S)+12, FEV_1, and mean total daily ICS dose will be evaluated using Mixed Model Repeated Measures (MMRM) modelling approaches including baseline ACQ-5 (for ACQ-5 only), visit, treatment, and visit × treatment.

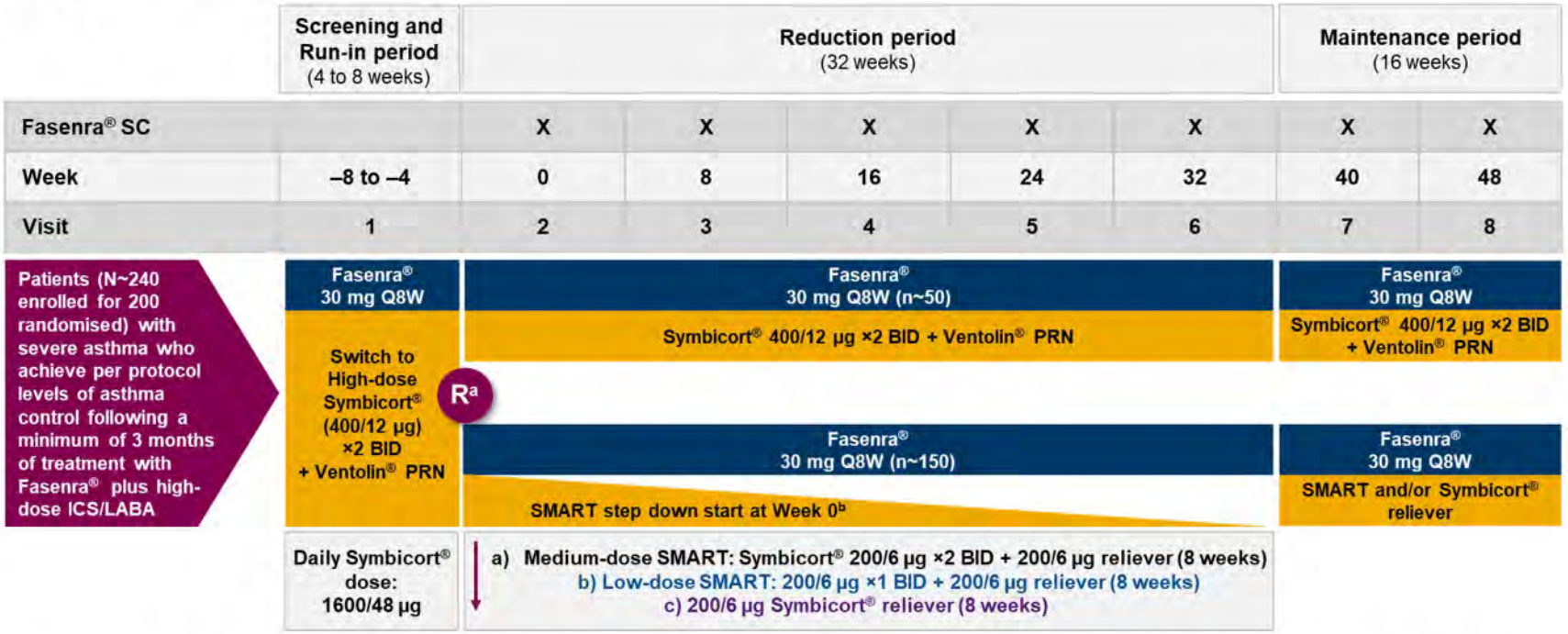
Safety data will be summarised for all patients in the SAF and data presented by actual treatment received.

Sensitivity analyses to assess the effect of missing data or drop-out on the primary endpoint will be outlined in the statistical analysis plan.

1.3 Schema

The 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) then the patient will screen fail.

[b] SMART step down should follow the dosing regimen and algorithm shown in Section 4.1.1.

2 INTRODUCTION

2.1 Study Rationale

The rationale for this study is to explore a new precision-based approach to treat severe eosinophilic phenotype asthma patients based on benralizumab (Fasenra®) maintenance treatment plus budesonide/formoterol (Symbicort® 200/6 µg) anti-inflammatory reliever as needed. Therefore, this study aims to assess the potential for Fasenra®-treated severe eosinophilic asthma patients to safely and effectively reduce their Symbicort® maintenance asthma treatment burden while maintaining asthma symptom control.

2.2 Background

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen, primarily centred around ICS, with the addition of LABAs in patients with more severe asthma (NAEPP 2007, GINA 2019). Approximately 5% to 10% of persons with asthma have a severe form of disease that is usually managed with high-dose ICS and bronchodilators (Bateman et al 2010, Chung et al 2014). Biologic therapies targeting immunoglobulin E (IgE), interleukin-5 (IL-5) or depletion of the eosinophil directly via IL-5Ra-directed antibody-dependent cell-mediated cytotoxicity are recommended as an add-on treatment in patients uncontrolled with ICS/LABA treatment (GINA 2019).

According to the Global Initiative for Asthma (GINA) 2019 guidelines, in patients who have had a good response to biologic therapy, the treating physician should consider reducing the ICS dose from high to medium dose (GINA 2019). GINA describes this guidance as "consensus advice" recognising that no data are available to guide this clinical decision. However, in future clinical practice, it is anticipated that treating physicians are likely to de-escalate the ICS dose significantly or completely at the behest of patients whose asthma becomes well controlled after the addition of biologic therapy, such as Fasenra®.

Optimisation with an ICS-formoterol maintenance and reliever prior to other add-on therapy strongly supports the use of Symbicort® anti-inflammatory reliever in uncontrolled GINA3-5 patients (GINA 2019). Data to guide clinicians on the speed and extent of the maintenance ICS de-escalation are lacking; similarly, de-escalation of maintenance ICS dose to zero with only a salbutamol reliever could expose patients to an increased risk of severe exacerbation (CAMP et al 2000, Guilbert et al 2006, Lemanske et al 2001, Waalkens et al 1993). The GINA guidelines acknowledge that overuse of short-acting β-agonists (SABAs; ≥3 canisters/year) is associated with an increased risk of severe exacerbations and recommend ICS-containing treatment, such as ICS-formoterol, should be initiated as soon as possible for the best outcomes (GINA 2019). To date, there is no clinical study published to assess the reduction of background SMART treatment in severe eosinophilic asthma patients while on

Fasenra® treatment. In addition, there is no standardised scheme of reduction of SMART treatment in these patients.

The proposed study is designed to address these evidence gaps and provide clear guidance on how to step down SMART while retaining the protective benefit from asthma worsening with Symbicort® anti-inflammatory reliever as needed in place of the maintenance ICS/LABA.

The objective of the study is to assess the potential for Fasenra®-treated eosinophilic phenotype asthma patients to safely and effectively reduce their Symbicort® maintenance asthma treatment burden from high-dose daily Symbicort® to 'Symbicort® anti-inflammatory reliever as needed' therapy while maintaining asthma symptom control. A parallel reference arm consisting of patients treated with Fasenra® Q8W and continuing on high-dose Symbicort® maintenance treatment (2 inhalations 400/12 µg BID), and Ventolin® reliever treatment, is included to help demonstrate that reduction of daily Symbicort® maintenance treatment can be achieved without meaningful loss of asthma control.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Fasenra®, Symbicort®, and Ventolin® are provided in their respective Summary of Product Characteristics (SmPC).

2.3 Benefit/Risk Assessment

Fasenra® is being studied in severe eosinophilic asthma where there are few treatment options for patients whose asthma remains uncontrolled on high-dose ICS/LABA and/or oral corticosteroids (OCSs) (GINA 2019). In adult patients whose asthma was poorly controlled by high-dose ICS/LABA therapy, Fasenra® 30 mg every 8 weeks produced improvements in multiple measures of asthma control including the annual rate of asthma exacerbations, lung function symptoms, and Asthma Control Questionnaire (ACQ) scores in 2 Phase III trials each approximately 1 year in duration (Bleeker et al 2016, FitzGerald et al 2016). In addition, Fasenra® has also been shown to reduce OCS dose (Nair et al 2017).

In Europe, Fasenra® is indicated as an "*add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus long-acting β-agonists*" (please refer to the Fasenra® SmPC). Fasenra® was developed as an add-on treatment to maintenance ICS/LABA treatment. To mitigate the risk of asthma deterioration or exacerbation during the reduction of ICS/LABA maintenance treatment, the following measures will be implemented:

- Careful assessment of asthma control before any tapering of ICS/LABA treatment (see Section 4.1.1).
- Weekly monitoring of asthma control and Symbicort® 200/6 µg use with alerts sent to patients, Investigators, and AstraZeneca (AZ) or delegate in the event of an ACQ-5 score

increase of at least 0.5 units compared to baseline or in the event of Symbicort® overuse (weekly average of >8 inhalations/day) [see Section 4.1.2].

- Daily monitoring of Symbicort® 200/6 µg use with alerts sent to patients, Investigators, and AZ or delegate in the event of an increase of Symbicort® use >12 inhalations/day for 2 consecutive days (see Section 4.1.2).

Potential risks of Fasenra® are as follows:

Malignancies have been reported at a low incidence in the completed and ongoing studies of Fasenra®. Eosinophils have been found in association with solid tumours, especially tumours of epithelial origin (breast and colon) and may play an active role in tumour defence by modulating host defences, or may be a bystander effect. However, the cause and consequences (ie, pro-tumorigenic versus anti-tumorigenic) of eosinophil recruitment and accumulation into tumours are unclear (Jacobsen et al 2012).

Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including Fasenra®. Anaphylaxis may be life-threatening. Risk minimisation includes a minimum of a 1-hour observation period at the clinical site following drug administration for the appearance of any acute drug reactions.

Development of anti-drug antibodies (ADA) to Fasenra® has been documented. Theoretical risks of developing ADA may include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease). There was no apparent impact of ADA on overall Fasenra® safety or efficacy in the previous Phase III studies in chronic obstructive pulmonary disease (COPD) patients.

Serious infections have been reported; however, a relationship between eosinophil depletion and serious infection has not been established. Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumours. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumours. Risk minimisation measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The Symbicort® Turbohaler is a well-known medication with efficacy and safety profiles established in numerous clinical studies and vast post-marketing experience. Symbicort® is effective as a reliever medication (Palmqvist et al 2001). In the SMART program using Symbicort 200/6 µg per inhalation as the metered dose (corresponding to a delivered dose of 160/4.5 µg per inhalation; please refer to the Symbicort® Turbohaler 200/6 µg SmPC), patients were allowed to use up to 12 inhalations per day (10 inhalations PRN in addition to

their maintenance treatment) and the safety profile of Symbicort® was no different from that of a fixed-dose maintenance treatment. Furthermore, in another study assessing 10 inhalations of Symbicort® Turbohaler 160/4.5 µg per inhalation as an addition to a daily Symbicort® maintenance dose of 640/18 µg, no new safety concerns compared to what was already known for ICS and LABA were identified (Ankerst et al 2003); this demonstrated that occasional high doses of Symbicort® Turbohaler are safe and well tolerated. More recently, the Phase III SYGMA trials demonstrated that Symbicort® Turbohaler as a reliever medication offered superior asthma symptom control compared to SABA reliever (34.4% vs. 31.1%) (O'Byrne et al 2018).

3 OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Primary Objective	**Endpoint/Variable**
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 (Week 32) to: ○ Medium-dose Symbicort® maintenance and reliever therapy (SMART), or ○ Low-dose SMART, or ○ Symbicort® anti-inflammatory reliever only.
Secondary Objectives	**Endpoint/Variable**
To assess changes in patient-reported outcomes for Fasenra®-treated patients while stepping down Symbicort® maintenance treatment	• Change from baseline in ACQ-5 score at the end of the reduction period. • Change from baseline in 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.
To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment	• Change from baseline in pre-bronchodilator FEV_1 during the study period.
To assess asthma exacerbation rate	• Annualised asthma exacerbation rate during the study period.
To assess the total 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 (Week 48) that they achieved at the end of the reduction period (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.

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, less than 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.
Safety Objective	**Endpoint/Variable**
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/Serious Adverse Events.
Exploratory Objectives	**Endpoint/Variable**
To assess changes in inflammation markers during and following stepping down Symbicort® maintenance treatment	• 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 stepping down Symbicort® maintenance treatment (sub-study)	• Change from baseline in airway oscillometry during the study period (sub-study).
To characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy (sub-study)	• Patient inflammatory biomarkers profile including eosinophils, microbiome, and sputum biomarkers (cytokines).

ACQ-5=Asthma control questionnaire-5 item; AQLQ(S)+12=Standardised asthma quality of life questionnaire for 12 years and older; FEV_1=Forced expiratory volume in 1 second; ICS=Inhaled corticosteroids; FeNO=Fractional exhaled nitric oxide; SMART=Symbicort® maintenance and reliever therapy

[a] Asthma symptom control is defined as 1) no asthma exacerbations since the last visit (as defined in Section 8.1.3), and 2) no increase in ACQ-5 ≥0.5 units in the last 4 weeks (compared to baseline; Visit 1) and no significant increase in Symbicort® use in the last 4 weeks (a weekly average of >8 inhalations of Symbicort®/day).

4 STUDY DESIGN

4.1 Overall 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.

For the purpose of this study, maintained asthma symptom control is defined as 1) no asthma exacerbations since the last visit (as defined in Section 8.1.3), and 2) no increase in ACQ-5

≥0.5 units in the last 4 weeks (compared to baseline; Visit 1) and no significant increase in Symbicort® use in the last 4 weeks (a weekly average of >8 inhalations of Symbicort®/day).

In this study, the ICS/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 3 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 OCSs, LTRAs, LAMAs 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.

Screening and run-in period: During the study period, patients will continue to receive Fasenra® 30 mg Q8W treatment. 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 BID + Ventolin® (salbutamol 100 µg) reliever 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.

Reduction period: At the randomisation visit (Visit 2b), 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) or whether they are screen failed from the study (see Section 5.4). 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).

- **Reference arm**
  Fasenra® 30 mg Q8W + high-dose Symbicort® maintenance ×2 inhalations BID + Ventolin® (salbutamol 100 µg) reliever PRN.

Treatment reduction arm: At the randomisation visit (Visit 2b) 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 4.1.1). If a patient is receiving medium-dose SMART and loses asthma control, they can be stepped up to high-dose Symbicort® maintenance treatment and Ventolin® reliever treatment (ie, returning to the study treatment provided during the run-in period).

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 prespecified algorithm (see Section 4.1.1). A patient will stop stepping down for the duration of the reduction period if 1) the patient experiences an asthma exacerbation since the last visit or 2) if the patient experiences a worsening of asthma control AND overuse of Symbicort® 200/6 µg treatment during the 4 weeks prior to each study visit.

Patients who are not on Symbicort® reliever only by Visit 4 will be given 1 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.

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

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.

Sub-study: A subset of patients who consent to participation in the sub-study (approximately 32 patients are to be included, spread across the 2 treatment arms) will undergo airway oscillometry to assess a measure of lung function and will undergo bronchoscopy and induced sputum sampling at specific timepoints (Table 1) for exploratory biomarker research. Patients will be enrolled from 1 study site in the UK and will be stratified into the sub-study separately from the main study with a 3:1 ratio by treatment arm (treatment reduction arm: reference arm).

Study completion/end of treatment: Patients will be considered to have completed the study if they complete Visit 8b (see Section 4.4). Patients who discontinue treatment prematurely will attend an end of treatment (EOT) visit, including the same assessments as in Visits 8a and 8b to exit the study.

Unscheduled Visit: Study site evaluations for asthma worsening may occur as an unscheduled visit or as part of a routine centre visit if the worsening happens to occur in line with a scheduled visit. A copy of the medical record should be obtained for asthma symptom worsening or asthma exacerbations evaluated and treated at non-study sites (eg, by the primary care provider or at an emergency department/hospital). Details should be entered into the exacerbation electronic case report form (eCRF) module in a timely fashion. Changes in concomitant medications due to asthma symptom worsening or asthma exacerbations must be recorded in the appropriate module of the eCRF.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3.

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

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

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

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.1.1 Treatment reduction arm tapering

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 3.

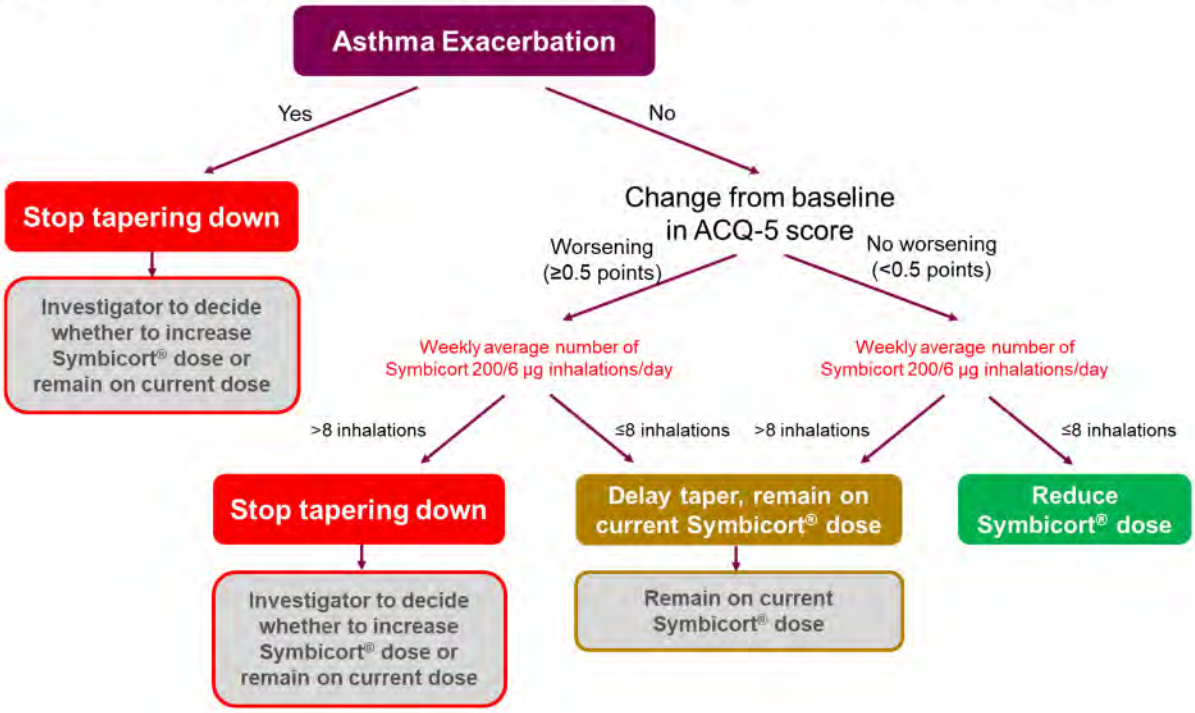
Table 3 Symbicort® dosing regimen for patients who maintain asthma control during the reduction period

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® 100µg
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

BID=twice per day.

The algorithm for stepping down or stepping up Symbicort® treatment is shown in Figure 2. 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 4 weeks prior to the study visit.

Figure 2 Algorithm for stepping down/up treatment in the Reduction Period



ACQ-5=Asthma control questionnaire-5 item.

A patient will stop stepping down for the duration of the reduction period if 1) the patient experiences an asthma exacerbation (see Section 8.1.3) since the last visit or 2) if during the last 4 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 4 weeks prior to each study visit 1) 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 2) the patient experiences no ACQ-5 worsening (<0.5 units compared to baseline) and has a weekly average of >8 inhalations of Symbicort®/day.

4.1.2 Monitoring asthma control and Symbicort® 200/6 µg use

To mitigate the risk of asthma deterioration or exacerbation during the reduction of Symbicort® maintenance treatment, 3 alerts (2 weekly alerts and 1 daily alert) will be used for this study:

Weekly Alerts

- If a patient's ACQ-5 score deteriorates (increases) by at least 0.5 units compared to baseline.
- If a patient has excessive total (maintenance and reliever) Symbicort® 200/6 µg use with a weekly average of >8 inhalations/day.

Daily Alerts

- If a patient has an excessive total (maintenance and reliever) Symbicort® 200/6 µg use of >12 inhalations/day for 2 consecutive days.

If an alert is triggered, the patient, Investigator, and AZ or delegate will receive an alert and the patient will be instructed to contact the study site or another healthcare provider as soon as possible.

4.2 Scientific Rationale for Study Design

In clinical practice, reduction of standard of care background asthma treatment medications is anticipated to be an increasingly common scenario in patients whose asthma becomes controlled following the addition of an asthma biologic like Fasenra®. Oral corticosteroids, ICS, and LABA each have potential safety and tolerability issues. It would be a potential benefit to patients if Fasenra® treatment could enable reduction in these therapies, while allowing patients to maintain asthma control and improving drug compliance. Whether treatment with Fasenra® can enable patients to reduce their standard of care asthma controller regimen while maintaining asthma control has not been previously evaluated.

This is a Phase IV, randomised, open-label, active-controlled study designed to further investigate the efficacy of Fasenra® (30 mg) administered subcutaneously (SC) in severe asthma patients with eosinophilic asthma on standard of care therapy (eg, high-dose ICS/LABA) to determine if the ICS/LABA dose can be safely reduced without loss of asthma control. A reference arm is included in which patients are maintained on standard of care high-dose ICS/LABA so that the degree of asthma control can be compared between the 2 arms. The 30 mg SC dose and every 8-week regimen of Fasenra® was shown to be effective across multiple measures of asthma control in this population, with an overall safety profile similar to placebo. Based on the previous Phase III experience, approximately 200 patients studied over a 32-week treatment period will be enough to detect differences from baseline for ICS dose and between treatment groups for ACQ-5.

The purpose of this proof-of-concept study is to assess the potential for reducing the use of Symbicort® maintenance treatment in asthma patients treated with Fasenra® 30 mg SC. This study will allow patients to reduce their high-dose Symbicort® maintenance treatment to the lowest dosage/day while being controlled on their asthma symptoms. This will eventually allow us to generate evidence to assess and explore:

- The potential for severe eosinophilic asthma patients treated with Fasenra® to safely and effectively reduce their Symbicort® asthma treatment burden.
- A new precision-based approach to treat eosinophilic phenotype patients based on maintenance treatment with Fasenra® plus anti-inflammatory reliever as needed (Symbicort® 200/6 µg, as needed).

4.3 Justification for Dose

The clinical efficacy of Fasenra® 30 mg SC was confirmed in 2 large Phase III global safety and efficacy trials in patients on high-dose ICS/LABA and blood eosinophil counts ≥300 cells/μL (Bleeker et al 2016, FitzGerald et al 2016). In these studies, Fasenra® was dosed every 8 weeks for approximately 1 year and produced significant decreases in asthma exacerbations (up to 51%), and improvements in forced expiratory volume in 1 second (FEV_1; up to 159 mL) and total daily asthma symptom scores. There was no apparent advantage to more frequent dosing (every 4 weeks) in these studies. Of note, the Phase III program also studied the efficacy of Fasenra® in patients with blood eosinophil counts <300 cells/μL and in an OCS-dependent asthma population (FitzGerald et al 2016, Goldman et al 2017, Nair et al 2017). The results of these prespecified and pooled analyses demonstrated broad efficacy in patients with blood eosinophil levels ≥150 cells/μL, and also supported an enhanced response to Fasenra® treatment when certain identifiable clinical features of the eosinophilic asthma phenotype are present. These features include OCS dependence, a history of frequent exacerbations, nasal polyposis, later onset of disease, and low lung function. The 30 mg dose of Fasenra® is approved in many countries worldwide, including the UK, France, and Germany, where the current study will be conducted.

All of the maintenance doses of Symbicort® that are proposed to be used in the current study are approved in many countries worldwide, including the countries intended for this study. The SYGMA trial 2 also suggested that the as needed use of Symbicort® in mild asthma could address patients' concerns about the risks of ICS treatment (O'Byrne et al 2018). Patient concern with safety is another issue that causes overreliance on SABAs and poor adherence to maintenance treatment with ICS. Patients are often more concerned than their healthcare providers about adverse effects of ICS, even when low inhaled doses are used. Conversely, patients are less concerned about their level of symptom control. Since Symbicort® used as needed was as effective as budesonide maintenance treatment in reducing exacerbation risk, without the need for regular twice-daily treatment, and resulted in only 17% of the inhaled glucocorticoid load, it would probably be more acceptable to patients who have this concern to use Symbicort® as needed.

Uncontrolled severe asthma patients on high-dose ICS/LABA are candidates to receive a biologic treatment (Step 5 of GINA 2019). High doses of budesonide dry powder inhaler is defined as a dose greater than 800 μg/day. The highest maintenance dose of Symbicort® is 400/12 μg BID (1 inhalation in the morning and in the evening); however, to achieve budesonide doses greater than 800 μg/day 2 inhalations BID of Symbicort® 400/12 μg are required (please refer to the Symbicort® SmPC). This is the dose administered during the run-in period of the study and maintained in the reference arm.

In addition, SMART is delivered with Symbicort® 200/6 μg for the reduction period in the treatment reduction arm; this dose is used as a maintenance treatment and is to be reduced by

50% at each step. Overall, this means that patients in the treatment reduction arm will be reduced from 200/6 µg 2 inhalations BID, through 200/6 µg 1 inhalation BID, and finally to 200/6 µg as anti-inflammatory reliever use only (see Section 4.1.1 and Figure 1).

4.4 End of Study Definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

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

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Patients will be recruited from secondary/tertiary care sites via internal databases, contact with hospital clinics, and referrals from other physicians and primary care centres.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion and randomisation criteria, and none of the exclusion criteria, for this study in order to be assigned/randomised to a study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

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

For procedures for withdrawal of incorrectly enrolled patients, see Section 7.3.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following inclusion and randomisation criteria, and none of the exclusion criteria apply:

Informed Consent

1 Provision of informed consent prior to any study-specific procedures.

The informed consent form (ICF) process is described in Appendix A 3.

Age

2 Patient must be aged 18 years old or above at the time of consenting to study participation.

Type of Patient and Disease Characteristics

3 Documented current maintenance treatment with high-dose ICS/LABA.

4 ACQ-5 score <1.5 at Visit 1.

5 Treatment with Fasenra® for the indicated diagnosis of severe eosinophilic asthma and has received at least 3 consecutive doses (>8 weeks) prior to Visit 1.

Sex

6 Male or female.

Reproduction

7 Negative serum pregnancy test at Visit 1 for women of childbearing potential (WOCBP).

8 WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration and within 12 weeks after the last dose of study treatment. Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation-oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation-oral, injectable, or implantable.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Sexual abstinence, ie, refraining from heterosexual intercourse (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient).
- Vasectomised sexual partner (provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomised partner has received medical assessment of the surgical success).

9 Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for ≥12 months prior to the planned date of randomisation without an alternative medical cause.

10 The following age-specific requirements apply:

11 Women <50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle stimulating hormone (FSH) levels in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the patient as WOCBP.

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

5.1.1 Randomisation criteria

For randomisation at Visit 2b, patients should fulfil the following criteria:

1 ACQ-5 <1.5 at Visit 2b.

2 No increase (worsening) in ACQ-5 of at least ≥0.5 units between Visit 1 and Visit 2b compared to baseline.

3 No asthma exacerbation (see Section 8.1.3) between Visit 1 and Visit 2b.

4 No use of Ventolin® for symptom worsening in >3 out of the 7 days prior to Visit 2b. Note: Use of Ventolin® for prophylactic reasons such as exercise is allowed.

5.2 Exclusion Criteria

Medical Conditions

1 As judged by the Investigator, any evidence of a severe or serious treatment-related AE during Fasenra® treatment which in the Investigator's opinion makes it undesirable for the patient to participate in the study.

2 History of exacerbation requiring systemic corticosteroids or hospitalisation during the last 3 months prior to Visit 1 or during the run-in period.

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

4 Current smokers or former smokers with a smoking history ≥20 pack/years.

5 History of alcohol or drug abuse within 12 months prior to Visit 1.

6 A helminth parasitic infection diagnosed within 24 weeks prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

7 History of anaphylaxis to any biologic therapy.

8 Known history of allergy or reaction to any component of the study treatment formulation.

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

10 Current malignancy, or history of malignancy, except for:

- Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
- Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.

Prior/Concomitant Therapy

11 Oral corticosteroid use during the last 3 months prior to Visit 1.

12 Receipt of LAMAs or theophyllines from Visit 1 until after Visit 8b, or LTRAs from Visit 2b until after Visit 8b (see Table 6).

13 Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months or 5 half-lives (whichever is longer) prior to the date informed consent is obtained.

14 Receipt of live attenuated vaccines 30 days prior to Visit 1.

15 It is recommended to allow receipt of inactive/killed vaccinations (eg, inactive influenza) provided they are not administered within 1 week before/after any study treatment administration.

16 It is recommended to allow receipt of coronavirus disease 2019 (COVID-19) vaccination prior to study start provided such patients are not randomized until >30 days after last vaccine dose.

17 It is recommended to allow allergen immunotherapy provided it is stable for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study visits.

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

19 Five-lipoxygenase inhibitors (eg, zileuton) are prohibited and are not allowed within 30 days of Visit 1 and until after Visit 8b.

20 Receipt of any marketed (eg, omalizumab) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer.

21 Receipt of systemic treatment with strong CYP3A4 inhibitors (eg, ketoconazole and itraconazole) from Visit 1 until after Visit 8b (for details, see Appendix D).

22 Receipt of beta-adrenergic blockers (including eye drops) from Visit 1 until after Visit 8b.

Prior/Concurrent Clinical Study Experience

23 Concurrent participation in another clinical study with an Investigational Product or a post-authorisation safety study.

Other Exclusions

24 Planned surgical procedures or other planned life events during the conduct of the study that would affect the patient's ability to comply with study treatment dosing or study assessments.

25 Involvement in the planning and/or conduct of the study (applies to both AZ staff and/or staff at the study site).

26 Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

27 Prior randomisation in the present study.

28 Currently pregnant, breast-feeding, or lactating women.

5.3 Lifestyle Restrictions

Patients enrolled in the study should adhere to the following conditions for the duration of the study. Any event likely to interfere with the conduct of the study will be communicated to the Investigator and reported without delay to the Sponsor.

5.3.1 Meals and dietary restrictions

Patients should avoid eating a large meal for at least 2 hours prior to all pulmonary function tests at the study site and patients should not eat or drink 1 hour prior to having the fractional exhaled nitric oxide (FeNO) test. Patients must fast for 6 hours prior to any bronchoscopy procedures.

5.3.2 Caffeine, alcohol, and tobacco

There are no protocol-specific restrictions to caffeine or alcohol intake. Smoking is not permitted as per exclusion criterion 4.

5.3.3 Activity

Patients should avoid strenuous exercise for at least 30 minutes before the planned visits to the study site.

5.3.4 Blood Donation

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent and for 12 weeks after last dose of study treatment.

5.4 Screen Failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to 1 of the 2 study treatment arms. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. These patients should have the reason for study withdrawal recorded in the eCRF.

Patients who do not fulfil the randomisation criteria (see Section 5.1.1) will be considered screen failed.

6 STUDY TREATMENTS

Study treatment is defined as any Investigational Product(s), marketed product, or placebo intended to be administered to utilised by a study participant according to the study protocol. Study treatment in this study refers to Fasenra®, Symbicort®, and Ventolin®.

6.1 Treatments Administered

6.1.1 Investigational products

Table 4 Study treatments

	Fasenra® (benralizumab)	**Symbicort®** (budesonide/formoterol)				**Ventolin®** (salbutamol)
		High-dose maintenance	**Medium-dose SMART**	**Low-dose SMART**	**Reliever only**	
Study treatment name:	Fasenra® 30 mg solution	Symbicort® Turbohaler® 400/12, inhalation powder	Symbicort® Turbohaler® 200/6, inhalation powder	Symbicort® Turbohaler® 200/6, inhalation powder	Symbicort® Turbohaler® 200/6, inhalation powder	Ventolin® pMDI
Dosage formulation:	Benralizumab 30 mg/mL, 1 mL fill volume	Budesonide 400 µg/formoterol fumarate 12 µg per inhalation	Budesonide 200 µg/formoterol fumarate 6 µg per inhalation	Budesonide 200 µg/formoterol fumarate 6 µg per inhalation	Budesonide 200 µg/formoterol fumarate 6 µg per inhalation	Salbutamol sulfate 100 µg per inhalation
Route of administration:	Subcutaneous injection	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation
Dosing instructions:	Q4W for first 3 doses (prior to study inclusion), Q8W thereafter	Maintenance: 2 inhalations BID, once in the morning and once in the evening	Maintenance: 2 inhalations BID, once in the morning and once in the evening. Reliever use: PRN	Maintenance: 1 inhalation BID, once in the morning and once in the evening. Reliever use: PRN	Reliever use: PRN	Reliever use: PRN
Maintenance total dosage: Budesonide (the Symbicort ICS compound)		1600 µg (Budesonide 400 µg × 2 inhalations BID)	800 µg (Budesonide 200 µg × 2 inhalations BID)	400 µg (Budesonide 200 µg × 1 inhalation BID)	200 µg (Budesonide 200 µg when needed)	

Table 4 Study treatments

	Fasenra® (benralizumab)	Symbicort® (budesonide/formoterol)				Ventolin® (salbutamol)
		High-dose maintenance	Medium-dose SMART	Low-dose SMART	Reliever only	
Packaging and labelling:	Fasenra® (benralizumab) will be provided by AZ or delegate in an accessorised pre-filled syringe (APFS)	Symbicort® (budesonide/formoterol) will be provided by AZ or delegate in a Turbohaler®				Ventolin® (salbutamol) will be provided by AZ or delegate in a pMDI
	All treatments will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.					

APFS=Accessorised pre-filled syringe; AZ=AstraZeneca; BID=Twice per day; GMP=Good manufacturing practice; pMDI=pressurised metered dose inhaler; PRN=As needed; Q4W=every 4 weeks; Q8W=every 8 weeks; SMART=Symbicort® maintenance and reliever therapy.

6.1.2 Medical devices

Medical devices provided for use in this study are the Hailie™ sensors for Ventolin® and Symbicort®, ERT MasterScope ™ Spirometry device, and Circassia NIOX Vero FeNO device.

6.1.2.1 Hailie™ Inhaler Device

The Hailie™ inhaler devices (manufactured by Adherium) are Bluetooth-enabled and automatically upload inhaler usage when they are near a smartphone that will be provided for this study. The Hailie™ inhaler sensors will be used to track the patients' use of Symbicort® Turbohalers® and Ventolin® pressurised metered dose inhalers (pMDIs).

The study site will ensure the Hailie™ inhaler devices are installed properly on the appropriate Turbohaler®/pMDI and that each device is properly paired with the smartphone to enable the Bluetooth-enabled device to sync and transmit data.

Patients will also be trained on how to use, remove, and replace the Hailie™ devices on refill Turbohalers®/pMDIs at Visit 1. From Visit 2b to Visit 7, additional training will be performed in the event of poor compliance.

6.1.2.2 Spirometry Device

The Spirometer used in this study is ERT MasterScope ™. This is the electronic portable medical device used to measure the lung function parameters FEV1 and FVC.

6.1.2.3 FeNO Monitoring Device

The FeNO measurement will be performed with the portable system Circassia NIOX Vero® connected to the MasterScope. It will be used to profile the patient's FeNO.

Instructions for medical device use are provided in device-specific Instructions for Use documents.

All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the Investigator throughout the study (see Section 8.4.5) and appropriately managed by the manufacturer.

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure,

environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Instructions for the preparation, handling, storage, and administration of Fasenra®, Symbicort®, and Ventolin® are provided in their respective SmPCs.

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

In the event of a malfunctioning accessorised pre-filled syringe (APFS), the centre should contact the study monitor to initiate a product complaint process according to applicable guidelines.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study and not blinded. All patients will be centrally assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

At Visit 2b, approximately 200 patients will be randomly assigned to 1 of the 2 treatment arms using a 3:1 randomisation ratio, with the randomisation stratified by whether or not the patient consents to participate in the sub-study (note this is equivalent to randomising patients in the sub-study separately in the same 3:1 ratio). Thus, approximately 50 patients will be randomised to the reference arm, and approximately 150 patients will be randomised to the treatment reduction arm. To ensure random allocation, each patient will be given the study treatment bearing the lowest available randomisation number at the site.

The Investigator(s) will:

- Obtain signed and dated informed consent from the patient before any study-specific procedures are performed.
- Assign the potential patient a unique enrolment number (E-code), beginning with 'E#'.
- Determine patient eligibility; see Sections 5.1 and 5.2.
- For patients fulfilling the eligibility and randomisation criteria at Visit 2b, the Investigator will assign a unique randomisation number.

Randomisation numbers will be assigned strictly sequentially as patients become eligible for randomisation. The randomisation numbers will be grouped in blocks at an overall level. The block size will not be communicated to the Investigators.

When the study is completed and the data verified and locked and the populations defined, the randomisation numbers will be made available for data analysis.

If a patient withdraws from the study, then his/her enrolment/randomisation number cannot be reused. Withdrawn patients will not be replaced.

6.4 Treatment Compliance

Fasenra® administration will take place at the study site and compliance will be recorded in the eCRF by the Investigator.

At Visit 1, instructions will be given to the patients on how to use the Symbicort® Turbohaler® and Ventolin® pMDI (inhalation technique) as well as the Hailie™ sensors (Section 6.1.2). Before taking the first dose of run-in medication, the patient will be instructed by the study personnel how to take the medication. In order to inhale properly according to the instructions, the patient will practice the inhalation technique with a training device, as many times as judged necessary by the supervising study personnel.

Symbicort® and Ventolin® compliance will be measured from the first dose (taken at Visit 1) until the end of the patient's participation in the study via the Hailie™ sensors (Section 6.1.2). From Visit 2b to Visit 7, additional training will be performed in the event of poor compliance.

Any change from the dosing schedule, such as dose interruptions, dose reductions, or dose discontinuations should be recorded in the eCRF.

The Investigator is responsible for managing the study treatment from receipt by the study site until the destruction or return of all unused study treatment. The Investigator(s) is responsible for ensuring that the patient has returned all unused study treatment.

6.5 Concomitant Therapy

Any medication or vaccine that the patient has received in the 3 months prior to the date of informed consent and/or is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.
- For COVID-19 vaccine, the vaccine brand also needs to be clearly indicated.

Table 5 Restricted medications

Allowed medication/class of drug	Usage
Inactive/killed vaccinations	Allowed provided they are not administered within 1 week before or after dosing with study treatment.
COVID-19 vaccination	Allowed provided they are not administered within 1 week before or after dosing with study treatment (Fasenra®), longer interval is advised when possible. If needed, administration of study treatment can be re-scheduled to allow for sufficient interval prior/post COVID-19 vaccination. Subsequent study treatment dose should be given in a different location from the vaccine.
Allergen immunotherapy	Allowed if patient has been receiving stable therapy for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study visits.
Prednisone/prednisolone	May be allowed as burst to treat asthma exacerbations, at the discretion of the Investigator.
Topical or nasal immunosuppressive medication	Topical or nasal administration may be allowed at the discretion of the Investigator.
Symbicort®	Withheld for 12 hours prior to study visits.
Ventolin®	Withheld for a minimum of 6 hours prior to study visits.

COVID-19=Coronavirus Disease 2019.

Table 6 Prohibited medications

Prohibited medication/class of drug	Usage
Marketed respiratory biologics	Any marketed respiratory biologic treatment other than Fasenra® (eg, omalizumab, mepolizumab, reslizumab) is not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1 and until after Visit 8b.
Non-respiratory marketed biologics or any investigational biologics	Any marketed (non-respiratory) or investigational biologic treatment is not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1 and until after Visit 8b.

Table 6 Prohibited medications

Prohibited medication/class of drug	Usage
Immunosuppressive medications	Use of immunosuppressive medications (including, but not limited to, methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, any experimental anti-inflammatory therapy, or oral/parenteral/intra-articular corticosteroids for reasons other than asthma) is not allowed except rescue use of systemic corticosteroids (oral, intravenous, or intramuscular) to treat an asthma exacerbation or to treat conditions other than asthma. Immunosuppressive medications must be discontinued 3 months or 5 half-lives (whichever is longer) prior to Visit 1; during the treatment period; and 3 months or 5 half-lives (whichever is longer) after the last dose of study treatment.
Blood products or immunoglobulin therapy	Receipt of immunoglobulin or blood products is not allowed within 30 days prior to Visit 1 and until after Visit 8b.
Live attenuated vaccines	Not allowed within 30 days of Visit 1, during the treatment period, and for 12 weeks (5 half-lives) after the last dose of the study treatment administration.
Lipoxygenase inhibitors	Five-lipoxygenase inhibitors (eg, zileuton) are prohibited and are not allowed within 30 days of Visit 1 and until after Visit 8b.
Systemic treatment with strong CYP3A4 inhibitors (eg, ketoconazole and itraconazole) [a]	Not allowed from Visit 1 and until after Visit 8b.
Beta-adrenergic blockers (including eye drops)	Not allowed from Visit 1 and until after Visit 8b.
LAMAs or theophyllines	Not allowed from Visit 1 and until after Visit 8b.
LTRAs	LTRAs are not allowed from Visit 2b and until after Visit 8b. LTRA washout may begin at or after Visit 1 and must be completed at least 1 week prior to Visit 2b.

AE=Adverse event; CYP=Cytochrome P450; LAMA=Long-acting muscarinic antagonist; LTRA=Leukotriene receptor antagonists; SAE=Serious adverse event.

[a] For details see Appendix D.

6.5.1 Other concomitant treatment

Other medication, other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.6 Dose Modification

This protocol allows the Symbicort® dose to be modified in the treatment reduction arm only (Table 3), in accordance with the stepping down/up treatment algorithm (Figure 2).

6.7 Treatment After the End of the Study

N/A.

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of Study Treatment

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- AEs that, in the opinion of the Investigator, contraindicates further dosing.
- Severe non-compliance with the clinical study protocol (CSP).
- Eligibility requirement found not to be fulfilled.
- Pregnancy.
- Lost to follow-up (see Section 7.2).
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the study treatment
  - Development of helminth parasitic infestations requiring hospitalisation
  - An asthma-related event requiring mechanical ventilation.

Generally, before discontinuation of a patient from the study treatment, a discussion between the AZ Study Physician or delegate and Investigator is encouraged, as much as feasible.

See the SoA (Table 1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment means that the patient must be withdrawn from the study. A patient who has discontinued study treatment, for any reason, does not need to complete further assessments or further planned visits for this study, however, they must attend a discontinuation visit to return all electronic devices used for the study and complete all EOT visit assessments.

The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the patient at their discontinuation visit. Patients permanently discontinuing study treatment

should be given treatment according to local medical practice, at the discretion of the Investigator.

7.2 Lost to Follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Lost to follow-up is when the following 3 attempts at contact have failed:
  - Three (3) attempts of either phone calls, faxes, or emails
  - Having sent 1 registered letter/certified mail
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up.

7.3 Withdrawal from the Study

A patient may withdraw from the study (eg, withdraw consent), at any time (study treatment **and** assessments) at his/her own request, without prejudice to further treatment.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up patients as medically indicated. The patient will return all devices used for the study.

See the SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

Patients who fail to meet the eligibility and/or randomisation criteria should not, under any circumstances, be randomised or receive study treatment. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility and/or

randomisation criteria must not be randomised or initiated on-treatment and must be withdrawn from the study.

When a patient does not meet all the eligibility and/or randomisation criteria but is randomised in error, or incorrectly started on-treatment, the Investigator should inform the AZ Study Physician or delegate immediately, and a discussion should occur between the AZ Study Physician or delegate and the Investigator regarding whether to continue or discontinue the patient from treatment. The AZ Study Physician or delegate must ensure all decisions are appropriately documented.

A patient will be withdrawn from the study if they withdraw consent to the analysis of mandatory biological samples. A patient will not be withdrawn from the study if they withdraw consent to the use of biological samples acquired as part of the voluntary sub-study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

The Investigator will ensure that data are recorded on the eCRF. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Electronic Patient-Reported Outcomes

This study includes 3 electronic Patient-Reported Outcomes (ePROs) that will be provided to the patient on a smartphone/tablet. The ePROs will be completed at the time points indicated in the SoA (Table 1); the ACQ-5 questionnaire will be completed mainly at home, the AQLQ(S)+12 and [redacted] will be completed at the study site. At Visit 1, the Investigator or authorised delegate will instruct the patients on how to complete each ePRO and answer any queries that the patient may have. From Visit 2b to Visit 7, additional training will be performed in the event of poor compliance.

Home completion of assessments for patients not visiting the study site due to COVID-19 and in case of early discontinuation of study treatment is allowed and described in the ePRO Manual.

8.1.1.1 Asthma Control Questionnaire-5 item

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 SABA use from the original ACQ assessment (see Appendix F).

Patients are asked to recall how their asthma has been during the previous week by responding to 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled).

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

8.1.1.2 Standardised Asthma Quality of Life Questionnaire for 12 years and older: 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).

The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli).

Patients are asked to recall their experiences during the previous 2 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 4 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).

8.1.1.3 CCI

8.1.2 Physiological asthma assessments

8.1.2.1 Pulmonary function tests (FEV_1 and FVC)

Pre-bronchodilator FEV_1 and forced vital capacity (FVC) will be performed at the study site and measured by spirometry using equipment provided by central vendor. Pulmonary function tests will be performed by the Investigator or authorised delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

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

Important! Symbicort® should be withheld for 12 hours prior to study visits. Ventolin® should be withheld for a minimum of 6 hours prior to study visits. If either condition is not met, the visit should be conducted when these conditions are met, either by delaying the time of the lung function evaluation or by re-scheduling the study visit.

Prior to pulmonary function tests at Visit 2b, the height of the patient will be measured.

8.1.2.2 CCI

CCI

CCI

CCI

8.1.2.3 CCI

CCI

8.1.3 Assessment of asthma exacerbations

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

- A temporary bolus/burst of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
- 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 Investigator must justify the decision for defining an event of worsening asthma as an exacerbation and record it in the source documents and eCRF. An asthma exacerbation that occurs within 7 days of the last dose of systemic steroids, prescribed for a prior exacerbation, will be counted as the same exacerbation event. The patient may remain in the study after an exacerbation and continue to receive study 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.

8.2 Safety Assessments

Clinical safety laboratory assessments, physical examinations, vital signs, electrocardiogram assessments, pregnancy testing, or other testing/procedures not required as part of this study may be conducted as part of routine clinical practice.

Only for patients participating in the sub-study: For patients participating in the sub-study, a nasal or throat swab will be done for SARS-CoV-2 testing prior to sputum induction. The testing will be done as per standard of care in participating site.

8.3 Collection of Adverse Events

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

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be recorded from the time of signing the ICF.

All SAEs will be recorded and reported to the Sponsor or delegate within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator shall, without any delay, report the SAE to the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

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

8.3.4 AE data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study treatment(s) (yes or no)
- Action taken with regard to study treatment(s)
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication.

8.3.5 Causality collection

The Investigator will assess causal relationship between study treatment and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study treatment?' for Symbicort®, Fasenra®, and Ventolin. Either none, or one, or more of the treatments may be selected as causal to any given AE or SAE.

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 AEs based on signs and symptoms

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

8.3.7 Disease under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of asthma. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnoea, breathlessness, and phlegm, will be recorded as AEs when:

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

Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of study treatment.

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of SAEs

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AZ representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AZ

representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AZ representative by telephone. The AZ representative will advise the Investigator/study site staff how to proceed.

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

8.4.2 Pregnancy

All serum pregnancy test analyses will be performed at a local laboratory.

All pregnancies and outcomes of pregnancy should be reported to AZ except for:

- If the pregnancy is discovered before the study patient has received any study treatment

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AZ representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is provided to the AZ Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.4.3 Overdose

For this study, any dose of Fasenra® greater than 200 mg, or formoterol greater than 90 µg, within 1 day will be considered an overdose.

AZ does not recommend specific treatment for an overdose.

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

Medication errors with AZ study treatments are collected in all studies where medication error is possible.

If a medication error occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AZ representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AZ representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is a SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Medical Device Deficiencies

In a combination drug-device study treatment (eg, APFS), the Device Constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

In this study, deficiency observed with any of study treatment devices (Ventolin® and Symbicort® inhalers and Fasenra® pre-filled syringes) will be collected and reported to the manufacturer using the form available on the Pharmacy manual (for more details please follow up Pharmacy manual).

For the third-party medical devices (Hailie™ sensors for Ventolin® and Symbicort®, ERT MasterScope ™ spirometry, CCI [redacted]) any deficiency or malfunction observed will be recorded on the eCRF form and reported to the manufacturers on a pre-defined basis.

The definition of a Medical Device deficiency can be found in Appendix H.

NOTE: Incidents and deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix H of the protocol.

8.4.5.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any medical device deficiency at any time after a patient has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting Medical Device Deficiency is provided in Appendix H.

8.4.5.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all patients, including those who discontinue study treatment.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

- New or updated information will be recorded on the originally completed form in eCRF with all changes signed and dated by the Investigator.

8.4.5.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies will be reported to the Sponsor within [24 hours] after the Investigator determines that the event meets the protocol definition of a medical device deficiency.
- The third-party medical device deficiency (Hailie™ sensors for Ventolin® and Symbicort®, ERT MasterScope ™ spirometry, [redacted]) will be reported by Investigator on the eCRF form. Study treatment devices deficiency (Ventolin® and Symbicort® inhalers and Fasenra® pre-filled syringes) will be reported over paper form and will be sent to the Sponsor by e-mail.
- The Sponsor will be the contact for the receipt of medical device deficiency reports.

8.4.5.4 Regulatory Reporting Requirements for Device Deficiencies

- The Investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the institutional review board (IRB)/ independent ethics committee (IEC).

For further guidance on the definition of an SAE, see Appendix H of the protocol.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

8.8.1 Sub-study biomarkers

All sub-study biomarker analyses will be reported separately from the Clinical Study Report (CSR).

Approximately 32 patients who have specifically consented to participate in the sub-study will undergo the following assessments.

8.8.1.1 CCI

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8.8.1.2 Induced sputum

Induced sputum will be collected for patients participating in the sub-study at Visit 2a (Week 0), Visit 8a (Week 47) or EOT, in accordance with the SoA (Table 1). Sputum will be analysed for pathogens and cytokines and a cell differential will be performed.

Briefly, before the induction procedure, a baseline post-bronchodilator FEV_1 test is performed (after inhalations of salbutamol); the measurement is done 3 times. The induction procedure includes inhalation of hypertonic saline solution by the patient for 5 minutes. After rinsing the mouth and throat and blowing the nose, the patient will cough sputum into a sterile plastic sputum pot using a deep cough. Following the sputum induction procedure, 1 FEV_1 measurement will be performed (3 measurements will be made if sputum FEV_1 falls by greater than 10% or 200 mL, whichever is less, compared with the best sputum post-bronchodilator FEV_1).

Nucleic acid analysis will be employed to determine the microbiome present in sputum samples. Protein analysis and cell differential analysis of induced sputum will be performed.

Details for conducting sputum collection will be described in a separate manual of procedures.

8.8.1.3 Serum samples for exploratory biomarkers

Blood samples for serum exploratory biomarkers will be collected. At each of the time points indicated in the SoA (Table 1), a maximum of 30 mL of blood will be taken for a full blood count (Visit 2b, Visit 6, and Visit 8b) and clotting (Visit 2b). The cellular profile of blood samples will be investigated using mass cytometry; RNA and protein analysis will be performed. Exploratory biomarker analysis may be performed on biomarker variants thought to play a role in severe eosinophilic phenotype asthma including, but not limited to, eosinophil granule proteins and inflammatory cytokines.

8.8.2 Blood sample for eosinophils

Blood eosinophil samples will be collected from all patients at all study visits indicated in the SoA (Table 1). If there is an EOT visit, a blood sample for eosinophils will be taken. Analysis will be performed at a local laboratory.

8.8.3 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. The results of the biomarker research in the sub-study will be reported separately from the CSR. The results of this biomarker research may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

8.9 Health Economics

After the exacerbation assessment at each visit, as shown in Table 1, the Investigator or authorised delegate will assess whether the patient has had any additional asthma-related healthcare resource utilisation event other than exacerbation-related events. If yes, information will be collected and recorded in the appropriate eCRF module.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

9.1.1 Estimation and testing strategy

The primary aim of this study is to assess the potential to reduce Symbicort® maintenance treatment while maintaining comparable asthma symptom control in 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).

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 and secondary outcome measures related to the reduction period will be analysed once all patients have completed the study (Week 48/EOT) (see Section 9.4.6). This will be described in more detail in the statistical analysis plan (SAP).

9.1.2 Baseline and change from baseline

In general, the last non-missing observation prior to randomisation 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 the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

In some assessments of the maintenance period around changes from end of the reduction period, the baseline will be defined as the visit the patient completed their reduction period.

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

9.1.3 Sensitivity analysis

Sensitivity analyses to assess the effect of missing data or drop-out on the primary endpoint will be outlined in the SAP.

9.2 Sample Size Determination

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 7 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% CI around the observed proportions with a half-width of less than 10 percentage points in the treatment reduction arm.

Screening failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to a study treatment arm at Visit 2b (Section 5.4).

Table 7 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%

CI=Confidence interval; SMART=Symbicort® maintenance and reliever therapy.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Patients Set (APS)	This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.
Full Analysis Set (FAS)	All randomised patients will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Patients who withdraw from the study will be included up to the date of their study termination. All efficacy analyses will be performed using the FAS. For consistency, demographic and baseline characteristics will be presented using the FAS.
Safety Analysis Set (SAF)	The safety analysis set consists of all randomised patients who have received at least one dose of study treatment. Erroneously treated patients (eg, those randomised to Treatment A but actually given Treatment B) are accounted for in the treatment group of the treatment they actually received. The SAF will be used for all safety analyses.

9.4 Statistical Analyses

Analyses will be performed by AZ or its representatives. A comprehensive SAP will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Patient disposition will be summarised using the APS. Demography, baseline, and patient characteristic data will be evaluated using the FAS. The efficacy endpoints will be evaluated using the FAS. All safety analyses will be performed using the SAF.

9.4.1 Outcome measures for analyses-calculation or derivation of efficacy variables

Symbicort® Maintenance Dose

The primary outcome variable is the Symbicort® maintenance dose prescribed at Visit 6 (Week 32).

The prescribed Symbicort® dose will be recorded at each post-baseline visit up to 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. For the 3 visits during the reduction period, the Investigator also records if the reduction is ended at that visit.

Asthma Control Questionnaire – 5 Item

Change from baseline ACQ-5 will be calculated as post-baseline ACQ-5 score minus baseline ACQ-5 score for all post-baseline ACQ-5 measurement points.

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

- Improvement: ACQ-5 score change from baseline ≤-0.5
- No Change: ACQ-5 score change from baseline >-0.5 and <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 time point will be considered asthma worsening responders at the timepoint.

Furthermore, patients will be categorised according to their ACQ-5 score defined asthma control status at post-baseline assessments using the following score thresholds (Juniper et al 2006):

- Well controlled: ACQ-5 score ≤0.75
- Partially controlled: 0.75<ACQ-5 score <1.5
- Not well controlled: ACQ-5 score ≥1.5.

Total ICS Dose Exposure

To assess the 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 total daily ICS dose on each day.
- 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.
- The patient's cumulative total daily ICS dose each day since the beginning of the maintenance period to the end of maintenance period.

In addition, the patient's mean total ICS dose (maintenance + reliever) during the previous 8 weeks will be derived during the study period at Week 0, 8, 16, 24, 32, 40, and 48 as the total recorded ICS dose (µg) divided by the number of days with recorded ICS dose (including any days with 0 µg ICS dose reported).

The within-patient change from baseline in mean total ICS dose for the previous 8 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 8 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 [Week 0]) / (the total daily ICS dose at baseline value).

AQLQ(S)+12

Change from baseline AQLQ(S)+12 will be calculated as post-baseline AQLQ(S)+12 score minus baseline (Visit 2b; Week 0) AQLQ(S)+12 score for all post-baseline AQLQ(S)+12 measurement points.

An AQLQ(S)+12 responder will be defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to end of treatment in AQLQ(S)+12 $\geq$0.5 and 0 otherwise.

Patients will also be categorised according to the following limits:

- Improvement: AQLQ(S)+12 (post visit– baseline) $\geq$0.5
- No change: -0.5 <AQLQ(S)+12 (post visit– baseline) <0.5
- Deterioration: AQLQ(S)+12 (post visit– baseline) $\leq$-0.5.

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.

Asthma Exacerbations

To calculate the number of exacerbations experienced by a patient during the treatment period, 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. In the primary analysis, the number of exacerbations observed for a patient during the 48-week study period 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 7 days in which neither criterion is fulfilled.

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 52-56 week treatment period according to the formula described below:

AER=Number of Exacerbations×365.25/(Follow-Up Date-First Fasenra® dose date+1).

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

Clinical Remission

Descriptive summaries of the number and proportion of patients meeting each composite endpoint criteria defining clinical remission (no exacerbations, less than 10% deterioration in FEV1 from randomisation and ACQ-5 ≤ 0.75 or ACQ-5 < 1.5) at 32 weeks (Visit 6b) and 48 weeks (Visit 8b) will be presented for both treatment arms. A remission score calculated for each patient 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
- Only exacerbation and ACQ-5 endpoints achieved

9.4.2 Efficacy analyses

9.4.2.1 Primary analysis

Reduction of Symbicort® Maintenance Treatment

The proportion of patients who reduce their Symbicort® maintenance treatment to either medium-dose SMART, low-dose SMART, or Symbicort® as anti-inflammatory reliever only 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 number and percentage of patients who do not reduce their maintenance treatment will also be included.

9.4.2.2 Secondary analysis

ACQ-5

Change from baseline ACQ-5 will be derived weekly up to Week 48 as post-baseline score minus baseline ACQ-5 score (Visit 2b; Week 0). The mean change from baseline ACQ-5 at the end of the reduction period is defined as at Week 32.

Change from baseline ACQ-5 to post-randomisation visits will be evaluated using a MMRM modelling approach including baseline ACQ-5, visit, treatment, and visit × treatment. The difference in average mean change from baseline ACQ-5 score at Week 32 (visits when the patient is in their maintenance period) will be presented together with 95% 2-sided CI.

The proportion of patients achieving an increase of <0.5 units compared to baseline in each treatment group at the end of the reduction period will be presented.

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 a MMRM approach including visit, treatment, and visit × treatment. The estimated mean change from baseline AQLQ(S)+12 during the reduction and maintenance periods will be presented by treatment and visit together with 2-sided 95% CI.

The proportion of patients achieving a decrease in AQLQ(S)+12 of <0.5 units compared to baseline in each treatment group at the end of the reduction period will be presented.

Change from Baseline FEV_1

Change from baseline pre-bronchodilator FEV_1 will be assessed at Week 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. The mean change from baseline pre-bronchodilator FEV_1 will be analysed using a MMRM approach including visit, treatment, and visit × treatment. The estimated mean change from baseline pre-bronchodilator FEV_1 during the reduction and maintenance periods will be presented by treatment and visit together with 2-sided 95% CI.

Asthma Exacerbation Rate

The annualised asthma exacerbation rate from Visit 2b (Week 0) up to Visit 8b (Week 48) will be estimated for each treatment arm and presented with 2-sided 95% CIs. Both crude rates and estimates based on a negative-regression model will be produced.

Total Daily ICS Dose

The cumulative daily total ICS dose (maintenance + reliever dose) will be presented for:

- The reduction period.
- The maintenance period.
- The study period.

The total daily ICS dose (maintenance + reliever dose) will be presented by treatment group for each day during the reduction and maintenance periods together with 2-sided 95% confidence bands.

The mean total daily ICS dose (maintenance + reliever) during the previous 8 weeks will be evaluated using a MMRM approach including visit, treatment, and visit × treatment.

9.4.3 Safety analyses

All safety variables will be summarised using the SAF. Safety data will be summarised for all patients in the SAF and presented by treatment group of the treatment they actually received.

9.4.3.1 Adverse events

An overall summary table will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories: AEs, deaths due to AE, SAEs, and AEs causing the discontinuation of study treatment (DAEs). 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 will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AstraZeneca or designee.

AEs, DAEs, and SAEs will be summarised by system organ class (SOC) and preferred term (PT) assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least 1 occurrence will be presented (ie, a patient with multiple occurrences of an AE will only be counted once). SAEs causing discontinuation of the study treatment/study will also be summarised.

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

A summary of the most common (ie, frequency of >5%) AEs will also be presented.

AEs of injection site reactions (high level term of administration and injection site) will be summarised by PT for the treatment period. In addition, if there is a sufficient number of hypersensitivity events (standardised MedDRA query of hypersensitivity), it will also be summarised by PT for the on-treatment period as well as the on-study period. Further details will be provided in the SAP.

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

9.4.4 Exploratory analyses

9.4.4.1 Change from baseline FeNO

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

9.4.4.2 Change from baseline in blood eosinophil count

The change from baseline blood eosinophil count will be assessed descriptively and using a MMRM approach including, treatment, visit, and treatment x visit. The estimated mean change from baseline eosinophil count during the reduction and maintenance 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.

9.4.4.3 CCI

9.4.4.4 Change from baseline in airway oscillometry during the study period

Airway oscillometry will be assessed in the sub-study only. See Section 9.4.5 for details of analysis.

9.4.5 Sub-study analysis

The sub-study consists of approximately 32 patients who will undergo airway oscillometry to assess asthma control and bronchoscopy and induced sputum sampling to characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy. The results of this sub-study biomarker research will be reported separately from the CSR.

9.4.6 Study read-out

The study will be analysed and read-out after the last patient has performed their last visit (Week 48/EOT). The full study will be analysed including both the reduction and maintenance periods. These analyses will include all study data from both the reduction and maintenance periods.

The unblinding, handling of data and results will be described in detail in the SAP and in the trial integrity document.

9.5 Interim Analyses

Not applicable.

9.5.1 Scientific Committee

A Scientific Committee will be utilised for this study. Appendix A 5 provides more details on the rationale for and the remit of the committee.

10 REFERENCES

Ankerst et al 2003
Ankerst J, Persson G, Weibull E. Tolerability of high dose of budesonide/formoterol in a single inhaler in patients with asthma. Pulm Pharmacol Ther 2003; 13(3): 147-151.

Bateman et al 2010
Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR *et al*. Overall asthma control: The relationship between current control and future risk. J Allergy Clin Immunol 2010; 125(3): 600-608.

Bleeker et al 2016
Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, *et al*. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016; 388(10056): 2115-2127.

CAMP et al 2000
Childhood Asthma Management Program Research Group, Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, *et al*. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med. 2000; 343(15): 1054-1063.

Chung et al 2014
Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43(2): 343-373.

FitzGerald et al 2016
FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, *et al*. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016; 388(10056): 2128-2141.

GINA 2019
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2019. [Accessed 12 April 2019]. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf.

Goldman et al 2017
Goldman M, Hirsch I, Zangrilli JG, Newbold P, Xu X. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017; 33(9): 1605-1613.

Guilbert et al 2006
Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, *et al*. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med. 2006; 354(19): 1985-1997.

Jacobsen et al 2012
Jacobsen EA, Helmers RA, Lee JJ, Lee NA. The expanding role(s) of eosinophils in health and disease. Blood 2012; 120(19): 3882-3890.

Juniper et al 1992
Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992; 47(2): 76-83.

Juniper et al 1994
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.

Juniper et al 1999
Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999; 115(5): 1265-1270.

Juniper et al 2005
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.

Juniper et al 2006
Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006; 100(4): 616-621.

Lemanske et al 2001
Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, *et al*. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA. 2001; 285(20): 2594-2603.

Miller et al 2005
Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A *et al*. Standardisation of Spirometry. Eur Respir J. 2005; 26: 319-338.

NAEPP 2007
National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007. [Accessed 01 March 2019]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

Nair et al 2017
Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, *et al*. Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma. N Engl J Med. 2017; 376(25): 2448-2458.

O'Byrne et al 2018
O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018; 378(20): 1865-1876.

Palmqvist et al 2001
Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. Pulm Pharm Ther 2001; 14(1): 29-34.

Waalkens et al 1993
Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, Gerritsen J, Duiverman EJ, Knol K, *et al*. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. Am Rev Respir Dis. 1993; 148(5): 1252-1257.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/ independent ethics committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Clinical Research Organisation (CRO) but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- The study will be performed in accordance with the AstraZeneca (AZ) policy on Bioethics and Human Biological Samples.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An Investigator who receives an 'Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator will explain the nature of the study to the patient and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient.

A 4 Data Protection

- Each patient will be assigned a unique identifier by the Sponsor. Any patient records or datasets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the patient in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A Scientific Committee consisting of internal AZ and external experts who have been involved in the design of the clinical study will advise the Sponsor on changes to the study

design and provide recommendations on issues related to the study conduct, if required. In addition, the committee will be involved in the review and interpretation of the study results. The Scientific Committee will be governed by a charter, detailing roles and responsibilities and processes of the Scientific Committee.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All patient data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to the Sponsor or delegate electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or delegate is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may

need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definitions of what constitutes source data can be found in the source data agreement and computerised data check list for electronic source data.

A 9 Study and Site Closure

The Sponsor or delegate reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. The study may be stopped if, in the judgement of AZ, trial patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant.
- Are assessed as causally related to study treatment.
- Are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

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

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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 or washout periods, even if no study treatment has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event (SAE) is an AE occurring during any study period (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent 1 of the outcomes listed above.

Adverse events for malignant tumours reported during a study should generally be assessed as serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a non-serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B 3 Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical treatment to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity Rating Scale:

1 Mild (awareness of sign or symptom, but easily tolerated)

2 Moderate (discomfort sufficient to cause interference with normal activities)

3 Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria

shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca (AZ) would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study (DUS) has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AZ study treatment that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding interactive voice/web response system [IVRS/IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors).

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

- Errors related to or resulting from IVRS/IWRS-including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product.

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody of Biological Samples

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

The Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca (AZ) will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AZ Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AZ is not obliged to destroy the results of this research.

As collection of the biological samples (ie, blood samples) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AZ
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AZ are informed about the sample disposal.

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt-all other materials with minimal risk of containing pathogens

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

Appendix D Classification of In Vivo Inhibitors of CYP3A4 Enzymes

Examples of CYP enzyme inhibitors

CYP enzyme	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil	Chlorzoxazone, cilostazol, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, tacrolimus, ticagrelor

CYP=cytochrome P450.
Note: Strong, moderate, and weak inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, ≥2 to <5-fold, and ≥1.25 to <2-fold, respectively.

Please note the following: This is not an exhaustive list. For an updated list, see the following link: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm080499.htm (accessed on 08 May 2019).

Appendix E AQLQ(S)+12

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

CCI

For further information:

PPD

CCI

CCI

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

PATIENT ID: _____

SELF-ADMINISTERED

DATE: _____

CCI

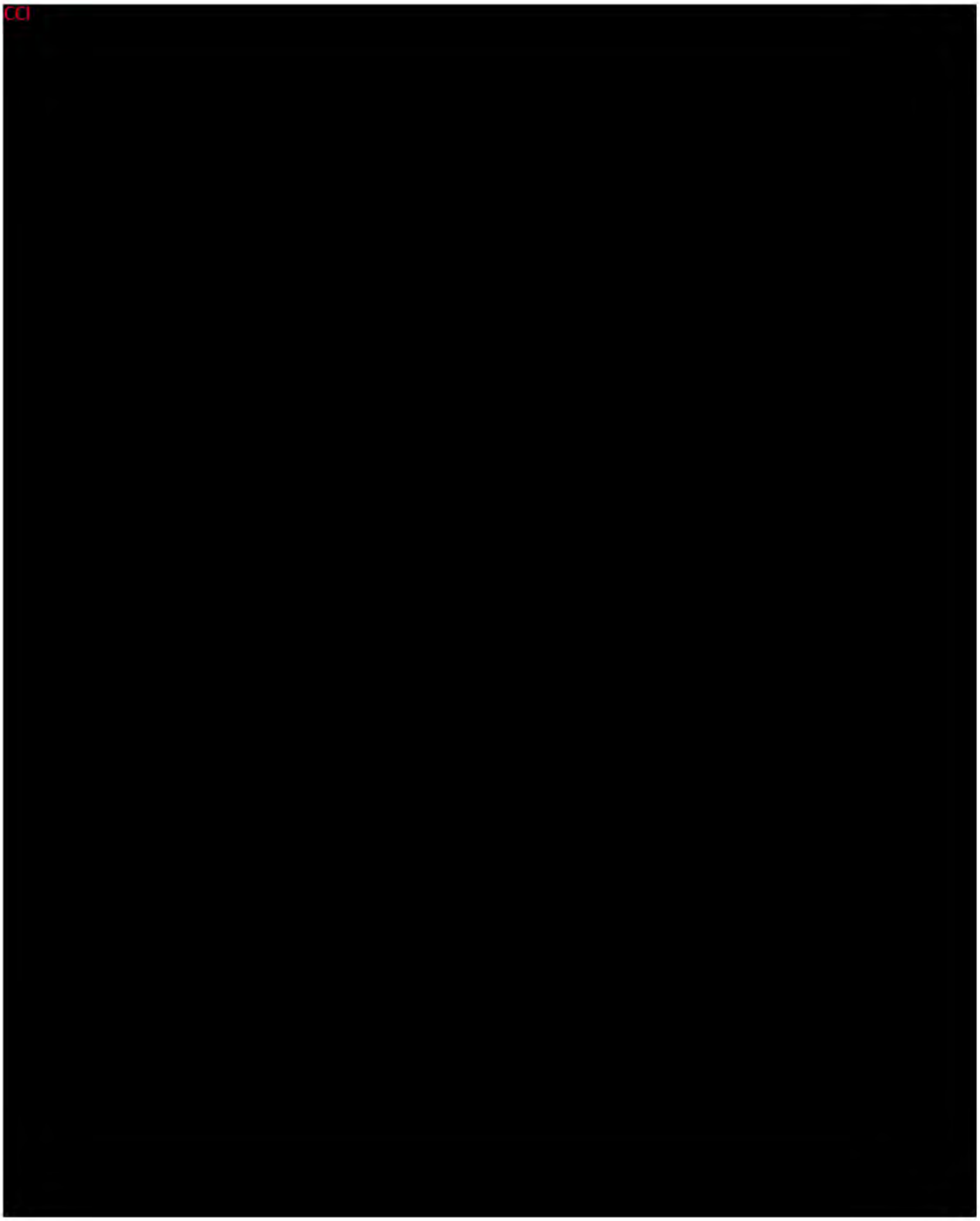
[redacted]

CCI

[redacted]

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____



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ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

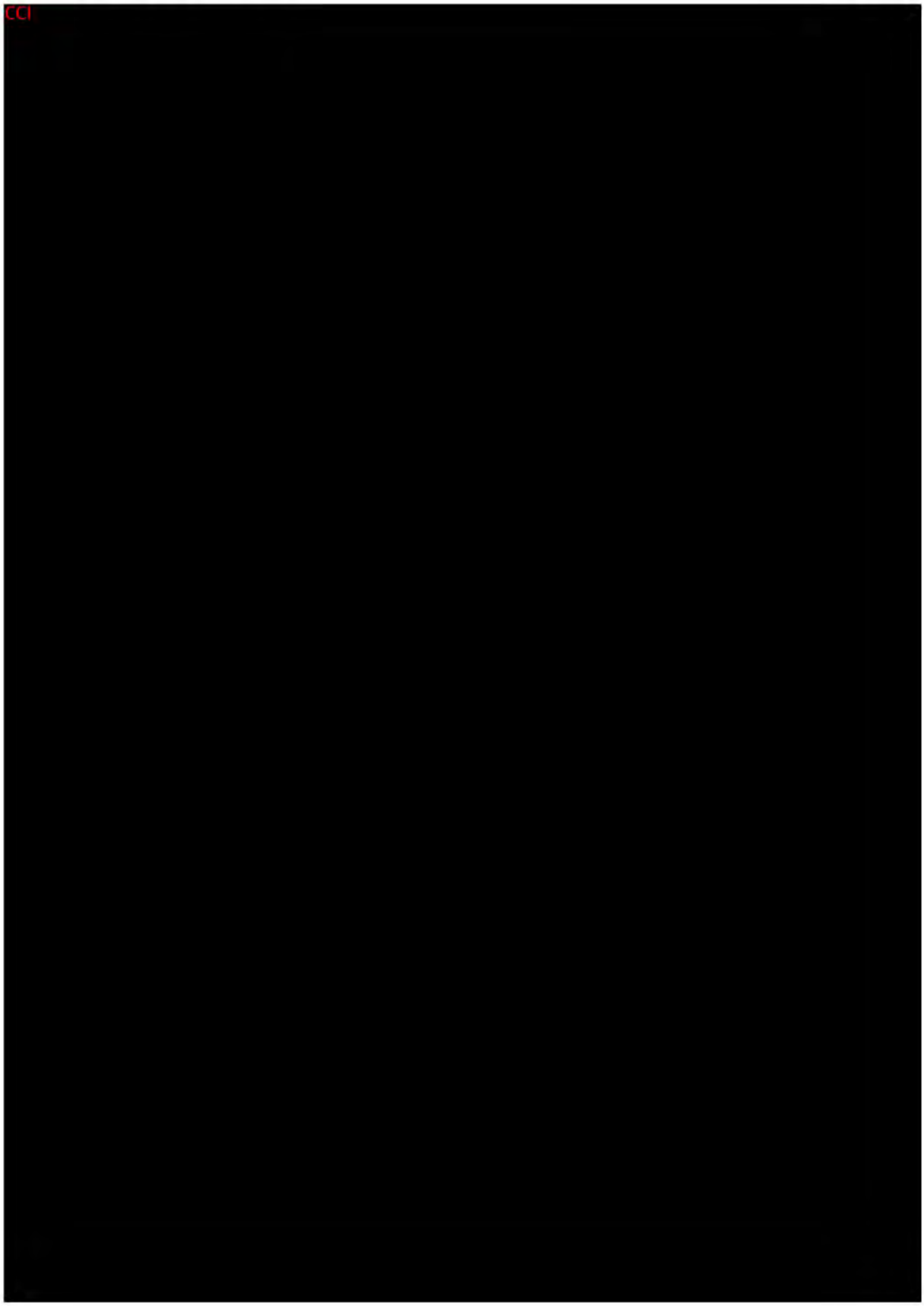
SELF-ADMINISTERED DATE: _____

Appendix F ACQ-5

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)

ASTHMA CONTROL QUESTIONNAIRE©



Appendix G Guidance on Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

G 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2 to G 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with investigational product. If this delay is outside the screening window specified in Table 1 the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4. The procedures detailed in Section 5 must be undertaken to confirm eligibility using the same randomization number as for the patient.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patients home/or other remote location as per local Standard Operating Procedures, as applicable. Supplies will be

provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP). If applicable, assessments will be performed according to the revised Schedule of Assessments (SoA).

G 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, and other information including efficacy data where relevant to be collected according to study requirements to be reported and documented. If applicable, safety procedures and blood sample collection may be performed according to the revised SoA in the Study Instructions for Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis.

G 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

G 5.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service may administer the IP at the patient's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

G 5.2 At-home or Remote Location IP Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location IP administration the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be

provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

G 6 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patient themselves.

Appendix H Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organisation for Standardisation 14155 and European MDR 2017/745 for clinical device research (if applicable).
- Both the Investigator and the Sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all Sponsor medical devices (see Section 6.1.1 for the related list) and all third-party medical devices (see Section 6.1.2 for the related list) provided for use in the study.

H 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study treatment, whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

H 2 Definition of Medical Device SAE, SADE, and USADE

A Medical Device SAE is an any SAE that:

a. Leads to death.

b. Leads to serious deterioration in the health of the patient, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.

- Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Leads to fetal distress, fetal death, or a congenital anomaly or birth defect.

SADE definition

Serious adverse device effect (SADE) is an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE. A SADE is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

H 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

H 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/medical device deficiency information in the patient's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the CRO/Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE/medical device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) or Product Information, for marketed products in his/her assessment.

- For each AE/SAE/medical device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

MDCG 2020 Guidance

For the purpose of harmonizing reports, each SAE will be classified according to five different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational[1] device or procedures.

1 Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device or the procedures.
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible.
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event.
- the event involves a body-site or an organ not expected to be affected by the device or procedure.
- the serious event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors).
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

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1 Investigational device: any device object of the clinical investigation, including the comparators

2 Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3 Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4 Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5 Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures.
- the event has a temporal relationship with investigational device use/application or procedures.
- the event involves a body-site or organ that
- the investigational device or procedures are applied to.
- the investigational device or procedures have an effect on.
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known).
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible).
- other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out.
- harm to the patient is due to error in use.
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AE/SAE/Medical Device Deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include

additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

H 5 Reporting of SAEs

SAE Reporting to Sponsor via Paper Data Collection Tool

- The SAEs, pregnancies and overdose to be reported in the EDC first. Only report on paper if EDC is unavailable. Fax cover sheet and SAE Report Form 243961-Shamal-SAE@parexel.com or Fax: + 1 833 944 0504 are to be used.
- Initial notification via EDC does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found on the paper SAE form available in the Site File.

H 6 Reporting of SADEs

SADE Reporting to Regulatory authorities

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any medical device deficiency that is associated with an SAE must be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the definition of a medical device deficiency.
- The Sponsor will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found on the paper SAE form available in the Site File.

Appendix I Abbreviations

Abbreviation or special term	Explanation
ACQ-5	asthma control questionnaire-5 item
ADA	anti-drug antibodies
ADE	adverse device effect
AE	adverse event
AER	annual exacerbation rate
APFS	accessorised pre-filled syringe
APS	all patients set
AQLQ(S)+12	standardised asthma quality of life questionnaire for 12 years and older
ATS/ERS	American thoracic society/European respiratory society
AZ	AstraZeneca
BAL	bronchoalveolar lavage
BID	bis in die (twice per day)
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRO	clinical research organisation
CSP	clinical study protocol
CSR	clinical study report
CYP	cytochrome P450
DAEs	AEs causing the discontinuation of study treatment
DNA	deoxyribonucleic acid
DUS	disease under study
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
eCRF	electronic case report form
EOT	end of treatment
ePRO	electronic patient-reported outcome
FAS	full analysis set
CCI [redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	good clinical practice
GINA	global initiative for asthma

HCP	Health Care Professional
IATA	international airline transportation association
ICF	informed consent form
ICH	international council for harmonisation
ICS	inhaled corticosteroids
IVRS/IWRS	interactive voice/web response system
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
OCS	oral corticosteroids
pMDI	pressurised metered dose inhaler
PRN	pro re nata (as needed)
PRO	patient-reported outcome
PT	preferred term
Q8W	every 8 weeks
RNA	ribonucleic acid
SABA	short-acting β-agonist
SADE	serious adverse device effect
SAE	serious adverse event
SAM	synthetic absorptive matrix
SAP	statistical analysis plan
SC	subcutaneous
SMART	Symbicort® maintenance and reliever therapy
SmPC	summary of product characteristics
SoA	schedule of assessments
TPV	Third-party vendor
USADE	unanticipated serious adverse device effect
UK	United Kingdom
WBDC	web based data capture
WOCBP	women of childbearing potential

Appendix J Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Clinical Study Protocol, Version 3.0, 17 September 2021

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

- To update minor discrepancies identified in the Global Clinical Study Protocol, Version 2.0 dated 10 Jul 2020.
- To add details of safety analysis set that is planned to be included in the study.
- To include recommendations regarding Coronavirus Disease 2019 (COVID-19) vaccination, as previously communicated to Investigators in the Investigator Letter dated 29 Jan 2021.
- To add details regarding the medical devices used in the study and also address medical device deficiencies as per AstraZeneca current processes for medical devices used in the studies and updated product safety information for Fasenra®.
- To include minor updates and clarifications in line with AstraZeneca current processes.
- To add Appendix H 'Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies' as per AstraZeneca current processes for medical devices used in the studies and updated product safety information for Fasenra®.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1, Table 1 Schedule of assessments	Updated to correct the days calculated for Visit 8a and Visit 8b	To align days calculation with weeks	Non-Substantial
Section 1.2, Synopsis	Updated the estimated date of last patient completed	Per extended study recruitment/timelines	Substantial
Section 1.2, Synopsis	Statistical methods in the synopsis were aligned with revised Section 9.3	For consistency with other sections	Substantial
Section 5.2, Exclusion Criteria	Added new criteria to include details about	To provide guidance on how to handle	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	patients who received COVID-19 vaccination	COVID-19 vaccinations in the patients participating in this study	
Section 5.3.4, Blood Donation	New section was added to explain restrictions related to blood donation	Per updated product safety information for Fasenra®	Substantial
Section 6.1.1, Table 4 Study Treatment	Added new row to include conversion of 200/6 and 400/12 Symbicort into 'total' µg	To add clarity on total doses of Symbicort	Substantial
Section 6.1.2, Medical devices	Updated to include a short description of spirometry device and [redacted]	To align with AstraZeneca current processes for medical devices used in the studies	Substantial
Section 6.1.2, Medical devices	Updated to include reference to Section 8.4.5 Medical Device Deficiencies	To align with AstraZeneca current processes for medical devices used in the studies	Substantial
Section 6.5, Concomitant therapy, Table 5 Restricted medications	Added details about COVID-19 vaccination	To provide guidance on how to handle COVID-19 vaccinations in the patients participating in this study	Substantial
Section 8.1.1, Electronic Patient-Reported Outcomes	Added wording about home completion of COVID-19-related-ePRO	To avoid data loss due to on-site visits not happening	Substantial
Section 8.3.2, Time period and frequency for	Added clarification that if the Investigator learns of any SAEs in	To align with current AstraZeneca SAE reporting processes	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
collecting AE and SAE information	a former study patient, these should be reported without any delay		
Section 8.4.5, Medical Device Deficiencies	Added new section	To align with AstraZeneca current processes for medical devices used in the studies and to align with updated product safety information for Fasenra®	Substantial
Section 9.3, Populations for Analyses	Added new population for analyses – Safety Analysis set	To align with statistical analysis	Substantial
Section 9.4.1, Outcome measures for analyses calculation or derivation of efficacy variables	ICS dose reported and recorded in mg updated to be reported and recorded in micrograms (µg)	To unify the units as per clinical practise and Statistical Analysis	Non-substantial
Section 9.4.3, Safety analyses	Updated to include Safety Analysis set	For consistency with Section 9.3	Substantial
Section 9.4.3.1, Adverse events	Added details about adverse events coding	To align with AstraZeneca standard processes for safety analyses	Non-Substantial
Appendix A, Regulatory, Ethical and Study Oversight Considerations	Updated to include some text missing in the protocol version 2.0 (dated 10 Jul 2020)	To align with AstraZeneca current processes	Substantial
Appendix H, Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device	Added new appendix	To provide definitions and procedures for AEs related to Sponsor and third-party medical devices, as	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies		well as medical device deficiencies, in line with current AstraZeneca processes for medical devices used in the studies	

Clinical Study Protocol, Version 2.0, 10 July 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

- To amend details for the sub-study. This includes removal of nasosorption sampling and addition of SARS-COV-2 test and induced sputum sampling.
- To update text concerning biomarker assessments, based on the latest version of the sub-study laboratory manual.
- To update minor discrepancies identified in the Global Clinical Study Protocol, Version 1.0 (dated 04 Jun 2019).
- To add language regarding study mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis which will provide sites with measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with Good Clinical Practice, and minimizing risks to the study integrity.
- The following appendices updated with latest AstraZeneca template language and requirements:
  - Appendix A Regulatory, Ethical and Study Oversight Considerations
  - Appendix B Adverse Event Definitions and Additional Safety Information
- Appendix D Deletion of 'Definitions of a Medical Device Incident' appendix.

Appendix G Addition of 'Guidance on Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis' appendix.

Summary of Changes
Clinical Study Protocol, Version 2.0, 10 July 2020

Throughout the document

- Updates made per the sponsor's current protocol template.
- Format and language changes, if deemed necessary.
- Visit 2 was split into Visit 2a and Visit 2b and Visit 8 into Visit 8a and Visit 8b, due to addition of assessments specific for the sub-study.

Section 1.1, Table 1 Schedule of assessments

- Addition of new columns to split Visit 2 into Visit 2a and Visit 2b and Visit 8 into Visit 8a and Visit 8b.
- Visit days have been corrected as follows: Visit 3, Day 57 (from Day 56); Visit 4, Day 113 (from Day 112); Visit 5, Day 169 (from Day 168); Visit 6, Day 225 (from Day 224); Visit 7, Day 281 (from Day 280); Visit 8a, 335.
- Addition of assessment of airway oscillometry (sub-study) at Visits 2b, 3, 4, 5, 6, 7, and 8b or end of treatment (EOT).
- Addition of SARS-CoV-2 testing (sub-study) and corresponding footnote.
- Addition of assessment of induced sputum (sub-study) at Visits 2a, 8a or EOT.
- Elimination of nasosorption sampling.
- Renumbering of existing footnotes subsequent to insertion of new assessments and new footnotes.
- Insertion of new footnote 'a' to indicate that Visits 2a and 8a and the assessments scheduled for these visits apply only to patients in the sub-study.
- Addition of new footnote 'b' explaining that although Visit 6 is listed under the reduction period, no further reduction of Symbicort® is permitted at this visit and that for statistical analysis purposes Visit 6 is the end of the reduction period and also the baseline visit for the maintenance period.
- Addition of footnote 'c' explaining that EOT visit is comprised of assessments at Visit 8a and Visit 8b.
- Addition of following text to footnote 'k': Prior to pulmonary function tests at Visit 2b, the height of the patient will be measured. Exceptionally, consistent with Appendix G, spirometry can be omitted under circumstances where it is not recommended because of precautions for infection control around pandemic disease.
- Revision of footnote 'l' to include the following: (treatment reduction arm : reference arm).
- Text in footnote 'n' concerning duration of fast changed from 'from midnight' to 'for 6 hours'.

Section 1.2 Synopsis and Section 3 Objectives and Endpoints

- Addition of the following exploratory endpoint/variable: Serum protein biomarkers (sub-study).
- Replacing of 'nasal biomarkers' with 'sputum biomarkers' as exploratory endpoint/variable.

- Addition of the following exploratory objective and corresponding endpoint/variable:
  - Exploratory objective: To assess the potential for Fasenra®-treated patients to maintain lung function while stepping down Symbicort® maintenance treatment (sub-study)
  - Endpoint/variable: Change from baseline in airway oscillometry during the study period (sub-study).

Section 1.2 Synopsis, Study Period:

- Revision of estimated dates of first patient enrolled and last patient completed.

Sections 1.2 Synopsis and Section 4.1 Overall Design

- Wording revised from:

  Sub-study: A subset of patients who consent to participation in the sub-study (approximately 32 patients are to be included, spread across the 2 treatment arms) will undergo bronchoscopy and nasosorption sampling at specific timepoints for exploratory biomarker research. Patients will be enrolled from 1 study site in the UK and will be stratified separately from the main study with a 3:1 ratio by treatment arm (treatment reduction arm: reference arm).

  to:

  Sub-study: A subset of patients who consent to participation in the sub-study (approximately 32 patients are to be included, spread across the 2 treatment arms) will undergo airway oscillometry to assess a measure of lung function and will undergo bronchoscopy and induced sputum sampling at specific timepoints for exploratory biomarker research. Patients will be enrolled from 1 study site in the UK and will be stratified into the sub-study separately from the main study with a 3:1 ratio by treatment arm (treatment reduction arm: reference arm).
- Addition of following:

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

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

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

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

Section 1.3 Schema

- Revision of footnotes to accommodate addition of new footnotes.

Section 5.1 Inclusion Criteria

Wording revised from:

- WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration and within 16 weeks after the last dose of study treatment. Highly effective forms of birth control include:

  to:

  WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration and within 12 weeks after the last dose of study treatment. Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Women <50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle stimulating hormone (FSH) levels in the postmenopausal range. Until FSH or luteininzing hormone is documented to be within menopausal range, treat the patient as WOCBP.

to: Women <50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle stimulating hormone (FSH) levels in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the patient as WOCBP.
Section 5.3.1 Meals and dietary restrictions • Wording revised from: CCI [redacted] [redacted] CCI [redacted]
Section 6.1.2 Medical devices The following text deleted: All medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the Investigator throughout the study (see Section 8.4.4).
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding • Wording revised from: At Visit 2, approximately 200 patients will be randomly assigned to 1 of the 2 treatment arms using a 3:1 randomisation ratio. to At Visit 2b, approximately 200 patients will be randomly assigned to 1 of the 2 treatment arms using a 3:1 randomisation ratio, with the randomisation stratified by whether or not the patient consents to participate in the sub-study (note this is equivalent to randomising patients in the sub-study separately in the same 3:1 ratio).

Section 6.5 Concomitant Therapy

Wording revised from:

Live attenuated vaccines: Not allowed within 30 days of Visit 1, during the treatment period, and for 16 weeks (5 half-lives) after the last dose of the study treatment administration.

to:

Not allowed within 30 days of Visit 1, during the treatment period, and for 12 weeks (5 half-lives) after the last dose of the study treatment administration.

Section 8.1.1.3 and Section 9.4.4.3 [redacted]

- [redacted]
- [redacted]

to:

CCI [redacted]
Section 8.1.2.1 Pulmonary function tests (FEV_1 and FVC) • Addition of the following text: Prior to pulmonary function tests at Visit 2b, the height of the patient will be measured.
Section 8.1.2.3 Airway oscillometry • Insertion of new Section 8.1.2.3 Airway oscillometry.
Section 8.2 Safety Assessments Addition of text regarding SARS-CoV-2 testing.
Section 8.4.2.1 Maternal exposure Wording revised from: The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy. to: The PREGREP module in the eCRF is used to report the pregnancy.
Section 8.4.4 Medical device incidents (including malfunctions) and Appendix D Section and appendix deleted.
Section 8.4.4 Medication error Following sentence deleted: For guidance, refer to AZ standard operating procedure (SOP) 'Reporting of Individual Safety Events in Clinical Studies'.
Section 8.8.1 Sub-Study biomarkers:

- Clarification that all sub-study biomarker analyses will be reported separately from the Clinical Study Report.
- Section 8.8.1.1 Bronchoscopy:
  - Wording revised from:

    Patients must fast from midnight prior to any bronchoscopy procedures.

    to:

    Patients must fast for 6 hours prior to any bronchoscopy procedures.
  - For sites participating in the sub-study, some data generated from biopsies and epithelial brushings will not be generated and analysed until after all patients in the sub-study have completed Visit 8b and therefore will be reported back from the analysing laboratories and transferred at the end of the study.

    to:

    Data generated from biopsies and epithelial brushings will not be generated and analysed until after all patients in the sub-study have completed Visit 8b and therefore will be reported back from the analysing laboratories and transferred at the end of the study.
  - Addition of nucleic acid/protein measurements, as well as cellular profiling, to the purpose of bronchoscopy sample collection (in addition to analysis of lung microbiome).
  - Clarification concerning the order of bronchoscopy samples and text rearranged accordingly.
  - Bronchoalveolar Lavage:

    Addition of text to method description.

    Clarification of purpose of sample collection and analyses used.
  - Bronchial Epithelial Brushing:

    Simplification of method description.

    Clarification of purpose of sample collection and data reporting.
  - Endobronchial Biopsy:

    Clarification of purpose of sample collection.
- Previous Section 8.8.1.2 Nasosorption sampling was deleted and replaced with Section 8.8.1.2 Induced sputum.
- Section 8.8.1.3 Serum samples for exploratory biomarkers:
  - Addition of following text: At each of the time points indicated in the SoA (Table 1), a maximum of 30 mL of blood will be taken for a full blood count (Visit 2b, Visit 6, and Visit 8b) and clotting (Visit 2b). The cellular profile of

blood samples will be investigated using mass cytometry; RNA and protein analysis will be performed.
Section 8.8.3 Storage, re-use and destruction of biomarker samples • Clarification that results of the biomarker research in the sub-study will be reported separately from the clinical study report.
Section 9.4.1 Outcome measures for analyses calculation or derivation of efficacy variables Wording revised from: • 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 $\leq$-0.5 and 0 otherwise. to: 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 $\geq$0.5 and 0 otherwise.
Section 9.4.4.2 Change from baseline in blood eosinophil count Wording revised from: The change from baseline blood eosinophil count will be assessed descriptively and using a MMRM approach including, treatment, visit, and treatment visit. to: The change from baseline blood eosinophil count will be assessed descriptively and using a MMRM approach including, treatment, visit, and treatment x visit.
Section 9.4.4 Exploratory analyses • Addition of Section 9.4.4.4 Change from baseline in airway oscillometry during the study period.
Section 9.4.5 Sub-study analysis • Text revised from: The sub-study consists of approximately 32 patients who will undergo bronchoscopy and nasosorption sampling to characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy. The results of this sub-study research will be reported either in the CSR itself or in a separate report. to:

• The sub-study consists of approximately 32 patients who will undergo airway oscillometry to assess asthma control and bronchoscopy and induced sputum sampling to characterise the effects of Fasenra® on airway inflammation after reducing daily Symbicort® therapy. The results of this sub-study biomarker research will be reported separately from the CSR.
Appendix A Regulatory, Ethical and Study Oversight Considerations Appendix updated to reflect current sponsor template.
Appendix B2 Definitions of Serious Adverse Events Appendix updated to reflect current sponsor template.
Appendix D Definitions of a Medical Device Incident • Appendix deleted.
Appendix G • Addition of guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.
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Initial creation

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