A 24-week Randomised Exploratory Open-Label Study Aiming To Characterise Changes In Airway Inflammation, Symptoms, Lung Function, And Reliever Use In Asthma Patients Using SABA (Salbutamol) Or Anti-Inflammatory Reliever (SYMBICORT®1) As Rescue Medication In Addition To SYMBICORT As Daily Asthma Controller

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Clinical Study Protocol	
Drug Substance	Budesonide/formoterol
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A 24-week Randomised Exploratory Open-Label Study Aiming To Characterise Changes In Airway Inflammation, Symptoms, Lung Function, And Reliever Use In Asthma Patients Using SABA (Salbutamol) Or Anti-Inflammatory Reliever (SYMBICORT®[1]) As Rescue Medication In Addition To SYMBICORT As Daily Asthma Controller

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2018-003467-64

[1] SYMBICORT is a trademark of the AstraZeneca group of companies.

VERSION HISTORY

Version 5.0, 02 Aug 2021
Section 1.2, Synopsis – Change in Principal Investigator. Section 5.1, Inclusion Criteria – removal of inclusion criterion number 8. Throughout – the SmartTouch™ device changed to the Hailie® device.
Version 4.0, 14 Apr 2021
Section 1.1, Table 1 – Schedule of Assessments – footnote typos corrected.
Version 3.0, 16 Sep 2020 Changes to the protocol are summarised below.
Section 1.1, Table 1 – Schedule of Assessments – the count of days between visits was corrected, baseline/start of treatment was clarified, collection of serious AEs and AEs leading to treatment discontinuation and/ or related to medical device incidents and concomitant medications was removed from the Run-in Period, FEV_1 now to be measured at the study site at screening only, CCI [redacted], Visit 3 was changed from a site visit to a telephone contact, and table footnotes were updated accordingly. Section 1.2 – Synopsis – was updated to reflect the changes described for Table 1. As a result of Visit 3 being changed to a telephone contact, randomised treatment for all at-home administration will be dispensed at Visit 2, and all drugs and devices will be returned by the patient at Visit 4 (unless needed to complete Event Visits). In addition, the secondary exploratory objective was removed. Section 3 - Objectives and Endpoints (and throughout the document) – the secondary exploratory objective has been removed. Section 4.1 – Overall Design - updated to reflect the changes described for Table 1 and Section 1.2. Section 4.1.1 – Study Conduct and Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis was added to the overall study design and describes study mitigation language measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue while minimising risk to the patient, maintaining compliance with Good Clinical Practice (GCP), and minimising risks to the study integrity. Section 6.1.2.4 (and throughout the document) – SmartTurbo™ changed to Turbu+™.

Section 6.5 – Concomitant Therapy: section was updated to add further guidance for Investigators in determining allowed, restricted, and prohibited medications.

Section 8.1.2.1 - Lung Function Measurement by Spirometry (FEV_1) was updated to reflect in-house FEV_1 measurement at screening only.

Section 8.8 – Biomarkers was updated to remove collection of spontaneous sputum.

Appendix C - Handling of Human Biological Samples: collection of spontaneous sputum was removed.

Appendix H - Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis was added.

Version 2.0, 12 March 2019

Changes to the protocol are summarised below.

Throughout (Number of inhalations/puffs of reliever medication): Clarification has been made for the number of inhalations/puffs of reliever medication that are required for the STIFLE App to trigger an "Event". When reliever medication is required, each administration consists of 1 inhalation for SYMBICORT and 2 puffs for VENTOLIN. The text has been updated to state 6 or more occasions of reliever medication use which is equivalent to 6 inhalations of SYMBICORT and 12 puff of VENTOLIN.

Appendix E (Asthma symptom diary): The diary questions related to the use of reliever medication during the night and during the day were updated to clarify the number of occasions of use.

Throughout (Reliever medication): Minor updates to clarify text where relevant to remove "inhalation" and state as "occasions of reliever medication use".

Section 1.1 (Schedule of Assessments, footnote j): Minor update clarifying the timing of eosinophil-derived neurotoxin blood sample collection.

Section 5.2 (Exclusion criteria 20): Updated to allow the Investigator flexibility when considering planned hospitalisations as part of patient eligibility.

Section 8.1.1.1 (Fractional exhaled Nitric Oxide [FeNO]): The time period for not using reliever medication before the FeNO assessment was reduced to 1 hour and the restriction of not performing the FeNO assessment following a respiratory infection removed.

Section 9.4 (Statistical Analyses): Clarification that the statistical analysis plan will be developed and approved before any statistical analyses are performed.

Throughout: A minor update to the terminology of serious adverse events and adverse events leading to discontinuation to also include related to medical device incidents to be consistent with the same definition later in the protocol. Throughout (Severe exacerbation definition): Minor updates to better present the definition.

Version 1.0, 09 November 2018
Initial creation

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

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Assessments

	Screening	Run-in period	Treatment period					
Visit	**1**	**-**	**2 (Baseline)**	**3** [a]	**4**	**Event Visits** [b] **(E1 to E4)**	**Premature discontinuation visit**	**Details in CSP section or Appendix**
Week	**-2**	**-2 to -1**	**1**	**12**	**24**	**Approx 4-day intervals from E1**	**On or after day of last study treatment administration**	
Day	**-14**	**-14 to -1**	**1**	**85**	**169**			
Window (days)	**-**		**±2**	**±4**	**±4**	**±2**		
Informed consent	X							Section 5.1
Eligibility criteria	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
Weight (BMI) and height	X							Section 8.2.2
Prior and concomitant medication	X		X	X	X	X [c]	X	Section 6.5
Routine safety measurements								
Serious AEs and AEs leading to treatment discontinuation and/ or related to medical device incidents	X		X	X	X	X	X	Section 8.3
Vital signs	X						X	Section 8.2.3
Physical examination	X						X	Section 8.2.2
Pregnancy test [d]	X							Section 5.1
Clinical chemistry/urinalysis assessments [e]	X				X		X	Section 8.2.1
Haematology assessments	X				X		X	Section 8.2.1
Asthma assessments at home								
FeNO assessment [f]	Daily (morning) including visit days							Section 8.1.1.1
Spirometry (PEF and FEV_1) [g]	Daily (morning and evening) including visit days							Section 8.1.1.2
Asthma symptom diary	Daily (morning and evening) including visit days							Section 8.1.1.3

	Screening	Run-in period		Treatment period				
Visit	**1**	**-**	**2 (Baseline)**	**3 [a]**	**4**	**Event Visits [b] (E1 to E4)**	**Premature discontinuation visit**	**Details in CSP section or Appendix**
Week	**-2**	**-2 to -1**	**1**	**12**	**24**	**Approx 4-day intervals from E1**	**On or after day of last study treatment administration**	
Day	**-14**	**-14 to -1**	**1**	**85**	**169**			
Window (days)	-		**±2**	**±4**	**±4**	**±2**		
Asthma assessments at site								
FEV_1	X							Section 8.1.2.1
Biomarker samples								
[redacted]				CCI [redacted]				
CCI [redacted]								
[redacted]								
[redacted]								
CCI [redacted]								
[redacted]								
Study treatment administration								
Devices given and training performed	X		X					Section 6.4
Devices collected					X		X	Section 7.3
Run-in treatment dispensed	X							Section 6.2
Run-in treatment collected			X					Section 6.2
Randomisation			X					Section 6.3
Randomised treatment dispensed			X					Section 6.2
Randomised treatment collected					X		X	Section 6.2

	Screening	Run-in period	Treatment period					
Visit	**1**	-	**2 (Baseline)**	**3 [a]**	**4**	**Event Visits [b] (E1 to E4)**	**Premature discontinuation visit**	**Details in CSP section or Appendix**
Week	**-2**	**-2 to -1**	**1**	**12**	**24**	**Approx 4-day intervals from E1**	**On or after day of last study treatment administration**	
Day	**-14**	**-14 to -1**	**1**	**85**	**169**			
Window (days)	-		**±2**	**±4**	**±4**	**±2**		
SYMBICORT as maintenance		SYMBICORT, × 2 BID (morning and evening)						Section 6.1
SYMBICORT/salbutamol as reliever medication		Salbutamol, PRN	Randomised SYMBICORT or salbutamol, PRN					Section 6.1

AEs=Adverse Events; CSP=Clinical Study Protocol; BID=twice per day; BMI=Body Mass Index; CCI [redacted]; FeNO=Fractional exhaled Nitric Oxide; FEV_1=Forced Expiratory Volume in 1 second; PEF=Peak Expiratory Flow; PRN=as needed.

a. Visit 3 will be conducted via a telephone call.
b. Patients will attend 4 Event Visits (E1 to E4); E1 will take place at the earliest possible date following the request to come to the study site for Event Visits. E2 to E4 will take place at approximately 4-day intervals. Investigators must make every effort to complete the series of 4 Event Visits when applicable (see Section 1.2). If a patient cannot attend Event Visits for their first event, then the Investigator will attempt to collect data for the next event instead. If Visit 4 is scheduled to occur during the Event Visit window, Visit 4 assessments must be conducted at the Event Visit that is closest to the date of the scheduled Visit 4. If the patient is required to complete the Event Visits during Week 23 or Week 24, the patient may participate in the study for 25 or 26 weeks, respectively.
c. Concomitant medication will be collected at Event Visits E1 and E4.
d. Women of childbearing potential should have a urine pregnancy test at Visit 1. If positive, the urine pregnancy test should be confirmed with a serum pregnancy test.
e. Positive dipstick findings should be confirmed with microscopic analysis.
f. Following training to use the device on Visit 1, FeNO assessments will be conducted at home every morning (prior to coming to the study site on visit days). Food consumption will be withheld for at least 1 hour before all FeNO assessments.
g. Spirometry must be conducted after the FeNO measurement.

CCI [redacted]

1.2 Synopsis

Principal Investigator:

Dr. Matthew Martin
City campus of Nottingham University Hospital
University of Nottingham
Hucknall Road
Nottingham
NG5 1PB
United Kingdom

Protocol Title:

A 24-week Randomised Exploratory Open-Label Study Aiming To Characterise Changes In Airway Inflammation, Symptoms, Lung Function, And Reliever Use In Asthma Patients Using SABA (Salbutamol) Or Anti-Inflammatory Reliever (SYMBICORT®[1]) As Rescue Medication In Addition To SYMBICORT As Daily Asthma Controller

Rationale:

The purpose of this exploratory study is to gain longitudinal insight on the possible relationship between the inflammatory profile, symptoms, lung function, and reliever use in groups of symptomatic adults (≥ 18 years of age) with moderate asthma, who are being treated with SYMBICORT®, a fixed dose combination (FDC) of inhaled corticosteroid (ICS; budesonide) plus a rapid-acting bronchodilator (formoterol) as maintenance therapy, and as reliever therapy (ie, SYMBICORT as Maintenance and Reliever Therapy [SMART]), compared to patients being treated with SYMBICORT maintenance therapy, treated with a short-acting β-agonist (SABA; salbutamol [VENTOLIN®, GSK]) as reliever therapy. Over the course of 24 weeks, this study will assess the inflammatory profile of patients, by measuring exhaled nitric oxide (FeNO), as well as their asthma condition by evaluating lung function, asthma symptoms, and reliever use.

Objectives and Endpoints:

Primary Objective:	Endpoint/Variable:
Descriptively characterise the relationship between inflammation, asthma symptoms, lung function, and reliever use measured daily over 24 weeks of treatment in the 2 treatment arms.	Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use for the 24 weeks of treatment.

[1] SYMBICORT is a trademark of the AstraZeneca group of companies.

Objectives and Endpoints:

Secondary Objective:	Endpoint/Variable:
Descriptively characterise the inflammatory, asthma symptoms, lung function, and reliever use profile surrounding an event in the 2 treatment arms.	Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use between 14 days prior and 28 days after an event. Events of interest are SevEx, CompEx (full criteria), a single day (in 24 hours) with 6 or more occasions of reliever medication use, and FeNO > 50 ppb.
Exploratory Objectives:	**Endpoint/Variables:**
CCI	CCI
CCI	CCI
CCI	

; FeNO=Fractional exhaled Nitric Oxide; FEV_1=Forced Expiratory Volume in 1 second; PEF=Peak Expiratory Flow; ppb=parts per billion.

Overall Design:

This is a randomised, active-comparator, open-label, parallel-group, multicentre phase IV exploratory study to characterise changes in airway inflammation, symptoms, lung function, and reliever use in asthma patients using short-acting β-agonist (SABA; salbutamol) or anti-inflammatory reliever (SYMBICORT) as reliever medication in addition to SYMBICORT as daily asthma controller. Eligible patients diagnosed with asthma at least 6 months prior to the Screening Visit (Visit 1) and fulfilling all of the inclusion criteria and none of the exclusion criteria will continue into the Run-in Period. At Visit 2, patients will be assessed for randomisation criteria and, if met, will be randomised to receive either SYMBICORT as maintenance and reliever treatment or SYMBICORT as maintenance treatment and salbutamol as reliever treatment in a 1:1 ratio. Randomisation will be stratified by the patient's ongoing dose of ICS (low or medium) or long-acting β_2-agonist (LABA) at study entry.

This study will include a minimum of 3 site visits. Patients may also attend up to 4 additional visits during the randomised Treatment Period for the first time that they meet one of the 3 criteria for Event Visits as detailed below. The duration of participation in the study will be 26 to 28 weeks (maximum) for each individual patient, including a 2-week Run-in Period, followed by a 24-week randomised Treatment Period and an additional follow-up period if the Event Visits fall within the final 2 weeks of the Treatment Period.

The study plans to randomise a minimum of 60 patients to a maximum of 80 patients to achieve at least 54 patients completing the study. A subset of up to 30 patients, who have specifically consented, will also participate in a sub-study on CCI [redacted].
The study will be conducted at no less than 2 sites in the United Kingdom (UK). The estimated study duration is approximately ~30 months.

The study will consist of a Screening Visit (Visit 1), a 2-week Run-in Period, a Baseline Visit (Visit 2) and a 24-week Treatment Period. During the Treatment Period, patients will attend a scheduled visit on Week 24 (Visit 4) of study treatment. If the patient meets the criteria for the Event Visits during the 24-week Treatment Period, 4 additional Event Visits (E1 to E4) will be scheduled (see the SoA [Table 1]). During the Run-in Period and Treatment Period, the patient will also perform daily asthma assessments at home, as described below.

Visit 1 (Screening): After signing the informed consent form (ICF), patients will have eligibility assessments, as well as safety evaluations (vital signs, physical examination, clinical chemistry, haematology, urinalysis, and pregnancy test) to assess the patient's medical condition, CCI [redacted] and FEV_1 will be measured using clinical spirometry equipment.

Patients who satisfy eligibility criteria will be requested to transition from their ongoing ICS/LABA asthma treatment to maintenance SYMBICORT (100/6 or 200/6 µg, × 2 BID) and reliever salbutamol (100 µg, as needed [PRN]). The selection of the SYMBICORT dose will reflect the patient's ongoing ICS (low or medium dose per the Global Initiative for Asthma [GINA] 2018 guidelines) or LABA regimen at study entry.

During this visit, patients will be given a patient kit containing a smartphone and 4 devices connected to the smartphone via the STIFLE App (1 spirometry sensor, 1 FeNO monitoring device, and 2 Adherium inhaler sensors). The Investigator (or trained study staff) will ensure all devices are connected properly and will instruct patients how to use each device and the STIFLE App. They will help patients perform their first spirometry measurements, FeNO measurement, and complete the asthma symptom diary.

Run-in period: The Run-in Period will last 14 days (±2 days) starting from Visit 1. Patients will take their run-in treatments (ie, maintenance SYMBICORT [100/6 or 200/6 µg, × 2 BID]) and reliever salbutamol [100 µg, PRN]) using the connected inhalers and complete the following daily assessments at home:

- In the morning before taking their study medication, patients will measure FeNO followed by spirometry assessments (Peak Expiratory Flow [PEF] and Forced Expiratory Volume in 1 second [FEV_1]) and will complete the asthma symptom diary.

- In the evening before taking their study medication, patients will measure spirometry assessments and complete the asthma symptom diary.

Data recorded during the Run-in Period from the spirometry sensor, FeNO monitoring device, connected inhalers, and asthma symptom diary will be used to evaluate compliance and reliever medication use, in order to confirm randomisation criteria at Visit 2.

Visit 2 (Baseline): After completing the Run-in Period, patients must continue to fulfil all eligibility criteria. In addition, randomisation criteria based on the evaluation of study compliance (≥ 80% of asthma assessments at home completed during the Run-in Period) and days with reliever medication use (a minimum of 2 to a maximum of 8 out of the last 10 days of the Run-in Period) will be checked. In order to assess randomisation criteria, the Investigator will be provided the patient's data regarding study compliance during the Run-in Period via the STIFLE system.

On the day of the visit, patients will perform their morning assessments at home as usual before coming to the study site. Patients should bring the run-in treatments and all devices (patient kit) to the study site.

Patients who are randomised in the study will be given their randomised study treatment and keep their patient kit (which contain the devices and was provided at Visit 1). They will have safety assessments (reporting of Adverse Events [AEs; serious or leading to discontinuation and/or related to medical device incidents only] and concomitant medications), CCI [redacted]

Patients who agree to participate in the CCI [redacted] sub-study will be shown how to collect the CCI [redacted] absorption sample and will be provided a kit and instructions for collecting samples at home.

Treatment period: Randomised patients will continue taking SYMBICORT (100/6 or 200/6 µg, × 2 BID) as their maintenance medication and will be randomly assigned to either SYMBICORT (same dose as maintenance, PRN) or salbutamol (100 µg, PRN) as their reliever medication. Randomised treatment for all at-home administration will be dispensed at Visit 2.

Patients will continue completing the following daily asthma assessments at home:

- In the morning before taking their study medication, patients will measure FeNO followed by spirometry assessments and will complete the asthma symptom diary.

- In the evening before taking their study medication, patients will measure spirometry and complete the asthma symptom diary.

Patients participating in the CCI absorption sub-study will also collect CCI samples every morning up to Day 30 post Visit 2.

Visit 3: A telephone contact will be conducted at Week 12 (Visit 3) to collect information regarding SAEs and AEs leading to treatment discontinuation and/or related to medical device incidents only, and concomitant medications.

Visit 4: Patients will attend a visit at the study site at Week 24 (Visit 4). Patients will perform their morning assessments as usual before going to the study site. Patients will have safety assessments (reporting of AEs [serious or leading to discontinuation and/or related to medical device incidents, only] and concomitant medications), and blood samples drawn for haematology, clinical chemistry, CCI . Patients will return all study medications and study devices to the study site (unless they still need to attend Event Visits).

Event Visits: Patients experiencing any one of the 3 criteria below will be requested to come to the study site for 4 additional Event Visits (E1 to E4) at approximately 4-day intervals beginning after the first visit (see the SoA [Table 1]). The patients will only attend the site for Event Visits once throughout the duration of the study. If a patient cannot attend Event Visits for their first event, then the Investigator will attempt to collect data for the next event instead.

Patients will attend the site for Event Visits if one of the below criteria is met:

1. A severe exacerbation (SevEx) defined as follows:

   – Use of systemic steroids for at least 3 days (an injection of depot glucocorticosteroid [GCS] due to asthma worsening is considered equivalent to at least 3 days of systemic GCS).

   Or

   – Emergency room visit (or other urgent unscheduled health care visit) due to asthma that required systemic corticosteroids.

   Or

   – Inpatient hospitalisation due to asthma.

   Note: Additional hospitalisations/emergency room treatments and systemic GCS treatments occurring during a severe asthma exacerbation should not be regarded as a new exacerbation. For a severe asthma exacerbation to be counted as a separate event, it must be preceded by at least 7 days in which no criteria for severe exacerbations are fulfilled.

2. Symptom worsening criteria based on CompEx evaluation - An asthma worsening identified by a combination of deteriorations in at least 2 of the following variables for at least 2 consecutive days.

- A decrease in PEF (morning or evening) of at least 15% compared with baseline (mean PEF [morning and evening separately] over 14-day run-in).

- An increase of reliever medication (documented in the morning or evening asthma symptom diary) of at least 1.5 occasions compared with baseline (mean reliever use per day [morning and evening separately] over 14-day run-in).

- An increase in asthma symptoms score (morning or evening) of at least 1 compared with baseline (mean symptom score [morning and evening separately] over 14-day run-in), or the absolute max score (= 3).

3. A single day (in 24 hours) with 6 or more occasions of reliever medication use.

When the PEF, reliever use, and symptom score criteria defined above are met, the patient and the Investigator will receive a notification from the STIFLE system. Patients will be instructed to contact the study site to arrange an Event Visit, as soon as they receive this notification or if they start using systemic steroids, attend the emergency room, or are hospitalised for their asthma. Patients may also come to the study site without meeting the criteria defined above if they believe they are experiencing an asthma exacerbation or if they are unable to complete the daily assessments due to asthma worsening. If the Investigator determines that the patient's condition satisfies criteria for Event Visits or that this is imminent, eg, the patient is in need of exacerbation treatment as per above, this will be considered as E1. Otherwise, this will not be considered as an Event Visit.

If possible, patients should perform their morning assessments as usual before going to the study site.

During Event Visits, the patients will have safety assessments (reporting of AEs [serious or leading to discontinuation and/or related to medical device incidents only] at all visits and concomitant medications at E1 and E4 only). CCI [redacted] Patients should inform the study staff if the CCI sample was already collected at home (as part of the CCI sub-study), as only 1 sample needs to be collected each day.

If possible, patients should perform their evening home assessments as usual, after returning from the study site.

If Visit 4 is scheduled to occur during the Event Visit window, Visit 4 assessments must be conducted at the Event Visit that is closest to the date of the scheduled Visit 4. If an event occurs during Week 23 or Week 24, the last Event Visit will be scheduled after Visit 4 (Week 24). In this case, the patient should continue taking study medication and performing daily assessments until the last Event Visit.

Study completion/premature discontinuation: Patients will be considered to have completed the study if they receive 24 weeks of study treatment and complete Visit 4. Patients who discontinue treatment prematurely will attend a premature discontinuation visit, including the

same assessments as Visit 4 and additional safety assessments (vital signs, physical examination, clinical chemistry, and urinalysis).

Study Period:

Estimated date of first patient enrolled: Q1 2019

Estimated date of last patient completed: Q1 2022

Number of Patients:

A minimum of 60 patients and maximum of 80 patients will be randomised into the study.

If the screening failure rate is approximately 40% (as per the previous SYGMA studies) the number of patients to be screened will be 100 to approximately 115 patients. Screening failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to an arm of study treatment (Section 5.4).

Primary objective: If 60 patients are randomised, the expected number of study completers will be 54 patients assuming a 10% dropout rate. This number of study completers is considered feasible to allow for individual patient plots to be generated and reviewed as per the primary objective of the study which relates to the 24-week Treatment Period. If during monitoring of the study data the dropout rate looks to be higher than 10%, up to 80 patients will be randomised to target 54 study completers. Patients will be considered to be study completers if they complete Visit 4 following the 24-week Treatment Period.

Secondary objective: As a rough estimate, if an average of 50% of patients (approximate average event rate across treatment arms observed in the development of CompEx) has at least one of the secondary objective events before dropping out of or completing the study, then analyses relating to this objective will be based on 30 patients. Analyses by treatment arm are likely to be unbalanced; more events may be seen in one treatment arm compared to the other.

Treatments and Treatment Duration:

During the Run-in Period, patients will stop their ongoing ICS (low or medium dose)/LABA asthma treatment and for 2 weeks, they will receive SYMBICORT as maintenance treatment and salbutamol as reliever treatment at the following doses:

- Patients on ICS (low-dose)/LABA prior to study entry (per GINA 2018 guidelines): SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID + salbutamol (100 µg) PRN.
- Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines): SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID + salbutamol (100 µg) PRN.

During the randomised Treatment Period, patients will be randomly assigned in a 1:1 ratio to 1 of the following group and receive treatments for 24 weeks:

- SYMBICORT as maintenance and reliever treatment:
  - Patients on ICS (low dose)/LABA prior to study entry (per GINA 2018 guidelines):
    SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance and PRN for relief.
  - Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines):
    SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance and PRN for relief.
- SYMBICORT as maintenance treatment and salbutamol as reliever treatment:
  - Patients on ICS (low dose)/LABA prior to study entry (per GINA 2018 guidelines):
    SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.
  - Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines):
    SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.

The duration of randomised treatment may be extended to a maximum of 26 weeks (182 days) for patients experiencing an event during Week 23 or Week24.

Patients will be provided commercially available SYMBICORT and salbutamol, with connected inhalers.

Statistical Methods:

Primary Analyses

The primary objective is to descriptively characterise the relationship between inflammation, asthma symptoms, lung function, and reliever use measured daily during 24 weeks of treatment in the 2 treatment arms.

Descriptive summaries of the primary outcome measures at baseline (Visit 2) and over time will be tabulated overall and by each treatment arm. Change from baseline summaries will be presented in a similar manner where appropriate.

Descriptive plots may include spaghetti plots showing trajectories for each patient, and mean plots for the outcome measures.

The focus of this outcome is to graphically characterise the variations in FeNO and how these relate to variations in other outcome measures over the 24 weeks of the study for each patient individually. For example, does variation in FeNO pre-empt variation in symptoms that

pre-empt variation in reliever use? Data will be scaled to allow for the presentation of multiple outcome measures in a single plot.

The variation in outcome measures between treatment arms will also be assessed in a similar manner.

Secondary Analyses

The secondary objective is to descriptively characterise the inflammatory, asthma symptoms, lung function, and reliever use profile surrounding an event in the 2 treatment arms. Events of interest are SevEx, CompEx (full criteria), a single day (in 24 hours) with 6 or more occasions of reliever medication use, and FeNO > 50 ppb.

For each event, available outcome measurements between 14 days prior and 28 days post the day of an event will be used in the analysis. The day of an event will be the earliest day used in the derivation of an event.

Descriptive summaries of the outcome measures around the event will be tabulated overall and by treatment arm; tables will include change from baseline data where appropriate.

Descriptive plots may include spaghetti plots showing trajectories for each patient and mean (or another relevant summary statistic such as area under the curve) plots for the outcome measures.

For each of the events the variation in FeNO will be characterised graphically, together with variations in other outcome measure, around the time of an event. Data will be scaled to allow for the presentation of multiple outcome measures in a single plot. Data will be presented for each patient individually, as well as by treatment arm for each event type.

Models allowing for a non-linear trend over time may also be explored.

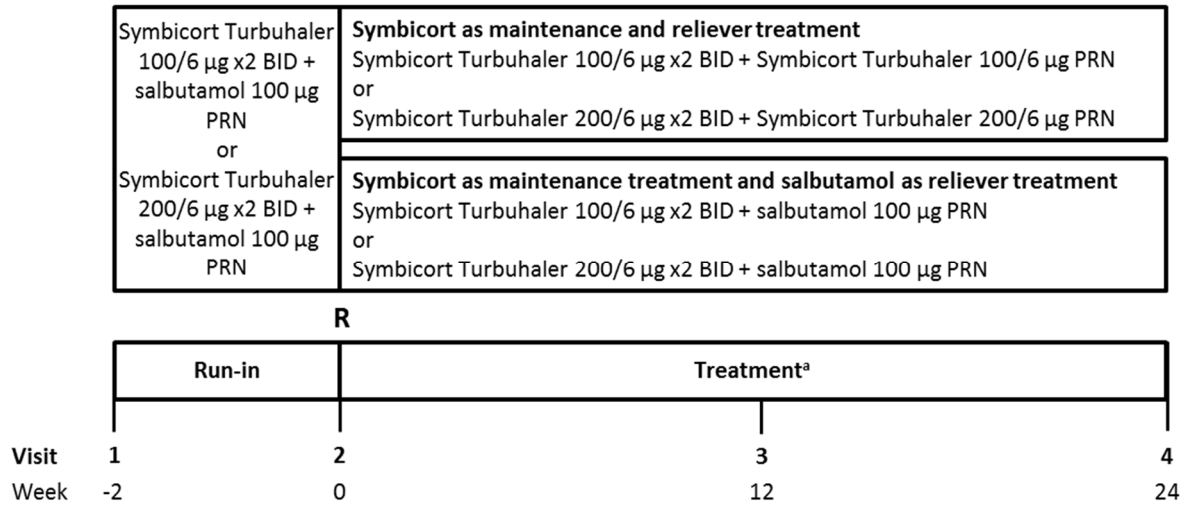
Exploratory Analyses

CCI [redacted]

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



BID=twice per day; PRN=as needed; R=Randomisation.

a Patients experiencing an event will attend the study site at the earliest possible date following the request to come to the study site for Event Visit E1 and attend 3 further visits (E2 to E4) at approximately 4-day intervals.

2. INTRODUCTION

2.1 Study Rationale

Airway inflammation is a key feature of in the pathophysiology of asthma which induces clinical signs and symptoms and leads to severe exacerbations. It is generally accepted that episodes of asthma worsening are due to unchecked and increased airway inflammation. The use of intermittent as needed (PRN) anti-inflammatory reliever (SYMBICORT®[1]), in combination with maintenance anti-inflammatory therapy (SYMBICORT), attenuates acute inflammation escalation, is able to control asthma, and induce a substantial reduction in severe exacerbations (Kuna et al 2007, O'Byrne et al 2005, Rabe et al 2006, Scicchitano et al 2004). Despite the evidence of reduction in severe exacerbations and improvement in asthma condition associated with the notion that the anti-inflammatory effect is the key mechanism of action, the actual changes in inflammation following treatment with SYMBICORT as maintenance and reliever medication has not been observed and described. This phase IV exploratory study is designed characterise the relationship between the daily inflammatory profile, symptoms, lung function,

[1] SYMBICORT is a trademark of the AstraZeneca group of companies.

and reliever use, in patients on SYMBICORT maintenance treatment using SYMBICORT or short-acting β-agonist (SABA) as reliever medication.

2.2 Background

Asthma is a complex, heterogeneous disease characterised by airway inflammation, reversible airway obstruction and airway hyper-responsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma continues to be a major health concern worldwide, with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 to 450 million people worldwide by 2025 (Masoli et al 2004, WHO 2017).

Combination inhaled corticosteroid (ICS)/ long-acting β_2-agonist (LABA) therapies have been a revolution and are now a cornerstone in the treatment of asthma (GINA 2018). With this combination, patients receive the benefit of the anti-inflammatory effect of a corticosteroid with the symptom relieving aspect of a β_2-agonist. Through proven trials, the combination of budesonide with the rapid-acting LABA, formoterol, led to the approval and successful implementation of SYMBICORT maintenance and anti-inflammatory reliever treatment (formerly SMART) across the globe (Kuna et al 2007, Rabe et al 2006, Scicchitano et al 2004, O'Byrne et al 2005, Bousquet et al 2007).

In a secondary analysis of the COMPASS trial, SYMBICORT maintenance and anti-inflammatory reliever therapy was compared to SYMBICORT maintenance therapy in terms of high (> 6 inhalations/day) PRN use. The SYMBICORT maintenance and anti-inflammatory reliever therapy group demonstrated a significant reduction ($p < 0.001$) in the percentage of patients who required a high amount of PRN inhalations for their symptoms (Buhl et al 2012). Additionally, it was demonstrated that along with the reduction in high PRN inhalations in SYMBICORT maintenance plus anti-inflammatory reliever therapy, there was a significant reduction in the number of severe exacerbation days in the 21-day post-index period.

While this evidence demonstrates the efficacy of maintenance plus anti-inflammatory reliever therapy, compared to maintenance therapy alone (plus salbutamol), there is a paucity of demonstrable mechanistic evidence to suggest that these improvements are directly due to an anti-inflammatory component. Inflammation needs to be monitored in a real-time fashion (daily), in order to gain a clearer picture of the process at hand.

Fractional exhaled nitric oxide (FeNO) is a highly sensitive and specific surrogate biomarker of Type 2 inflammation in the lung. Because of its non-invasive nature, ease of teaching/implementation in the home environment, and predictive nature in the pathology asthma, FeNO has been instituted, deployed, and widely used in asthma clinical trials for nearly 2 decades (Jones et al 2001, Harkins et al 2004, Gelb et al 2006, Anderson et al 2012, Saito et al 2014). FeNO, however, in not a 'catch-all' when it comes to determining

inflammation (Kuperman and Schleimer 2008, Takatsu et al 2009). Other techniques for measuring inflammation have also been successfully investigated in asthma, including CCI [redacted] (Hansel et al 2017).

A detailed description of the chemistry, pharmacology, efficacy, and safety of SYMBICORT is provided in the Summary of Product Characteristics (SmPC).

Salbutamol will be used for reliever treatment in the comparator arm as it is an effective and safe SABA reliever medication in asthma (GINA 2018).

2.3 Benefit/risk Assessment

The SYMBICORT TURBOHALER®[2] is a well-known medication with efficacy and safety profiles established in numerous clinical studies and vast postmarketing experience.

SYMBICORT is effective as a reliever medication (Palmqvist et al 2001). In the SYMBICORT SMART programme, 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, another study with patients taking 10 inhalations of SYMBICORT TURBOHALER 160/4.5 µg per inhalation as an addition to a daily SYMBICORT maintenance dose of 640/18 µg revealed no new safety concerns compared to what was already known for ICS and LABA (Ankerst et al 2003), demonstrating 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 (34.4% vs. 31.1%) compared to SABA reliever (O'Byrne et al 2018).

During the study, all patients will monitor their asthma daily using devices to evaluate pulmonary function (PEF and FEV_1) and use of reliever medications. They will attend site visits at 24 weeks of treatment. They will also attend the site for the first time during the study that they experience severe asthma exacerbation or worsening of their asthma (due to symptom worsening criteria based on CompEx evaluation or a single day [in 24 hours] with 6 or more occasions of reliever medication use) is detected during daily monitoring with the devices.

[2] TURBOHALER is a registered trademark of the AstraZeneca group of companies.

Furthermore, the patients will be instructed to contact the Investigator at any time they feel like they are experiencing a severe exacerbation (SevEx).

To conclude, the overall benefit/risk ratio is considered acceptable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SYMBICORT may be found in the SmPC.

3. OBJECTIVES AND ENDPOINTS

Table 2 Study Objectives

Primary Objective:	**Endpoint/Variable:**
Descriptively characterise the relationship between inflammation, asthma symptoms, lung function, and reliever use measured daily over 24 weeks of treatment in the 2 treatment arms.	Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use for the 24 weeks of treatment.
Secondary Objective:	**Endpoint/Variable:**
Descriptively characterise the inflammatory, asthma symptoms, lung function, and reliever use profile surrounding an event in the 2 treatment arms.	Individual patient profiles of daily variations over time in FeNO (morning), asthma symptom scores (morning and evening), PEF and FEV_1 (morning and evening), and occasions of reliever medication use between 14 days prior and 28 days after an event. Events of interest are SevEx, CompEx (full criteria), a single day (in 24 hours) with 6 or more occasions of reliever medication use, and FeNO > 50 ppb.
Exploratory Objectives:	**Endpoint/Variables:**
CCI [redacted]	CCI [redacted]

Table 2 Study Objectives

CCI	CCI

CCI ; CCI ; FeNO=Fractional exhaled Nitric Oxide; FEV_1=Forced Expiratory Volume in 1 second; PEF=Peak Expiratory Flow; ppb=parts per billion.

4. STUDY DESIGN

4.1 Overall Design

This is a randomised, active-comparator, open-label, parallel-group, multicentre phase IV exploratory study to characterise changes in airway inflammation, symptoms, lung function, and reliever use in asthma patients using SABA (salbutamol) or anti-inflammatory reliever (SYMBICORT) as reliever medication in addition to SYMBICORT as daily asthma controller. Eligible patients diagnosed with asthma at least 6 months prior to the Screening Visit (Visit 1) and fulfilling all of the inclusion criteria and none of the exclusion criteria will continue into the Run-in Period. At Visit 2, patients will be assessed for randomisation criteria and, if met, be randomised to receive either SYMBICORT as maintenance and reliever treatment or SYMBICORT as maintenance treatment and salbutamol as reliever treatment in a 1:1 ratio. Randomisation will be stratified by the patient's ongoing dose of ICS (low or medium)/LABA at study entry.

This study will include a minimum of 3 site visits. Patients may also attend up to 4 additional visits during the randomised Treatment Period for the first time that they meet one of the 3 criteria for Event Visits as detailed below. The duration of participation in the study will be 26 to 28 weeks (maximum) for each individual patient, including a 2-week Run-in Period, followed by a 24-week randomised Treatment Period, and an additional follow-up period if the Event Visits fall within the final 2 weeks of the Treatment Period.

The study plans to randomise a minimum of 60 patients to a maximum of 80 patients to achieve at least 54 patients completing the study. A subset of up to 30 patients, who have specifically consented, will also participate in a sub-study on CCI .

The study will be conducted at no less than 2 sites in the UK. The estimated study duration is approximately 30 months.

The study will consist of a Screening Visit (Visit 1), a 2-week Run-in Period, a Baseline Visit (Visit 2) and a 24-week Treatment Period. During the Treatment Period, a telephone contact will be made at Week 12 (Visit 3), and patients will attend a scheduled visit at Week 24 (Visit 4) of study treatment. If the patient meets the criteria for the Event Visits during the 24-week Treatment Period, 4 additional Event Visits (E1 to E4) will be scheduled (see the SoA [Table 1]).

During the Run-in Period and Treatment Period, the patient will also perform daily asthma assessments at home, as described below.

Visit 1 (Screening): After signing the ICF, patients will have eligibility assessments, as well as safety evaluations (vital signs, physical examination, clinical chemistry, haematology, urinalysis, and pregnancy test) to assess the patient's medical condition, CCI [redacted] and FEV_1 will be measured using clinical spirometry equipment.

Patients who satisfy eligibility criteria (Sections 5.1 and 5.2) will be requested to transition from their ongoing ICS/LABA asthma treatment to maintenance SYMBICORT (100/6 or 200/6 µg, × 2 BID) and reliever salbutamol (100 µg, PRN). The selection of the SYMBICORT dose will reflect the patient's ongoing ICS/LABA regimen (low or medium dose per GINA 2018 guidelines) at study entry (Section 6.1.1).

During this visit, patients will be given a patient kit containing a smartphone and 4 devices connected to the smartphone via the STIFLE App (1 spirometry sensor, 1 FeNO monitoring device, and 2 Adherium inhaler sensors, see Section 6.1.2). The Investigator (or trained study staff) will ensure all devices are connected properly and will instruct patients how to use each device and the STIFLE App. They will help patients perform their first spirometry measurements, FeNO measurement, and complete the asthma symptom diary.

Run-in period: The Run-in Period will last 14 days (±2 days) starting from Visit 1. Patients will take their run-in treatments (ie, maintenance SYMBICORT [100/6 or 200/6 µg, × 2 BID]) and reliever salbutamol [100 µg, PRN]) using the connected inhalers and complete the following daily assessments at home:

- In the morning before taking their study medication, patients will measure FeNO followed by spirometry assessments (PEF and FEV_1) and will complete the asthma symptom diary.
- In the evening before taking their study medication, patients will measure spirometry assessments and complete the asthma symptom diary.

Data recorded during the Run-in Period from the spirometry sensor, FeNO monitoring device, connected inhalers and asthma symptom diary will be used to evaluate compliance and reliever medication use, in order to confirm randomisation criteria at Visit 2.

Visit 2 (Baseline): After completing the Run-in Period, patients must continue to fulfil all eligibility criteria. In addition, randomisation criteria (Section 5.1.1) based on the evaluation of study compliance (≥ 80% of asthma assessments at home completed during the Run-in Period) and days with reliever medication use (a minimum of 2 to a maximum of 8 out of the last 10 days of the Run-in Period) will be checked. In order to assess randomisation criteria, the

Investigator will be provided the patient's data regarding study compliance during the Run-in Period via the STIFLE system.

On the day of the visit, patients will perform their morning assessments at home as usual before coming to the study site. Patients should bring the run-in treatments and all devices (patient kit) to the study site.

Patients who are randomised in the study will be given their randomised study treatment and keep their patient kit (which contain the devices and was provided at Visit 1). They will have safety assessments (reporting of AEs [serious or leading to discontinuation and/or related to medical device incidents, only] and concomitant medications), CCI

Patients who agree to participate in the CCI sub-study will be shown how to collect the CCI absorption sample and will be provided a kit and instructions for collecting samples at home.

Treatment period: Randomised patients will continue taking SYMBICORT (100/6 or 200/6 µg, × 2 BID) as their maintenance medication and will be randomly assigned to either SYMBICORT (same dose as maintenance, PRN) or salbutamol (100 µg, PRN) as their reliever medication. Randomised treatment for all at-home administration will be dispensed at Visit 2.

Patients will continue completing the following daily asthma assessments at home:

- In the morning before taking their study medication, patients will measure FeNO followed by spirometry assessments and will complete the asthma symptom diary.
- In the evening before taking their study medication, patients will measure spirometry and complete the asthma symptom diary.

Patients participating in the CCI absorption sub-study will also collect CCI samples every morning up to Day 30 post Visit 2.

Visit 3: A telephone contact will be conducted at Week 12 (Visit 3) to collect information regarding SAEs and AEs (leading to treatment discontinuation and/or related to medical device incidents, only), and concomitant medications.

Visit 4: Patients will attend a visit at the study site at Week 24 (Visit 4). Patients will perform their morning at-home assessments as usual before going to the study site. Patients will have safety assessments (reporting of AEs [serious or leading to discontinuation and/or related to medical device incidents, only] and concomitant medications), and blood samples drawn for haematology, clinical chemistry, CCI .

Patients will return all study medications and study devices to the study site (unless they still need to attend Event Visits).

Event Visits: Patients experiencing any one of the 3 criteria below will be requested to come to the study site for 4 additional Event Visits (E1 to E4) at approximately 4-day intervals beginning after the first visit (see the SoA [Table 1]). The patients will only attend the site for Event Visits once throughout the duration of the study. If a patient cannot attend Event Visits for their first event, then the Investigator will attempt to collect data for the next event instead.

Patients will attend the site for Event Visits if one of the below criteria is met:

1. A severe exacerbation (SevEx) defined as follows:

   - Use of systemic steroids for at least 3 days (an injection of depot GCS due to asthma worsening is considered equivalent to at least 3 days of systemic GCS).

   Or

   - Emergency room visit (or other urgent unscheduled health care visit) due to asthma that required systemic corticosteroids.

   Or

   - Inpatient hospitalisation due to asthma.

     Note: Additional hospitalisations/emergency room treatments and systemic GCS treatments occurring during a severe asthma exacerbation should not be regarded as a new exacerbation. For a severe asthma exacerbation to be counted as a separate event, it must be preceded by at least 7 days in which no criteria for severe exacerbations are fulfilled.

2. Symptom worsening criteria based on CompEx evaluation - An asthma worsening identified by a combination of deteriorations in at least 2 of the following variables for at least 2 consecutive days.

   - A decrease in PEF (morning or evening) of at least 15% compared with baseline (mean PEF [morning and evening separately] over 14-day run-in).

   - An increase of reliever medication (documented in the morning or evening asthma symptom diary) of at least 1.5 occasions compared with baseline (mean reliever use per day [morning and evening separately] over 14-day run-in).

   - An increase in asthma symptoms (morning or evening) of at least 1 compared with baseline (mean symptom score [morning and evening separately] over 14-day run-in), or the absolute max score (=3).

3. A single day (in 24 hours) with 6 or more occasions of reliever medication use.

When the PEF, reliever use, and symptom score criteria defined above are met, the patient and the Investigator will receive a notification from the STIFLE system. Patients will be instructed to contact the study site to arrange an Event Visit, as soon as they receive this notification or if they start using systemic steroids, attend the emergency room, or are hospitalised for their asthma. Patients may also come to the study site without meeting the criteria defined above if they believe they are experiencing an asthma exacerbation or if they are unable to complete the daily assessments due to asthma worsening. If the Investigator determines that the patient's condition satisfies criteria for Event Visits or that this is imminent, eg the patient is in need of exacerbation treatment as per above, this will be considered as E1. Otherwise, this will not be considered as an Event Visit.

If possible, patients should perform their morning assessments as usual before going to the study site.

During Event Visits, the patients will have safety assessments (reporting of AEs [serious or leading to discontinuation and/or related to medical device incidents, only] at all visits and concomitant medications at E1 and E4 only), CCI [redacted] Patients should inform the study staff if the CCI sample was already collected at home (as part of the CCI sub-study), as only 1 sample needs to be collected each day.

If possible, patients should perform their evening home assessments as usual, after returning from the study site.

If Visit 4 is scheduled to occur during the Event Visit window, Visit 4 assessments must be conducted at the Event Visit that is closest to the date of the scheduled Visit 4. If an event occurs during Week 23 or Week 24, the last Event Visit will be scheduled after Visit 4 (Week 24). In this case, the patient should continue taking study medication and performing daily assessments until the last Event Visit.

Study completion/premature discontinuation: Patients will be considered to have completed the study if they receive 24 weeks of study treatment and complete Visit 4. Patients who discontinue treatment prematurely will attend a premature discontinuation visit, including the same assessments as Visit 4 and additional safety assessments (vital signs, physical examination, clinical chemistry, and urinalysis).

4.1.1 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 (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 (COVID-19) 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 (GCP), and minimise 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 patients. The Investigator should confirm this with the designated study physician.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

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

4.2 Scientific Rationale for Study Design

The purpose of this exploratory study is to gain longitudinal insight on the possible relationship between the inflammatory profile, symptoms, lung function, and reliever use in groups of symptomatic adults (≥ 18 years of age) with moderate asthma who are being treated with SYMBICORT, a FDC of ICS (budesonide) plus a rapid-acting bronchodilator (formoterol) as maintenance therapy, and as reliever therapy (ie, SMART), compared to patients being treated with SYMBICORT maintenance therapy, treated with a SABA (salbutamol) as reliever therapy. This study also aims to explore the aforementioned characteristics in patients who are experiencing an event.

The primary outcome measures (see Section 3) of inflammation, symptoms, lung function, and reliever use are commonly accepted measures for clinical studies of asthma. Exhaled nitric oxide (FeNO) will be a key determinant of assessing daily inflammation in the patient population. While FeNO has been implemented in many studies in asthma over the past decade, the methods that will be used during this study in assessing the inflammatory profile of a patient to determine variability and comparison to other primary endpoints in a real-time environment while comparing maintenance anti-inflammatory therapy to maintenance plus as-needed anti-inflammatory therapy is novel. Additionally, studying these endpoints during the course of an event will conceivably provide insight into the mechanisms of an exacerbation's inflammatory nature, and the effect an anti-inflammatory reliever medication might have, compared to conventional reliever therapy (salbutamol).

The study patient population (adults, moderate asthma, symptomatic) will provide an ideal population to assess the inflammatory profile, and the effect of a maintenance anti-inflammatory medication with or without PRN anti-inflammatory reliever medication on the inflammatory profile surrounding the time of an exacerbation. Because this is an exploratory study, investigating several endpoints, the feasible patient population sample size was determined by expert consensus to gain insight on the inflammatory profile and exacerbations.

4.3 Justification for Dose

The population of asthma patients selected for this study will be receiving Step 3 or Step 4 (ICS [medium-dose]/LABA, only) treatment prior to enrolment as per the stepwise approach to control symptoms and minimise future risk (GINA 2018). The preferred controller choice for this patient population is ICS (low- or medium-dose)/LABA, and is consistent with the low- (budesonide/formoterol 100/6 µg × 2 BID) or medium-dose (budesonide/formoterol 200/6 µg × 2 BID) SYMBICORT treatment proposed in this study. Patients requiring Step 4 ICS (high dose)/LABA were not selected for this study as this would present a large range of severity in the population that would limit the conclusions that may be drawn from the results of this study.

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.

Patients will be considered to have completed the study if they receive 24 weeks of study treatment and complete Visit 4.

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 contact with primary care centres.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted as per AstraZeneca policy. Any major/minor protocol violations should be brought to the AstraZeneca Study Physician's attention immediately.

Each patient should meet all of the eligibility and randomisation criteria for this study in order to be randomised to a study intervention. 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 sign informed consent at Visit 1 and receive an E-code number. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

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

5.1 Inclusion Criteria

Informed Consent

1. Provision of signed and dated, written ICF prior to any study-related procedures, sampling, and analyses (at Visit 1).

The ICF process is described in Appendix A 3.

Age

2. Patient must be ≥ 18 years of age at the time of signing the ICF.

Type of Patient and Disease Characteristics

3. A physician diagnosis of asthma for a minimum ≥ 6 months prior to Visit 1.

4. Use of ICS (low or medium dose)/LABA (GINA 2018 guidelines) for asthma for ≥ 3 months prior to Visit 1.

5. Episode of asthma symptom worsening requiring overuse of reliever (more than the standard for the individual patient) at least once during the last 30 days prior to Visit 1.

6. The patient must be able to read speak, and understand local language; and be able to, in the Investigator's judgement, comply with the study protocol.

7. Able to perform home FeNO and spirometry assessments and complete the asthma symptom diary on a regular basis during the conduct of the study.

Sex

8. Male and/or female.

Reproduction

9. Negative pregnancy test (urine) for female patients of childbearing potential at Visit 1.

Note: For inclusion criterion 4, GINA 2018 guidelines define low, medium, and high daily doses of ICS in adults and adolescents (12 years and older) as follows:

Drug	Daily dose (µg)		
	Low	Medium	High
Beclometasone dipropionate (CFC) [a]	200-500	> 500-1000	> 1000
Beclometasone dipropionate (HFA)	100-200	> 200-400	> 400
Budesonide (DPI)	200-400	> 400-800	> 800
Ciclesonide (HFA)	80-160	> 160-320	> 320
Fluticasone furoate (DPI)	100	NA	200
Fluticasone propionate (DPI)	100-250	> 250-500	> 500
Fluticasone propionate (HFA)	100-250	> 250-500	> 500
Mometasone furoate	110-220	> 220-440	> 440
Triamcinolone acetonide	400-1000	> 1000-2000	> 2000

CFC=chlorofluorocarbon propellant; DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; NA=not applicable.

[a] Beclometasone dipropionate CFC is included for comparison with older literature.

5.1.1 Randomisation Criteria

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

1. Symptoms requiring reliever medication use for a minimum of 2 to a maximum 8 days out of the last 10 days of the Run-in Period.

2. At least 80% overall compliance rate for performing FeNO and spirometry assessments and completing the asthma symptom diary during the Run-in Period.

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

5.2 Exclusion Criteria

Medical Conditions

1. Any significant disease or disorder, or evidence of drug/substance abuse which in the Investigator's opinion would pose a risk to patient safety, interfere with the conduct of study, have an impact on the study results, or make it undesirable for the patient to participate in the study.

2. Any asthma worsening requiring change in asthma treatment other than the patient's prescribed reliever medication (SMART therapy, SABA, and/or short-acting anticholinergic agent) within 30 days prior to Visit 1.

3. Medical history of life- threatening asthma including intubation and intensive care unit admission.

4. Medical conditions (other than allergic rhinitis) or medications (other than ICS) that will influence FeNO, as judged by the Investigator.

5. Concurrent respiratory disease: presence of a known pre-existing, clinically important lung condition other than asthma (eg, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension).

6. Acute upper or lower respiratory infections requiring antibiotics or antiviral medication within 30 days prior to the date informed consent is obtained (Visit 1) or during the screening/Run-in Period.

7. A severe asthma exacerbation (defined by an exacerbation resulting in ≥ 3 days of oral corticosteroids [or one depot intramuscular injection of a glucocorticosteroid], an urgent care or emergency room visit that results in systemic corticosteroids, or an inpatient hospitalisation due to asthma) within 30 days prior to screening.

8. Any disease state or procedure that may necessitate the use of oral/systemic corticosteroids during the Treatment Period, other than asthma.

9. Malignancy: a current malignancy or previous history of cancer in remission for less than 12 months prior to Visit 1 (patients that had localised carcinoma of the skin which was resected for cure will not be excluded).

10. Patients with a history/treatment of malignancy, and which in the Investigator's opinion could compromise the safety of the patient.

11. Other concurrent medical conditions: patients who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.

12. Current smokers: previous smokers are allowed to be included provided that they stopped smoking > 12 months prior to Visit 1 AND have a smoking history of ≤ 10 pack-years.

13. Alcohol/substance abuse: a history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.

Prior/Concurrent Clinical Study Experience

14. Participation in another clinical study with any marketed or investigational biologic drug within 4 months or 5 half-lives (whichever is longer) prior to Visit 1.

15. Participation in another clinical study with a non-biologic investigational product or new formulation of a marketed non-biologic drug during the last 30 days prior to Visit 1.

16. Patients with a known hypersensitivity to the study drugs or any of the excipients of the products.

Other Exclusions

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

18. Previous randomisation in the present study.

19. For women only: currently pregnant (confirmed with positive pregnancy test), breast-feeding or planned pregnancy during the study. Fertile women not using acceptable contraceptive measures, as judged by the Investigator. Periodic abstinence, spermicides only, and the lactational amenorrhoea method are not acceptable methods of contraception.

20. Planned hospitalisation during the study that would interfere with study objectives as judged by the Investigator.

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 consuming food or drinks for 1 hour prior to conducting FeNO assessment. Patients will be recommended to conduct the FeNO assessments first thing upon awakening. If they eat first, they should wait for 1 hour before performing FeNO assessments (see Section 8.1.1.1).

5.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions to caffeine as there is no evidence that caffeine affects FeNO measurements (Taylor et al 2004). There are no protocol-specific restrictions to alcohol intake. Smoking is not permitted as per exclusion criterion 12.

5.3.3 Activity

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

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 study treatment. 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 be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed. Any rescreening of patients should be in discussion and approval from the AstraZeneca Study Physician or designee.

These patients should have the reason for study withdrawal recorded in the electronic case report form (eCRF).

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study patient according to the study protocol. Study treatment in this study refers to SYMBICORT treatment for maintenance and reliever treatment or SYMBICORT for maintenance treatment and salbutamol as reliever treatment. Patients will receive a low or medium dose of SYMBICORT (Table 3) depending on the dosage of ICS/LABA they were receiving prior to study inclusion.

6.1 Treatments Administered

6.1.1 Study Treatments

During the Run-in Period, patients will stop their ongoing ICS/LABA asthma treatment (low or medium dose) and for 2 weeks, they will receive SYMBICORT as maintenance treatment and salbutamol as reliever treatment at the following doses:

- Patients on ICS (low dose)/LABA prior to study entry (per GINA 2018 guidelines): SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID + salbutamol (100 µg) PRN.

- Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines): SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID + salbutamol (100 µg) PRN.

During the randomised Treatment Period, patients will be randomly assigned in a 1:1 ratio to 1 of the following group and receive treatments for 24 weeks:

- SYMBICORT as maintenance and reliever treatment:

    - Patients on ICS (low dose)/LABA prior to study entry (per GINA 2018 guidelines):
      SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance and PRN for relief.

    - Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines):
      SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance and PRN for relief.

- SYMBICORT as maintenance treatment and salbutamol as reliever treatment:

    - Patients on ICS (low dose)/LABA prior to study entry (per GINA 2018 guidelines):
      SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.

    - Patients on ICS (medium dose)/LABA prior to study entry (per GINA 2018 guidelines):
      SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.

Patients will be provided commercially available SYMBICORT and salbutamol and both treatments will be used according to their approved indication during the study.

Table 3 Study Treatments

	SYMBICORT (budesonide/formoterol)		VENTOLIN (salbutamol)
	Low Dose	**Medium Dose**	
Study treatment name:	SYMBICORT TURBOHALER 100/6, inhalation powder	SYMBICORT TURBOHALER 200/6, inhalation powder	VENTOLIN pMDI
Dosage formulation:	Budesonide 100 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:	Oral inhalation	Oral inhalation	Oral inhalation
Dosing instructions:	Maintenance: 2 inhalations twice per day, once in the morning and once in the evening Reliever use: Inhalation as needed		Reliever use: Inhalation as needed
Packaging and labelling:	Commercially available SYMBICORT (budesonide/formoterol) will be provided by AZ or designee in a TURBOHALER.		Commercially available VENTOLIN (salbutamol) will be provided by AZ or designee in a pMDI.
	All treatments will be labelled according to Annex 13 and per UK country regulatory requirements with a reduced label on the secondary container only.		

pMDI=pressurised metered dose inhaler, UK=United Kingdom.

6.1.2 Medical Devices

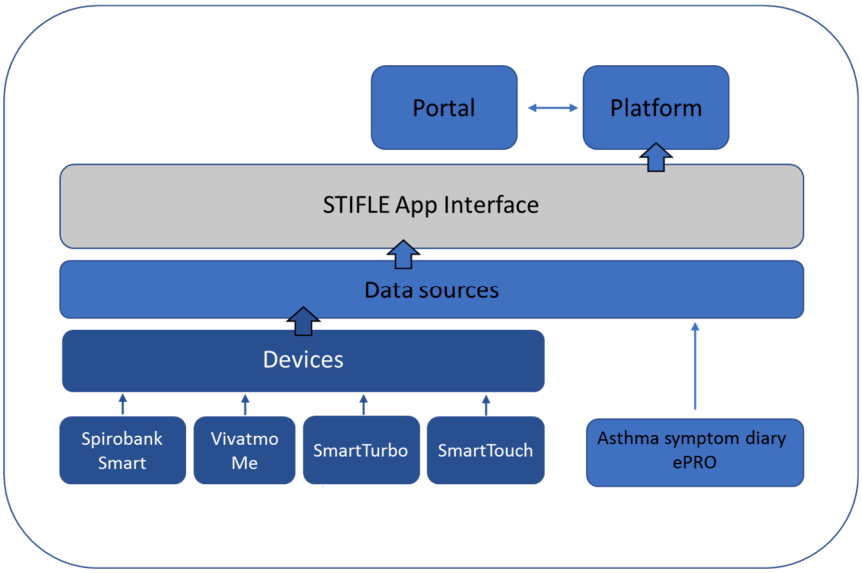
6.1.2.1 Overview

This study comprises 4 devices that need to be effectively paired to a mobile application (the STIFLE App), which itself will be installed on a Samsung smartphone that will be provided to the patient (see Appendix F). The Samsung smartphone used for this study will be locked to prevent the patient from modifying content outside of the STIFLE App. Location tracking services will be blocked.

The 4 devices selected for use in the study are: the Vivatmo Me (Bosch) used for measurement of exhaled nitrous oxide, the Spirobank Smart™ (MIR) used for measurement of PEF and FEV_1 and the Turbu+™ (SmartTurbo™ and Hailie® inhaler sensors (Adherium) used for measurement of inhaled medication actuation.

The STIFLE App is a custom software application provided by AstraZeneca for the STIFLE Study (Figure 2).

Figure 2 Integrated Approach to Data Collection



FeNO=Fractional exhaled Nitric Oxide; ePRO=electronic patient reported outcome.

The devices and software application will be provided to each patient within a kit. The kit will contain:

- 1 Samsung smartphone with the STIFLE App (a mobile application) installed
- 1 spirometry sensor (Spirobank Smart™)
- 1 FeNO monitoring device (Vivatmo Me)
- 2 inhaler sensors (Turbu+™ for SYMBICORT TURBOHALER and Hailie® for salbutamol pressurised metered dose inhaler [pMDI])

The kit number for each kit will be recorded by the study site as it is assigned to a patient at Visit 1.

During Visit 1, the Investigator or trained study staff will install the STIFLE App and pair all devices, instruct the patients how to use each device and the STIFLE App, help patients perform their first spirometry measurements, FeNO measurement, and complete the asthma symptom diary, and leave the patient with all materials as well as a number to contact the Technical Support Call Centre in case of technical difficulties with devices or the STIFLE App. The study sites will also be provided with technical support to assist with technical issues related to device handling, communication, and data flow.

Data collection will follow an integrated approach whereby data from the 4 connected devices and an embedded asthma symptom diary electronic patient reported outcome (ePRO) will be

collected in the STIFLE App and sent to the AstraZeneca Clinical Study Digital Data Collection Platform.

Patients will be blinded to all data collected from the devices via the STIFLE App and they will not have access to the asthma symptom diary data after they are submitted. However, the STIFLE App will show reminders for assessments to be completed and their average compliance rate with completing their daily assessment.

The Investigator will not have access to the raw data collected but will have access to the following information via a web portal during the course of the study:

- At the end of the Run-in Period, the Investigator will have access to a dashboard showing the following patient data:
    - Overall compliance rate for performing FeNO and spirometry assessments and completing the asthma symptom diary during the Run-in Period.
    - Days using reliever medication during the Run-in Period as recorded by the patient's diary.
- During the randomised Treatment Period, the Investigator and patients will receive a notification when patients should attend Event Visits due to symptom worsening criteria based on CompEx evaluation (PEF, reliever use, and symptom score criteria) or a single day (in 24 hours) with 6 or more occasions of reliever medication use (see Section 4.1). The Investigator will continue to see the patient compliance data via a dashboard. Once the Event Visits have been completed, the Investigator and patients will continue to receive notifications when patients meet the criteria outlined above. Patients should contact the study site when they receive a notification.

Instructions for device use will be provided in device-specific Instructions for Use documents.

All 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).

Appendix F of this protocol contains detailed information regarding the regulatory status of each system component; however, a brief summary of device functions is provided below.

6.1.2.2 Spirometry Sensor

The spirometry sensor (Spirobank Smart™) is an electronic, handheld home spirometer connected to the STIFLE App. It will be used to measure the patient's FEV_1 and PEF at home.

6.1.2.3 FeNO Monitoring Device

The FeNO monitoring device (Vivatmo Me) is a battery powered device with an electronic data logger connected to the STIFLE App. It will be used to profile the patient's FeNO.

6.1.2.4 Turbu+™ and Hailie® + Connected Inhalers

The Turbu+™ and Hailie® inhaler devices are Bluetooth®-enabled and automatically upload inhaler usage data to the STIFLE App when they are near the Samsung phone provided for this study:

- The Turbu+™ inhaler medication sensor will be used to track the patients' use of SYMBICORT TURBOHALERs.
- The Hailie® inhaler medication sensor will be used to track the patients' use of salbutamol pMDIs.

The study site will ensure the Turbu+™ and Hailie® inhaler devices are installed properly on the appropriate TURBOHALER/pMDI and that each device is properly paired with the STIFLE App, enabling the Bluetooth-enabled device to sync and transmit data.

Patients will also be instructed how to remove and replace the Turbu+™ and Hailie® devices on refill TURBOHALERs/pMDIs as needed.

Patients will not receive notifications from these devices. Patients will be instructed to use their TURBOHALER/pMDI as they normally would if they were not participating in the study.

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).

6.3 Measures to Minimise Bias: Randomisation and Blinding

PAREXEL will be responsible for generating the randomisation scheme through the AZRand programme. At Visit 2, approximately 60 patients will be randomly assigned to one of the two treatment arms using a 1:1 randomisation, stratified by dose of ICS/LABA the patient received prior to study enrolment (50% low and 50% medium dose in each arm). Thus, approximately 30 patients will be assigned to each treatment 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:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

2. Assign potential patient a unique enrolment number (E-code), beginning with 'E#'.

3. Determine patient eligibility; see Sections 5.1 and 5.2.

4. For patients fulfilling the eligibility and randomisation criteria at Visit 2, 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.

Randomisation data will be kept strictly confidential. The randomisation list will only be provided to AstraZeneca or delegated personnel responsible for preparing the sequentially numbered opaque sealed envelopes.

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.

This is an open-label study; potential bias will be reduced by the following steps: central randomisation and blinded envelopes for allocation. Patients will not have a direct access to data recorded on the STIFLE App via the devices (FeNO, spirometry, and study treatment use) or reported by the patients (asthma symptom diary) after responses are submitted in the STIFLE App.

6.4 Treatment Compliance

At Visit 1, instructions will be given to the patients on how to use the TURBOHALER (inhalation technique). 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 instructions, the patient will practice inhalation technique with a training device, as many times as judged necessary by the supervising study personnel.

From the day of Visit 1 to end of treatment, the administration of all study treatment will be recorded via Turbu+™ inhaler medication sensor for SYMBICORT TURBOHALERs and the

Hailie® inhaler medication sensor for salbutamol pMDIs. Treatment compliance will be monitored via data logging in the STIFLE App.

Any change from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations will be assessed using the data recorded via the Turbu+™ Hailie® inhalers in the STIFLE App.

The following actions must be taken if any of the patient's daily assessments fail to register data for ≥ 3 days during the run-in and treatment periods:

- The site must attempt to contact the patient and counsel the patient on the importance of maintaining the frequency of study assessments.

During the Run-in Period, study compliance will be assessed for the completion of daily FeNO, spirometry and asthma symptom diary questionnaire entry. Patients must be ≥ 80% compliant with their asthma assessments at home to meet the eligibility criteria.

6.5 Concomitant Therapy

Any of the following treatments taken prior to signing of the ICF must be recorded in the Prior and Concomitant Medication eCRF page:

- Any ICS/LABA taken at least in the 3 months prior to Visit 1
- Any systemic corticosteroids (intramuscular, intravenous, or oral) in the 12 months prior to Visit 1
- Any change in asthma treatment other than the patient's prescribed reliever medication (SMART therapy, SABA, and/or short-acting anticholinergic agent) within 30 days prior to Visit 1

From Visit 1, any new treatments taken or any change in ongoing medications during the participation in the study, apart from study treatment, will be transcribed onto the corresponding eCRF page by the Investigator or designee.

Any medication or vaccine including over-the-counter or prescription medicines that the patient is receiving at the time of enrolment or receives during the study must be recorded in the case report form (CRF).

Allowed and Prohibited medications are described in Table 4 and Table 5, respectively. Restricted medications, ie, medication that can be used only under certain circumstances during the study, are described below and are listed in Table 6.

- The following drugs are **allowed during the whole study** provided ongoing at study entry and continued throughout the study: leukotriene modifiers/antagonists, xanthines/methylxanthines

- The following drugs are **allowed to be introduced during the study** after 3 months if intensification of treatment is needed, and only in the SYMBICORT medium-dose arm: leukotriene modifiers/antagonists, xanthines/methylxanthines (eg, theophylline) (See guidance in Section 6.6).

  Note 1: These drugs may also be used as part of treatment of a severe exacerbation.
  Note 2: Long-acting anticholinergics (eg, tiotropium) are prohibited at study entry but may be introduced at any time during the study if there is a sustained drop in asthma control.

- The following drugs are prohibited at study entry and only allowed during the study as part of treatment of a severe exacerbation (note, a concomitant severe exacerbation should be recorded): oral steroids, intramuscular corticosteroids, intravenous corticosteroids, cromoglycates (inhaled route), nedocromil (inhaled route), any ICS or β_2-agonist other than study medication, oral β_2-agonists and short-acting anticholinergics.
  Note: SABA may be used as part of treatment of a severe exacerbation if advised by local treatment guidelines.

Table 4 Allowed Asthma/Allergy Medications

Mucolytics and expectorants not containing bronchodilators.
Beta-adrenergic blockers including eye drops.
Patients on allergen-specific immunotherapy (desensitisation) must have been on a maintenance regimen for at least 4 weeks prior to Visit 2 and remain on a maintenance regimen during the study. Patients should not begin allergen-specific immunotherapy during the course of the study.
Topical, nasal, or ocular formulations of GCS, disodium cromoglycate and/or nedocromil sodium.
Other anti-inflammatory treatments that are not prohibited (Table 5) or restricted (Table 6) according to this section of the protocol. If needed, contact the AstraZeneca Study Physician for advice.

GCS=glucocorticosteroids.

Table 5 Prohibited Medications

Prohibited medication
Rectal GCS
Beta-adrenergic blockers (with the exception of eye drops)
Phosphodiesterase inhibitors
Omalizumab or any other monoclonal or polyclonal therapy for any reason
Systemic treatment with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole and ritonavir). NSAIDs usually do not interfere with CYP3A4.

CYP3A4=cytochrome P450; GCS=glucocorticosteroids; NSAID=nonsteroidal anti-inflammatory drug.

Table 6 Restricted Medications

Medication	Use After Randomisation
Inhaled short-acting β_2-agonist (SABA)	- SABA may be used as part of treatment of a severe exacerbation in both study arms if advised by local treatment guidelines. (Otherwise, patients randomised in SYMBICORT reliever arm should use the SYMBICORT study drug as a reliever and not a SABA.)
Leukotriene modifiers/ antagonists	- Allowed during the study if ongoing at study entry and continued through the study. - Allowed to be introduced during the study after 3 months if intensification of treatment is needed, and only in the SYMBICORT medium-dose arm (See guidance in Section 6.6). - Allowed as part of treatment of a severe exacerbation.
Xanthines/methylxanthines	- Allowed during the study if ongoing at study entry and continued through the study. - Allowed to be introduced during the study after 3 months if intensification of treatment is needed, only in the SYMBICORT medium-dose arm (See guidance in Section 6.6). - Allowed as part of treatment of a severe exacerbation.
Long-acting anticholinergics	Can only be introduced during the course of the study in patients taking the medium dose of SYMBICORT if there is a sustained drop in asthma control.
Oral steroids, intramuscular/intravenous corticosteroids	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)
Any ICS or β_2-agonist other than study medication	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)
Oral β_2-agonist	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)
Cromoglycates (inhaled route)	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)
Nedocromil (inhaled route)	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)

Medication	Use After Randomisation
Short-acting anticholinergic	Only allowed during the study as part of treatment of a severe exacerbation. (Note, a concomitant severe exacerbation should be recorded.)

6.6 Dose Modification

After 3 months of treatment, dose intensification may be considered as per GINA guidelines.

Randomised treatment:	Dose intensification:
SYMBICORT low-dose treatments	
SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.	Increase to medium dose SYMBICORT: SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.
SYMBICORT (budesonide/formoterol 100/6 µg) × 2 BID for maintenance and PRN for relief.	Increase to medium dose SYMBICORT: SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance and PRN for relief.
SYMBICORT medium-dose treatments	
SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance + salbutamol (100 µg) PRN for relief.	Add tiotropium, leukotriene antagonist, or theophylline to attain asthma control. Patients requiring an ICS (high dose)/LABA regimen to attain asthma control should be withdrawn from the study and followed up appropriately. Note: For patients taking medium dose SYMBICORT, the maximum daily dose of budesonide is 800 µg. This limit of 800 µg only includes the maintenance dose. If SYMBICORT is used as maintenance and reliever medication (ie, SMART), the patient will be using extra doses of budesonide, occasionally and the daily dose may exceed 800 µg of budesonide.
SYMBICORT (budesonide/formoterol 200/6 µg) × 2 BID for maintenance and PRN for relief.	

6.7 Treatment After the End of the Study

After discontinuation of study treatment patients will receive asthma medication prescribed according to the Investigator's judgement and local medical practice.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of Study Treatment

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

- Patient decision: the patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance with the CSP with the exception of poor study treatment adherence.
- Failure to meet randomisation criteria: violations of inclusion and/or exclusion criteria detected after randomisation. See Section 7.3 for patients not fulfilling inclusion/exclusion criteria but detected after randomisation.
- Lost to follow-up: see Section 7.2 for details.
- Pregnancy: in case of pregnancy the female patient will be immediately discontinued from study treatment.
- ICS (high dose)/LABA regimen required to attain asthma control.
- Safety reason as judged by the Investigator and/or AstraZeneca.
- Study cancellation.
- Patient withdrawal due to death.

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

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

The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that 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 study site 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.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, eg, repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- 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 with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the Study

A patient may withdraw from the study (eg, withdraw consent), at any time (investigational 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 electronic devices used for the study.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly

available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

See SoA, Table 1, for data to be collected at the time of study discontinuation 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 AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

A patient will be withdrawn from the study if they withdraw consent to the use 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 CCI absorption subgroup.

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 system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRF 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.

The Investigator will not have direct access to the raw data recorded by the devices (FeNO, spirometry, asthma symptom diary, and study treatment use) but will have access to the patient's data on study compliance via the STIFLE web portal.

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 Asthma Assessments at Home

8.1.1.1 Fractional Exhaled Nitric Oxide

FeNO will be measured by the patient using a FeNO monitoring device (Vivatmo Me, see Section 6.1.2.3).

At Visit 1, patients will be given the FeNO monitor, they will be trained to perform FeNO measurements and will receive written user instructions. Then, daily measurements (morning) will be performed by the patient at home.

Patients will be instructed to perform FeNO measurements, in the morning first thing upon awakening. The FeNO assessment must be performed prior to spirometry. Patients should not eat or drink 1 hour prior to having the FeNO assessment. Where possible patients should avoid using their reliever medication within 1 hour prior to the FeNO measurement.

8.1.1.2 Lung Function Measurement by Spirometry (PEF and FEV_1)

Peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) will be measured by the patient using a spirometry sensor (Spirobank Smart™, see Section 6.1.2.2).

At Visit 1, patients will be given the spirometer, they will be trained to perform PEF and FEV_1 measurements. Then, daily measurements (morning and evening) will be performed by the patient at home.

Patients will be instructed to perform PEF and FEV_1 measurements before taking their study medication and after performing FeNO measurements (for morning assessments, only).

The forced expiratory manoeuvre should start with a maximal inspiration and then be followed by a fast and forceful expiration that should last for at least 6 seconds. Patients should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing.

8.1.1.3 Asthma Symptom Diary

The asthma symptom diary is an ePRO that will be completed by the patient using a smartphone application (STIFLE App installed on a Samsung smartphone, Appendix F).

At Visit 1, patients will be given a smartphone installed with the application and will be trained to complete the asthma symptom diary. Then, the asthma symptom diary will be completed by the patient at home, in the morning and in the evening.

The asthma symptom diary will include daily recordings of asthma symptoms, reliever use, and nights with awakenings due to asthma symptom (Appendix E).

Asthma symptoms during night time and daytime will be recorded by the patient twice daily in the asthma symptom diary, according to the following scoring system:

0 = no asthma symptoms

1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms

2 = your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep)

3 = you are unable to do your normal activities (or to sleep) because of your asthma

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Reliever medication usage will be recorded by the patient in the asthma symptom diary twice daily. The usage between the evening and morning lung function assessments will be recorded in the morning. The usage between the morning and evening lung function assessments will be recorded in the evening. Reliever medication usage is captured in the asthma symptom diary as the number of occasions the reliever inhaler was used. An occasion is defined as 2 puffs for salbutamol or 1 inhalation for SYMBICORT.

Night time awakenings due to asthma symptoms will be recorded by the patient in the asthma daily symptom diary each morning by answering the question whether the patient woke up during the night due to asthma symptoms by a "yes" or "no" response.

8.1.1.4 Use of Reliever Medications

During the Run-in Period and the randomised Treatment Period, the use of reliever medications will be measured automatically by the Turbu+™ and Hailie® inhaler devices and by the asthma symptom diary (see Section 6.1.2.4 and Section 8.1.1.3).

8.1.2 Asthma Assessments at Study Site

8.1.2.1 Lung Function Measurement by Spirometry (FEV_1)

FEV_1 will be measured by qualified site staff at screening. Daily home spirometry assessments will be performed by the patient, FEV_1 will be performed locally by site personnel according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria (Miller et al 2005). Sites will use their own spirometry equipment which must comply with the ATS/ERS criteria. Data will be entered into the eCRF.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Clinical Safety Laboratory Assessments

See Table 7 for the list of clinical safety laboratory tests to be performed and to the SoA (Table 1) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA. The results of tests performed at the screening (Visit 1) or baseline (Visit 2) visits can be regarded as baseline data.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory. The central laboratory will provide the centre with the necessary material and instructions for the sampling. In exceptional circumstances and upon discussion with the Sponsor, local laboratory assessments may have to be undertaken to collect key information supporting an AE or SAE.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

Table 7 Laboratory Safety Variables

Haematology/Haemostasis (whole blood) at screening and Visit 4 (or at premature discontinuation visit)	**Clinical Chemistry (serum or plasma) at screening and Visit 4 (or at premature discontinuation visit)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick [a]) at screening	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)

[a] Positive dipstick findings should be confirmed with microscopic analysis.

Pregnancy testing should be performed as detailed in the SoA (Table 1).

8.2.2 Physical Examinations

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

Body weight and height will be measured at screening (Visit 1) for calculation of Body Mass Index (BMI). Patients should be in light indoor clothes without shoes.

Physical examination will be performed at timelines as specified in the SoA (Table 1), Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital Signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed as outlined in the SoA (Table 1).

Blood pressure and pulse measurements will be assessed when the patient is in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by approximately 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

Vital signs will be measured in a semi-supine position after approximately 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

8.2.4 Electrocardiograms (ECGs)

No ECGs will be recorded for the purpose of the study.

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.

The AE will be reported by the patient.

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 that are serious, leading to treatment discontinuation, and/or related to medical device incidents will be collected from the start of run-in medication and throughout the Treatment Period including Visit 4/premature discontinuation visit and last Event Visit.

The SAEs will be recorded from the time of signing of the ICF.

All SAEs will be recorded and reported to the Sponsor or designee 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 may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE (that are serious, leading to discontinuation, and/or related to medical device incidents) 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 (that are serious or leading to discontinuation and/or related to medical device incidents) will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs (that are serious, leading to discontinuation, and/or related to medical device incidents) and 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. AstraZeneca retains the right to request additional information for any patient with ongoing AEs that are serious or leading to discontinuation and/or related to medical device incidents at the end of the study, if judged necessary.

8.3.4 Adverse Event Data Collection

The following variables will be collected for each AE (that is serious, leading to discontinuation and/or related to medical device incidents):

- 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 medications.

8.3.5 Causality Collection

The Investigator will assess causal relationship between study treatment and each AE (that is serious, leading to discontinuation, and/or related to medical device incidents), 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 SAEs, causal relationship will also be assessed for other medication, study procedures and/or AstraZeneca Medical device. 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 Adverse Events 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 Adverse Events Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and physical examination should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the study treatment.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.8.

8.3.8 Disease Under Study (DUS)

Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded when:

- the sign or symptom is serious according to definitions, and/or
- the patient discontinues the study due to the sign or symptom.

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 AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca 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 pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study drug.
- Pregnancies in the partner of male patient.

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, the 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 abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.2) 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 and the PREGOUT is used to report the outcome of the pregnancy.

8.4.3 Overdose

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

AstraZeneca 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 AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no** later **than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca 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 Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purpose of monitoring daily assessments (FeNO, spirometry, maintenance and reliever medication use). In order to fulfil regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix D.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3 and Appendix B of the protocol.

8.4.4.1 Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident 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 incident 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 incidents is provided in Appendix D.

8.4.4.2 Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.2). This 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 incident.

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

8.4.4.3 Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the Sponsor by the patient using the STIFLE App. If the patient reports the incident to the Investigator, then the Investigator must report the incident to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device incident.

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.2). If an investigational medical device is used, the Study Representative will send the SAE report to AstraZeneca Data Entry Site (DES) within one calendar day.

8.4.4.4 Regulatory Reporting Requirements for Medical Device Incidents

- The Investigator will promptly report all incidents 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 incidents to the institutional review board (IRB) or independent ethics committee (IEC).

8.4.5 Medication Error

Medication errors are collected in all studies where medication error is possible. Refer to the Project Specific Safety Requirements (PSSR) or other appropriate project document for specific considerations for collection of medication errors.

For guidance, refer to AstraZeneca Standard Operating Procedure 'Reporting of Individual Safety Events in Clinical Studies'.

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

The designated AstraZeneca representative 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 an 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.

8.5 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

CCI [redacted]

CCI [redacted]

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[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

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8.9 Health Economics

Health economic parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

This study is exploratory in nature with no formal hypothesis pre-specified. The objectives are as specified in Table 2 and below in Section 9.4.

This exploratory study is not designed or powered to test statistical hypotheses for the difference between treatment arms; findings will be used to generate hypotheses for future research.

9.2 Sample Size Determination

A minimum of 60 patients and maximum of 80 patients will be randomised into the study.

If the screening failure rate is approximately 40% (as per the previous SYGMA studies) the number of patients to be screened will be 100 to approximately 115 patients. Screening failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to an arm of study treatment (Section 5.4).

Primary objective: If 60 patients are randomised, the expected number of study completers will be 54 patients assuming a 10% dropout rate. This number of study completers is considered feasible to allow for individual patient plots to be generated and reviewed as per the primary objective of the study which relates to the 24-week Treatment Period. If during monitoring of the study data the dropout rate looks to be higher than 10%, up to 80 patients will be randomised to target 54 study completers. Patients will be considered to be study completers if they complete Visit 4 following the 24-week Treatment Period.

Secondary objective: As a rough estimate, if an average of 50% of patients (approximate average event rate across treatment arms observed in the development of CompEx) has at least one of the secondary objective events before dropping out of or completing the study, then analyses relating to this objective will be based on 30 patients. Analyses by treatment arm are likely to be unbalanced; more events may be seen in one treatment arm compared to the other.

It is an inclusion criterion of the study that patients should be "Able to perform home FeNO and spirometry assessments and complete the asthma symptom diary on a regular basis during the conduct of the study", and it is assumed that patients will have these data collected regularly that will provide adequate data for the analyses of the primary and secondary objectives with regards to the aforementioned numbers of patients.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Patients Analysis Set	All patients screened for the study will be used for reporting of disposition and screening failures.
Full Analysis Set (FAS)	All randomised patients who had at least one post baseline measurement 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.

9.4 Statistical Analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and approved before any statistical analyses are performed. The SAP will describe the patient populations to be used for the analyses, any

sensitivity analyses, and any procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints. Any deviations from this protocol-defined plan will be reported in the CSR.

9.4.1 Analyses of Endpoints

All data analyses will be performed on the FAS population except summary of the patient disposition and screen failures presented on the All Patient Analysis Set. Continuous variables will be summarised using the mean, two-sided 95% confidence interval (CI) of the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method, where necessary. No multiplicity adjustment will be applied in the statistical analysis.

Primary Analyses

The primary objective is to descriptively characterise the relationship between inflammation, asthma symptoms, lung function, and reliever use measured daily during 24 weeks of treatment in the 2 treatment arms.

The outcome measures are as follows:

Category	Measure	Notes
Inflammation	FeNO	Daily (AM)
Symptoms	Asthma symptom questions	Daily (AM and PM)
Lung function	PEF and FEV_1	Daily (AM and PM)
Reliever use	Occasions of reliever medication use	As needed

AM=morning; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; PM=evening.

Descriptive summaries of the primary outcome measures from baseline (Visit 2) and over time will be tabulated overall and by each treatment arm. Change from baseline summaries will be presented in a similar manner where appropriate.

Descriptive plots may include spaghetti plots showing trajectories for each patient, and mean plots for the outcome measures.

The focus of this outcome is to graphically characterise the variations in FeNO and how these relate to variations in other outcome measures over the 24 weeks of the study for each patient individually. For example, does variation in FeNO pre-empt variation in symptoms which pre-empt variation in reliever use? Data will be scaled to allow for the presentation of multiple outcome measures in a single plot.

The variation in outcome measures between treatment arms will also be assessed in a similar manner.

Secondary Analyses

The secondary objective is to descriptively characterise the inflammatory, asthma symptoms, lung function, and reliever use profile surrounding an event in the 2 treatment arms.

Events of interest are SevEx, CompEx (full criteria), a single day (in 24 hours) with 6 or more occasions of reliever medication use, and FeNO > 50 ppb.

CompEx (Full Criteria)

A composite endpoint for exacerbations (severe) in asthma (CompEx) will be derived and analysed. CompEx is an extended definition of asthma exacerbations combining diary-based event with traditionally defined severe exacerbations. The definitions for both types of events are as follows:

- Severe exacerbation: events leading to one or more of the following; ≥ 3 days of oral corticosteroids (or one depot intramuscular injection of a GCS), an urgent care or emergency room visit that results in systemic corticosteroids, or an inpatient hospitalisation due to asthma.
- Diary-based events: objective measures of a worsening of PEF assessed in the morning and evening, increased reliever use assessed in the morning and evening, worsening of asthma symptoms assessed morning and evening (asthma symptom diary), and awakenings assessed in the morning (asthma symptom diary); in total 4 different variables. The algorithm for determining CompEx is based on predefined threshold values and slopes as described by Fuhlbrigge et al. (Fuhlbrigge et al 2017).

The outcome measures are as follows:

Category	Measure	Notes
Inflammation	FeNO	Daily (AM)
Symptoms	Asthma symptom diary	Daily (AM and PM)
Lung function	PEF and FEV_1	Daily (AM and PM)
Reliever use	Occasions of reliver medication use	As needed

AM=morning; FeNO=fractional exhaled nitric oxide; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow; PM=evening.

For each event, available outcome measurements between 14 days prior and 28 days post the day of an event will be used in the analysis. The day of an event will be the earliest day used in the derivation of an event.

Descriptive summaries of the outcome measures and around the event will be tabulated overall and by treatment arm; tables will include change from baseline data where appropriate.

Descriptive plots may include spaghetti plots showing trajectories for each patient and mean (or another relevant summary statistic such as area under the curve) plots for the outcome measures.

For each of the events the variation in FeNO will be characterised graphically, together with variations in other outcome measure, around the time of an event. Data will be scaled to allow for the presentation of multiple outcome measures in a single plot. Data will be presented for each patient individually, as well as by treatment arm for each event type.

Models allowing for a non-linear trend over time may also be explored.

9.4.2 Safety Analyses

Safety outcome will be reported descriptively. A detailed description will be included in the SAP.

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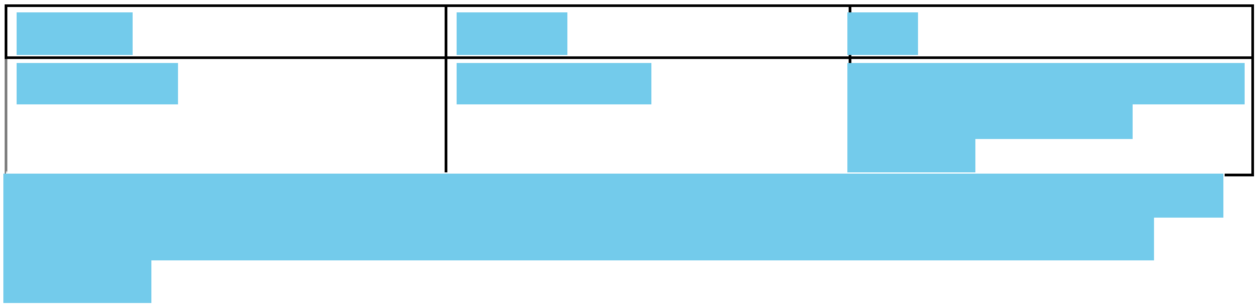
PPD



9.5 Interim Analyses

No interim analysis is planned for this study.

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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 Organisations 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, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB/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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- 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), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

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 or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, 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 or the patient's legally authorised representative.

Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the collection of additional samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow the collection of additional samples for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. 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 already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data Protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets 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 must also be explained to the patient.

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

There will be no steering committee, data monitoring committees or internal/external scientific advisory committee as this is an exploratory study to assess changes in inflammation associated with reliever use using study treatment commercially available for the treatment of asthma.

A 6 Dissemination of Clinical Study Data

A description of this clinical trial will be available on *http://astrazenecaclinicaltrials.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 CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory and STIFLE App data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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 designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 CRF 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 designee 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. 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 IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study intervention development

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

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

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 SAE, 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 one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring 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 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 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 AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances 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 patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

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

- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

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 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 AstraZeneca 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, AstraZeneca is not obliged to destroy the results of this research.

As collection of the mandatory biological samples (ie, CCI absorption samples at study site, and CCI samples for CCI) is an integral part of the study, if the patient withdraws consent to the use of these donated biological samples then the patient is withdrawn from further study participation.

As collection of the additional biological samples (ie, CCI) is an optional part of the study, if the patient withdraws consent to the use of these donated biological samples then the patient may continue in the study.

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- 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 AstraZeneca are informed about the sample disposal.

AstraZeneca 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 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 UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (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 Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

D 1 Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all Sponsor provided medical devices provided for use in the study (see Section 6.1.2) for the list of Sponsor-provided medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the Instructions for Use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the treatment of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical treatment to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Examples of Incidents:

- A patient, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A patient's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A patient's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical device incident documentation

- Any medical device incident occurring during the study will be documented in the patient's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the CRF.
- For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix B.
- The CRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the Sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the Sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- 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 an incident. This includes any amendment to the device design to prevent recurrence.

Appendix E Asthma Symptom Diary

Daily Questionnaire - Morning Diary

Instructions: Please complete ALL questions by selecting the response that best describes your asthma. Asthma symptoms could include, but are not limited to, shortness of breath, wheezing, coughing, and/or chest tightness.

The following questions ask about your asthma during the night. During the night refers to the period of time between the evening lung function assessment yesterday and the morning lung function assessment today.

1. Please record your asthma symptoms during the night:

    0 – No asthma symptoms

    1 – You were aware of your asthma symptoms but you can easily tolerate the symptoms

    2 – Your asthma was causing you enough discomfort to cause problems with sleep

    3 – You were unable to sleep because of your asthma

2. Did you use rescue medication in response to worsening symptoms during the night?

    No

    Yes

2a. On how many separate occasions did you use rescue medication in response to worsening symptoms during the night? (Occasion – 2 puffs for VENTOLIN, or 1 inhalation for SYMBICORT)

    Occasions

3. Did your asthma cause you to wake up during the night?

    No

    Yes

Daily Questionnaire - Evening Diary

Instructions: Please complete ALL questions by selecting the response that best describes your asthma. Asthma symptoms could include, but are not limited to, shortness of breath, wheezing, coughing, and/or chest tightness.

The following questions ask about your asthma during the daytime today. Daytime refers to the period of time between the morning lung function assessment and the evening lung function assessment.

1. Please record your daytime asthma symptoms:

    0 – No asthma symptoms

    1 – You were aware of your asthma symptoms but you can easily tolerate the symptoms

    2 – Your asthma was causing you enough discomfort to cause problems with normal activities

    3 – You were unable to do your normal activities because of your asthma

2. Did you use rescue medication in response to worsening symptoms during the daytime today?

    No

    Yes

2a. On how many separate occasions did you use rescue medication in response to worsening symptoms during the daytime today? (Occasion – 2 puffs for VENTOLIN, or 1 inhalation for SYMBICORT)

    Occasions

Appendix F STIFLE Devices and Software Application

STIFLE System Description:

As described within the main body of the protocol, the study proposes to collect patient information using medical devices, in-vitro diagnostic devices, and a software application. The table below summarises the components of the STIFLE system as well as their intended use within the study:

Device, Manufacturer	Image	Intended Use
Spirobank Smart™, MIR		Record and transmit spirometry values (FEV_1 and PEF).
Vivatmo Me, Bosch		Record and transmit exhaled nitrous oxide (FeNO) values.
Turbu+™ (SmartTurbo™) SYMBICORT® TURBOHALER®, Adherium		Record and transmit actuations of SYMBICORT inhaler.
Hailie® for **VENTOLIN® HFA**, Adherium		Record and transmit actuations of VENTOLIN inhaler.
STIFLE App, AstraZeneca	No Image Available	Receive data from devices for post hoc analysis, present electronic symptom survey information for patient entry, and direct patients for additional biomarker sampling if conditions are met.

Regulatory Status of System Components:

As the STIFLE system is proposed for use in a medicinal product investigation, it is important to account for the regulatory status of the products used within the study. The sections below contain details regarding the classification of system components as a medical devices or in-vitro diagnostic devices as well as commercial marketing status, if applicable.

Spirobank Smart™ Spirometer

The Spirobank Smart™ Spirometer provides a physical interface for the patient to record spirometry readings during the course of the study. The Spirobank Smart™ device does not provide spirometry values directly on the device and is intended by the manufacturer to transmit readings to a compatible software interface. Within the proposed study, the device will transmit readings to the STIFLE App, however these readings will not be displayed to the patient. The Spirobank Smart™ device is CE marked as a Class IIa medical device according to the Medical Device Directive.

Vitamo Me FeNO Device

The Vitamo Me device provides a physical interface for the patient to record exhaled nitrous oxide readings during the course of the study. The device will transmit readings to the STIFLE App, however the version of the device designed for use within the proposed study does not permit patients to view exhaled nitrous oxide readings directly on the device. Additionally, the STIFLE App will not display nitrous oxide readings to the patient. The Vitamo Me device is currently undergoing a conformity assessment and will meet applicable elements of the In Vitro Diagnostic Medical Device Directive prior to use in the proposed study.

Turbu+™ and Hailie® Inhaler Monitoring Devices

The Turbu+™ and Hailie® devices provide a physical interface for the patient to record actuation of asthma maintenance and rescue medication inhalers during the course of the study. The Turbu+™ and Hailie® devices are intended by the manufacturer to transmit actuation data to a compatible software interface. Within the proposed study, the devices will transmit readings to the STIFLE App, however these readings will not be displayed to the patient. The Turbu+™ and Hailie® inhaler monitoring devices are CE marked as Class I medical devices according to the Medical Device Directive.

STIFLE App

The STIFLE mobile application will be used within the proposed study to receive readings from these medical devices and in-vitro diagnostic devices and relay the information to study databases. The mobile application also provides an interface for the patient to view device Instructions for Use and complete electronic surveys of their symptoms and quality of life. The mobile application serves only to receive information from the devices and patients. The mobile application will not control or display information from the devices and will not provide a historical view of past information, however it will display a history of data collection compliance (eg, a record showing the days where the patient performed their daily readings and symptom survey). In addition to these functions, the software will contain a feature that alerts Investigators and patients if a patient's medical device, in-vitro diagnostic, or sensor information

diverge from their baseline or across pre-set limits. If an alert is triggered, the patient will be instructed to contact the site.

The software is not intended to/will not have the following functions:

- The software will not provide any recommendations to the patient or the Investigator to inform or influence treatment.
- The software will not control, either directly or indirectly, any component of the investigational system (eg, the medical devices and in-vitro diagnostic device do not receive information from the mobile application).
- The software will not display information from the devices and will not provide a historical view of past device or symptom information.

The Sponsor has communicated with Medicines and Healthcare products Regulatory Agency (MHRA)'s Devices Regulatory Group on the status of the STIFLE App as a medical device. The Sponsor proposed that the STIFLE App would not meet the definition of a medical device according the Medical Device Directive (MDD). The Sponsor's rationale included:

- The software has been developed for use only in the subject study and is not intended for commercial use.
- The software is not intended to influence the assessment or treatment of the patients.
- The software does not act as an accessory to medical devices or in-vitro diagnostics.

After discussing the details of the software application, the MHRA's Devices Regulatory Group agreed with the Sponsor's assessment that the STIFLE App does not meet the definition of a medical device according to the MDD.

Conclusion

As described within the sections above, each of the medical device and in-vitro diagnostic device components of the STIFLE system will be legally marketed in the EU prior to use within the study and will be used according to their labelled use. The STIFLE App does not meet the definition of a medical device as listed in the MDD and is therefore considered a digital investigational tool.

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
AM	morning
ATS	American Thoracic Society
BID	bis in die (twice per day)
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CCI	[redacted]
CSP	clinical study protocol
CSR	clinical study report
DES	Data Entry Services
DUS	disease under study
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
CCI	[redacted]
ePRO	electronic patient reported outcome
ERS	European Respiratory Society
FAS	full analysis set
FDC	fixed dose combination
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
GCP	good clinical practice
GCS	glucocorticosteroid
GINA	global initiative for asthma
IATA	International Airline Transportation Association
ICF	informed consent form

Abbreviation or special term	Explanation
ICH	international conference on harmonisation
ICS	inhaled corticosteroids
IEC	independent ethics committee
IRB	institutional review board
LABA	long-acting β_2-agonist
MDD	Medical Device Directive
MHRA	Medicines and Healthcare products Regulatory Agency
PEF	peak expiratory flow
PM	evening
pMDI	pressurised metered dose inhaler
ppb	parts per billion
PRN	pro re nata (as needed)
PSSR	Project Specific Safety Requirements
SABA	short-acting β-agonist
SAE	serious adverse event
SAP	statistical analysis plan
SMART	SYMBICORT as Maintenance and Reliever Therapy
SmPC	summary of product characteristics
SoA	schedule of assessments
TBL	total bilirubin
UK	United Kingdom
ULN	upper limit of normal

Appendix H 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 (COVID-19) or a 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.

H 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section H 2. 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.

H 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. 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 enrolment into the study, beginning the Run-in Period, or beginning the Treatment Period. The patient may need to be rescreened to reconfirm eligibility before commencing study procedures, and may need to restart the Run-in Period prior the Treatment Period. This provides another possible scenario for rescreening a patient in addition to that described in Section 5.4**.** The procedures detailed in the SoA (Table 1) must be completed to confirm eligibility using the same randomisation number for the patient.

H 3 Telemedicine Visit to Replace On-site Visit (where applicable)

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

During a civil crisis, natural disaster, or public health crisis, onsite 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 and concomitant medication to be reported and documented.

H 4 Data Capture During Telemedicine

Data collected during telemedicine will be captured by the qualified HCP from the study site or TPV service, or by the patients themselves in their study diary.

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.