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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Statistical Analysis Plan	
Study Code	D589BC00018
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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®) As Rescue Medication In Addition To SYMBICORT As Daily Asthma Controller

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Parexel Study Statistician

PPD

Date

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AZ Study Statistician

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Biometrics Team Lead

PPD Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
ATC	anatomical therapeutic chemical classification system
AUC	area under the curve
AM	morning
BID	bis in die (twice per day)
BMI	body mass index
CI	confidence interval
CompEx	composite endpoint for severe exacerbations of asthma
COVID-19	Coronavirus Disease 2019
CCI	[redacted]
CSP	clinical study protocol
CSR	clinical study report
CV	Coefficient of Variation
DRM	Data Review Meeting
eCRF	electronic case report form
CCI	[redacted]
ePRO	electronic patient reported outcome
ER	emergency room
FAS	full analysis set
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCS	glucocorticosteroid
GINA	global initiative for asthma
ICF	informed consent form
ICS	inhaled corticosteroids
L	litres
LABA	long-acting β_2-agonist
LTRA	leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
PDF	portable document format
PEF	peak expiratory flow
PM	evening
pMDI	pressurised metered dose inhaler
PN	predicted normal
ppb	parts per billion
PRN	pro re nata (as needed)
PT	preferred term
SABA	short-acting β-agonist
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SevEx	severe exacerbation
SMART	SYMBICORT® as Maintenance and Reliever Therapy
SoA	schedule of assessments
SOC	System Organ Class
STIFLE	name of study
ULN	upper limit of normal
WHO	World Health Organisation

AMENDMENT HISTORY

Date	Description of change	Rationale
17 Apr 2019	N/A	Version 1.0 of the Statistical analysis plan.
29 Apr 2021	List of major changes can be found in appendix 8.2.	Updated to reflect changes in the CSP and changes to analyses.
14 Apr 2022	Added clarification that if more than one FeNO is performed in a day, then the first measure is used for analyses.	Only one measurement should be used per day, first assessment gives most reliable results.
14 Apr 2022	Updated in-text tables 3 and 9, and text throughout to modify analysis day definitions. For all parameters a day is now made up of am and pm assessments from the same day.	To be consistent within the project.
14 Apr 2022	Added clarification that if less or more than the 3 protocol defined spirometry assessments are performed at a given time point, then the highest measure is used for analysis.	Only one measurement should be used per timepoint.
14 Apr 2022	Removed forced vital capacity conversion factors from spirometry section.	Conversion factors are only needed for at home assessments, FVC not done at home and so not needed.
28 September 2022	Updated rule for if more than one FeNO is performed in a day. We will now use the average of all measures for analyses.	ERS/ATS recommendation is do minimum 2 measurements and take the average
28 October 2022	Updated CompEx derivation to clarify what events will be considered.	Updated after discussion with AZ CompEx programming team.
23 May 2023	Updated to add swimmer plot, present nasal biomarkers on the log10 scale, add coefficient of variation to summary statistics. Add details surrounding the exclusion of outlier data.	Updates following dry run comments and improve useability of outputs for CSR

This statistical analysis plan (SAP) is based upon the following study documents:

- Study Protocol, Version 3.0 (April 14, 2021)
- electronic Case Report Form (eCRF), Version 4.0 (October 15, 2020)
- AZ Corporate CSRHLD Reporting Standards, Version 3.0 (September 30, 2018)
- AZ Corporate CSRHLD Listings Templates, Version 1.0
- AZ Corporate CSRHLD Figures Templates, Version 3.0
- AZ Corporate CSRHLD Tables Templates, Version 3.0
- AZ Respiratory TA Population and Efficacy Output Templates, Version 2.2
- AZ Respiratory TA Safety Output Templates, Version 2.1
- AZ Corporate Pandemic CSRHLD Table and Listing Templates Version 1.0 (July 03, 2020)

1. STUDY DETAILS

1.1 Study Objectives

Table 1 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 fractional exhaled nitric oxide (FeNO) (morning), asthma symptom scores (morning and evening), peak expiratory flow (PEF) and forced expiratory volume in 1 second (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 severe exacerbation (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]
CCI [redacted]	CCI [redacted]

CCI [redacted]; FeNO=Fractional exhaled nitric oxide; FEV_1=Forced expiratory volume in 1 second; PEF=Peak expiratory flow; ppb=parts per billion.

1.2 Study 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, 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 inhaled corticosteroids (ICS) (low or medium)/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 nasal absorption biomarkers.

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 schedule of assessments (SoA) [Table 2]). 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, blood samples collected for CCI [redacted], and FEV_1 will be measured using clinical spirometry equipment.

Patients who satisfy eligibility criteria (see clinical study protocol [CSP]) 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 (low or medium dose per the Global Initiative for Asthma [GINA 2018] guidelines) or LABA regimen at study entry (see CSP).

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 fractional exhaled nitric oxide [FeNO] monitoring device, and 2 Adherium inhaler sensors, see CSP). 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 (see CSP) 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), blood samples

for CCI [redacted]

Patients who agree to participate in the nasal biomarker sub-study will be shown how to collect the nasal 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 administrations 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 nasal absorption sub-study will also collect nasal 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 [redacted]

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 2]). 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. 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 defined as 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 one 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.

If criteria 2 or 3 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), collection of nasal absorption samples for

CCI [redacted] and collection of blood samples for CCI [redacted]. Patients should inform the study staff if the nasal sample was already collected at home (as part of the nasal biomarker sub-study), as only one sample needs to be collected each day.

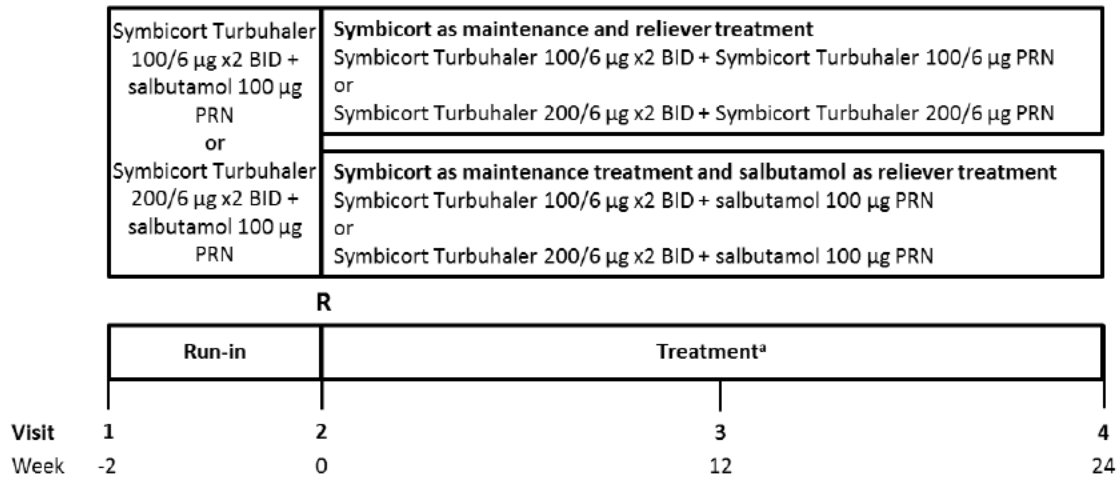
If possible, patients should perform their evening home assessments as usual, after returning from the study site.

If Visit 4 is scheduled to occur during the Event Visit window, the 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 be study completers if they complete Visit 4 following the 24-week Treatment Period. 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).

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.

Table 2 Schedule of Assessments

Visit	Screening	Run-in Period	Treatment Period				Premature discontinuation visit	Details in CSP section or Appendix
	1	-	2 (Baseline)	3 [a]	4	Event Visits [b] (E1 to E4)		
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

Table 2 Schedule of Assessments

Visit	Screening	Run-in Period	Treatment Period				Premature discontinuation visit	Details in CSP section or Appendix
	1	-	2 (Baseline)	3 [a]	4	Event Visits [b] (E1 to E4)		
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]				
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[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

Table 2 Schedule of Assessments

Visit	Screening	Run-in Period	Treatment Period				Premature discontinuation visit	Details in CSP section or Appendix
	1	-	2 (Baseline)	3 [a]	4	Event Visits [b] (E1 to E4)		
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 of CSP). 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]

1.2.1 Potential Bias

- It is recognised that some patients may have baseline values indicative of lack of control at baseline. If during the observational period such patients gain control and then deteriorate they may not meet the criteria for secondary objective events; particularly those for CompEx where derivation are in reference to change from baseline (ie, it is too hard to meet the change from baseline criteria given an initial lack of control at baseline). As such the number of patients with an event may be undercounted, and such patients will not be included in any secondary event analyses because they will not have met the criteria for an event.
- If patients do not record data on home devices at the time that they are, for example, hospitalised, or at home not feeling well, important data around a deterioration in asthma control may be missed.
- Given the above, and if more deterioration is observed in 1 treatment arm compared to the other then more missing data may be observed in 1 treatment arm compared to the other around an event.
- For the secondary objective, if a patient experiences more than 1 event, their data may be included more than once in any data analyses.
- When deriving change from baseline in reliever medication use, patients randomised to receive SYMBICORT as reliever medication in the Treatment Period will have received salbutamol in the Run-in Period, whereas patients randomised to receive salbutamol as reliever medication in the Treatment Period will have also received salbutamol in the Run-in Period; baseline is based on data from the Run-in Period. Data are however analysed in terms of occasions of use, defined as 2 puffs for salbutamol or 1 inhalation for SYMBICORT.
- CCI methods for nasal biomarkers may CCI . Any interpretation is deemed exploratory.

1.3 Number of Patients

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

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 patients 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.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

2.1.1 All Patients Analysis Set

The All Patients Analysis Set is defined as all patients screened for the study who signed the informed consent form. All disposition and screening failure analyses will be based on the All Patients Analysis Set.

2.1.2 Full Analysis Set

The FAS is defined as all patients randomised who had at least 1 post-baseline measurement, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed as randomised, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be based on the FAS.

The following subsets of the FAS are defined to assess the secondary and exploratory objectives:

2.1.2.1 FAS – Secondary Objective

Patient population who have reported at least 1 of the secondary objective events is defined as FAS - Secondary Objective.

CCI [redacted]

CCI [redacted]

2.1.3 Safety Analysis Set

The Safety Set (SS) is defined as all patients who received at least 1 dose of investigational product. Patients will be classified according to the treatment they actually received.

All safety summaries will be based on the SS.

2.2 Violations and Deviations

Deviations from the CSP will be assessed as "Important" by Parexel in conjunction with AstraZeneca. Important protocol deviations will be identified before database hard lock. Important protocol deviations are defined in the project-specific Protocol Deviation Specification, however, will include the following:

- Violation of inclusion and/or exclusion criteria;
- Patients who developed withdrawal criteria during the study but were not withdrawn;
- Wrong study treatment or incorrect dose administered;
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.

Upon database release, before database hard lock, protocol deviation and analysis population outputs will be produced and will be sent to AstraZeneca for review. A Data Review Report will be created, and, if required, a Data Review Meeting (DRM) will be arranged to discuss the outputs and consolidate decisions prior to database hard lock and will be documented in the Data Review Report and approved by AstraZeneca.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary and Secondary Objective Variables

3.1.1 Fractional exhaled Nitric Oxide

FeNO will be collected as the outcome measure for inflammation and will be measured by the patient using a FeNO monitoring device (Bosch Vivatmo Me). The concentration of FeNO will be measured in units of ppb. An increase in FeNO values suggest reduced asthma control.

FeNO will be performed daily (in the morning) during the Run-in and Treatment Periods as specified in the SoA (see Table 2), and will be summarised in terms of observed values, change from baseline and percentage change from baseline over time. If more than one FeNO is performed in a day, then the average of the measures is used for analysis purposes. Due to the skewed nature of the data, geometric mean and 95% CI will also be presented based on back-transformation (to original scale) of log-transformed values.

3.1.2 Spirometry

3.1.2.1 PEF and FEV_1

PEF and FEV_1 will be collected as the outcome measures for lung function and will be measured by the patient using a spirometry sensor (MIR Spirobank Smart™). PEF will be measured in units of L/min, and FEV_1, in units of L. A decrease in PEF or FEV_1 values suggest reduced asthma control.

PEF and FEV_1 will be performed daily (morning and evening) during the Run-in and Treatment Periods as specified in the SoA (see Table 2).

Morning and evening PEF and FEV_1 will be summarised in terms of observed values, change from baseline and percentage change from baseline over time, as appropriate.

As per the CSP, patients should perform 3 successive peak flow manoeuvres for each morning/evening session; for summaries and analysis of PEF and FEV_1, the best (highest)

results of the 3 manoeuvres performed at each morning/evening session will be used. Three assessments are specified per protocol at a given timepoint, if less than 3 or more than 3 assessments are recorded then the highest will still be used for analyses purposes.

Unit conversion factors for PEF, and FEV_1 data will be applied, as required, in order to align the received vendor data for home assessments with the standard reporting units:

- PEF, collected as cL/s:
  - 1 cL/s to L/min = 0.6 L/min.
- FEV_1, and PEF, collected as cL:
  - 1 cL = 0.01 L
  - 1 cL = 10 mL.

3.1.3 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).

The morning and evening asthma symptom diary data will include daily recordings of asthma symptoms, reliever use, and nights with awakenings due to asthma symptoms.

Asthma symptom diary data will be summarised in terms of observed values, change from baseline and percentage change from baseline over time, as appropriate.

3.1.3.1 Reliever Medication Use

Occasions of reliever medication use will be collected as the outcome measure for reliever use. Patients will be provided with Ventolin® Evohaler® (salbutamol, pMDI), as reliever medication, to be used as needed, starting from Visit 1. From Visit 2, patients will be provided with either SYMBICORT Turbohaler® (budesonide/formoterol) or salbutamol, as reliever medication, to be used, as needed, according to their randomised treatment arm. The recommended reliever usage is to take 2 puffs of salbutamol or 1 inhalation of SYMBICORT, as needed, upon symptoms.

Patients will record their use of reliever medication twice daily (morning and evening) during the Run-in and Treatment Period as specified in the SoA (see Table 2) in the asthma symptoms diary. 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. The total reliever use will also be evaluated by patient.

3.1.3.2 Asthma Symptom Score

Asthma symptom score will be collected as the outcome measure for symptoms. During the Run-in and Treatment Periods, patients will record the severity of their asthma symptoms during night time and day-time each morning and evening, as specified in the SoA (see Table 2), in the asthma symptom diary. Asthma symptoms are scored on a scale of 0 to 3, where higher scores represent more severe impairment/symptoms (reduced asthma control).

The total asthma symptom score, on a scale of 0 to 6, where higher scores represent more severe impairment/symptoms (reduced asthma control), will be derived and summarised by treatment arm.

3.1.3.3 Night Time Awakening

Patients will record every morning if they had any awakening because of asthma during the last night in the asthma symptom diary during the Run-in and Treatment Period.

3.1.4 Baseline for Primary and Secondary Objective Variables

For primary outcome measure variables, baseline will be defined as mean value over the 10 days prior to randomisation (over the Run-in Period). As per CSP, patients must be ≥80% compliant with their asthma assessments (FeNO, spirometry and asthma symptoms) during the Run-in Period at home to meet the eligibility criteria for randomisation. This means the baseline value should not be affected too much by missing data. The mean value over the 10 days prior to randomisation will be derived as follows, and calculated separately for variables collected in the morning and evening:

$$\frac{Sum\ of\ non\text{-}missing\ values\ over\ 10\ days\ prior\ to\ randomisation}{Number\ of\ days\ with\ non\text{-}missing\ data\ over\ 10\ days\ prior\ to\ randomisation}.$$

Table 3 shows the Run-in Period sessions that will be used to derive the baseline value:

Table 3 Outcome Measure Variables at Baseline

Collection Day	Collection Time	Analysis Day
Day -10	Morning	Day -10
Day -10	Evening	
Day -9	Morning	Day -9
Day -9	Evening	
Day -8	Morning	Day -8
Day -8	Evening	
Day -7	Morning	Day -7
Day -7	Evening	
Day -6	Morning	Day -6
Day -6	Evening	
Day -5	Morning	Day -5
Day -5	Evening	
Day -4	Morning	Day -4
Day -4	Evening	
Day -3	Morning	Day -3
Day -3	Evening	
Day -2	Morning	Day -2
Day -2	Evening	
Day -1	Morning	Day -1
Day -1	Evening	

3.2 Safety Variables

3.2.1 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken as specified in the SoA (see Table 2).

The laboratory variables to be measured are presented in Table 4.

The results of the most recent tests performed at the Screening Visit (Visit 1) or Baseline Visit (Visit 2) visits will be regarded as baseline data.

Table 4 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 will be performed as specified in the SoA (see Table 2).

3.2.2 Physical Examinations

Physical examination will be performed at timelines as specified in the SoA (see Table 2). 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 as specified in the SoA (see Table 2) for calculation of Body Mass Index (BMI).

3.2.3 Vital Signs

Vital signs will be collected at the times as specified in the SoA (see Table 2). The vital sign parameters to be assessed (prior to study treatment administration) are oral temperature (ºC), pulse rate (bpm), respiratory rate (bpm), and blood pressure (mmHg) measurements.

The results of tests performed at the Screening Visit (Visit 1) will be regarded as baseline data.

3.2.4 Adverse Events

Data relating to all AEs that are serious, leading to discontinuation or related to medical device incidents will be collected from the start of run-in medication and throughout the Treatment Period as specified in the SoA (see Table 2).

3.2.5 Medical Device Incidents

Data relating to medical device incidents will be collected from the start of run-in medication and throughout the Treatment Period as specified in the SoA (see Table 2).

3.3 Exploratory Variables

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

3.3.2 Spirometry Measured at Site

FEV_1 (L), FVC (L) and percent of predicted values of FEV_1 (% predicted normal [PN]) will be performed at site during Visits 1, 2, 3, and 4 as per CSP Version 2.0 (March 12, 2019) only.

Under CSP Version 3.0 (September 16, 2020) FEV_1 (L), FVC (L) and FEV_1 (% PN) will be performed at site during Visit 1 only, as indicated in the SoA (see Table 2). If there is a premature discontinuation visit, spirometry will be performed.

4. ANALYSIS METHODS

4.1 General Principles

This study is exploratory in nature with no formal hypothesis pre-specified. 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.

'Study Day' will be calculated relative to the date of randomisation, ie,

if Assessment Date < Randomisation Date then;

$$Study\ Day\ =\ Assessment\ Date - Randomisation\ Date.$$

Else if Assessment Date ≥ Randomisation Date then;

$$Study\ Day = Assessment\ Date - Randomisation\ Date + 1.$$

All visit-based summaries using data recorded on the eCRF will use analysis visits. All post-randomisation scheduled and unscheduled visits (excluding premature discontinuation visit), will be mapped to an appropriate analysis visit. Details of which can be found in Table 5.

Table 5 Analysis Visit Mapping Based on Study Day

eCRF visit	Target day	Protocol Visit Window	Actual assessment day	Analysis Visit
Visit 2 (Baseline)	D1		D1	Baseline
Visit 3 (Week 12)	D85		D2 to D126	Week 12
Visit 4 (Week 24)	D169		D127 to D172	Week 24
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Listings will display all values contributing to a time point for a patient. For visit-based summaries, if there is more than 1 value per patient within a time window, then the closest

value will be summarised, or the earliest in the event the values are equidistant from the nominal visit date. The listings will highlight the value for that patient that went into the summary table, wherever feasible.

In the table, listing and figure outputs, treatment will be presented using nominal dose and the treatment labels to be used are described in Table 6.

Table 6 Treatment Arm Labels

Study Period	Dose Level*	Treatment Arm Description	Treatment Label
Run-in Period/ Treatment Period	Low	SYMBICORT (100/6 µg) + salbutamol (100 µg) PRN	SYMBICORT + salbutamol PRN
	Medium	SYMBICORT (200/6 µg) + salbutamol (100 µg) PRN	
Treatment Period	Low	SYMBICORT (100/6 µg) + SYMBICORT PRN	SYMBICORT + SYMBICORT PRN
	Medium	SYMBICORT(200/6µg) + SYMBICORT PRN	

* ICS/LABA dose prior to study entry per GINA 2018 guidelines.

Continuous data will be summarized in terms of the number of non-missing observations, mean, standard deviation (SD), two-sided 95% confidence interval (CI) of the mean (except safety data), median, minimum and maximum unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, two-sided 95% CI of the mean, SD and median, will be reported to one more decimal place than the raw data recorded in the database. For derived continuous data, a maximum of four decimal places will be used for all summary statistics.

For FeNO, CCI [redacted] biomarker data will be summarised using arithmetic mean, SD, median, minimum and maximum, along with geometric mean (Roenfeldt K 2018), geometric coefficient of variation, and the associated two-sided 95% CI, 1st and 3rd quartile, in order to describe the lognormal distribution of the skewed data.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages, as well as a two-sided 95% CI for proportions computed using exact Clopper-Pearson method, where necessary.

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

SAS® Version 9.3 or higher will be used for the data analysis. Raw data listings will be appended to the final clinical study report (CSR). All tables, figures and listings will be presented in portable document format (PDF) documents without any manual editing; ie, they will appear unmodified as programmed by means of the statistical package.

4.1.1 Rules for Handling Missing Data

If smoking start date, date of asthma diagnosis, medical history start/end dates or AE start/end dates are partially missing they will be imputed. If start day is missing, this will be set to the first day of the month, "01", unless month is the same as month of the first dose of study drug, in that case, impute as first dose date. If month is missing for the start date, this will be set to the first month of the year, "January". If day and month are missing for the start date, this will be set to "1st January" unless year is the same as first dose date, then impute as first dose date. If year is missing or the whole date is missing, then the date will be left as missing.

If end day is missing, this will be set to the last day of the month unless the month is the same as month of first dose of study drug, then impute last dose date. If the day and month are missing, impute as 31st December unless year is the same as first dose date, then impute as last dose date. If the whole date is missing, then the date will be left missing.

Missing or partially missing AE dates will be assumed to be occurring during the Treatment Period, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the start of the Treatment Period.

If either morning or afternoon (AM/PM) scores or reliever use is missing, the respective total score or total reliever use will be set to missing.

4.1.2 Outlier data exclusion

Outlier data due to the high variability of measures, as confirmed statistically or clinically by the sponsor team, will be excluded from figures to aid interpretability. The outlier data which is excluded will be presented in a separate listing for transparency.

The following criteria is used for the exclusion of outliers:

Parameter	**Exclusion criteria**
FeNO	Exclude data >150
PEF (morning)	Exclude value <80
PEF (evening)	Exclude value >900
CCI [redacted]	[redacted]

Note that nasal biomarker data should be logged using the logarithm base 10 since the data is skewed. Further details of exclusion handling will be specified in the Analysis Dataset Specification.

4.2 Analysis Methods

4.2.1 Patient Disposition

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

The following summaries will be provided:

- A table of the number of patients enrolled into the study, and the number and percentage of patients entering the Run-in Period, randomised, treated and not treated, and completing the study, by treatment arm and overall. In addition, reasons for not completing the study will be summarised by treatment arm (Analysis population: All Patients Analysis Set)
- A table of the number of patients randomised per centre, by treatment arm (Analysis population: All Patients Analysis Set)
- A table of stratification factors, i.e. ICS (low/medium dose)/LABA at study entry by treatment arm (Analysis population: Full Analysis Set).

Study disposition will also be presented in a figure.

By-patient listings of disposition details for discontinued patients and patients completing the study will be provided. In addition, a by-patient listing of the randomisation scheme and codes will be provided.

4.2.2 Analysis Sets

The following summaries will be provided:

- A table of the number and percentage of patients in each analysis set by treatment arm. Exclusions from each analysis set will also be summarized by reason.

By patient listings of patients excluded from each analysis set and the data excluded from Full Analysis Set (FAS) will be provided.

4.2.3 Violations and Deviations

The following summaries will be provided:

- A table of the number and percentage of patients with an important protocol deviation by treatment arm and by type of deviation (Analysis population: Full Analysis Set).

A by patient listing of important protocol deviations for all randomised patients will also be provided.

Protocol deviations confirmed to be due to Coronavirus Disease 2019 (COVID 19) will be summarised. See Section 4.2.10 for more information.

4.2.4 Demographic and Other Baseline Characteristics

Summaries of demographic and baseline characteristics, and medical history data will be performed on the FAS. Summaries of demographic and baseline characteristics, and medical history will also be performed on the FAS subsets of patients defined in Sections 2.1.2.1 to 2.1.2.3 (ie, FAS-Secondary Objective, FAS-Nasal Biomarker and FAS-Event Visit) to support secondary and exploratory objective analyses.

The following summaries will be provided:

- A table of demographic characteristics by treatment arm
- A table of patient characteristics by treatment arm (height, weight, BMI)
- A table of asthma characteristics at baseline by treatment arm
- A table of diary data at baseline by treatment arm
- A table of lung function at baseline by treatment arm
- A table of relevant medical history by SOC, PT and treatment arm

By-patient listings of demographic characteristics, patient characteristics, asthma characteristics, and baseline lung function data detailed above will be provided.

Screening values for laboratory assessments, pregnancy tests and blood pressure will not be presented in the tables corresponding to demographic and screening characteristics but together with the corresponding assessments after baseline and with the changes from baseline (where relevant) to ease the interpretation of these safety outcomes.

4.2.4.1 Demographic and Patient Characteristics

Demographic characteristics to be assessed are age (years), sex, race and ethnic group. The following age groups will also be presented for EudraCT reporting:

- Adults (18-64 years)
- Adults From 65 years
  - Elderly (From 65-84 years)
  - Elderly 85 years and over.

Patient characteristics to be assessed are height (cm), weight (kg) and BMI (kg/m^2). BMI will be calculated as follows:

$$\frac{weight\ (kg)}{height\ (m)^2}$$

4.2.4.2 Asthma Characteristics

Asthma characteristics to be assessed include:

- Asthma duration (years), calculated as:

$$\frac{(date\ of\ randomisation - date\ of\ diagnosis\ of\ asthma) + 1}{365.25}.$$

- Prior use of ICS (low/medium dose)
- Number of exacerbations treated with systemic corticosteroids experienced in last 12 months prior to Visit 1
- Number of exacerbations treated with systemic corticosteroids leading to emergency room visits experienced in last 12 months prior to Visit 1
- Number of exacerbations treated with systemic corticosteroids leading to hospitalisation experienced in last 12 months prior to Visit 1
- Time since last of these exacerbations (days), calculated as:

$$date\ of\ randomisation - date\ of\ most\ recent\ exacerbation.$$

- Smoking consumption (total number of pack-years)
- Smoking status (non-smoker, current smoker, former smoker)

4.2.4.3 Baseline Asthma Symptom Diary Data

Baseline asthma symptom diary data to be assessed include:

- Average morning reliever medication use (number of occasions)
- Average evening reliever medication use (number of occasions)
- Average total reliever medication use (where the total on Day_n is derived as the morning and evening values on Day_n)
- Average morning asthma symptom score
- Average evening asthma symptom score
- Average total asthma symptom score (where the total on Day_n is derived as the morning and evening values on Day_n)
- Percentage of night time awakening days
- Percentage of asthma control days
- Percentage of reliever-free days
- Percentage of symptom-free days

Baseline for the above data will be derived as per Section 3.1.4.

4.2.4.4 Baseline Lung Function Data

Baseline lung function data to be assessed by device measurements and derived as per Section 3.1.4 will be summarised for:

- Average morning PEF (L/min)
- Average evening PEF (L/min)
- Average morning FEV_1 (L)
- Average evening FEV_1 (L)
- Average FeNO (ppb).

Observed values of the FEV_1, including percent of predicted normal values, and FVC collected at site at Visit 1 will also be summarised. Percent of predicted normal values of FEV_1 collected at site at Visit 1 will also be summarised by group:

- Group 1: FEV1 ≥80% predicted
- Group 2: 60% <FEV1 <80% predicted
- Group 3: FEV1 ≤60% predicted.

4.2.4.5 Medical History

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

4.2.5 Prior and Concomitant Medications

All medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of World Health Organisation (WHO) Drug Dictionary.

The following treatments taken prior to signing of the ICF will be considered as prior asthma medications:

- 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 (SYMBICORT as Maintenance and Reliever Therapy [SMART] therapy, SABA, and/or short-acting anticholinergic agent) within 30 days prior to Visit 1
- A table of the number and percentage of patients who used any prior asthma medication by therapeutic category and by treatment arm.

Medications for any other indication other than asthma taken by the patient during the 2 weeks prior to signing the ICF and prior to the first dose date of study run-in treatment will be considered prior medication.

Prior asthma medications will be tabulated by therapeutic categories for FAS, FAS – Secondary Objective, FAS – Nasal Biomarker and FAS – Event Visit, with the medication summaries done for any prior asthma medications taken prior to signing of the ICF and for any prior asthma medications taken between signing of the ICF and Visit 2. The therapeutic categories to be considered are (based on GINA 2018 guidelines):

- ICS (low)
- ICS (medium)
- ICS (low)/LABA combination
- ICS (medium)/LABA combination
- Leukotriene Receptor Antagonists (LTRAs)
- Theophylline

- Tiotropium
- Others.

Therapeutic categories will be identified during medical review. The dose levels for prior use of ICS will be identified using the clinical comparability of doses detailed in Table 7 as taken from the CSP.

Table 7 Estimated Clinical Comparability for Low and Medium Doses of Inhaled Corticosteroids

Drug	Daily dose (mcg)	
	Low	Medium
Beclometasone dipropionate (CFC)*	200-500	>500-1000
Beclometasone dipropionate (HFA)	100-200	>200-400
Budesonide (DPI)	200-400	>400-800
Ciclesonide (HFA)	80-160	>160-320
Fluticasone furoate (DPI)	100	Not applicable
Fluticasone propionate (DPI)	100-250	>250-500
Fluticasone propionate (HFA)	100-250	>250-500
Mometasone furoate	110-210	>210-440
Triamcinolone acetonide	400-1000	>1000-2000

CFC: Chlorofluorocarbon propellant; DPI: Dry powder inhaler; HFA: Hydrofluoroalkane propellant
* Beclometasone dipropionate (CFC) is included for comparison with old literature
Source: Global Strategy for Asthma Management and Prevention. Updated 2018. Available from http://www.ginasthma.org/ (accessed on 24 March 2018).

Any medication taken from Visit 1 until Visit 2 (randomisation) will be considered as Run-in concomitant medication. Any medication taken from Visit 2 until the end of the study participation, will be considered concomitant medication.

The following summaries will be provided:

- A table of prohibited concomitant medications during run-in by ATC (level 3), PT, and treatment arm. This will be produced for the FAS and the 3 FAS subsets.
- A table of prohibited concomitant medications during study treatment by ATC (level 3), PT, and treatment arm. This will be produced for the FAS and the 3 FAS subsets.
- A table of all allowed concomitant medications during study treatment by ATC (level 3), PT, and treatment arm. This will be produced for the FAS and the 3 FAS subsets.

The identification of prohibited concomitant medications will be conducted as part of the medical review.

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

4.2.6 Compliance

By-patient listings of treatment administration and patients receiving the various batches of maintenance treatment, as well as randomised treatment allocation and actual treatment received will be provided.

4.2.6.1 Compliance to Daily Measures

Compliance to daily measures during the Treatment Period for an assessment will be calculated using the following equation:

$$Compliance\ to\ daily\ measures\ (\%) = \frac{Number\ of\ sessions\ with\ actual\ complete\ data}{Number\ of\ expected\ sessions\ with\ complete\ data} \times 100.$$

Compliance to daily measures will be calculated for the following assessments:

- FeNO (morning only)
- PEF (morning and evening separately)
- FEV_1 (morning and evening separately)
- Asthma symptom diary score (morning and evening separately).

The number of expected days with complete data is equal to one session, twice per day for morning and evening collection, or once per day for morning collection only, throughout the duration of the study for each patient, eg, would be 28 or 14 sessions if a patient completes the Run-in Period, 336 or 168 sessions if a patient completes the Treatment Period and 364 or 182 sessions if a patient completes the study.

- A table of the compliance to daily measures, by month and overall, by treatment arm (Analysis population: Full Analysis Set)

4.2.7 Analyses of Endpoints

All primary objective summaries and analyses will be based upon the FAS as defined in Section 2.1.2. The secondary objective summaries and analyses will be based upon the appropriate FAS subset, as defined in Section 2.1.2.1 and the exploratory endpoint summaries and analyses will be based upon the FAS or the appropriate subset, as defined in Section 2.1.2.

By-patient listings of the individual primary/secondary analyses response data and assessments will be provided.

4.2.7.1 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 defined in Table 8.

Table 8 Efficacy Outcome Measures

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

AM=Morning; FeNO=Fractional exhaled Nitric Oxide; FEV_1=Forced Expiratory Volume in 1 second; PEF=Peak Expiratory Flow; PM=Evening.

See the following sub-sections for derivation of each outcome measure.

Analysis table

A summary of the average observed values and change from baseline (including percent change from baseline) in each primary outcome measure over the Treatment Period will be tabulated by week and treatment arm. For FeNO and nasal biomarker data, a geometric mean will be presented along with 1st and 3rd quartiles of the data, as outlined in Section 4.1 (note that for nasal biomarker data, the geometric coefficient of variation will be presented)

FeNO values below the limit of detection, i.e. below 5, are recorded in the device as 0. They will be analysed as 3.5ppb.

The asthma symptom diary sessions, used to derive the analysis weeks, are described in Table 9. Data from the date of randomisation, i.e. Day 1, will not be used for any analysis purposes.

Table 9 Diary Variables Weeks

Analysis Week	First Session Included	Last Session Included
Baseline	-D10 Morning	-D1 Evening
Week 1	D2 Morning	D7 Evening
Week 2	D8 Morning	D14 Evening
Week 3	D15 Morning	D21 Evening
Week 4	D22 Morning	D28 Evening
Week 5	D29 Morning	D35 Evening
Week 6	D36 Morning	D42 Evening
Week 7	D43 Morning	D49 Evening
Week 8	D50 Morning	D56 Evening

Table 9 Diary Variables Weeks

Analysis Week	First Session Included	Last Session Included
Week 9	D57 Morning	D63 Evening
Week 10	D64 Morning	D70 Evening
Week 11	D71 Morning	D77 Evening
Week 12	D78 Morning	D84 Evening
Week 13	D85 Morning	D91 Evening
Week 14	D92 Morning	D98 Evening
Week 15	D99 Morning	D105 Evening
Week 16	D106 Morning	D112 Evening
Week 17	D113 Morning	D119 Evening
Week 18	D120 Morning	D126 Evening
Week 19	D127 Morning	D133 Evening
Week 20	D134 Morning	D140 Evening
Week 21	D141 Morning	D147 Evening
Week 22	D148 Morning	D154 Evening
Week 23	D155 Morning	D161 Evening
Week 24	D162 Morning	D168 Evening
Week 25	D169 Morning	D175 Evening
Week 26	D176 Morning	D180 Evening
Treatment Period	D2 Morning	D180 Evening

Outcome Measures

Inflammation

For the summary table of inflammation by week and treatment arm, average morning FeNO values will be derived for each patient.

Average morning FeNO will be derived as follows:

$$\frac{Sum\ of\ morning\ FeNO\ values\ in\ period}{Number\ of\ days\ morning\ FeNO\ was\ completed\ in\ period}.$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Baseline will be defined as average morning FeNO over the 10 days prior to randomisation (see Table 3).

Symptoms

For the summary table of symptoms by week and treatment arm, average morning and evening asthma symptom scores, as well as total asthma symptom scores and night time

awakenings due to asthma symptoms, as defined in Section 4.2.9.7, will be will be derived for each patient.

Average morning asthma symptom score will be derived as follows:

$$\frac{Sum\ of\ morning\ asthma\ symptom\ scores\ in\ period}{Number\ of\ days\ morning\ Diary\ was\ completed\ in\ period}.$$

Average evening asthma symptom score will be derived as follows:

$$\frac{Sum\ of\ evening\ asthma\ symptom\ scores\ in\ period}{Number\ of\ days\ evening\ Diary\ was\ completed\ in\ period}.$$

Average total asthma symptom score will be derived as follows:

$$\frac{Sum\ of\ total\ asthma\ symptom\ scores\ in\ period}{Number\ of\ days\ total\ asthma\ symptom\ score\ available\ in\ period},$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Baseline will be defined as mean daily asthma symptom score over the 10 days prior to randomisation (see Table 3).

Lung Function

For the summary table of lung function by week and treatment arm, average morning and evening lung function values will be derived for each patient.

PEF

Average morning PEF will be derived as follows:

$$\frac{Sum\ of\ morning\ PEF\ values\ in\ period}{Number\ of\ days\ morning\ PEF\ was\ completed\ in\ period}.$$

Average evening PEF will be derived as follows:

$$\frac{Sum\ of\ evening\ PEF\ values\ in\ period}{Number\ of\ days\ evening\ PEF\ was\ completed\ in\ period}.$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Baseline will be defined as average morning or evening PEF over the 10 days prior to randomisation (see Table 3).

FEV_1

Average morning FEV_1 will be derived as follows:

$$\frac{Sum\ of\ morning\ FEV_1\ values\ in\ period}{Number\ of\ days\ morning\ FEV_1\ was\ completed\ in\ period}.$$

Average evening FEV_1 will be derived as follows:

$$\frac{Sum\ of\ evening\ FEV_1\ values\ in\ week}{Number\ of\ days\ evening\ FEV_1\ was\ completed\ in\ week}.$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Baseline will be defined as average morning or evening FEV_1 over the 10 days prior to randomisation (see Table 3).

Reliever Medication Use

For the summary table of reliever medication use by week and treatment arm, average morning and evening use will be derived for each patient, based on diary data.

Average morning use of reliever medication will be derived as follows:

$$\frac{Sum\ of\ number\ of\ morning\ occasions\ of\ reliever\ medication\ used\ in\ period}{Number\ of\ mornings\ Diary\ was\ completed\ for\ reliever\ use\ in\ period}.$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study. Average evening use of reliever medication will be derived in a similar manner to that for morning use.

The derivation of overall average daily measurements will follow that of the total asthma symptom score, as outlined on page 39. Symptoms where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Baseline will be defined as average daily use of reliever medication (number of occasions) over the 10 days prior to randomisation (see Table 3).

Daily reliever medication use will be derived as follows:

$$\frac{AM\ reliever\ medication\ use\ on\ Day_n + PM\ reliever\ medication\ use\ on\ Day_n}{2}.$$

Average daily reliever medication use will be derived as follows:

$$\frac{Sum\ of\ daily\ reliever\ medication\ use\ in\ period}{Number\ of\ days\ with\ non\text{-}missing\ daily\ reliever\ medication\ use\ in\ period}'$$

where period is defined as per Table 9 for the weekly measurements, as well as for the overall duration of the study.

Reliever medication use will be presented as a line graph over the duration of the Treatment Period, by treatment arm, for morning, evening and average daily measurements at weekly intervals, as per the schedule in Table 9.

Analysis Figures

Panel Plots

For each patient, plots of the observed primary outcome measure values over time (daily data, 24-week Treatment Period) will be presented as panel plots by outcome measure. The event start date of each secondary objective event of interest that a patient experiences will also be flagged on the panel plots for each patient.

For the lung function, reliever use and symptoms outcome measures, AM, PM, and total, if appropriate, values will be presented on the same plot panel.

Spaghetti Plots with Mean Curve

For each outcome measure, spaghetti plots of the individual patient outcome measure values over time (24-week Treatment Period) will be presented with separate plots for each treatment arm. A curve for the mean (± SE) outcome measure values for the treatment arm over time (daily data, 24-week Treatment Period) will also be presented on the spaghetti plot (overlay) for each treatment arm and outcome measure combination. If there is a considerable different between the mean and median outcome measure values, then the median curve will be presented instead of the mean curve. If the data allows, a loess smoothing curve will also be presented on the spaghetti plot (overlay).

4.2.7.2 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. See the following sub-sections for derivation of each event and definitions of "surrounding an event", multiple events and overall event.

The outcome measures are as detailed in Table 8 and presented for the FAS – Secondary Objective, as defined in Section 2.1.2.1, unless otherwise specified.

Analysis Table

For each event type, the observed values for patients who had an event in each outcome measure will be summarised, by treatment arm, for each day from 7 days prior to the event start date and 7 days post the average duration of the event stop date.

Analysis Figures

Panel Plots

For each event type and each patient who had an event, plots of the observed outcome measure values over time will be presented as panel plots by outcome measure. If a patient experiences the same event more than once, then a separate plot for each event will be produced. The event start date of each secondary objective event of interest (not including the event type being plotted) that a patient experiences will also be flagged on the panel plots for each patient.

The panel plots for each patient will also be presented for all events combined. If a patient experiences multiple events, their data for each outcome measure around each event will be included in this plot so they will be included more than once.

For the lung function and symptoms (including night time awakenings, as defined in Section 4.2.9.7) outcome measures, AM and PM values will be presented on the same plot panel.

Combined Plots

A figure for variations in FeNO compared to variations in the other outcome measures over the Treatment Period will be presented for each patient who had an event separately for each treatment arm. Data will be normalized to allow for the presentation of multiple outcome measures in a single plot. The following equation for normalization will be used for each outcome measure:

$$Normalised\ change\ at\ time\ X\ (\%) = \frac{Value\ at\ Time\ X - Minimum\ Value}{Maximum\ change\ from\ Minimum\ value} \times 100.$$

, where "Minimum value" is the minimum value recorded surrounding an event and where "Maximum change from minimum value" is the maximum value surrounding the event minus the minimum value. The definition of "surrounding an event" is provided in Section 0.

For each event type, a plot showing the mean standardised percentage change from baseline in each occasion of each outcome measure over time will be presented for each treatment arm separately; ie, one plot per treatment with separate lines indicating the mean standardised percentage change from baseline time profile for each outcome measure (including night time awakenings, as defined in Section 4.2.9.7).

The combined plots for each treatment will also be presented for all events combined. If a patient experiences multiple events, their data for each outcome measure around each event will be included in this plot so they will be included more than once.

Exploratory sensitivity analyses looking at different methods for scaling/standardisation of the outcome measures may be explored.

Spaghetti Plots with Mean and Loess Curves

For each event type, spaghetti plots of the individual patient outcome measure values (for patients who had an event) over time will be presented with separate plots for each treatment arm. A curve for the mean outcome measure values for the treatment arm over time and a loess smoothing curve will be presented on the spaghetti plot (overlay) for each treatment arm, outcome measure and event type combination.

The spaghetti plots (with mean curves) for each outcome measure and treatment arm will also be presented for all events combined. If a patient experiences multiple events, their data for each outcome measure around each event will be included in this plot so they will be included more than once.

Swimmer Plot

A swimmer plot will be presented showing each patient who observed any secondary objective event of interest. All secondary objective events of interest experienced by each subject will be presented. The plot will be sorted by event start date and duration of first event (if there are multiple subjects with first events occurring on the same day).

Events of Interest

SevEx

Asthma exacerbations will be evaluated by the investigator at each visit and will be recorded on the EXACA eCRF page.

A severe exacerbation (SevEx) event is 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.

The start date of a SevEx event is defined as the earliest date of the above criteria start dates which meets the definition.

The end date of a SevEx event is defined as the latest date of the above criteria end dates which meets the definition. The duration of a SevEx will be summarised by treatment arm.

CompEx (diary 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:

- SevEx
- 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 and worsening of asthma symptoms assessed morning and evening (asthma symptom diary); in total 3 different variables.

Events in the period from randomisation to the maximum of (the last scheduled visit date, treatment end date +7) will be considered.

The algorithm for determining CompEx is based on predefined threshold values and slopes as developed by AstraZeneca (Fuhlbrigge et al 2017).

A patient will be considered to have a CompEx diary event during the planned Treatment Period if the patient has the following:

1. An objective deterioration, which is defined as either the threshold criterion or the slope criterion (or both), as defined below, being met for ≥2 consecutive days.

For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For the diary data (which is captured twice during the day), one day will be defined by the morning/evening pairing for consistency with published precedent for the CompEx endpoint. (Note: other diary endpoints in this trial will use an evening/morning pairing to define one day.) The morning diary recordings captured on the first day of treatment will not be included in the calculation of the CompEx endpoint.

Threshold criterion:

a. ≥15% decrease from baseline in either morning or evening home-based PEF, *and* at least one of the following:
b. ≥1.5 occasions increase from baseline in reliever medication in either the morning (for preceding night) or evening (for preceding day)
c. ≥1 score increase from baseline, or the absolute maximal symptom score, in either the morning or evening.

For (b), the number of doses of reliever medication is defined as the number of occasions of inhaler recorded in the morning and evening, respectively.

For (c), the asthma symptom score (scored 0-3) as described in Section 3.1.3.2 will be used, recorded in the morning and evening, respectively. The maximal symptom score is therefore 3.

Assessment of the threshold criterion in any rolling 2-day consecutive period will be based on the available data during that period. The threshold criterion can be met with non-missing values for fewer than the 6 variables specified above, provided those non-missing values meet the criterion.

Slope criterion:

One of (a), (b) or (c) above is met for ≥2 consecutive days *and* the regression slope requirement over the preceding 5 days is also met.

The regression slope requirement in the preceding 5 days is that all of the following are met:

- Morning PEF slope ≤ -3%/day
- Evening PEF slope ≤ -3%/day
- Morning (preceding night) rescue medication slope ≥ 0.3 doses/day
- Evening (preceding day) rescue medication slope ≥ 0.3 doses/day
- Morning asthma symptom score slope ≥ 0.2 score/day
- Evening asthma symptom score slope ≥ 0.2 score/day.

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the observed values of each of the 6 variables separately against day number, with no other variables included in the regression model.

For morning and evening PEF, the regression slope thus obtained will first also be divided by the baseline PEF value before applying the above criterion. Table 10 shows how the timing for the 5-day requirement for the regression slopes fits with the 2-day consecutive requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2-day consecutive assessment is made:

Table 10 Timing For Assessment Of CompEx Slope Criterion

	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1
Threshold (a), (b), (c)					x	x
Slope	x	x	x	x	x	

A regression slope will be calculated provided there are at least 2 non-missing values in the required 5 days. If 1 or more of the 6 variables above does not have at least 2 non-missing values in the required 5 days, then the slope requirement therefore cannot be met.

The start date of a CompEx diary event is defined as the objective deterioration start date. Objective deterioration start date is defined as the earliest Day 0 (in notation from Table 10)

from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

The end date of a CompEx event is defined as the objective deterioration end date. Objective deterioration end date is defined as the latest Day 1 (in notation from Table 10) from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

If the end date of the first CompEx diary event and the start date of the second CompEx diary event are less than 7 days apart for any patient, then these will be counted as 1 CompEx diary event.

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

Derived from the number of occasions of reliever medication use recorded in the asthma symptom diary (STIFLE App).

The start date of an event is defined as the earliest date where the patient fulfils the above criteria.

FeNO > 50ppb

Derived from FeNO measurement recorded with FeNO monitoring device (STIFLE App).

The start date of an event is defined as the earliest date where the patient fulfils the above criteria.

Surrounding an event

For secondary objective analyses data will be analysed "surrounding an event" for each event of an event type.

For plots that look at individual patient events, "Surrounding an event" is defined as -14 days prior to start of event (event day 0) to +7 days post end of event. For analyses that look at overall events, or multiple events for the same patient, "Surrounding an event" is defined as -14 days prior to start of event (event day 0) to +7 days post the average duration of the event. The average duration will be calculated separately for each event type. The event should be within the observational period. For events close to the start / end of the observational period, data will be truncated at the date of the start / end of observational period.

Start date of event is defined as event day 0. End date of event is defined as the last consecutive day that the subjects meet the criteria for that event type; although see also the rules for multiple events below.

Multiple events

For each event type, a subject may meet the criteria for an event more than once. As such the following rules should be followed.

- For each event type, the first event starts on the date that the subject first meets the criteria for that event type.
- For each event type, the first event stops on the date that the subject last meets the criteria for that event type prior to not meeting the criteria for that event type for >7 days.
- For each event type, a subsequent event starts on the date that the subjects first meets the criteria for that event type again after not meeting the criteria for that event type for >7 days after stop date of prior event.
- For each event type, the stop date of a subsequent event follows the same rules as for stop date of first event.

Figures which present event duration for multiple events per subject will present the average duration.

Refer to Appendix 8.1 for example of coding.

Overall event

For secondary objective analyses, in addition to analysing data "surrounding an event" for each event type, data will be analysed "surrounding an event" for each overall event. An overall event accounts for the fact that there are multiple event types, and a patient is likely to have an event for more than one event type simultaneously. By definition an overall event will be made up of events relating to at least two event types. As such not all subjects who have an event will have an overall event.

- The first overall event starts on the date that the patient first meets the criteria for at least one of the four event types.
- The first overall event stops on the date that the patient last meets the criteria for at least one of the four event types, prior to not meeting the criteria for all four of the event types for >7 days.
- A subsequent overall event starts on the date that the patients first meets the criteria for at least one of the four event types again, after not meeting the criteria for all four of the event types for >7 days after stop date of prior overall event.
- The stop date of a subsequent overall event follows the same rules as for stop date of first overall event.

Refer to Appendix 8.1 for example of coding.

4.2.8 Safety Analyses

All safety summaries and analyses will be based upon the SS, as defined in Section 2.1.3.

Change from baseline will be calculated as the differences between the post-dose value at each time point and the screening value recorded at Visit 1.

Individual safety and tolerability data will be provided in data listings and summarised as appropriate by treatment. Continuous variables (laboratory parameters and vital signs) will be summarised using descriptive statistics (n, mean, SD, minimum, median, and maximum) as appropriate by scheduled assessment time point. Where applicable, data will be summarised for the observed value, and for the corresponding change from baseline/screening. Categorical variables will be summarised in frequency tables (counts and percentage) as appropriate by scheduled assessment time point too.

4.2.8.1 Extent of Exposure to reliever treatment

The duration of exposure (days) for each reliever treatment (SYMBICORT/salbutamol) will be derived as follows based on date of first and last occasions of use from the asthma symptoms diary:

$$Duration\ of\ exposure\ (days) = Date\ of\ last\ dose - Date\ of\ first\ dose + 1.$$

Note that because reliever use for either treatment is as-needed, duration may include days where no reliever is used.

The daily dose (including days with zero use) for each reliever treatment (SYMBICORT/salbutamol) will be derived as follows based on delivered dose:

$$Daily\ dose\ (\mu g/day) = \frac{Total\ number\ of\ occasions \times delivered\ dose\ (\mu g)}{Duration\ of\ exposure\ (days)}.$$

For patients randomised to SYMBICORT as reliever, the metered dose is 100/6 µg per occasion (1 inhalation) for patients on low dose, and 200/6 µg per occasion (1 inhalation) for patients on medium dose. The delivered doses are 80/4.5 µg and 160/4.5 µg respectively (of budesonide/formoterol).

The following extent of exposure summaries will be provided:

- A table of the duration of exposure to as-needed reliever use (days) during treatment period by treatment arm, dose level (low/medium/overall).
- A table of mean daily dose of reliever treatment during treatment period.

4.2.8.2 Adverse Events

AEs will be coded by system organ class (SOC) and preferred term (PT) using the latest version of MedDRA.

AEs with an onset date on or after the date of first dose of randomised treatment and up to and including 1 day following the date of last dose of randomised treatment will be included in summary tables. Any AE occurring outside this period will be included in the data listings but will not be included in the summary tables of AEs.

The following AE summaries will be provided:

- A table of the number and percentage of patients reporting an AE in any category by treatment arm
- A table of the number of AEs reported in any category by treatment arm
- A table of the number and percentage of patients reporting a non-serious adverse event occurring in greater than 5% of patients by treatment arm, SOC and PT
- A table of the number of AEs reported by treatment arm, SOC and PT
- A table of the number and percentage of patients reporting an AE by treatment arm, SOC and PT.

AE summaries will be ordered in terms of international order for SOC, and alphabetically for PT within SOC.

For each patient and each AE, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst causality will be attributed and used in the by-causality summaries. Multiple occurrences of an AE in the same patient will only be counted once overall in patient-level summaries. All occurrences of an AE in the same patient will be counted in event-level summaries.

A by-patient listing of all AEs will be provided. This listing will be presented by treatment arm and ICS dose level (low/medium) and will include patient identifier, treatment, age, sex, race, AE (PT, and verbatim term), study day of onset, duration, intensity, seriousness, action taken, causality, outcome and concomitant medication given (including CM number).

4.2.8.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

AEs will be included in the summary tables below.

The following AE summaries will be provided:

- A table of key patient information for patients reporting AE with outcome of death
- A table of the number of serious adverse event (SAEs) reported by treatment arm, SOC and PT
- A table of key patient information for patients reporting a SAE
- A table of key patient information for patients reporting an AE leading to discontinuation of investigational product, by treatment arm and PT
- A table of the number and percentage of patients reporting AE related to medical device incidents by treatment arm, SOC and PT.

4.2.8.4 Clinical Laboratory Evaluation

Laboratory variables are described in Section 3.2.1.

The following summaries will be provided:

- A table of the observed values and change from baseline in each haematology and clinical chemistry laboratory parameter by treatment arm and time point.

By-patient listings of all laboratory data will be provided including patient identifier, treatment, age, sex, race, visit, category, lab test name, result and standard units. Laboratory reference ranges will also be listed and out of range values will be flagged.

4.2.8.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital sign variables are described in Section 3.2.3. Physical examination variables are described in Section 3.2.2. Medical device incident variables are described in Section 3.2.5.

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each applicable scheduled visit will be summarised.

The following summaries will be provided:

- A table of the observed values in each vital sign parameter by treatment arm and time point
- A table of the number and percentage of patients reporting a medical device incident by treatment arm.

By-patient listings of vital sign parameters, medical device incidents and weight, height and BMI will also be provided.

Any clinically relevant new physical examination findings or worsening of a pre-existing physical examination finding were to be recorded as an AE and will be presented with the AEs.

4.2.9 Exploratory Analyses

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4.2.9.3 Spirometry Measured at Site

The observed values in FEV_1, FVC and FEV_1 (% PN) measured at site at Visit 1 will be tabulated by treatment arm, following CSP Version 3.0 (September 16, 2020).

4.2.9.4 Seasonal Effect

FeNO over the Treatment Period will be summarised by season, month, and treatment arm.

Seasons are defined as follows:

- Winter: December, January, February

- Spring: March, April, May
- Summer: June, July, August
- Autumn: September, October, November.

A box and whisker plot of FeNO values by month they were collected in (irrespective of year) will be presented. Months will be grouped as seasons defined above.

4.2.9.5 Secondary Objective Events and Durations

The number of patients with at least 1 secondary objective event and number of secondary objective events by event type will be tabulated by treatment arm. Duration of events will be calculated as follows:

$$(last\ day\ of\ event - first\ day\ of\ event) + 1.$$

4.2.9.6 Symptom-free Day

A symptom-free day is defined as a day that fulfils all of the below criteria:

- A day with no asthma symptoms (ie, asthma symptom score = 0, for both the morning and evening assessments)
- A night with no awakenings due to asthma symptoms (the answer to the question "Did your asthma cause you to wake up last night" should be 'No').

This means for defining symptom-free for Day_n, the morning and evening assessments for Day_n will be used.

Percentage of symptom-free days will be derived as follows:

$$\frac{Number\ of\ symptom\text{-}free\ days\ in\ week}{Number\ of\ days\ Diary\ was\ completed\ in\ week} \times 100.$$

Baseline will be defined as average percentage of symptom-free days over the 10 days prior to randomisation (see Table 3).

The observed value and change from baseline in percentage of symptom-free days over the Treatment Period will be tabulated by treatment arm.

4.2.9.7 Night Time Awakenings

Percentage of night time awakening days will be derived as follows:

$$\frac{Number\ of\ days\ in\ period\ where\ patient\ recorded\ a\ night\ time\ awakening}{Number\ of\ days\ Diary\ was\ completed\ in\ period} \times 100.$$

Baseline will be defined as the percentage of night time awakening days over the 10 days prior to randomisation (see Table 3).

The observed value and change from baseline in percentage night time awakening days over the Treatment Period will be tabulated by treatment arm.

4.2.9.8 Reliever-free Day

A reliever-free day is defined as a day with no use of reliever medication (ie, both morning and evening asthma symptom diary entries indicate no reliever medication was taken, ie, zero occasions recorded).

This means for defining reliever-free for Day_n, the morning and evening assessments for Day_n will be used.

Percentage of reliever-free days will be derived as follows:

$$\frac{Number\ of\ reliever\text{-}free\ days\ in\ observational\ period}{Number\ of\ days\ Diary\ was\ completed\ in\ observational\ period} \times 100.$$

Baseline will be defined as the average percentage of reliever-free days over the 10 days prior to randomisation (see Table 3).

The observed value and change from baseline in percentage of reliever-free days over the Treatment Period will be tabulated by treatment arm.

4.2.9.9 Asthma control

An asthma control day is defined as a day that fulfils all of the below criteria:

- A day with no asthma symptoms (ie, asthma symptom score = 0, for both the morning and evening assessments)
- A night with no awakenings due to asthma symptoms (the answer to the question "Did your asthma cause you to wake up last night" should be 'No')
- A day with no use of reliever medication (ie, both morning and evening asthma symptom diary entries indicate no reliever medication was taken, ie, zero occasions recorded).

This means for defining asthma control for Day_n, the morning and evening assessments for Day_n will be used.

Percentage of asthma control days will be derived as follows:

$$\frac{Number\ of\ asthma\ control\ days\ in\ period}{Number\ of\ days\ Diary\ was\ completed\ in\ period} \times 100.$$

Baseline will be defined as average percentage of asthma control days over the 10 days prior to randomisation (see Table 3).

The observed value and change from baseline in percentage of asthma control days over the Treatment Period will be tabulated by treatment arm.

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4.2.10 Impact on Analyses Due To COVID-19 Pandemic

Given the COVID-19 pandemic, the proposed analyses relating to the exploratory objective of this study may need to be adapted if insufficient biomarker data are available because patients are unable to attend for scheduled site visits and/or event visits for biomarker sampling. Primary and secondary objectives are not likely to be impacted by the pandemic since data are collected daily at home.

COVID-19 related disruptions will be summarised by treatment arm and overall. A by-patient listing of COVID-19 related issues in the Clinical Trial Management System will be presented.

5. INTERIM ANALYSES

No interim analyses are planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Safety Analysis Set (SS) (Section Safety Analysis Set2.1.3) added to Section 2.1 and all associated safety reporting outputs previously reported on the FAS, or the FAS subsets, will be reported on the SS instead, as per Sponsor request. Full Analysis Set subgroups have been added (Sections 2.1.2.1, 2.1.2.2, 2.1.2.3).

7. REFERENCES

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8. APPENDIX

8.1 Coding Example for Events and Overall Events

Example Patient

Event Type
First event for event type
Second event for event type
Third event for event type
Unique event

Study day	Date	FeNO criteria indicator variable	Reliever use critiera indicator variable	SevEx criteria indicator variable	CompEx criteria indicator variable	FeNO event variable	Reliever use event variable	SevEx event variable	CompEx event variable	Overall Event variable
21	21/04/2021	0	0	0	0	0	0	0	0	0
22	22/04/2021	1	0	0	0	1	0	0	0	1
23	23/04/2021	1	1	0	1	1	1	0	1	1
24	24/04/2021	0	1	0	1	1	1	0	1	1
25	25/04/2021	0	1	1	1	1	1	1	1	1
26	26/04/2021	1	0	1	1	1	0	1	1	1
27	27/04/2021	1	0	1	1	1	0	1	1	1
28	28/04/2021	0	0	1	1	1	0	1	1	1
29	29/04/2021	0	0	1	1	1	0	1	1	1
30	30/04/2021	0	0	0	1	1	0	0	1	1
31	01/05/2021	1	0	0	1	1	0	0	1	1
32	02/05/2021	1	0	0	0	1	0	0	0	1
33	03/05/2021	0	0	0	0	0	0	0	0	1
34	04/05/2021	0	0	0	0	0	0	0	0	1
35	05/05/2021	0	1	0	0	0	2	0	0	1
36	06/05/2021	0	1	0	0	0	2	0	0	1
37	07/05/2021	0	1	0	0	0	2	0	0	1
38	08/05/2021	0	0	0	0	0	2	0	0	1
39	09/05/2021	0	0	0	0	0	2	0	0	1
40	10/05/2021	0	0	0	0	0	2	0	0	1
41	11/05/2021	0	1	0	1	0	2	0	1	1
42	12/05/2021	0	1	1	1	0	2	2	1	1
43	13/05/2021	0	1	1	1	0	2	2	1	1
44	14/05/2021	0	1	0	1	0	2	0	1	1
45	15/05/2021	0	1	0	0	0	2	0	0	1
46	16/05/2021	0	0	0	0	0	0	0	0	0
47	17/05/2021	0	0	0	0	0	0	0	0	0
48	18/05/2021	0	0	0	0	0	0	0	0	0
49	19/05/2021	0	0	0	0	0	0	0	0	0
50	20/05/2021	0	0	0	0	0	0	0	0	0
51	21/05/2021	0	0	0	0	0	0	0	0	0
52	22/05/2021	0	0	0	0	0	0	0	0	0
53	23/05/2021	0	0	0	0	0	0	0	0	0
54	24/05/2021	1	0	0	0	2	0	0	0	2
55	25/05/2021	0	0	0	0	0	0	0	0	2
56	26/05/2021	0	1	0	0	0	3	0	0	2
57	27/05/2021	0	1	0	0	0	3	0	0	2
58	28/05/2021	0	0	0	0	0	0	0	0	0
59	29/05/2021	0	0	0	0	0	0	0	0	0
60	30/05/2021	0	0	0	0	0	0	0	0	0
61	31/05/2021	0	0	0	0	0	0	0	0	0
62	01/06/2021	0	0	0	0	0	0	0	0	0
63	02/06/2021	0	0	0	0	0	0	0	0	0
64	03/06/2021	0	0	0	0	0	0	0	0	0
65	04/06/2021	0	0	0	0	0	0	0	0	0
...										

8.2 Amendment History

Details of amendments made between version 1.0 and version 2.0.

Description of change
Updates and clarifications to wording throughout to be consistent with protocol and throughout document in general.
References to sputum biomarker collection and analysis removed throughout.
Text related to enrolment period duration removed. Study duration updated.
Event Criteria 2 text amended. Text related to Event visit criteria 2 and 3 amended.
FEV1 collected at Visit 1 using study site equipment only, all other FEV1 measurements done using patient devices throughout the study under CSP version 3.0.
Visit 3 added as telephone visit only. Visit 4 description and assessments performed updated.
Text related to patient screening and screening failure rate removed from the SAP.
"and safety" removed from FAS definition. All safety analyses reporting will be done based on SS, defined in Section 2.1.3.
Safety Analysis Set added.
Protocol deviation text related to COVID-19 added.
Text related to exclusion of patients and/or patient data and patient exclusion from analyses has been removed
Text added to summarise how FeNo, PEF and FEV1 data will be analysed, in term of observed values, changes from baseline and percentage changes from baseline.
Text related to exposure summaries and use of reliever medication measurements has been removed.
Total asthma symptom score has been added.
Text related to additional safety sample collection has been removed.
CCI [redacted]
[redacted]
Rules for imputation of partial start/end dates added.
Compliance to Daily Measures – Total asthma symptom score added to list of assessments to be presented. Table of compliance to daily measures moved from Section 4.2.6.
Reliever Medication Use – Clarification of reliever data coming from the diary only. Daily reliever and average daily reliever derivations added.

Description of change
Symptoms subsections updated to include total asthma symptom score and night time awakenings due to asthma symptoms
Analysis Table – All references to Area Under the Curve (AUC) removed from the SAP.
SevEx – Definition of SevEx end date and duration of SevEx summary tables added.
Events of interest – definitions of “surrounding an event”, “multiple events” and “overall event” added
Tables of number and percentage of patients reporting AE with outcome death, SAE and DAE by SOC and PT removed.
Secondary objective on exploration of steroid exposure removed.
Target days updated in line with CSP, thus will no longer deviate from Schedule of Assessments.
Addition of SS and change from the FAS to SS in reporting of safety summaries added.

SIGNATURE PAGE

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